A Practical Guide to Managing Breast Cancer

for Low- and Middle-Income Countries

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Preface

A Practical Guide to
Managing Breast Cancer for
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Addressing Breast Cancer Globally

Cancer burden in low-middle-income countries (LMICs) is a hidden crisis that has largely gone underreported, undiagnosed, and untreated. Cancer has emerged as a significant public health problem for many of the LMICs. According to the World Health Organization (WHO), by 2020, nine million of the 15 million people with cancers will be living in developing countries. More than 50% of new cancer cases and 60% of cancer deaths occur in these countries. In fact, cancer kills more people each year than AIDS, tuberculosis, or malaria and is now one of the leading causes of death in the LMICs. Morbidity and mortality from cancer are mainly influenced by health literacy and poverty. According to the Lancet Commission, approximately 1.5 billion people lack access to safe, affordable surgical and anesthesia care when needed. That is more than four times the population of the United States of America.

Breast cancer is the most common cancer in women globally. Nearly one in every four women with cancer in the world is diagnosed with breast cancer. Worldwide, over one million

women will be diagnosed with breast cancer annually. Breast cancer is now the second leading cause of cancer death in LMICs, with over 450,000 women who will succumb to the disease.

Outcomes for patients with breast cancer in the LMICs are dismal. While the 5-year overall survival for breast cancer patients in the United States is greater than 80%, it is approximately 30% for women in sub-Saharan Africa. These facts have serious societal implications because, in many poor societies, women play an important role not only in the domestic realm (i.e., educating and disciplining the children) but also are the economic engines for their families and the nation. Deaths due to breast cancer not only disrupt these important societal roles but also force adolescent girls to assume the responsibility of their deceased mothers. These children often are forced to abandon school as they work to support their families. Poverty begets poverty, and the vicious cycle of poverty fuels itself for perpetuity.

The causes of the disparity in breast cancer outcomes between the developed and LMICs are multiple: cost, access, technology, culture, belief systems, health literacy, trust, national infrastructure, public health, and medical education. The knowledge gap at the point of medical care can be remediated. Although there are many excellent textbooks written on breast cancer, most of them are too expensive and/or overwhelmingly comprehensive to be of any practical use to those in developing countries. For example, a discussion on the merits of screening mammograms may not be germane for a nation that does not have the infrastructure or the resources for such a program. Similarly, a dedicated chapter on the art of oncoplastic surgery is impractical for a country that sees mainly patients with locally advanced breast cancer.

The Lancet Commission aimed to achieve 80% coverage of essential surgical and anesthesia services per country by 2030. To take the first step on the long journey of effectively

addressing these challenges, we editors have decided to embark on this project, namely "A Practical Guide to Managing Breast Cancer for the Low-Middle Income Countries," which we hope will precisely distill the essence of managing breast cancer into a more pragmatic form. In addition to the chapters that will specifically address the different aspects of breast cancer care, we will also add a brief chapter on how to prospectively collect and analyze data using affordable methodologies.

Although we have endeavored diligently on this project, we recognize our work's limitations. We hope that the readers will make such limitations apparent so that we might improve future editions.

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Chapter 1

Addressing the Global Burden of Breast Cancer: A Population Health Perspective

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Abstract

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-associated death in women worldwide. An exploration of the global burden of breast cancer dataset revealed a dramatic increase in total disability-adjusted life years (DALYs) from 1990 to 2019 in low, low-middle, and middle sociodemographic index (SDI) countries. The most significant increase was attributed to the rising number of chronic (noncommunicable) diseases, with a reduction in women's deaths from infectious diseases and pregnancy-related mortality. By 2040, an estimated 28.4 million new breast cancer cases are projected worldwide. This aging population of women with breast cancer, coupled with inadequate breast care resources, will have dire consequences. The looming crisis requires innovative approaches to navigating this population health crisis within complex, resource-limited global health systems. An emphasis on value-based population health management (VBPHM) will help progress toward the goal of

early breast cancer detection worldwide. Ultimately, adaptive leadership is required to promote the national and international early breast cancer detection agenda.

Introduction

We face severe gaps in healthcare delivery needs worldwide[1]. The increasing burden of non-communicable diseases (NCDs) falls disproportionately on resource-limited countries or subpopulations within a country[2,3,4]. Cancer ranks among the top five causes of global death among NCDs threatening all populations[4]. In 2018, Globocan reported 18 million new cancer diagnoses worldwide, with about 11% or 2.1 million newly diagnosed female breast cancers, the leading cause of cancer-related mortality of women in low- and middle-income countries (LMIC) and the leading cause of death in developed countries[5,6]. In 2040, an estimated 28.4 million new cancer cases are projected worldwide, with a 33.8% increase in breast cancer from 2020 (Figure 1; 7). Since the original 2001 Institute of Medicine observation that “between the health care we have and the healthcare, we could have lies not just a gap but a chasm,” the subsequent 2018 report recognized that the global chasm has grown even greater[8,9]. All stakeholders' organized national and global strategic effort is essential to “bend the curve” away

from the looming crisis[10, 11].

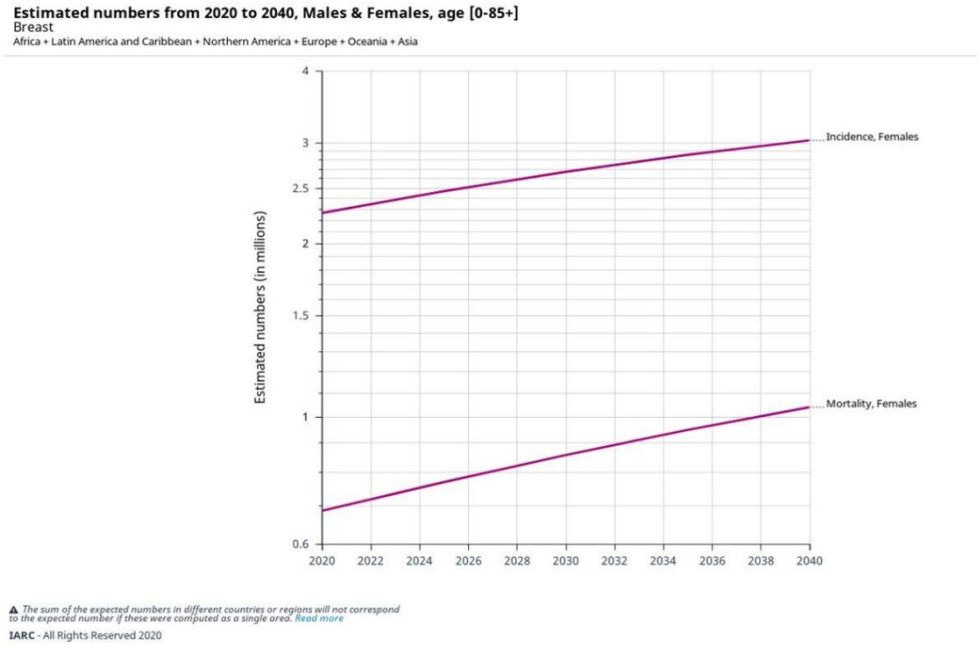

Figure 1: Estimated new cancer cases worldwide

Multiple barriers to improving breast healthcare persist in LMIC[12, 13, 14]. Fifty percent of women in resource-limited countries present with clinical stage III breast cancer compared to 10% in resource-abundant countries[11]. Studies highlight the demand for adaptive strategies to tackle this growing burden of breast cancer in low-resource countries[15]. To reduce worldwide breast cancer deaths, there is a dire need to address the unequal distribution of medical resources and accessibility to breast care delivery[16]. A global goal of improving access to breast care with the early detection of breast cancer is essential[15, 17]. The Breast Cancer Initiative 2.5 outlines its commitment to overcoming barriers in eliminating breast health disparities worldwide (Table 1, 17). However, the problem of fragmentation in health care is shared by all countries, whether high-, middle-, or low-income, resulting in the vast majority of health system failures. The lack of a practical "system thinking" approach impedes excellence in global care delivery and

illustrates the limitations of the traditional method of dividing complex problems into basic units[18, 19]. Systemic conditions—such as fragmentation, unclear goals, unreliable supply chains, burdensome rules, inadequate information flows, and lack of valuable data, contribute to health inequities[9].

Barriers	
Structural	
	Geographic location of services
	Transportation needs
	Insufficient diagnostic or treatment services
	Insufficient or undertrained workforce
	Ineffective referral networks
	Inadequate patient navigation
Sociocultural	
	Myths and misconceptions about the causes and treatment of cancer, stigma, language, discrimination, social class, gender, and religious beliefs
Personal	
	May include mistrust of the health system, fear of a cancer diagnosis, low health literacy and competing family and work obligations
	Supportive care to help reduce psychosocial barriers to treatment
Financial	
	Access to care issue from need for out-of-pocket payment for services as well as indirect costs such as transportation, housing, childcare, and lost wages

Table I: Barriers to Eliminating Breast Health Disparities

The magnitude and cost of the "global quality chasm" is reflected by health disparities within and across countries[9, 20, 21]. Awareness of this "cancer divide," with a substantially higher burden of disease and worse outcomes in socioeconomically disadvantaged populations, has resulted in an intense emphasis on global oncology by the international health community[21]. The World Health Organization's (WHO) Millennium Development Goals (MDG) has concentrated on health, development, and poverty reduction and encouraged the scale-up of investments in

interventions worldwide. Unfortunately, the MDGs largely overlooked inequalities within nations and placed insufficient emphasis on improving conditions for the most impoverished populations in both low-and middle-income nations[3]. As a successor to the MDGs, the global community adopted the Sustainable Development Goals (SDGs) in 2015 to address the unfinished agenda of the MDG era by setting forth comprehensive economic, social, and environmental targets[20, 21, 22]. Available quality data is essential for global health-related SDG monitoring[23, 24]. A national- or community-level commitment to enact socially equitable policies can result in equitable opportunities that ultimately lead to improved population health outcomes[12].

Approaching population health involves improving "the aggregate health outcome of health-adjusted life expectancy of a group of individuals in an economic framework that balances the relative marginal returns of the multiple determinants of health"[25, 26, 27]. Thus, population health improvement seeks to eliminate gaps in global health through upstream interventions directed at health drivers, boosting health outcomes[28]. A data-driven approach employing summary measures of health outcomes facilitates the study of diseases, conditions, and impairment[29, 30, 31]. Gibbs et al. (2020) introduced the term “Value-based focused Population Health Management” (VBPHM) as a comprehensive population-level, quality-focused, and resource-responsive care delivery framework for all global communities to address gaps in healthcare[32, 33]. Effective VBPHM relies on coordinating and investigating various care interventions, including health promotion, prevention, screening, behavioral change, and consumer education, with a particular emphasis on self-management, disease management, and chronic care management[33]. It is well recognized that social determinants of health have a dramatic influence on global health inequity[33, 34, 35, 36]. The WHO Commission on Social

Determinants of Health's (CSDH) goal is to close the health gap and promote health equity worldwide[34].

The Global Burden of Disease (GBD) project is a worldwide collaborative effort initially described in the World Development Report 1993 to measure health programs' impact on populations[37, 38, 39]. The GBD project is the most comprehensive global study, led by the Institute of Health Metrics and Evaluation (IHME). The study dataset provides a platform for monitoring health-related SDG indicators across demographic and geographic regions[40, 41, 42]. The GBD offers a means to educate physicians, researchers, and policymakers, foster transparency, and improve lives worldwide by monitoring progress within and across countries. The GBD study highlights the interplay between human health, health policy, and economic development (38,40) that links with the foundational principles of population health management. The project demonstrated national epidemiological profiles of cancer burden that reveal significant disparities resulting from different risk factor exposures, economics, lifestyles, and access to treatment and screening. Policymakers and other stakeholders can use the GBD study findings to build and strengthen national cancer control to meet global goals and improve care equity.

In this chapter, we outline a strategic framework to address the global burden of breast cancer using population health management and adaptive leadership principles. This framework can guide interventions toward closing the global gap in access to treatment and early detection of breast cancer at the national, regional, and local decision-making levels.

Global Burden of Breast Cancer

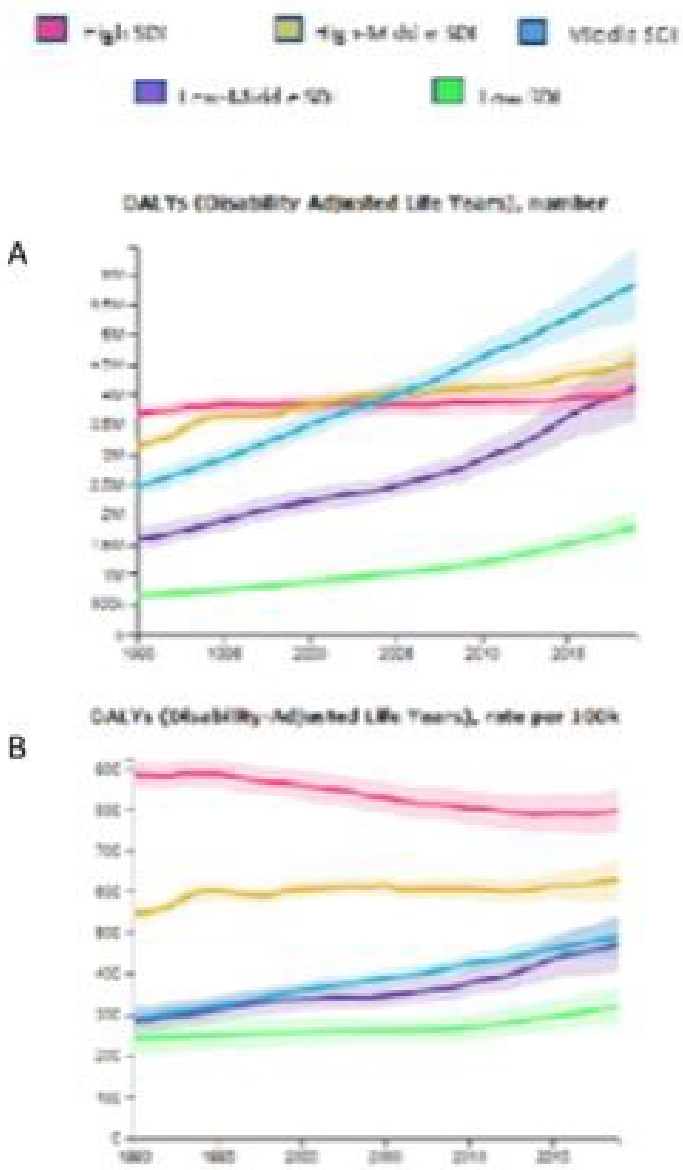

Figure 2: Total DALYs in low, low-middle, and middle SDI regions from 1990 to 2019.

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-associated death in women worldwide[5]. Annual estimates of breast cancer incidence, mortality, and disability-adjusted life-years (DALYs) by age and sex and temporal trends across regions and countries are provided. According to the GBD study, breast cancer remains a significant

public health issue worldwide. Between 1990 and 2017, the age-standardized incidence rates (ASIRs) increased while the age-standardized mortality rates and DALY rates decreased. However, breast cancer burden patterns varied by socioeconomic status, with breast cancer mortality and DALY rates falling in developed and developing countries, owing to disparities in access to new medicines and the implementation of clinical guidelines.

Given the trend of inequalities in incidence, mortality, and DALY rates found across regions and countries, policies to assign adequate breast cancer healthcare services at national and local/regional levels should be implemented[7]. Ji et al. (2020) analysis revealed that breast cancer incidence, mortality, and DALY trends were heterogeneous across regions and countries mainly based on socioeconomic status[43]. The authors attributed a portion of the increased incidence of breast cancer to Westernization in lower SDI countries. Subsequently, widespread screening and increased life expectancy in lower SDI countries will result in a higher detection rate[43]. Additionally, the age-standardized DALY rates increased in lower SDI countries, with a stable

proportion of DALYs attributable to years of life lost (YLL) and years living with disability (YLD) thought to be due to underdiagnoses of aggressive breast cancers[43].

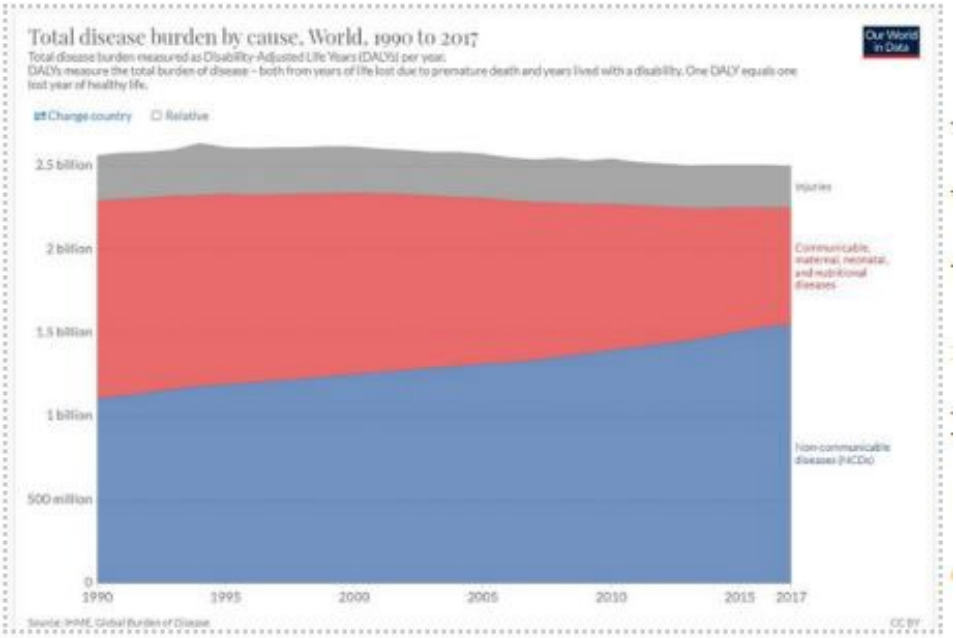

Figure 3: Total Disease Burden by Cause

The GBD database was explored, taking a broader view of the total burden of all global female breast cancers DALY (1990-2019) by SDI level of development (http://ghdx.healthdata.org/gbd-results-tool). We noted a dramatic increase in the total DALYs in low, low-middle, and middle SDI regions from 1990 to 2019 (Figure 2). The most significant change occurred in the middle SDI region. The rate of increase from 1990-2019 reflects the transition from the reduction in communicable, maternal, neonatal, and nutritional diseases (CMNN) related mortality rates to increased chronic (noncommunicable) disease[22] (Figure 3). For example, the global maternal mortality ratio (MMR, the number of maternal deaths per 100,000 live births) declined by 2.9% every year between 2000 and 2017[24]. The World Health Statistics 2020 report found that chronic (noncommunicable) disease in 2016 accounted for 71%

of all global deaths and 85% of the 15 million premature deaths (ages 30 to 70) occurring in LMICs[24]. Several studies have similar patterns of change in the increased total DALYs in 1990 and 2017 in various settings[44, 45, 46, 47]. Although our exploratory analysis did not evaluate the change in the global health environment nor interactions among multiple predictor variables, multiple GBD studies provide a putative correlation between total DALYs and GBD. The lack of comprehensive research on clusters of chronic diseases makes it difficult to provide definitive information[4].

A GBD 2016 study reported the epidemiological transition in healthy life expectancy and the global burden of total DALYs from CMNN to chronic (noncommunicable) disease[45]. Females had more DALYs due to NCD relative to CMNN causes than males. Population growth has resulted in a significant increase in total DALYs due to chronic disease coupled with a high total DALY burden, leading to an overall increasing toll on health systems. The increased population of chronic diseases influences a country's ability to implement resource-specific policies[46, 47]. Fitzmaurice et al. (2018) evaluated several cancer types' incidence, mortality, YLLs, YLDs, and DALYs[46, 47]. The prevalence of YLDs for each sequela was disability weight adjusted for cancer-related outcomes. Overall, incident cases increased by 43% due to population growth (contributing an additional 13%) and aging (contributing 15%)[46]. The odds of developing breast cancer were one in five in the lowest SDI quintile. SDI quintiles were used to group similar countries based on their development status. The number (95% UI) of incident cases increased in all SDI quintiles between 2005 and 2015 for nearly all cancers. The most significant increase in cancer incident cases between 2005 and 2015 occurred in low SDI countries, of which population growth contributed 33%, changing age-specific incidence rates 13%, and changing age structure 4%[46, 47]. The second-largest increase occurred in the low-middle SDI quintile, with

a 40% increase, followed by high SDI countries, with a 36% increase; high-middle SDI countries, with a 28% increase; and middle SDI countries, with a 27% increase.

Hu et al. (2016) assessed breast cancer-related health inequalities according to socioeconomic development factors[6]. A woman's residence and socioeconomic status are significant determinants of the odds of developing breast cancer[6]. Although breast cancer rates are higher in high SDI countries, the low incidence rates in low-middle SDI cancers have not translated into lower cancer-related mortality rates. Both breast cancer incidence and related mortality increased in resource-poor settings or countries partially due to reproductive patterns and delays in diagnosis and treatment[6]. The authors describe patterns and trends by combining SDI data with breast cancer incidence and mortality. They hypothesized that it would enable a comprehensive investigation of the distribution of breast cancer-associated health inequalities[6]. The Gini index, representing income inequality within a nation, measures social gradients and cancer-associated health inequalities. The Gini coefficient for the incidence of breast cancer continuously decreased (1990 to 2016).

Similarly, the Gini coefficients using mortality rates showed marked declines across most age groups. Patterns and trends in breast cancer incidence and mortality correlated with the SDI levels. The effectiveness of the mortality-to-incidence ratio (MIR) and its association with SDI across interregional and interstate patterns identify heterogeneity in geographic variation in rates of breast cancer burden[48]. Using the MIR may allow better identification of the heterogeneity in breast cancer burden and implementation of effective cancer control programs within countries. Decision-makers should implement more sensitive and cost-effective detection and treatment interventions.

Population Health Strategies to Address Global Breast Cancer

To address the current global burden of breast cancer, health advocates, leaders, and managers must approach global cancer care with new paradigms. The conventional reliance on resource-intensive management available in many high incomes has resulted in a focus on technical care not feasible for many LMICs. Improving breast cancer care delivery in low-resource countries requires an adaptive approach to recognizing problems and challenges in differing contexts. Context is important in complex adaptive system thinking in understanding intervention outcomes[62]. The Adaptive Leadership Framework (AL) provides a novel perspective on conceptualizing, studying, and providing care that could help catalyze global health change by better characterizing its problems and developing innovative solutions. It presents an unconventional view of leadership developed to solve a broad range of chronic social challenges.

Worldwide, There is a shift in the emphasis of population health research toward the study of interventions to reduce health inequities[49, 50]. For example, given resource constraints, Roberts et al. describe “five control knobs” for designing effective national system-level interventions involving financing, payment, organization, regulation, and behavior to increase the effectiveness and equity of global health However, for any intervention to be adopted, analytic research is required to understand global breast cancer disparities, promote individualization of breast management, and improve breast cancer survival and care coordination in LMIC. Central to this aim are implementation research and population health intervention research roles.

Level of Resources	Public Education and Awareness	Detection Methods	Evaluation Goals
Basic	Development of culturally sensitive, linguistically appropriate local education programs for target populations to teach early detection, breast cancer risk factors, and breast health awareness	Clinical history and CBE	Breast health awareness regarding value of early detection in improving breast cancer outcomes
Limited	Culturally and linguistically appropriate targeted outreach/education encouraging CBE for age groups at higher risk at district/provincial level using local healthcare providers	Diagnostic breast U/S ± diagnostic mammography in women with positive CBE; Mammographic screening of target group*	Downsizing of symptomatic disease in women
Enhanced	Regional awareness programs regarding health linked to general health and women's health programs	Mammographic screening every 2 years in women ages 50-69*; consider screening ever 12-18 mos. In 40-49	Downsizing and/or downstaging of asymptomatic disease in women in highest yield target groups
Maximal	National awareness campaigns regarding breast health using media	Consider annual mammographic screening in women ages 40 and older; other imaging technologies as appropriate for high-risk groups	Downsizing and/or downstaging of asymptomatic disease in women in all risk groups

Table 2: BHGI Four-tiered system for Resource Allotment

The National Cancer Institute defines implementation research as "the use of strategies to adopt and integrate evidence-based health interventions and change practice patterns within specific settings"[51]. Implementation Science provides a multidisciplinary framework and methodology to promote the integration of scientific evidence into healthcare practice, policy, and research. It focuses on various theories and methods used to determine factors that promote or impede the adoption, adaptation, and maintenance of healthcare interventions by individuals, providers, payers, and communities[53, 54]. Population health intervention research (PHIR) is a relatively new field involving scientific methods to produce knowledge about interventions within or outside the health sector to impact health outcomes[52]. PHIR involving awareness and education, detection method, and evaluation goals can be assessed as important areas in early

breast cancer detection. PHIR integrated with implementation research has the ability to affect its translation into practice at a system level.

The Breast Health Global Initiative (BHGI) resource-specific stratification framework to improve all aspects of breast cancer management is an ideal foundation for developing system-level global strategies using PHIR and implementation research principles. At BHGI's first conference in 2002, an emphasis on early detection was articulated[12]. Although mammography is the goal standard for early detection, it is not feasible in many poor resource regions. BHGI applies a resource allotment focus on a four-tiered system that consists of basic, limited, enhanced, and maximal options for determining the feasibility of implementation, cost, level of complexity, and demands of global breast health care (Table 2, Table 3)[12, 13, 14]. It strives to "achieve a next level of resource-based service delivery[15]. In particular, breast health awareness and other detection methods are necessary.

	Basic	Limited	Enhanced	Maximal
Services	• Diagnostic & pathology • Nursing • Medical & Surgical Oncology • Palliative • Psychosocial • Primary care	• Imaging services • Peer support service • Radiation oncology services	• Cancer follow up • Group support • Screening programs • Rehabilitation services • Survivor services	• Universal access to screening • Individual psychosocial care
Human resource capacity- building education	• Primary care provider (diagnosis, treatment, and detection) • Nursing (cancer patient management and emotional support) • Pathology technician (specimen handling & preparation)	• Nurse education (diagnosis, treatment, and management) • Imaging technician (technique and quality control)	• National volunteer network • Specialized nursing oncology training • Home care nursing • Physiotherapists and lymphedema therapists • On-site cytopathologist	• Organization of national medical breast health groups
Patient & family education	• General education	• Group or 1-on-1 counseling involving family and peer support	• Educational programs • Survivorship • Lymphedema • Home-care	
Patient navigation	• Field nurse, midwife or health care provider triages patients to central facility for diagnosis and treatment	• On-site patient navigation	• navigator team supporting patient "handoff" during transition among providers to ensure completion of therapy	
Record keeping	• Individual medical records & service-based patient registration	• Facility-based medical records & centralized patient registration • Hospital-level cancer registry	• Resource area for education/outreach facility-based follow up • regional cancer registry	• Representative national cancer registry
Cancer care facility	• Health • Operating Center • Outpatient • Pharmacy • Home Hospice Support • External consultation pathology laboratory	• Clinical information systems • Health system network • Imaging facility • Radiation therapy	• Centralized cancer referral center(s) • Establishment of a "basic" external beam radiotherapy service with brachytherapy referred elsewhere	• Satellite (non-centralized or regional) cancer centers
Breast cancer center	• Breast care access integrating into existing health care infrastructure	• "Breast Center" with clinician, staff and imaging access	• Multidisciplinary programs • Oncology nurse specialists • Physician assistants	

Table 3: System for Determining the Feasibility of Implementation

The BHGI objective for any intervention program is to improve women's quality of life and prolong life expectancy[12]. The initiative endorses a research agenda using evidence-based

guidelines and implementation science to support advanced theoretical models applicable to resource-poor settings[55]. In 2017, the United Nations General Assembly charged the WHO "to develop or adapt stepwise and resource-stratified guidance for the implementation of comprehensive cancer prevention and control programs," In response, the BHGI established a consensus report addressing systematic, evidence-based "phased implementation" for breast cancer early detection[56, 57, 58]. The BHGI phased implementation aims to provide a "meaningful and realistic" approach for a health system to build capacity at any resource level[56].

Ultimately, this approach to population health requires interventions that impact people groups by changing underlying risk conditions and reducing health inequities. Applied to global health, these strategies provide a means to understanding the complex, dynamic properties inherent to healthcare systems[59-62].

Conclusion

The dramatic rise in breast cancer cases and an aging population with multiple chronic diseases will challenge resource-limited global health systems. Population health management and adaptive leadership principles, supported by a data-driven framework utilizing evidence-based policies and interventions, can help improve outcomes in global cancer care. The BHGI phased implementation approach for early breast cancer detection is an example of a potentially viable, evidence-based strategy. However, successful dissemination requires input from stakeholders at all levels. Leaders who can adapt and thrive in challenging environments applying evidenced-based policies are needed to navigate this population health crisis within complex global health systems.

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Chapter 2

Global Epidemiology of Breast Cancer

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Background

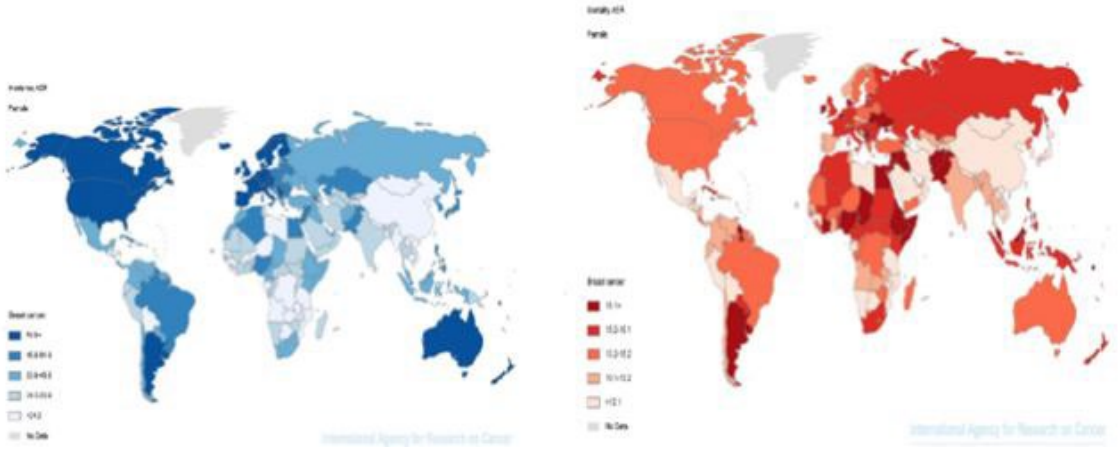
International Variation in Breast Cancer Incidence and Mortality

Globocan International, a project of the International Agency for Research on Cancer, is the primary source of published data regarding population-based breast cancer incidence and mortality in various countries worldwide. The accuracy of these data invariably depends upon the ability of each nation/region to contribute reliable information regarding overall population demographics and cancer burden[1-3]. More affluent countries such as the United States have invested in robust national census programs and population-based cancer registries such as the Surveillance, Epidemiology, and End Results (SEER) Program. Low- and Middle-Income Countries (LMIC) are unable to support comparable public health registries; the data on cancer control in these populations is, therefore, likely to be less definitive. The statistics generated by Globocan have been vetted to the greatest extent possible; while the estimations of substantial increases in the worldwide breast cancer burden are alarming (and particularly in LMIC)[4], it can be assumed that any data inaccuracies for LMIC reflect disease underestimation as a consequence of lower cancer detection rates. Rising breast cancer incidence in LMIC is likely

multifactorial in etiology but is at least partly explained by the adoption of reproductive, dietary, and physical activity patterns that are prevalent among Westernized and more affluent nations[5,6].

Approximately 2.1 million new breast cancers are estimated to have been diagnosed in 2018, accounting for nearly one-quarter of all cancers in women[7]. Globocan also documents the worldwide cancer burden correlated with the economic development of various countries and regions, using a four-tier scale called the Human Development Index (HDI). The more affluent countries of North America (the United States; and Canada) and Europe are included in the Very High HDI tier. Most countries of sub-Saharan Africa (e.g. Ghana; Nigeria; Ethiopia; and the Democratic Republic of Congo) are included in the Low HDI tier. Mexico is an example of a High HDI country, and South Africa is an example of a Medium HDI country. The continents of South America and Asia are notable for featuring countries across the spectrum of HDI tiers. Among Very High- and High-HDI regions, breast cancer has the highest age-standardized incidence rates (54.4 per 100,000), followed by cancers of the colorectum (20.9 per 100,000) and lung (19.1 per 100,000)[7]. Among Low- and Medium-HDI regions, breast cancer is the highest-incidence malignancy (31.3 per 100,000) but is followed by cervical cancer (18.2 per 100,000) and colorectal cancer (5.9 per 100,000)[7]. Age-standardized mortality rates have a somewhat different pattern, with lung cancer being the most deadly cancer among women in Very High- and High-HDI regions (14.3 per 100,000), followed by breast (11.6 per 100,000) and colorectal cancer (8.5 per 100,000)[7]. In Low- and Medium-Income regions, age-standardized mortality rates are highest for breast cancer (14.9 per 100,000), followed by cervical cancer (12.0 per 100,000) and lung cancer (4.2 per 100,000)[7]. Hereafter this chapter will use the common acronym LMIC to denote countries belonging to the Low- and Medium-HDI

regions.



Figures 1 and 2 depict Globocan International incidence and mortality rates for breast cancer, respectively.

Figures 1 and 2 demonstrate that breast cancer incidence is highest in relatively affluent countries of North America and Europe but lowest in the LMIC of Africa and Southeast Asia. Also have relatively high mortality rates, but the highest mortality rates are seen in LMIC of Africa and South America. While breast cancer incidence rates reflect disease-attributable risk factors, including lifestyle, exposures, and hereditary genetics, mortality largely reflects the ability of a country's healthcare system to detect the disease at early stages and to provide appropriate treatment. As shown in Table 1, the incidence-to-mortality rate ratios are, therefore, highest in the populations of LMIC, where financially constrained public health systems are unable to screen for disease and have limited resources for treatment.

The patterns of incidence and mortality described above are especially concerning given expectations that breast cancer incidence will steadily increase among LMIC where the ability to treat is most impaired—thereby resulting in rising global breast cancer mortality rates. It is therefore, appropriate to carefully assess strategies that can mitigate this predicted excessive

mortality burden. Some of these approaches include the dissemination of cost-efficient screening and treatments; others involve understanding risk factors that can be modified and/or addressed.

Region	Incidence	Mortality	Incidence-to-Mortality Ratio
Western Europe	92.6	15.5	5.97
Northern Europe	90.1	14.1	6.39
North America	84.8	12.6	6.73
Southern Europe	80.3	13.3	6.04
Micronesia/Polynesia	58.2	19.1	3.05
South America	56.8	13.4	4.24
Eastern Europe	54.5	15.5	3.52
Caribbean	50.2	18.1	2.77
Northern Africa	48.9	18.4	2.66
Southern Africa	46.2	15.6	2.96
Western Asia	45.3	13.6	3.33
Eastern Asia	39.2	8.6	4.56
Central America	38.3	10.1	2.72
Southeast Asia	38.1	14.1	2.70
Western Africa	37.3	17.8	2.10
Eastern Africa	29.9	15.4	1.94
Middle Africa	27.9	15.8	1.77
South Central Asia	25.9	13.6	1.90

Table 1. Worldwide Incidence-to-Mortality Rate Ratios for Breast Cancer[7].

Expansion of the workforce available to manage the worldwide breast cancer burden must also be taken into consideration. For example, it is estimated that between 2018 and 2040, the number of cancer patients requiring chemotherapy will increase from 9.8 million to 15.0 million, with nearly two-thirds of these cases residing in LMIC. Breast cancer, being the second most common malignancy (after lung cancer) will require a large proportion these treatments[8]. It is also estimated that the number of cancer physicians available worldwide to deliver chemotherapy will need to increase from the current volume of 65,000 to approximately 100,000 by the year 2040[8]. However, a detailed discussion of the financial costs of breast cancer screening as well as treatments are beyond the scope of this chapter. This discussion will focus on lifestyle and genetic factors for breast cancer that are potentially measurable and/or modifiable.

We will review the factors that are likely to explain the high burden of breast cancer that is seen in relatively affluent populations, as well as risk factors that may be explaining the increasing incidence rates that have already been observed and that are predicted to continue in LMIC.

Breast Cancer and International Variation in Life Expectancy

Regardless of nationality, breast cancer risk increases as women age. In the United States, one in eight women is expected to be diagnosed with breast cancer over the expected lifespan of 85 years. For a 30-year-old American woman, the likelihood of developing invasive breast cancer within the next ten years is 1 in 209 (0.5%); for a 70-year-old woman, the likelihood is 1 in 25 (4.1%) over the following ten years; and over the expected 80-plus years longevity of an American female, the lifetime likelihood of developing breast cancer is 1 in 8 (12.8%)[9]. Breast cancer is, therefore, less common among younger women and is expected to be a lower-burden disease among populations with an overall younger age distribution. Longevity for individuals born/residing in LMIC of Africa and Asia is notably shorter. For example, Ghanaians have a life

expectancy of 67 years, Ethiopians 62.6 years, and Nigerians 55.9 years[10]. Indians have a life expectancy of 68.8 years, Pakistanians 68.1 years, and Afghanistanians 51.7 years[10]. As LMICs develop advances in health care technology and improved treatments/prophylaxis for communicable diseases such as malaria and tuberculosis, their life expectancy is increasing[11], and their breast cancer burden will rise accordingly.

Breast Cancer and International Variation in Obesity

Obesity and its closely associated additional adverse lifestyles of inactivity and non-balanced, high-fat diet are directly linked to breast cancer risk and are unfortunately rising to epidemic levels both in the United States and in the world[12]. The World Health Organization defines obesity as having a body mass index (BMI) of at least 30 $kg/m^{2,}$ and its prevalence has doubled in at least 73 different countries over the past forty years, while steadily rising in most others (Figure 3)[13].

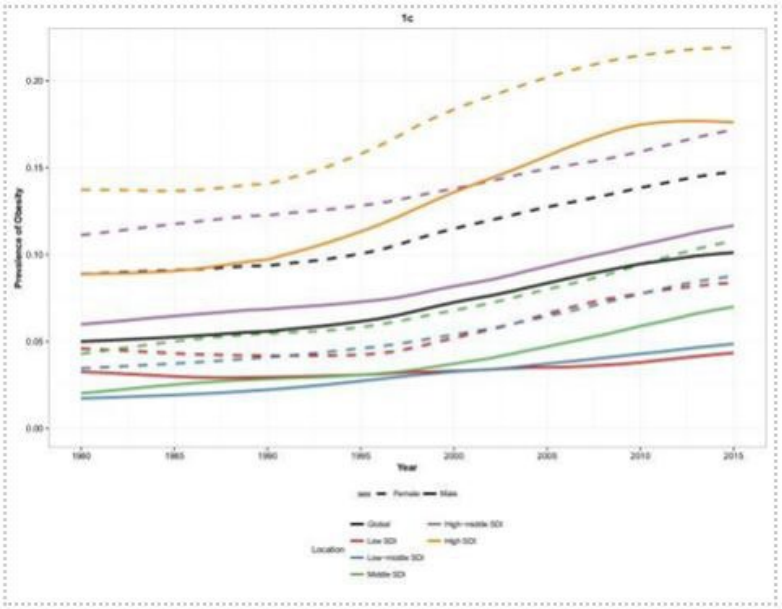


Figure 3 depicts the rising obesity rates of countries across the spectrum of socioeconomic development.

Obesity (especially central obesity) is an essential element of metabolic syndrome, and the cluster of risk factors belonging to this syndrome (i.e., insulin resistance, dyslipidemia, and hypertension) are strongly correlated with a spectrum of medical problems, including breast cancer. Obesity and metabolic syndrome are thought to promote breast cancer pathogenesis through complex interactions between adipokines (biologically active hormones produced by adipose tissue), the microbiome, and the mammary microenvironment.[14]

Obesity is most closely linked to an increase in the risk of postmenopausal breast cancer. Whereas menstrual breast cancer risk factors such as parity are correlated specifically with estrogen receptor-positive disease, obesity appears to increase the risk of estrogen receptor-positive and triple-negative breast cancer[14,15]. Obesity is furthermore associated with increased mortality among breast cancer patients[14,15].

Breast Cancer and International Variation in Parity/Hormone Exposure

The hormonally-based etiology of breast cancer is readily apparent in its gender predisposition, with fewer than 1% of all breast cancers occurring in men[17]. There are genetic factors that alter the hormonal milieu of adult males and increase breast cancer risk, such as Klinefelter's Syndrome (trisomy 47XXY)[18]. Cirrhosis can result in altered hepatic hormone metabolism, and parasitic causes of liver dysfunction, such as bilharzial cirrhosis, has been implicated in the higher male breast cancer burden reported in selected international regions, such as Egypt[19]. Other risk factors for male breast cancer include the presence of pathogenic hereditary susceptibility mutations in the BRCA1 and BRCA2 genes, obesity, therapeutic chest wall radiation, and exogenous hormone exposure[18].

In women, hormonal balance is also associated with breast cancer risk. Post-menopausal hormone replacement therapy was a common primary care strategy for women in North America and in Europe during the latter part of the twentieth century. Large-scale abandonment of this practice following the release of data from the Women's Health Initiative in 2003[20] definitively linking prolonged combination hormone replacement therapy with postmenopausal breast cancer risk is widely credited with accounting for substantial declines in population-based breast cancer incidence rates observed in these continents. Postmenopausal hormone replacement therapy has been a consistently less common practice among LMICs, contributing to the overall lower incidence rates of breast cancer in these areas during both the twentieth and twenty-first centuries[4].

Parity and menstrual history also influence breast cancer risk[4]. Breast cancer incidence is higher in populations that experience prolonged lifetime estrogen exposure through ovarian production, explaining the higher risk of breast cancer in women who experience menarche younger than age eleven years, women who experience menopause at an age older than 55 years, and women that

have fewer interruptions of ovarian cycles because of nulliparity or delayed initiation of childbearing. In general, these reproductive and menstrual risk factors influence incidence rates of estrogen receptor-positive breast cancer[21]. Childbearing patterns associated with increased risk of breast cancer tend to be more common among affluent countries of North America and Europe. Women residing in LMIC are more likely to initiate childbearing at relatively younger ages and to have more pregnancies. These population-based patterns of parity contribute to relatively lower breast cancer incidence rates in LMIC, but the adoption of Westernized lifestyles in these communities is contributing to the rising burden of disease[4].

The association between parity and breast cancer risk persists within populations of LMIC. For example, studies from India[22] and China[23] have demonstrated higher breast cancer risk among nulliparous compared to women having multiple pregnancies. The correlation between shifts in parity trends and population-based breast cancer incidence is particularly interesting in China, where breast cancer incidence has historically been lower than rates seen in Western countries, but since the 1990s, incidence rates have risen more than twice as fast as international rates-–a trend at least partly attributed to national birth control efforts such as the one-child policy[24].

Lactation is closely linked to parity and protects against breast cancer risk, at least in part through the amplified reduction in ovarian cycles associated with prolonged nursing following multiple pregnancies. Extended lactation is more prevalent among resource-poor LMICs and is thought to contribute to the lower breast cancer incidence of women in these countries[25]. Interestingly, lactation confers protection against estrogen receptor-positive as well as triple-negative breast cancer, yet selected LMICs such as those of western sub-Saharan Africa have a relatively higher frequency of triple-negative breast cancer compared to other parts of the

world[26]. This paradoxical association supports the need for additional research regarding germline ancestral genetics and breast cancer risk.

Breast Cancer and International Variation in Alcohol Intake

Alcohol consumption of more than one drink per day is associated with a higher likelihood of developing breast cancer compared to abstention, and this risk rises progressively with increasing quantities of alcoholic beverage intake. Populations of relatively more affluent countries tend to have higher rates of modest as well as excessive alcohol intake compared to rates in LMIC[27,28], thereby contributing to differences in breast cancer incidence. As noted previously, however, populations of LMIC have been increasingly adopting Westernized lifestyles, including rising rates of alcoholic beverage consumption[28]. It has also been noted that some herbal preparations commonly ingested in LMIC can contain ethanol. For example, "paraga mixtures" consumed in Nigeria can have alcohol content ranging from 1.2%-20.8%[29]. Better documentation of these products can contribute to an improved understanding of breast cancer risk factors internationally and will also be important information as a control measure in public health related to motor vehicle driving.

Breast Cancer and International Variation in Breast Cancer Phenotypes

It is now well-established that breast cancer is comprised of a spectrum of distinct tumor subtypes associated with phenotype-specific biology, prognoses, and therapeutic options. Most of our understanding of breast cancer risk factors is based upon epidemiologic studies of hormone receptor-positive disease, as this phenotype accounts for the high majority of disease in women from westernized countries where these studies have been performed.

More recent studies conducted among internationally-diverse populations suggest that the frequency of non-estrogen receptor-positive disease- and in particular triple negative breast cancer- varies by country. In particular, triple-negative breast cancer is relatively more common among women with Western, sub-Saharan African ancestry, including African Americans and women from countries such as Ghana and Nigeria[26]. These patterns suggest that genetic ancestry, which can be quantified by Ancestry Informative Markers, can be a useful tool in understanding phenotype-specific breast cancer risk[30].

Studies of triple-negative breast cancer in diverse populations indicate that African ancestry is also associated with a broader spectrum of triple-negative tumor subtypes compared to studies in more homogeneous populations[31]. Furthermore, the AIM genetic variant known as Duffy-null (which represents an evolutionary selection pressure pattern that confers resistance to malaria) is also linked to the risk of triple-negative breast cancer[32]. Studies of Latina/Hispanic admixed populations in the United States and in Latin America have demonstrated that extent of Indigenous American genetic ancestry is associated with a reduced risk of breast cancer[33,34].

Future Directions: Need for Breast Cancer Research Internationally

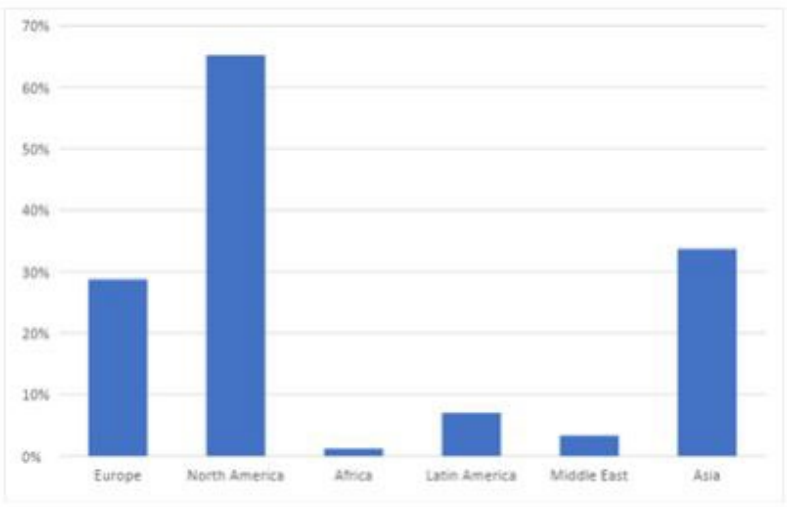


Figure 4. Proportion of 933 Phase I, II and III clinical trials registered with ClinicalTrials.gov that are available in various international sites[35].

Optimizing the generalizability of results is a bedrock principle of any human clinical research project. The response or effectiveness of a novel breast cancer treatment or prevention strategy might vary because of toxicity, tumor biology/genetics, compliance, and/or cost. Any combination of these factors might be relevant to different degrees in population subsets residing in various parts of the world. Striving for diverse accrual in clinical research studies is the primary method for achieving generalizable results. Unfortunately, however, breast cancer clinical trials have been lacking in diversity both domestically and internationally. As demonstrated by Barrios et al. [35] in a review of 933 Phase I, II, and III breast cancer clinical trials listed with ClinicalTrials.gov, fewer than 2% are available in Africa and only 7% in Latin America (Figure 4).

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Chapter 3

Socioeconomic barriers to breast cancer early diagnosis and treatment

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Keywords: breast cancer, diagnosis, early detection, guideline, health care systems, health planning, international health problems, low-resource countries, pathology, public policy, recommendations, resource allocation, screening, treatment Socioeconomic barriers, Religious barriers, Geographic Barriers, Alternate Medicine, China, Africa, Middle East, India, and Caribbean

Overview

Breast cancer is the most common cause of cancer-related death among women worldwide, with case fatality rates highest in low resources countries. Despite significant scientific advances in its management, most of the world faces resource constraints that limit the capacity to improve early detection, diagnosis, and treatment of the disease. In the next few decades, breast cancer will become a leading global public health problem as it increases disproportionately in low- and middle-income countries (LMICs). Cancer affects more every

year, and in tandem with the global trend, its incidence in these regions is increasing, led mainly by factors such as urbanization, population aging, and the so-called westernization of lifestyles[1,2,6].

Like other regions, Latin America, Asia, Africa and the Middle East need to increase knowledge for the implementation and assessment of preventive and early detection policies. We must analyze how primary and secondary prevention can be accompanied by better timing of policies within the setting of health care services. In terms of treatment, there are barriers that limit access for the region's most vulnerable groups who depend on public health care coverage. In addition, it is necessary to consider the limitations that patients who live in rural or less accessible regions, with restricted access to health care systems, must face. In these regions, higher mortality can result from insufficient access to the health care system for early diagnosis and specific treatment[6].

Regarding access to treatment, patient organizations play a key role by guiding the family in their search for resources available in public entities; informing patients of their rights and helping them assert these rights. Finally, the care of survivors must be considered a guiding principle for controlling the disease. Survivors' reinsertion into the community and an active life and their role as an example for others should be encouraged through patient organizations[3,4].

The development of research in LMICs, the encouragement of independent academic research, and the improvement of access to clinical trials while increasing patient participation and involvement. Although breast cancer research priorities vary in different socioeconomic scenarios, identification of both global and regional needs is mandatory. Collaboration strategies are essential and should be designed[5,6].

In this chapter, we present a case example followed by a series of regional scenarios illustrating common socioeconomic barriers, some of which are ubiquitous around the globe.

Case Presentation

A 30-year-old female, clinically T2 N0 breast cancer, African descent, no family history of breast cancer presented to our Breast Unit after repeatedly being told that she is too young to have breast cancer. She was triaged as RED, (suspicious for breast cancer). Ultrasound, mammogram and core needle biopsy confirmed diagnosis (luminal Triple negative, Ki 67 75%). Radiology T2 N1

Tumor board decision: primary neoadjuvant (preoperative) chemotherapy. Her booking date for oncology was for 4 weeks later at a location far from her. Her family advised that she seeks counsel from the elders before commencing treatment. She returned 3 months later after attending spiritual cleansing ceremonies as advised by her elders. Clinically now T3 N1 breast cancer. Navigation counseling by community navigators explained the implicated cultural issues to the clinicians, and the importance of being non-judgemental.

She eventually underwent primary neoadjuvant chemotherapy and achieved a complete clinical response. She had not been examined during her treatment and no markers had been placed. She was sent back a week after her last session, resulting in the ideal window of 3 to 6 weeks for surgical booking being compromised. She was referred back to radiology where little documented evidence of her breast cancer was seen.

After much debate; a breast saving conserving surgery was performed; including an immediate local parenchymal flap. It took 6 weeks to receive the final histology and she was

then referred for radiation. The centralized radiation department promised to call her but they did not. A year later she returned to the breast unit with nodal breast recurrence and metastatic workup revealed disease in the lung. She is on the second line oncology waiting list for chemotherapy and the outcome is not good.

Indian Scenario

Garvit Chitkara, Vani Parmar, Nita Nair, Gauravi Mishra, Shalaka Joshi, Purvi Thakkar, Rajesh Dixit, Rajendra Badwe

Epidemiology

As India underwent epidemiological transition because of economic development in the last three decades, an increase in incidence rates of breast cancer has been observed in rural as well as in urban regions. The increase is, however, more and statistically significantly greater in Metropolitan cities compared to smaller cities and rural areas. The difference in incidence and trends in rural and urban areas can be attributed to differences in prevalence of "Westernized" risk factors (obesity, late age at first pregnancy, less breast feeding, etc.) in rural and urban areas and changes in risk factor prevalence over the years. Breast cancer incidence rates are much higher in older women (age at diagnosis >50 years) compared to younger women, which becomes more apparent with the increased use of mammographic screening. The variation in incidence of breast cancer for rural and urban region is less among younger women compared to older women[8].

Number of breast cancer cases in India will continue to increase, even if rates remain unchanged. Given the current population projection that people aged over 60 at 7.7% in 2020 will rise to 12.6% in 2025, one could predict a doubling in the number of breast cancer cases

assuming no further increase in age-adjusted rates. Therefore, future planning should target prevention and early detection and followed by effective treatment to reduce rising burden and mortality. As the increase is predominantly among older women, any planning for early detection to reduce mortality should target older women aged 50 and above[9].

Social barriers and religious barriers

Spiritual beliefs are often at odds with the medical practices in Indiae of medicine. The attribution of cancer to punishment for a 'sin' committed earlier is not an uncommon belief in the rural areas. A large number of women from rural India even may believe that God works through doctors to cure breast cancer and will leave the whole deciding powers unto the treating doctor and accept everything unquestioned. Some of them may also believe that medical treatment is unnecessary based on fatalistic beliefs because only God could cure breast cancer. Shame and stigma of being diagnosed with cancer and fear of being outcast and losing out their family and social support may also contribute to women concealing the condition and forgoing care until their disease is advanced, thus increasing mortality rates amongst these at-risk individuals[13].

Although Indian families are mostly structured on a joint family system, lately there has been an increase in the unit family structure with limited physical, emotional and financial support. Both family structures have their associated strengths and weaknesses. The joint family structure in India predominantly has a patriarchal system and with men in the family assuming a dominant role in deciding need and type of treatment being offered to the women diagnosed with breast cancer. The decision to undergo mastectomy may actually stem from the decision delivered by the male head of family, at times the spouse or father/father-in-law, and the wish to undergo breast conservation or even a whole breast reconstruction is considered as more a fashion-related unwarranted desire by the affected woman, and not related to the basic need to

maintain a body image. On the flip side, a joint family system may sometimes actually work well when it comes to the emotional, social, financial and overall support which is much more and therefore, compliance to treatment is better. Women in such families are happy letting men take major decisions regarding their own treatment and accept it too without much ado. The unit family structure fails where social and emotional support is concerned with caregiver burnout and financial strain are very frequent. But it may be easier on the individual level to decide on what treatment strategy and where to receive the treatment[10].

Another commonly encountered issue is reluctance by the immediate family members to reveal the diagnosis to the patient, lest it may lead to depression, denial and withdrawal from undergoing cancer treatment, or may lead to rejection by the society. This also appears to be more in the male dominated societies where all decisions are taken by the male member who is also the bread earner. There is apparent stigma associated with the term 'cancer' and a clear lack of understanding of patients' coping capabilities. However, the acceptance of appropriate surgical treatment decisions and compliance with adjuvant systemic and radiation therapy is far superior in women who are well informed from the start and are kept aware of their disease status. A better informed patient may also be more compliant with treatment recommendations, translating into overall improved outcomes. In a study conducted at the Tata Memorial hospital on 250 diagnosed cancer patients and 250 caregivers it was found that Patients with cancer preferred full disclosure of their diagnoses and prognoses, whereas the family caregivers preferred nondisclosure of the same to their patients[11].

The large proportion (82%) of population of women below 50 yrs age in India also makes mammography screening in India a poor screening option. Alternative methods of breast cancer screening by clinical breast examination have been tested in a randomized setting in India and

have shown an increase in detection rate but again no definite benefit in reducing mortality. The actual population risk of developing breast cancer is a quarter of the observed risk in the west and screening in this population does not seem to reduce mortality due to breast cancer. But, it definitely reduces the stage of detection of breast cancers and will therefore translate into better survival in diagnosed cases. An increase in social awareness itself works a long way in women presenting earlier for diagnosis and treatment of cancer with obvious improved survival. The current national practice is targeted at raising awareness of breast cancer and screening is not included in national health programmes[11].

The social barriers to screening in India are of many frequent depending on societies among some social groups. Embarrassment felt to activities relating to breast examination, fear of loss of breast and knowledge of breast cancer were tested through a self-completion questionnaire in a study comparing two cities Chennai and Ranchi. The study aimed to map the barriers to screening in young, educated, well-off Indian women with good access to healthcare facilities and define the influence of the sociocultural environment of the subject on the barriers to screening. They were also tested for their knowledge of breast cancer through ten questions answered in true/false format. Five questions measured embarrassment. Briefly the results showed that 35% could refuse breast examination by a male doctor, 46% will hide a breast lump from their sons, 40% would refuse a mammogram because it is too embarrassing, and 76% may ignore any advice regarding breast examination due to embarrassment. 49% would not demand breast prosthesis, 62% would not feel any restriction in their choice of dress, 77% would not feel deformed, and 71% fear the cancer more than the deformity after mastectomy[10].

Different studies have reported different social and religious barriers to breast cancer screening. In a service program conducted in slums of Mumbai for breast cancer screening, it has

been demonstrated that Muslim women and women with a mother-tongue other than Marathi or Hindi were negative predictors of participation in screening. A study conducted in Trivandrum showed similar findings that women belonging to Muslim religion had lesser participation. Trivandrum study also demonstrated that women who are educated (college and above) and whose monthly household income is more than 5000 had lesser participation. The Mumbai study of CBE screening has also demonstrated that women belonging to the Muslim community, women with higher education, higher-income women, women speaking a language other than Hindi and Marathi, single unmarried women had lower participation in screening. It has been observed that the other reasons for nonparticipation in screening are, belief that cancer is incurable, low perceived risk of getting cancer, belief that screening is not necessary if they have no symptoms, fear that the screening test may be harmful, embarrassment and discomfort, fear of a positive diagnosis, perceived inefficiency of screening, belief that family physician will tell them if a screen is necessary and poor health status of the women[11].

Geographical and financial barriers

The objectives of health care related policies are to improve both the quality of available health care and make it more accessible. Barriers related to knowledge, economic condition, geography, and cultural aspects impact the outcome of a large majority of women treated with breast cancer in our country. In India geographical and economic barriers play a significant role to the management, right from patient presenting to treatment options.

Several studies have documented that the distance or travel time from hospitals result in delays in diagnosis and can influence the choice of treatment of a variety of common cancers. The need for multiple visits, support of a caregiver, distance from health care provider, all result in loss of work days and impact treatment choices made by a patient. For example, patients with

early breast cancer often opt for a mastectomy to avoid radiation therapy, to limit cost and loss of daily wages. Numerous retrospective studies examining the association between the travel distance to radiation and patient's choice for breast-conserving surgery (BCS) have demonstrated a statistically significant decrease in the likelihood of undergoing BCS among women with early-stage breast cancer living more than 15 miles from a hospital with radiation therapy[11]. There is a geographic variation in access to care in India, with a significant urban- rural divide. Thus various organizations are instituting efforts to increase the local diagnostic infrastructure especially in rural India, so only positive cases are then referred to regional cancer centers. Thus reducing the distance traveled for diagnosis and encouraging patients to seek early health care and present in early stages of cancer.

In addition to the cost of travel and lost work hours, the increasing cost of cancer care is also a concern. The increasing cost is often associated with the rise in availability and use of targeted therapies. Trastuzumab, pertuzumab, T-DM1, lapatinib and neratinib are the currently approved HER2 targeted therapies, of which trastuzumab and pertuzumab have a defined role in non-metastatic disease. Unfortunately, these treatments are expensive, and many eligible patients worldwide lack access. A large tertiary cancer center in India that draws patients from many parts of India and a significant proportion (> 50%) of those patients belong to underprivileged sections of society, published their patients' access to Trastuzumab in 2008 as low as 8.61%. Over the years that has improved with the use of shorter courses of trastuzumab and biosimilar, allowing more patients access to optimal care and improving outcomes to breast cancer, but still limited by available philanthropic support[8].

Optimal cancer care is no longer just based on patient and tumor characteristics and toxicity to therapy but physicians and policy makers must also account for the financial toxicity to the patient and family.

Alternate therapy and avoidance of allopathy

Alternative or Complementary therapy is a broad domain of theories and practices believed to have the healing effects of allopathic medicine which may be used instead of or along with mainstream treatment methods respectively. NIH National Center for Complementary and Alternative Medicine (NCCAM) defines Complementary and Alternative Medicine as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine". Such therapies work on general principles of holistic care and overall health promotion and may involve use of less invasive or less toxic practices which make them attractive. However, they are usually untested by scientific methods for efficacy and safety[12].

In various surveys across populations, the prevalence of use of CAM therapy has been reported to be around 40%. It varies depending on the practices included and the indication studied. If prayer as a mode of therapy is included, the proportion is higher in the range of 60%. In India, the most common CAM therapy resorted to includes Ayurveda and Homeopathy. In the United States the commoner practices include natural healing products and breathing practices.

Prevalence of TCAM in India

In India, various alternative therapies such as Ayurveda, Unani, Siddha, Homeopathy etc. have been practiced since ancient times. Significant proportions of cancer patients in developed countries use complementary therapies as adjuncts to conventional symptom management to

improve their quality of life. However, the situation in less-developed countries such as India, is quite different. In remote parts of the country, due to lack of access to medical services, many are forced to try alternative medicines including naturopathy, home remedies, hydrotherapy, acupuncture, vipassana etc. In a survey conducted on 825 cancer patients in Delhi, 34.3% had sought traditional, complementary and alternative medicine (TCAM) causing a significant delay in seeking help from clinical medicine.12.8% of patients waited for 3 months or longer after noticing symptoms due to cancer and resorted to TCAM in the beginning[16]. As such, 75% of cancers are diagnosed at an advanced stage in developing countries such as India. When early diagnosis offers potentially curative treatment, the delay caused by use of alternative practices is detrimental to cure in developing countries where more than 50% of patients diagnosed with cancer die in the first 12 months. There are concerns regarding the potential interaction between the TCAM medication and routine allopathic care, with respect to the common presence of high percentage of heavy metals in them. Case reports of such interaction with serious adverse events are reported in the literature[8].

Streamlining research in alternative therapies in India

However, Alternative therapies may indeed be complementary to allopathy and herbal remedies may hold the potential to strengthen or replace the results of traditional cancer care. A striking example of this is the recent worldwide interest in herbal cannabis preparation which has resulted in FDA approval of plant-based cannabis extracts in the treatment of pain in multiple sclerosis as well pediatric refractory epilepsy[12].

The Government of India formed the AYUSH ministry in 2014 with a view to provide focused attention for the development of Education and Research in Ayurveda, Yoga, Naturopathy, Unani, Siddha and Homoeopathy. The objective was to obtain a time-bound

research program on various diseases with the use of the Indian System of Medicines and to draw up schemes for promotion, cultivation and regeneration of medicinal plants used in these systems. In 2013, there was a declaration by the South-East Asian countries to explore the role of traditional medicine and medicinal plants in the planning and implementation of health care and research[16].

The practice of modern allopathic medicine is based on strong scientific research and evidence. The Traditional Medical systems in India as well as the rest of the world lack systematic research and documentation of effect. However, several complementary therapies such as Yoga may be helpful in improving the outcome of cancer. And herbal medicine therapy needs scientific research to improve its pharmacopeial standards.

Tata Memorial Centre studied the effect of Yoga and conventional exercise in a randomized control study on patients of early breast cancer as compared to conventional exercise alone. In a secondary endpoint analysis the authors found that although yoga did not show a significant difference in global QOL but had a major benefit reaching statistical significance in fatigue, emotional score and pain. More such studies are required to be able to include the alternate practices in the treatment of cancer[14].

Population based screening strategies

There are no organized screening programmes for cervix and breast cancers in India. Cervix Cytology and Mammography based screening programmes are difficult to organize in India because of issues related to absence of trained man-power, infrastructure, logistics, quality assurance, frequency of screening and costs involved. Population based mammographic screening has its pitfalls in that nearly 25-30% over diagnosis of in situ lesions and low grade

invasive breast cancers without really changing the number of advanced cases. The contribution of clinical breast examination (CBE) was never systematically studied until the results of the Canadian National Breast Screening Study were published wherein mammography did not contribute to decreasing mortality over and above CBE. In May 1998, supported by a grant from the NCI (US), the Tata Memorial Center, started a cluster-randomized, controlled, screening-trial for cervix and breast cancer using trained primary health workers to provide health-education, visual-inspection of cervix (with 4% acetic acid-VIA) and clinical breast examination (CBE) in the screening arm, and only health education in the control arm. At the end of 3 rounds of 2 yearly screening, a significant down staging was achieved in the screened arm ($p < 0.004$). With further follow-up, we may see a difference in mortality in the screened vs unscreened arm. With just one round of health education, there was a significantly better symptomatic referral in the non-screened arm; suggesting that in the absence of even VIA and CBE, effective health education and availability of resources and treatment options may be an effective strategy in reducing cervix and breast cancer mortality[11].

Latin American Scenario

Maurício Magalhães Costa, Eduardo Cazap

Epidemiology

In 2018, of the 18 million new cancer cases diagnosed, female breast cancer was the second most frequent, corresponding to 11% of all cancer cases. The incidence of breast cancer in Latin American countries is lower than that in more developed countries, whereas the mortality rate is higher[6]. These differences probably are related to differences in screening strategies and access to treatment.

Clinical burden

Breast cancer (BC) is a high-burden malignancy in Latin American women with ≈200,000 new cases per year and accounting for more than 52,000 deaths yearly. The high mortality in this region may be explained by reasons such as late stages at diagnosis, lack of access to specialized cancer centers and limited health insurance coverage of high-cost drugs (2). Enhanced treatments and earlier diagnoses explain progresses made during past years. The available data show a 5-year survival rate in Latin America that fluctuates around 70%, and this difference in survival is caused mainly by the late stage at diagnosis, which is an important predictor for overall survival. In countries like Peru, Colombia, or Mexico, approximately 50% of detected breast cancer occurrences are in advanced stages. Late stage at diagnosis negatively affects survival rate and notably increases per-case health expenditures[5].

Social and economic burden

The costs of breast cancer are directly related to stage of diagnosis, where annual health care costs for a patient with stage IV breast cancer in Latin America are three to four times higher than the cost of treatment for a patient with stage I disease. The increased morbidity and mortality of patients with metastases greatly increase overall expenses throughout the healthcare system. The ample majority of women are diagnosed when they are still at working ages, so productivity losses as a result of younger age at death are exacerbated by the increased morbidity that results from younger age at diagnosis. Because of insufficient funding, some patients are undiagnosed, unattended, untreated, and uncared for—and others receive suboptimal treatment. General health care expenditure in Latin America is far below European and U.S. standards, not only in absolute but also in relative terms[2,4]. Annual expenditures per breast cancer occurrence in Europe are approximately $40,000; conversely, in Latin American countries, such as in Brazil

for example, values can vary depending on insurance type, from $4,800 in the Sistema Unico de Saude (Brazil's publicly funded health system) to 16,400 in a private facility[1,5].

Screening

In Latin America, there has been increasing activity in breast cancer screening during the past decade. Currently, almost all Latin American countries in which breast cancer is the leading cause of cancer mortality among women have national recommendations or guidelines; however, no country in the region has a screening system that meets all the criteria of organized screening programmes[3]. Most countries use mammographic screening combined with clinical breast examination (CBE) and breast self-examination (BSE); half of the countries recommend mammography for women younger than 50 years. Screening participation rates vary enormously across and within countries, with large differences between urban and rural areas and by income level[1]. There is intensive advocacy activity, and information is provided by governments, NGOs, and the media, which appear to have induced a good level of breast awareness, although in a non-coordinated manner[2].

Social and Cultural Barriers: Deterrents of Care-Seeking Behavior

Fear. Fear of finding disease or embarrassment from the exam is an important deterrent in Brazil and, to a lesser extent, in Chile. However, Peruvian women reported that, if their CBE had negative findings, their sense of fear and willingness to discuss breast health improves, as does their willingness to urge others to have the examination.

Self-neglect and fatalism. Articles from Chile and Mexico cited the term flojera—self-neglect from laziness or limited time—as a reason for nonperformance[1,2]. In Brazil, women similarly referred to negligence or laziness as a reason given by nearly half in one study for

mammography nonperformance. Women in Mexico and Brazil cited forgetfulness and disinterest as additional reasons for nonperformance. A study from Mexico noted other obligations, such as work and family, that led to decreased time for screening adherence[5].

Physical barriers and availability of technology

In most cases that mentioned financial barriers, cost was prohibitive to access; these included accounts from Peru, Chile.

Diagnosis and treatment

Because there is low commitment to population-based mammography screening, in Latin American countries, most breast cancer occurrences are self-detected when women seek care after they notice a breast lump[7]. Early detection is an opportunity for improvement, but there is no consistent strategy for breast cancer prevention or detection in the region. Actions are being taken in countries like Mexico, Costa Rica, Argentina, Uruguay, and Brazil, where population-based programs have been or are being implemented[4,5]. Contrary to the low commitment to mammographic screening, post-diagnostic screening with hormone receptor and biologic marker determination seems widespread in Latin America[2].

With regard to medical therapy, all systemic treatments are licensed, but budget considerations constrain the use of some effective treatments. Adjuvant chemotherapy reduces the relative risk of death each year by almost 40% for women younger than age 50 years and by 20% for women aged 50 to 69. Use of modern drugs greatly differs from country to country and by insurance type. Chemotherapy treatments with anthracyclines are widely accepted, as is tamoxifen, for patients with estrogen receptor–positive tumors. However, new-generation

hormonal treatments like aromatase inhibitors and the biologic therapy trastuzumab are not accessible to all women[4].

In metastatic breast cancer, medical treatment is the most important consideration. Access to modern drugs is critical but often unavailable. Targeted therapies, such as trastuzumab, bevacizumab, or lapatinib, are important treatment options for patients with advanced breast cancer. Access to these drugs follows restrictions similar to those mentioned for early breast cancer, which leaves patients with few therapeutic alternatives, uncontrolled disease progression, and consequently poor outcomes[6].

Locally advanced breast cancer (LABC) is a term used to define a wide and heterogeneous group of large-sized tumors, node-positive or inoperable BC with often unfavorable prognosis. Its management remains challenging and involves a multidisciplinary team of cancer physicians. Although recent advances in systemic treatment have improved the operability rates and the outcome of LABC, these benefits have not necessarily been seen in Latin American patients[2].

Caribbean Scenario

Wesley Francis, Katura Horton -Perinchief

Epidemiology

Breast cancer is the most prevalent cancer, among women, and the third leading cause of cancer mortality across the Caribbean region[2]. Breast cancer is the leading cause of death among women in the region and continues to show rising incidence across the Caribbean[3].

The varied socioeconomic structures across the Caribbean region may help to explain some of the discrepancies seen from country to country. Although CARICOM describes all member countries to be 'classified as developing countries', members and associate members range from very low on the UN's Human Development Index (ie. Haiti = 0.503) to very high (ie. Bahamas = 0.805). Social determinants of health may indicate differences in access to care within a country including screening and specific treatment modes and could have a host of implications for the capacity to effectively diagnose, monitor and treat breast cancer. For the purposes of this review, four Caribbean countries of varied HDI grading were analyzed[15,17].

Genetic considerations

The region has been considered a hot spot for genetic predisposition as a significant risk factor for breast cancer. Hurley and Colleagues first reported that approximately 23% of unselected cases of breast cancer cases in the Bahamian population are attributable to a founder mutation in the BRCA 1 gene[17]. Hurley also reported a BRCA mutation rate in 9.5% of unselected cases and a PALB2 mutation in .1% of cases in Trinidad and Tobago[15]. A relatively high frequency of PALB2 mutations (2.8%) among Jamaican breast cancer patients compared to BRCA1 and BRCA2 mutations (1.7%)[9]. The rate of PALB2 mutations in unselected cases in Jamaica is the highest reported to date.

The increase in genetic predisposition is possibly to be due to the African Ancestry which is predominant within the region. In Caucasian non-founder populations, the prevalence of BRCA mutations in unselected breast cancer patients is reported to be 3-4%. Among BRCA1 carriers, the average cumulative risk of breast cancer by age 70 years is 65% and among BRCA2 carriers is 45%[17]. After a first breast cancer, BRCA1 and BRCA2 carriers also have a substantial risk of contralateral breast cancer[19]. PALB2 mutation carriers have a lifetime breast cancer risk

of between 33 and 58%[20]. Therefore, genetics has a significant influence on Breast Cancer incidence, clinical characteristics and outcomes within the region. Recommendations for routine genetic testing among women with a family history of breast cancer have been proposed in most of the major territories.

Clinicopathologic features

Chin and Colleagues at the University Hospital of the West Indies, reviewed 121 patients presenting to the oncology clinic in Jamaica. The median age of breast cancer diagnosis was 52 years[15]. Sixty-five patients were referred after definitive breast cancer surgery, 20% were referred for neoadjuvant chemotherapy and 15% for metastatic disease. Among patients referred for adjuvant therapy 91% initially presented because of symptoms and 9% were screen detected. The most common finding was a breast lump. Seventy-seven percent of women underwent a modified radical mastectomy and 23% had breast conservation, all patients had full axillary dissection. Estrogen receptor positive cases made up 62% of cases and triple negative cases were 33%[15,16].

Mungrue reviewed a total of 640 patients in Trinidad and reported that the age group ranging from 51-60 years had the highest proportion of breast cancer[16]. The cohort consisted of 62.2% patients that were postmenopausal. Breast Cancer was also more common among women of African ancestry and the most common stage at presentation was Stage IIA. All women were diagnosed by symptoms and no patients had cancer detected by mammography. The unilateral mastectomy rate was reported as 70% and of these patients 34.5% had axillary nodal clearance. It was not clear if the sentinel lymph node biopsy was a technique utilized. The author noted that in 25 years the pattern of surgical care had not changed and mastectomy with nodal clearance

was the preferred approach in the management. Patients received multimodal therapy, 69% of patients received chemotherapy and 36.2 % received radiation therapy[16].

The Barbados National Cancer Study group reported on risk factors for breast cancer in a black population. The BNCS consisted of 241 incident BC cases and 481 age-matched female controls with a mean ages of 57 and 56 respectively. The BNCS reported that older age at full term pregnancy, nulliparity, history of benign breast diseases and family history of BC were among the most significant risk factors among the population. Their results strongly suggested genetic influences in BC development. Among the women in the study population, 45% presented with tumors at stage IIB or higher and 54% had ER negative cancers[15].

The author (WF) reviewed 200 patients over a 10-year period with a median age of 50 years (range 28-87), 22.5% were BRCA mutation carriers, 62% of which also had a positive family history. Seventy percent of patients presented with symptomatic breast cancer. The most common stage at presentation was clinical IIA (33.5%), only 3% presented at stage 0. Infiltrating ductal ca was the most common pathology (79.5%) and 9.5% of patients had DCIS. Estrogen Receptor positive rates were 52 % and 21.8% were ER negative. HER2 Positive rate was 43.7% with 29.9% of patients being HER-2 negative. Patients with triple negative tumors were 21%. The unilateral mastectomy rate was 33.5%, 21% had a bilateral mastectomy and 15% underwent Breast conservative surgery. Most patients had multimodal therapy, Seventy-one percent underwent chemotherapy of which 40% in a neoadjuvant fashion. Forty seven percent underwent Radiation therapy[15].

The common theme among all the major territories is the fact that at presentation most patients are symptomatic. Screen detected breast cancer outcomes far outweigh those patients

who present with symptoms. An overview of published screening trials report a reduction in breast cancer mortality of 21% in women who are screened[15]. Screening is thought to enable breast cancer diagnosis at an earlier stage of the disease. This lead time allows for earlier introduction of curative measures and identification of disease with less nodal involvement. With the majority of patients presenting at stage IIA and IIB, this significant stage migration has poorer prognostic implications[16].

Cultural Barriers

There are many cultural barriers which do exist but have not been captured in published literature. Studies are lacking which may review overall attitudes toward screening within the region. Anecdotal data would suggest that even women with Private health insurance and those who can afford to pay out of pocket still do not participate in routine screening. The index case presented is an example of a patient with resources and easy access to care but still did not participate in screening. Even with obvious progressing symptoms, she did not present until her disease had progressed to skin ulceration. This presentation is very common and it may be related to fear of the diagnosis and often religious beliefs that the disease may disappear without treatment. There is also a factor of denial among women in the Caribbean and a fear of chemotherapy which results in seeking any alternative therapy including herbalist and naturopathic practitioners. The end result is delay in diagnosis with very late stage presentations. This is an area that is desperately in need of further studies[16].

Chinese Scenario

Xishan Hao, Hong Liu, Liren Liu, Huiqin Liu

In China, the incidence of breast cancer has continually increased in the past 40 years, due primarily to the changes in lifestyle accompanying the rapid social and economic development, such as westernization of diet, reduction of physical labor and decline in fertility and breast-feeding rates.

The incidence of breast cancer varies across different geographical areas in China, attributable to the imbalance of economic and social development. Breast cancer incidence in urban areas is significantly higher than that in rural areas, and in eastern regions it is significantly higher than that in central and western regions. Consistently, the proportion of breast cancer onset before the menopause in China is higher than in Europe and the United States. At present, early-stage breast cancer only accounts for a small number of newly diagnosed cases in China. Ductal carcinoma in situ, for example, has been diagnosed proportionally much less commonly in China (<1%) than that in Euramerican countries (20%-30%)[25]. Correspondingly, the average 5-year survival rate for breast cancer patients is approximately 73% in China compared with 90% that can be achieved in Euramerican countries when breast cancer is diagnosed and treated earlier[22].

To date, no nationwide early screening program exists for breast cancer in China, most women with breast cancer have a palpable tumor at the time of first consultation, among which more than 60% are diagnosed at the intermediate or advanced stage[22]. Furthermore, the awareness rate of breast cancer in Chinese women remains relatively low. According to a recent study, the awareness rate of breast cancer is less than 30 % among urban Chinese women, and their knowledge about risk factors, prevention, diagnosis and treatment of breast cancer is thereby rendered poor and inaccurate. Compared with that of urban women, the awareness rate of breast cancer among rural women is even lower (only 15%), and their knowledge about breast

cancer is more deficient due in part to them having had less chance to receive higher education. Moreover, in rural areas, most of the patients with basic health insurance nevertheless obtained medical care largely at their own expense, suggesting that the low coverage of newer treatments under the health insurance directly affects the care-seeking behavior in this population. Some rural women tend to give priority to alternative therapies during illness, which may cause them to lose the opportunity for early diagnosis and treatment. Given the large population of China, breast cancer has become a significant burden of illness, and the specialized equipment for diagnosis and treatment of breast cancer, such as breast X-ray machine, breast B-ultrasound machine and radiotherapy devices, are relatively insufficient, especially in the vast rural areas. Besides, the lack of well-trained specialists who can master cutting-edge technology constitutes another major obstacle to the optimal treatment for breast cancer patients in China. According to statistics from Tianjin Medical University Cancer Institute & Hospital in 2016, of more than 6000 breast cancer patients who underwent surgery in the hospital, only 1298 (21.5%) and 245 (4.0%) patients received breast-conserving surgery and postmastectomy breast reconstruction surgery, respectively[23].

Nowadays, with the rapid social and economic development, the general quality of healthcare in China has greatly improved. More than 95% of the Chinese population has been covered by basic social health insurance schemes since 2011, although the coverage provided by different types of social medical insurance in the country varies greatly. Meanwhile, several large population-based pilot projects for breast cancer screening have recently been carried out. For example, from 2008 to 2011, the Chinese Anti-Cancer Association (CACA) and Tianjin Medical University Cancer Institute & Hospital jointly conducted a breast screening project that covers 829,000 rural and 432,000 urban women, among which 431 and 307 cases of breast

cancer were diagnosed in rural and urban population, respectively. Notably, of those newly diagnosed cases, early-stage breast cancer (stage 0-I) accounts for 46.15% and 38.76% cases in rural and urban patients, respectively, which was significantly higher than that in patients attending the hospital (17%). An interesting finding from the project is that breast ultrasonography (BUS) provides advantages in breast cancer screening for Chinese women, since most of them have dense breast tissues. As an important complement to mammography, BUS was shown to increase the positive rate of screening by 11.9% when it was used in addition to screening the mammographic negative population[20].

Based on the results of this project, the first large population-based "breast cancer screening guidelines for Chinese women" were released in 2019[23]. Due to the characteristics of an early peak age of onset in Chinese women, the guideline suggests a 5-year earlier starting age for breast screening compared to that in Euramerican guidelines. Chinese women aged 45-69 years with average risk of breast cancer are advised to undergo regular mammography screening every 2 years. Among these, the ones with mammographic negative results and dense breasts are advised to have additional BUS screening. As for those who have a family history of breast cancer, mammography plus BUS screening once a year from the age of 40 are recommended. Under this screening program, it now costs about $30,000 to save a patient with breast cancer in China, which meets the standard of three times GDP per capita recommended by WHO[21].

To further increase the early diagnosis and cure rates of breast cancer in China, there are still many areas yet to be improved. Firstly, to promote the implementation of a nationwide breast cancer screening program with a continuous updating scheme. Secondly, to pay special attention to health literacy to spread the knowledge about breast cancer, promoting healthy lifestyle habits. Thirdly, to strengthen the training on prevention, early diagnosis, and

standardized treatment of breast cancer for clinicians and to expand the program for training breast cancer specialists, with the support of the National Cancer Clinical Research Center as well as other social organizations. Fourthly, to provide sufficient specialized devices for breast cancer screening, such as BUS and mammography equipment, based on the needs of each local population. Finally, to further strengthen international exchange and cooperation to keep abreast of cutting-edge technology as well as novel ideas for early diagnosis and treatment of breast cancer[22,23].

Middle East Scenario

David Atallah, Malak Moubarak

Epidemiology

The Middle East region is characterized by low, but increasing cancer incidence rates, which could be explained by lifestyle changes such as late marriage, delayed first pregnancy, lower parity, use of oral contraceptives, lack of physical activity, and smoking. In 2007, a systematic review estimated that breast cancer accounts for 13–35% of all female cancers in Arab countries. They also noted a trend toward earlier age of onset as well as presentation at advanced stages among Arab women. Among 7455 patients included in the study[28] found that the average age at diagnosis of breast cancer was 48 (range: 43–52) in women from the Arab nations. These findings appear to be a decade earlier than in Western countries. In the Middle East, the age-standardized incidence rate (ASIR) of breast cancer in women varies between 24.9 and 97.6 per 100,000 Lebanon has the highest incidence rate among Arab nations with an ASIR of 97.6 per 100,000 (Globocan 2018)[25]. In parallel, countries such as Egypt, Morocco, and Iraq, which have large populations, had the highest total number of deaths. The ASIR of breast cancer

in Western Asia and North Africa are 45.3 and 48.9 per 100,000, respectively. The low incidence numbers could be explained by the low participation in breast cancer screening (BCS) or inadequate screening programs in these countries with low incidence rates. No adequate mortality records and disease-specific mortality rates are available in most of the countries[24].

Furthermore, quality of life varies among Arab women with breast cancer. Women over this geographical area have different education and socioeconomic status making the epidemiology of breast cancer in this region very complex and involving multiple risk factors of breast cancer. Besides, some countries are low-income countries with poorly developed health care systems which do not allow the detection of some cases. Besides, the continuous political and civil instabilities that this region suffers from may also increase not only the burden of the disease but also the delay of its detection[26].

Cultural Aspects

Unfortunately, breast cancer is still considered a taboo by a large segment of the population in this area and some people avoid mentioning it by calling it 'the other disease'. This fear of having the disease or acquiring it may preclude a lot of women from participating in national screening programs, if these are really developed in the country. According to a cross-sectional quantitative survey of 1,063 Arab speaking women in Qatar, participants had different conceptions of cancer occurrence and cause. While some thought that people get cancer because of unhealthy lifestyle, not breastfeeding one's baby or hereditary factors, others ascribed cancer to fate. Only 42.8% believed that cancer is preventable and less than 20% considered that cancer is a punishment from God, bad luck or contagious. These social and cultural beliefs may severely influence the cancer perception and consequently the adherence and participation to BCS programs[27].

For religious reasons, some women have gender preference for the health care provider and accept to be examined only by a woman and may skip an annual examination in case of non-availability of a female physician.

Besides, the developing world is witnessing a shift in lifestyle by following the steps of the Western countries with an increase in social factors like smoking, alcohol, lack of exercise, and obesity. Since women are more involved in the work field, hormonal risk factors are more prominent such as delayed first pregnancy, having fewer children and reduced breastfeeding[27]. On a similar note, a recent review has suggested that the rising incidence of female breast cancer could be related to excess body weight[26].

Barriers for the Early Diagnosis and Treatment

A major barrier to BCS is low perceived risk and pessimistic views related to cancer. Actually, women with lower education levels may fear to undergo a screening examination that might detect cancer and are not aware that an early detection of cancer is beneficial.

Unfortunately, no effective health infrastructure is available for BCS in these countries. National programs implemented by the health authorities lack in most of the countries and are only developed in countries with a high socio-demographic index. Some countries have developed guidelines for BCS examinations which are undergone by women who are self-motivated or encouraged by their health practitioner. For example, in Lebanon, the guidelines for BCS recommend a mammography scan every year starting the age of 40 years, women with family history of breast cancer should start screening 10 years prior to the onset of the first case in the family, all women are to have an annual clinical breast examination (CBE) with mammography and one CBE every three years between the age of 20 and 40, all women are to

perform breast self-examination once per month starting at the age of 20, two routine views are needed for a valid mammography which include craniocaudal and lateral oblique, and finally ultrasound is not recommended for asymptomatic women[28].

Screening expenses are not always covered by governmental or private insures. Otherwise, the existing screening centers are not being sufficiently monitored neither for safety nor results. Due to lack of national screening programs, awareness campaigns at institutional levels try to involve the media and increase the participation of patients to BCS by organizing lectures, physician interviews, and sometimes offering screening mammograms at reduced prices. These efforts have contributed in some countries to a reduction of detection rates at advanced stages[28].

Health care professionals have a positive impact on the attitude and beliefs of the general public. Therefore, health care workers should have adequate knowledge and be aware of the risk factors and recommendations of BCS to positively influence the patients' attitude. Unfortunately, recent studies in the Arab World showed low knowledge levels and adherence to screening examinations among health care professionals while they are supposed to spread the knowledge and encourage female patients to participate in screening programs[24].

Improving Quality of Care:

Unfortunately, the modified radical mastectomy remains the most common performed operation amounting to 45–82% of cases. This could be related to the presentation at advanced stages and the low number of radiation centers since radiation therapy is essential in case of conservative treatment. The availability of radiotherapy services in the Arab world is far below international standards and varies significantly among different countries. There are only 84

radiation therapy centers, 256 radiation oncologists and 473 radiation technologists in all the Arab countries, as compared with 1,875, 3,068 and 5,155, respectively, in the USA, which has an equivalent population of about 300 million[27].

In some countries, huge efforts are made to improve the detection as well as the treatment of breast cancer patients. For instance, earlier stages of the disease constituted two-thirds of the cases in the Lebanese population, with survival rates exceeding 80–90% according to a recently published study[28].

Multidisciplinary approach is the keystone in the management of breast cancer and only few centers practice it in the developing and Arab countries. Implementation of multidisciplinarity, proper access to tumor boards in cancer institutions are still needed in this region to improve breast cancer care. Also, the medical community in this region is urged to publish more findings to adapt screening and treatment modalities.

South Africa and Sub-Saharan Africa Scenario

Carol Ann Benn

Background

The latest South African National Cancer Registry, in 2014 showed that breast cancer was the most commonly diagnosed cancer among women, with an age-adjusted incidence rate of 29.75 per 100,000 women and a lifetime risk of 1 in 27. In 2014, 8,230. This data is based on people presenting symptomatically to clinics with a small minority of women engaging in screening programs. While the presentation of breast cancer in most lower middle income environments is locally advanced breast cancers (LABC) with more palpable disease, clinical

assessment remains an equally useful screening tool and probably as effective as two yearly mammography screening in reducing mortality in limited resource areas. For South Africa, given the large proportion of women who present with clinically detectable, later-stage cancer, clinical breast examinations conducted in primary health clinics – for all symptomatic women and asymptomatic women over age 35 – is a low-cost option for population-level screening in the medium term. The international trend of screening based on risk and not age can be effectively trialed in LMIC. The concept of going back to basics and ensuring breast self examination (BSE) and primary care access to breast assessment is encouraged. This is a cost effective way of improving breast disease detection, which can be taught to both public and healthcare providers[29].

Cultural Aspects

Perceptions of breast cancer have changed over the last 30 years, with the realization that it occurs in any race, age, or culture. Awareness in South Africa has involved both successful and failed community education projects, mainly by media directed public health campaigns, and breast cancer advocacy and support groups. Health awareness education and support projects based on American and European models, driven largely through pharmaceutical and cosmetic firms whose corporate-social initiatives provide printed leaflets and posters (primarily in English), have achieved limited success[29]. Listening to patient navigators from the community highlighting the reasons for failure of these projects and redirecting information based on local cultural belief systems resulted in an increase in patient attendance to treatment centers. Initial problems such as the diversity of languages spoken, poor literacy in English, and an inherent suspicion of accepting advice from women of a different cultural background were corrected by involvement of the navigator, through provision of personalized information and training within

their community. This training included understanding preconceptions and beliefs around the cause of cancer, which were resulting in symptomatic women not accessing care[32].

Barriers of Early Diagnosis and Treatment

Historically and currently access to breast cancer screening and treatment in SA, as also seen in other lower middle income sub saharan countries, is characterized by regional and socioeconomic disparities. These differences, as in many LMIC often start with the relatively low levels of knowledge of the disease in certain geographic areas and within certain communities around issues such as "how breast cancer presents" with the resultant late presentation at health facilities. This is further hampered by the still vertical medicinal model of acceptance of health care provider assessment of the health concern. If the patient is advised that this is not a concern she may decide not to seek health care advice despite a genuine health risk issue .A continent-wide review of surgical management of breast care in Africa described a disproportionate amount of black African patients presented with locally advanced and metastatic disease (stage 3 or 4). Only 25 % presented with early-stage disease (stage 1 or 2) . Since then a change in awareness and access to care has doubled the percentage of women presenting with stage 2 cancer or lower to 46%. Still, significant disparities and barriers to accessing services persist in comparison to the United States, where 82% of women are diagnosed with stage 2 cancer or lower[30].

Lack of clear direction as to where patients with health concerns should present; as well as apathy if no clear answers are given result in compounded access delays. Patients waiting for bookings for chemotherapy or radiation accept excuses such as "the next available date is in 4 month's time" and "we will call you", and don't push back when not receiving calls.

Whilst delays regarding access to health care services are due to both patient- and provider-factors; understanding barriers to receiving healthcare are complex, with both doctor and patient factors contributing to the problem . Patient (mis)beliefs and cultural factors; including suspicion of the biomedical model exacerbated by economic, geographical, psychosocial, cultural, financial and medical influences all affect delays to treatment. Investment in breast cancer research and treatment in LMICs should be a global health priority[31].

Medical influences more commonly understood as 'Provider delay' (defined as the structural or provider-dependent factors which impact negatively on time from the first presentation to a healthcare practitioner to receiving primary treatment, be that surgical or non-surgical) make a not insignificant contribution to limitations in accessing health care in many LMIC. For example, in South Africa, restrictions to access of the healthcare system and delays in service delivery mechanisms will most positively affect the outcome regarding diagnosis, management and ultimately cancer survival. Data suggest that patients presenting with advanced disease, with a delay of more than 60 days from tissue diagnosis to primary treatment may have an adverse impact on mortality. A meta-analysis studying delay from surgery to adjuvant therapy found a backlog of more than four weeks to chemotherapy as well as delays to radiation adversely affecting patient outcomes[31]. These delays are often seen in LMIC. Delays to care in environments where there is a patient driven advocacy results in forced improvement of services. Delays to care in environments with a historic acceptance of poor service and fatalistic attitude to cancer compound the problems of poor service delivery. If walk-in access was prioritized at specialist centers, women could also initiate their diagnosis process at the specialist centers directly, reducing appointments and patient costs. Regardless, quick, coordinated referral would contribute to reductions in delays to treatment. Regionalizing oncology services would also

improve access to care and compliance as time and distance stressors would be avoided. It can thus be seen that interventions are required at multiple levels to ensure access and availability to affordable care in sub-Saharan Africa[32].

Improving Quality of Care

Service delivery is a key concept to ensuring reasonable health care outcomes.

South African models that have been instituted in a few government units have undergone fundamental improvements ensuring better clinical care in some settings over the last twenty years. Service delivery models and how they impact on the result are critical issues; this is where navigation programs particularly with community-based navigators that understand the logistic and psycho-social issues is important. Perpetuating a service delivery model whereby trained primary care healthcare workers could immediately refer women with suspected breast concerns to specialist centers where diagnostic radiology and/or an ultrasound and biopsy could be performed as needed. More publications about breast cancer services in LMIC are needed.

Training of primary care physicians; clinical associates; primary care nurses and community-based patient navigators (those from the community who have experienced breast cancer, either self or with close family, and have an increased understanding of geographical and cultural logistical challenges) is critical.

Service delivery in SA as with other LMI countries has progressed considerably in some cosmopolitan urban cities. In these public sector units diagnosis now includes the global gold standard: triple assessment (i.e., clinical breast examination, imaging by ultrasound or mammography or both, and biopsy). Quality of the radiology and pathology service may be variable affecting the efficacy and reliability of the triple assessment. In Kenya the development

of a national strategy for the prevention and control of noncommunicable diseases 2015-2020 provides a roadmap to improve (breast) cancer care and the quality of life of all Kenyans[32].

In South Africa, access to diagnostic, treatment and surgical services are not homogenous. Late-stage presentation of disease continues to prohibit individual management approaches, such as

BCT and a lack of treatment facilities and specialist capability to perform these procedures in the public sector limit access for many women.

A national-level policy document on breast cancer screening and treatment has been drafted and launched in South Africa. The policy document addresses options for improving access to breast cancer-related services under a new policy. It looks at the current environment regarding breast cancer-related care. Barriers to the implementation of equitable access – including perceived costs – are discussed, and health delivery models which could help achieve South Africa's goals are suggested. The aim is to decrease current provider-dependent delays. Increased availability of multidisciplinary teams functioning in specialist centers should improve access and thus decrease the numbers of LABC presenting with a knockdown effect on decreasing low survival rates. The policy document hopes to improve patient access; improved communication between regional and central units with more timely access to all treatment modalities[31].

Conclusions

Breast cancer is the most common cancer, and it kills more women than any other cancer in Low and middle income countries. The economic burden is also great, and it is clearly

observed that countries today allocate insufficient resources to tackle the disease. Women remain undiagnosed, uncared for, or treated with suboptimal therapies, all of which result in high morbidity and the associated societal costs. Universal health care coverage is still not the rule in LMICs; even in those countries where the entitlement to breast cancer health services are guaranteed by law, it is not accompanied by the necessary resources. Vast inequities in access to breast cancer health in different regions of countries, exist, which translate to unequal results in breast cancer outcomes. Data about survival are scarce and fragmented; what is available shows a wide dispersion across and also within countries. Yet, the evidence signals that only a few countries have 5-year survival outcomes that surpass 70%. The reduced survival results in part from diagnosis of approximately 30% to 40% of patients when the disease is already in metastatic phases III and IV.

Key messages

Education, awareness, prevention, and early diagnosis are priorities to be considered for all actions performed as part of the breast cancer control continuum.

• Because of the demographic transition, breast cancer rates will approach epidemic proportions with great economic impact. Health systems and physicians must be prepared to face this critical situation.

• Lack of data about the disease is common. It is important to promote better information from reliable data that originates from Latin American countries.

• Access and affordability to proper diagnosis and care are important limiting factors. National general or specific breast cancer plans are fundamental for an organized governance, financing, and health care delivery.

• Evidence-based treatment guidelines are published in most countries by governmental authorities, cancer institutes, or scientific associations. The challenge is the implementation of policies and mechanisms to ensure a consistent compliance with these guidelines across the whole population.

• Practice of alternative medicine in the absence of adequate evidence can be harmful. Scientific studies should be undertaken to generate evidence that amalgamates both traditional practices and modern medicine.

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Chapter 4

Causes and Risk Factors for Breast Cancer

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Abbreviations:

BMI: body mass index
EPIC: European Prospective Investigation into Cancer
ER: estrogen receptor
IARC: International Agency from Research on Cancer
IGF: insulin-like growth factor
PR: progesterone receptor
SHBG: sex hormone binding globulin

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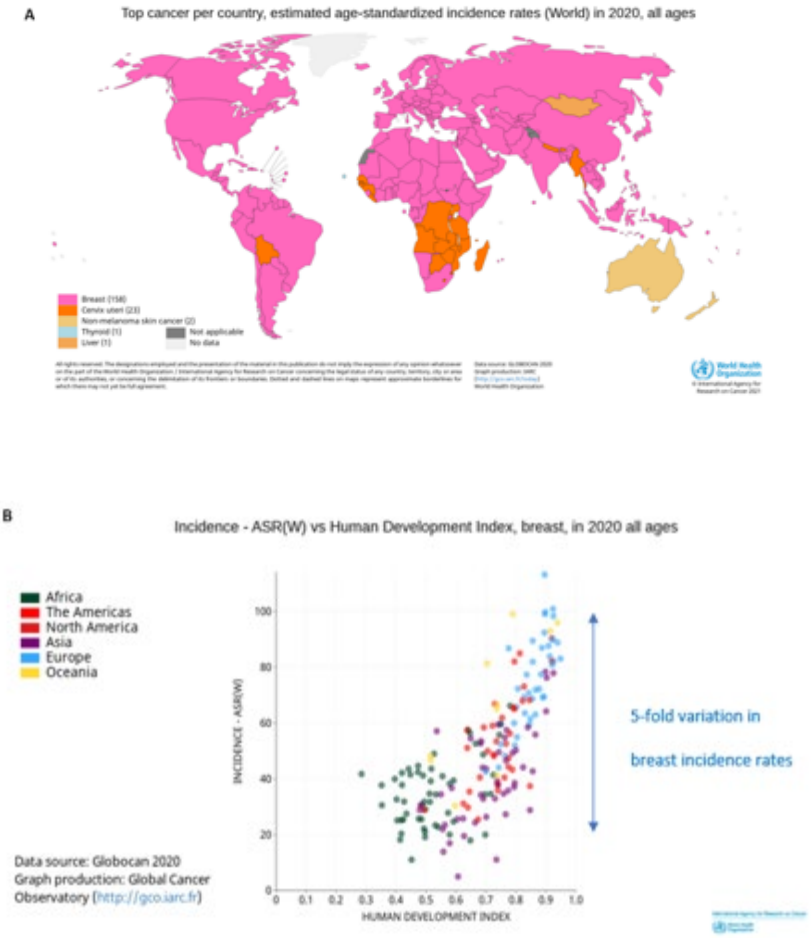
Introduction

Breast cancer is a common cancer in every country worldwide, ranking first or second most common cancer diagnosed in women (Figure 1A). This fact means that, without exception, in every national cancer control plan worldwide, the prevention, early detection/diagnosis, and treatment of breast cancer requires special attention. Despite this common predominance of breast cancer in women, as seen in Chapter 2, incidence rates display immense variations internationally (Figure 1B). Notably in 2020, there were over four-fold variations in age-standardized incidence rates between the lowest and highest incidence countries e.g. from 26.2 and 32.7 per 100,000 women in South Central Asia (including India) and Middle Africa to 90.7 in Western Europe and 95.5 in Australia and New Zealand (1). Even under the age of 45 years, when the impact of screening on incidence is minimal, these international variations are of the

order of 3-fold differences in rates. What accounts for these differences? The mammary gland is under strong hormonal influence for the fulfillment of the biological function of lactation, and breast cancer, too, has a strong hormonal pathogenesis. Early clues to this fundamental etiology were first identified as early as the 1700s when an Italian occupational epidemiologist, Bernardrino Ramazzari, observed that nuns had particularly high mortality rates from this disease and, conversely, they had very low - near zero - rates of cervical cancer (2).

Figure 1: A. Breast cancer features as the most common cancer in most countries worldwide and B Variation in breast cancer incidence rates by human development index



Since then, knowledge of breast cancer risk factors responsible for this observation in nuns, which also drive immense international variations in incidence, has been unveiled. They primarily pertain to features of the reproductive life. Here we provide a brief overview of these significant established risk factors for primary incident breast cancer and the pathways through

which they act. Note that the risk factors for a second primary breast cancer or breast cancer recurrence are not included here. The research landscape on breast cancer etiology is wide, thus where possible, we have based this summary on large international collaborative re-analyses, meta-analyses, large cohort studies, or reputed comprehensive evaluations, such as those performed by the World Cancer Research Fund and the International Agency for Research on Cancer's (IARC) Monograph program. The chapter is structured as follows: (1) the complexity of breast cancer etiology across the life-course; (2) sex; (3) inherited genetic susceptibility; (4) early-life factors; (5) reproductive factors; (6) endogenous and exogenous hormones; (7) lifestyle factors; (8) ionizing radiation; (9) history of breast diseases and (10) breast density and breast tissue aging.

The complexity of breast cancer etiology over the life course

Breast cancer etiology is complicated by several factors, including disease heterogeneity and the timing of exposures and of disease onset. Concerning the first of these, as will be seen in Chapter 12, breast tumor subtypes differ not only in prognosis and therapeutic management but also in their etiology. That is, a given factor can differentially affect the risk of different **molecular subtypes**, typically defined by estrogen (ER) and progesterone receptors (PR), HER2, tumor gene expression profiles, proliferation indices, or histology. For example, breastfeeding appears to be more protective against hormone receptor-negative than hormone receptor-positive breast cancer (3). Attention to disease heterogeneity has been a primary focus of etiological studies because a risk factor may not be detected, or its impact on disease risk may be greatly underestimated if all subtypes are combined. Secondly, risk factors can impact risk differentially according to the timing of exposures and the timing of disease onset. The period of breast development and ductal morphogenesis during puberty and up until the first pregnancy

represents a particularly susceptible window of exposure, as complete mammary cell differentiation is not achieved until the first pregnancy. Evidence of this **critical exposure window** was seen in the Hiroshima and Nagasaki atomic bomb survivors of the Life Span study Japan. In the follow-up of this cohort, for the same radiation exposures, increased breast cancer risk was greatest for women who were exposed at younger than at older ages (4). Pregnancy, a period of extensive epithelial cellular proliferation and differentiation rates in the mammary gland - stimulated by synergistic increases in prolactin and progesterone levels - may also be another window of susceptibility to environmental risk factors. Finally, etiology also differs by the **timing of disease onset**, as defined by age or menopausal status, e.g., women with higher adult body mass index have lower risk of breast cancer at pre-menopausal ages, but an increased risk post-menopausally.

Sex

Sex is the strongest risk factor for breast cancer, with over 99% of cases occurring in women. Thus, most of this chapter will concern the etiology of this cancer in women. Here we briefly summarize the rare occurrence of **breast cancer in men**. Age-standardized incidence rates for breast cancer in men are generally less than 1 per 100,000 man-years. Based on high-quality population-based cancer registry data in IARC's Cancer in Five Continents, international variations in male breast cancer incidence rates are present, with the highest in Israel (1.24) and lowest in Thailand (0.16). Interestingly, a positive correlation has been observed between breast cancer incidence rates in men and women, possibly pointing to a partially shared etiology (5). Many breast cancer case series have summarized male-to-female sex ratios, which typically range from about 1:100 to 1:30. However, this sex ratio has limited interpretational potential as a standalone measure of absolute incidence rates in men as it reflects variations in incidence in

each sex group, i.e., in terms of numbers of cases, a male to female ratio of 1:30 or 1:100 within a case series can originate from two settings with exactly the same incidence rates in men. Concerning risk factors for male breast cancer, genetic predisposition plays an important role. The strongest relative risks are seen for men with Klinefelter syndrome (RRs > 20), i.e., men having XXY chromosomes, as well as in those carrying mutations in/pathogenic variants of the BRCA1 and BRCA2 genes. The Klinefelter syndrome is known to be associated with lower androgen and higher estrogen levels and, consequently, a higher risk of gynecomastia. Independent of Klinefelter syndrome, however, gynecomastia is also a risk factor for male breast cancer (RR>10). For risk factors with modest effects, due to the rarity of male breast cancer, the pooling of many studies has been necessary, such as in the Male Breast Cancer Pooling Project. In this project, increased risks were observed among men with a higher body weight, higher body mass index and taller adult height, and possibly with excessive alcohol drinking, but there was no clear association with tobacco use (6, 7). There is also emerging evidence of a potential link to diabetes, cryptorchidism, having never had children, and a history of fractures at older ages (7).

Inherited genetic susceptibility

A family history of breast cancer is a strong risk factor, pointing to the role of inherited susceptibility to the disease (8). Extensive research on the mutations responsible for this hereditary predisposition first identified several moderate and highly penetrant genes. They include mutations in genes such as **BRCA1, BRCA2**, CHEK2, PTEN, TP55, CDH1 and STK11. The highest lifetime risks, at the individual level (up to 80% risk), are conferred by mutations in the BRCA1 (increasing ER-negative risk) and BRCA2 genes which are implicated in the hereditary breast and ovarian cancer syndrome (HBOC). TP53 mutations are present in the rare

Li-Fraumeni syndrome and PTEN in Cowden's syndrome, two other rare genetic syndromes that are associated with an increased risk of breast and other cancers. At the population level, however, moderate and high-penetrance genes account only for a small fraction of breast cancer patients (<10%, with between population variations).

Further, these genes can only be identified in a minority (up to 30%) of familial cases. Indeed, models of inherited genetic risk suggest that, for the majority of breast cancer patients, susceptibility arises from the combination of a large number of much lower penetrance non-coding genetic variants. Discovery of these more common single nucleotide polymorphisms (SNPs) implicated in breast cancer is much more challenging, requiring large genome-wide association studies with hundreds of thousands of patients, such as in the Breast Cancer Association Consortium (9, 10). Each SNP confers a small increased risk, but when combined with **polygenic risk scores**, individuals ranked with the highest scores have substantially increased risks. Such scores currently include a few hundred SNPs. Polygenic risk scores are frequently being updated with larger sample sizes, by breast cancer subtype, and importantly, in understudied populations and ethnicities to capture relevant and greater genetic diversity (11). These scores, or those that combine inherited susceptibility variants with non-genetic risk factors such as mammographic density (12), help to stratify women into higher vs lower risk and are hoped to improve breast cancer primary or secondary prevention strategies in high-risk women. Primary prevention may be through lifestyle modification or through chemoprevention, e.g., with tamoxifen, raloxifene, exemestane, and anastrozole. For the latter approach, among women with a higher breast cancer risk, it has been estimated that up to 50% of breast cancers could be prevented among high-risk women (13). The above advances are being incorporated in the determination of risk in women with a strong family history and, among breast cancer patients,

for contralateral breast cancer risk. Screening for pathogenic variants at an accurate population-wide scale requires careful consideration of the costs, counseling, infrastructure, personnel, and real-life implementation needs and consequences (14).

Early-life factors: growth and development

Let us now move beyond inherited germline mutations to how exposures that occur during life, starting from conception, affect risk. In 1990 the Greek epidemiologist Trichopoulos elaborated the hypothesis that influences on breast cancer risk commence as early as in the *in utero* period (15). This hypothesis stemmed from several observations. The first of these was from the observed effects of **diethylstilbestrol** (DES), a synthetic pro-estrogenic drug. Notably, in the daughters of mothers who were prescribed this drug during pregnancy in the 1940s-1960s, in the then belief that it would reduce the risk of miscarriage, there was an increase in breast cancer risk in the lifetime of daughters of DES-exposed mothers, with relative risks ranging from modest increases (~1.3) to a doubling of risk (16). This risk increased in a dose-response fashion. Negative health effects also extend to a range of adverse reproductive events (17).

Nevertheless, the increased breast cancer risk was present after adjusting for age at first birth and parity. Millions of women, mainly in the US and Europe, had been prescribed the drug before its ban from 1971 onwards. The proposed mechanism explaining the DES-associated risks is through DNA methylation leading to increased levels of estrogen in utero and a more significant number of breast stem cells at risk of mutational transformation later in life.

Other aspects of the typical pregnancy hormonal milieu also influence breast cancer risk. In terms of large-scale epidemiological studies, widescale data on such exposures have relied upon

measures routinely recorded during pregnancy or at birth, including birth size, mostly birth weight. In this regard, a large pooled re-analysis of 32 studies with 22,058 breast cancer cases examined the associations of **birth weight**, birth length, and ponderal index (a measure of weight for size relevant to infants in kg/m^3) in relation to breast cancer (18). Higher birthweight was associated with an increase in breast cancer risk of 6% (95% CI: 2% to 9%) per 500 grams (approximately one standard deviation) increase in birth weight (adjusted for gestational age, reproductive factors, and adult height). Slightly stronger associations were found for birth length. Birth size can be viewed as an early measure of infant and child development at the start of the **body growth trajectory** from conception to childhood, through adolescence, and to adulthood. In the discipline of life-course epidemiology, several metrics along the trajectory of physical growth and development are associated with increased risk – namely greater height and but lower BMI at age 14, younger age at **peak height velocity** (i.e. a younger age at maximum growth spurt), height gain between age 8 and 14 years, and **greater adult height** (19). Of note in relation to adult height is that taller stature is positively linked to the higher incidence of many types of cancer, not just breast, but its association with breast cancer is more robust than that for other cancers (20).

Independent of these factors, women who had **earlier menarche** and those who had a later menopause have a 5% (per one year earlier menarche) and 3% (per one year later menopause) increase in risk. The stronger association for early menarche than last menopause suggests that the relevant risk factor goes beyond a lengthening of the reproductive life span when the ovarian function generates cycles of exposure to high sex steroid levels (21); instead the time between menarche and first birth may be critical due to susceptibility of the mammary gland prior to complete cell differentiation at pregnancy. Finally, whilst the relevance of these associations

with birth size, growth, and development may seem somewhat obscure at first because they do not represent modifiable factors in today's adult women, their importance in the primary prevention of breast cancer may be critical for longer-term prevention in future generations of women (22). Early life balances of nutrition, physical activity, and energy are likely behind the mechanisms driving these associations. Secular trends in many Western countries over the past century are towards taller adult height, earlier menarche, and more recently, higher BMI in childhood and during adult life. Thus at the population level, the early-life period has had an increasing contribution to incidence rates over time.

Reproductive factors

Since the observations of Ramazzini in the eighteenth century, there is clear epidemiologic evidence demonstrating that a woman's reproductive life has a significant impact on her risk of developing breast cancer. Relevant features include the number of pregnancies, age at the first pregnancy, and breastfeeding habits for each pregnancy. Indeed, **nulliparous women** have a 30% higher risk of developing breast cancer compared to parous women (23). Women bearing a **child at a younger age** have a lower risk of breast cancer compared to those having their first child later in life: women having their first full-term pregnancy after the age of 35 have a 40% higher risk of developing breast cancer compared to those having their first child before the age of 20 (23). In an analysis conducted in the UK Million Women's study, a prospective cohort of more than one million middle-aged women, a more substantial increase in breast cancer risk with increasing age at first birth was observed for lobular breast cancers compared to other histological subtypes (24). Concerning parity, among parous women who never breastfed, a greater number of full-term pregnancies is associated with a lower breast cancer risk, each birth

corresponding to a 7% decrease in risk (25). Pregnancies that end as spontaneous or induced abortion do not increase the risk of breast cancer (26).

Mothers who breastfed their children have additional protection against breast cancer, and each cumulative year of **breastfeeding** is associated with a 4% decrease in breast cancer risk (25). Indeed, larger family size and longer breastfeeding duration in developing countries account for a large part of their lower incidence rates compared to developed countries, with breastfeeding patterns estimated to be responsible for two-thirds of this difference (25). Amidst trends towards delayed and less childbearing, which have multiple overall benefits on the lives of women, the associated increases in breast cancer risk can be partially curtailed through breastfeeding.

A meta-analysis that explored the above associations according to estrogen and progesterone receptor status of the tumor found significant reductions in risk associated with parity and younger age at first birth for ER-positive PR-positive breast cancer but no association for ER-negative PR-negative breast cancer (27). On the contrary, breastfeeding decreased the risk of both ER-positive/PR-positive and ER-negative & PR-negative breast cancers, suggesting different and partly hormone-independent mechanisms of action. In a pooled analysis of nine prospective cohorts, being parous was associated with a decreased risk of luminal-type breast cancer but with an increased risk (+23% compared to nulliparous) of triple-negative breast cancer (28). In this same analysis, the risk of triple-negative breast cancer was not related to number of children or age at first birth. A longer duration of breastfeeding seems, however, to be associated with a lower risk of all breast cancer subtypes, including triple-negative breast cancers (29).

Although parity protects against breast cancer development overall, it should be noted that a **transient increase** in breast cancer risk is observed after a pregnancy. A recent pooled analysis of 15 prospective cohorts conducted by the Premenopausal Breast Cancer Consortium observed that, compared to nulliparous women, parous women have an increased risk of breast cancer that peaked five years after childbirth and lasts for more than 20 years before the pregnancy-conferred protection is achieved (30). This pattern was more pronounced among women with a family history of breast cancer and for women older at first birth and with more births. The delayed pregnancy-conferred protection was also specific to hormone-receptor-positive breast cancer; for ER-negative cancers, risks were increased after a pregnancy, but there was no subsequent protective effect, even more than 30 years after the birth.

The timing and type of **menopause** are also an important factor for breast cancer. Premenopausal women have a higher risk of breast cancer compared to postmenopausal women of the same age, and the older a woman reaches menopause, the higher her risk of developing breast cancer: every year older at menopause is associated with a 3% increased risk of developing breast cancer (21). This seems to be particularly the case for hormone-receptor-positive breast cancers. Menopause signals cessation of ovarian function and a substantial reduction in sex hormone levels. Thus, an earlier menopause reduces the lifetime exposures to these proliferation hormones. Correspondingly, women who have a bilateral prophylactic salpingo-oophorectomy (for breast cancer prophylactic reasons in BRCA carriers, for example, or for other reasons) also have a substantial reduction of 50% in breast cancer risk (31)

Endogenous and exogenous hormones

Endogenous hormones

Sex, growth, and metabolism hormones are known to play a critical role in breast cancer etiology. The role of estrogens in the development of breast cancer has been known for more than 100 years. Mechanisms by which estrogens are involved in breast carcinogenesis include mitogenic properties and metabolic activation of estrogens to genotoxic metabolites (32). Androgens may also play a role through their conversion to estrogens or through a direct effect on cell proliferation and growth (33). Insulin-like growth factor-I is a peptide that stimulates mitosis, inhibits apoptosis, and is involved in metabolism and growth (34). Results from the literature over the last decades have shown that endogenous estrogens, androgens, prolactin, and insulin-like growth factor-I (IGF-I) are associated with an increased risk of breast cancer, but their association may differ by menopausal status and receptor status.

At postmenopausal ages, several publications from cohort studies (including women not taking exogenous hormones at blood donation) over the last decades have constantly shown an overall increase in the risk of breast cancer with increasing blood concentrations of endogenous **estrogens and androgens** and a decreased risk with increasing concentrations sex hormone binding globulin (SHBG), a protein that regulates the availability of these hormones (35, 36). Results from the large European Prospective Investigation into Cancer and Nutrition cohort (37) (EPIC), including 554 women who developed invasive breast cancer with information on receptor status and 821 matched control subjects, showed that women in the highest tertile of estradiol and testosterone concentrations had a breast cancer risk that was more than doubled compared to that of women in the first tertile. This association was stronger in women who developed ER-positive PR-positive cancer but was also significant in women developing hormone-receptor-negative cancers. A recent publication from the UK Biobank cohort, including 2,997 women who developed breast cancer during follow-up, and 133,294 controls, with

endogenous testosterone and SHBG measurements available, showed a 20% increase in breast cancer risk with increasing testosterone levels (per 0.5 nmol/L increment), and more than 10% decrease with increasing SHBG levels (per 30 nmol/L increment) (38). Further, a pooled analysis of 17 prospective studies published by the Endogenous Hormones and Breast Cancer Collaborative Group indicated a 30% increase in estrogen receptor-positive breast cancer risk with increasing pre-diagnostic **IGF-I levels** (i.e., approximately a doubling) (39). Finally, higher postmenopausal levels of the pituitary gland hormone **prolactin** important in breast development and lactation, increase breast cancer risk at these ages (40).

The role of exogenous hormones in breast cancer risk at pre-menopausal ages is more challenging to decipher because there are fewer studies of endogenous sex steroids in pre-menopausal women not taking oral contraceptives at blood collection. A further complexity when studying the role of endogenous hormones at these ages is the very high estrogen variations during the menstrual cycle, which makes it difficult to characterize a woman's exposure over a long period of time based on measurements on a single blood sample. A reanalysis of seven prospective studies published by the Endogenous Hormones and Breast Cancer Collaborative Group (Endogenous Hormones Breast Cancer Collaborative Group *et al.*, 2013), including more than 700 women diagnosed with breast cancer who were under age 50 at blood donation and who developed breast cancer during follow-up, and more than 1600 matched controls, indicated a 20% increased risk with doubling concentrations of both androgens and estrogens and no association with SHBG. Results from the EPIC study, including a total of 801 cases and 1132 controls, confirmed increased risk with increasing testosterone concentrations and no association with estrogen levels and showed no heterogeneity by receptor status of the tumors (42). Recent findings from the UK Biobank, including 527 premenopausal women who

developed cancer during follow-up, and more than 30,000 controls, did not show any association between endogenous testosterone levels and breast cancer risk but indicated a 20% increase in breast cancer risk with increasing IGF-I levels per 5 nmol/L increment (38). A similar increase in risk with increasing IGF-I concentrations was also observed in large pooled analyses (39).

Exogenous hormones

The IARC monograph program has classified the use of combined estrogen–progestogen oral contraceptives as carcinogenic to humans with sufficient evidence for breast cancer (43). However, this risk is only increased in present and recent users compared with never users, and ten years after cessation of use, the risk is similar to that in never users. Moving to later in a woman's reproductive life, hormone replacement therapy (HRT) started to be commercialized during the 1970s and has been widely used to treat post-menopausal symptoms and to prevent chronic diseases such as osteoporosis. As for oral contraceptives, a wide range of compositions of replacement therapies (estrogen alone, estrogens plus progestogens, tibolone) were marketed, with different routes of administration (oral, transdermal, implanted formulations). The IARC working group concluded that the use of estrogen-only, or the use of combined estrogen–progestogen menopausal therapy is carcinogenic to humans, with sufficient evidence of an increased risk of breast cancer (44).

Lifestyle and environmental exposures

Beyond differences in reproductive and hormonal factors, the variations observed in breast cancer incidence also result from contrasting lifestyles. Unless referenced otherwise, most of the statements below on diet and physical activity were sourced from the World Cancer Research Fund Continuous Update Project (45). **Excess adiposity** is an established risk factor for postmenopausal breast cancer (46), with an increase in the risk of 12% per 5 kg/m² increase in

body mass index (BMI), and a comparable increase per 10 cm in waist circumference and 0.1 unit in waist-to-hip ratio. Adult weight gain is also associated with an increase in risk of postmenopausal breast cancer, estimated at 6% per 5 kg weight gain. These associations are observed mainly for hormone receptor-positive tumors and are likely limited to women not using exogenous hormones. The most likely biological mechanisms driving these associations involve the endocrine function of the adipose tissue, which becomes the main source of endogenous estrogen production after menopause when the ovaries cease to fill this role.

Further pathways may include chronic low-grade inflammation induced by obesity and increased insulin resistance observed in the context of excess adiposity (47) and in relation to the increased breast cancer risk among women with Diabetes Mellitus. With the rising epidemic of obesity and sedentary lifestyles globally, the above associations are of concern for increasing breast cancer risks. Already in 2012, and assuming a 10-year lag period, it was estimated that 10% of postmenopausal breast cancers, or 114,000 cases worldwide, were attributable to excess body mass index (48).

Physical activity is defined by the WHO as "any bodily movement produced by skeletal muscles that requires energy expenditure." This exposure is challenging to evaluate in epidemiological studies, primarily based on self-reported activity levels. Nevertheless, there is strong evidence that being physically active decreases breast cancer risk, especially for vigorous physical activity, with a 10 to 17% reduction of breast cancer risk in women with the highest versus lowest physical activity levels (45, 49). Physical activity plays an important role in avoiding excess body fat but is also thought to benefit the metabolic pathways previously mentioned independent from body fat (48). Insufficient physical activity is currently more common in high-income than low-income countries, and women have a higher prevalence than men due to more

sedentary occupations and leisure time. However, its prevalence is evolving in low and middle-income countries with lifestyle changes, and some countries, such as South Africa and parts of Latin America, already have high obesity prevalence in women.

Alcohol consumption is an established risk factor for breast cancer: a 10 g/day increase in ethanol consumption (which corresponds to approximately one standard drink/day (~ 10g ethanol)) is associated with a 5 to 9% increase in breast cancer risk. A sizeable collaborative reanalysis of individual data from 53 epidemiological studies demonstrated that for an intake of 45 g ethanol/day (compared to never-drinkers), breast cancer risk was increased by 46%. This risk is limited to estrogen-receptor-positive tumours (45). Despite its harmful effects, alcohol use in women has been increasing worldwide since 1990, partly due to an increasing share of middle-income countries in the global volume of alcohol consumed (50).

Concerning **tobacco**, evidence for its role in breast carcinogenesis has emerged only recently. Going back to 2004, although smoking is clearly a Group 1 carcinogen – i.e., it causes cancer in humans, and indeed it causes many types of cancer - at that time, the IARC monograph evaluation concluded that there was evidence suggesting a lack of carcinogenicity for breast cancer (51). Since then, large cohort studies have reported positive associations with ever-smoking, either passive or active, which were stronger if smoking commenced before the woman's first birth or commenced at a young age (52, 53). For example, in the UK Generations Study, ever-smoking raised breast cancer risk by 14% overall and by 24% if smoking was initiated within four years of menarche (53). In this study, the effect of tobacco was also stronger among women with a family history of breast cancer. Further recent suggestive evidence derives from a Mendelian randomization study, which is a design less prone to conventional confounding. Genetic variants associated with a higher lifetime amount of smoking were

associated with increased breast cancer risk by 13% (95% CI: 0 to 26%) per one standard deviation increase (54).

Ionizing radiation

Ionizing radiation is an established risk factor for breast cancer (55). As mentioned in the comments on critical exposure windows, the effects of radiation on the breast derive predominantly from studies of atomic bomb survivors, such as the Life Span Study in Japan, which demonstrated that the radiation-related risk was highest if the radiation exposure occurred at a young age, under age 20 (4). Breast cancer risk increases in a dose-response relationship with the radiation dose received, with no minimum threshold. Increased breast cancer risks have also been found in other radiation circumstances, including medical radiation for non-cancer conditions, radiotherapy for cancer (i.e., in cancer survivors), and in radiation workers. Another radiation exposure setting is mammography itself. The IARC Handbook of Cancer Prevention on Breast Cancer Screening provides a comprehensive assessment of studies that compare the number of breast cancer deaths prevented through mammography screening to mammography radiation-induced breast cancers. The benefits of mammography screening in reducing breast cancer mortality outweigh any small increase in mammography-induced breast cancers (56).

Breast density, age, and unifying models for breast tissue age

Breast density is a measure of the fibro-glandular tissue in the breast as opposed to fatty tissue. This attribute was introduced because of the differential appearance of breasts on mammograms (among women free from cancer and free from breast disease). Some women have very fatty breasts, with little fibroglandular tissue – often older women after breast involution. Others have extensive fibroglandular tissue, i.e., extensive ductal and stromal tissue. Fibroglandular tissue attenuates X-rays and thus appears as radio-dense white areas on a mammogram, whereas fatty

tissue does not and appears black. Breast density is thus often referred to as mammographic density. John Wolfe described four patterns of increasing breast density, and in 1976 he conducted the first study linking mammographic parenchymal patterns to breast cancer (57). Since then, repeated studies have confirmed this positive association. Women with over 75% breast density have a 4-fold increase in subsequent breast cancer risk compared to women of the same age and BMI with less than 10% density (58). Unfortunately, women with dense breasts have the compounded disadvantage, beyond their raised breast cancer risk, of the lower sensitivity of mammography, i.e., it is more difficult to detect a tumor amidst a background of dense tissue than a tumor arising within a fatty breast. For this reason, ultrasound or other imaging modalities are often used to detect cancer in younger women when breast density is higher.

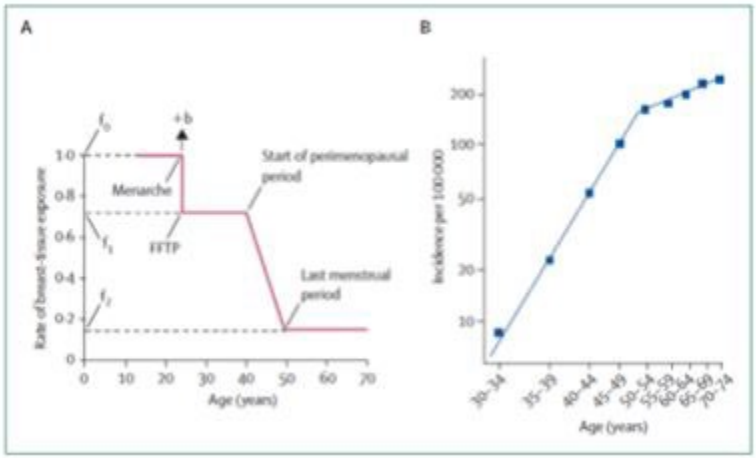


Figure 2: Pike model of breast-tissue ageing (A) and loglog plot of age-specific incidence of breast cancer in the USA (B) FFTP=first full-term pregnancy. B-variable is used to calculate age at menarche. F0, f3, and f2 are variables in the model. Reproduced from Pike Nature 1983.

The epidemiology of breast density partially mirrors that of breast cancer. Notably, breast cancer and breast density share many risk factors such as nulliparity or low parity, alcohol, HRT use,

and some genetic determinants, illustrating that breast density is modifiable and suggesting that breast density may be an intermediate tissue-specific biomarker of the effects of some breast cancer risk factors. One clear apparent anomaly among the determinants of breast cancer risk and breast density is age. Breast cancer incidence rates increase linearly (on a log-log scale) with increasing age and at a slower rate after menopause (known as Clemmesen's hook). In contrast, breast density declines with age, particularly at menopause. Although this may seem contradictory at first, these features can be linked. In 1983 Pike introduced a model for breast tissue ageing, reproduced in Figure 2, proposing that breast tissue does not age linearly but rather the tissue ages at different rates through life (59). His model describes how breast cancer risk factors, notably reproductive features, influence the rate of breast tissue aging, linking these factors to the shape of the age-incidence curve for breast cancer. Subsequently, in 2005 when the emerging epidemiology of breast density had been unveiled, Pike's model was linked by Boyd et al. to breast density (60). Notably, breast density also declines during the menopausal transition and with aging. Thus, breast density may be a tissue-specific marker of the biological process underlying the rate of breast tissue aging and, ultimately, of breast cancer incidence rates. The nature and drivers of the cumulative breast density profile thus become of interest to inform periods in life when breast density reductions may be best targeted. Complimentary research is underway on molecular measures of breast tissue age, such as the breast epigenetic age (61).

Summary

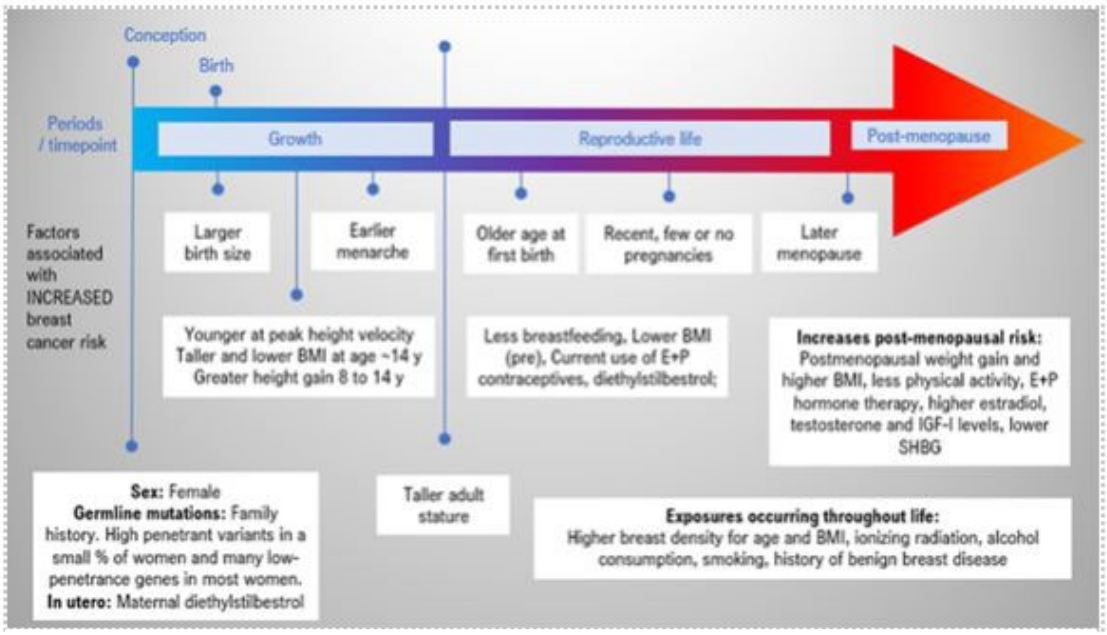


Figure 3: Summary of the established risk factors for breast cancer

In summary, breast carcinogenesis is a complex multifactorial disease with genetic and lifestyle/environmental influences on the proliferation and differentiation of mammary epithelium. Figure 3 summarizes the established risk factors presented in this chapter, emphasizing the accumulation of risk along the entire life course. The risk factors summarized only include established factors. Many other factors still require further investigation, including endocrine disruptors present in the environment (e.g., certain pesticides), dietary factors (e.g., starchy vegetables, dairy products, diets high in calcium), and occupational exposures (e.g., night shift work). Moving back to an international perspective, many of the risk factors summarized account for variations in breast cancer incidence rates. As many low- and middle-income countries undergo epidemiological transitions, including an increasing cancer incidence as populations expand and age, rises in breast cancer incidence are projected. Within this increasing

burden, an epidemiologic breast cancer transition is also expected, involving an evolving dominant molecular subtype.

Finally, how can we use the information on breast cancer risk factors to reduce risk? Whilst a disease-specific or molecular subtype-specific focus is needed for an understanding of the etiology of breast cancer, primary prevention of the disease necessitates a broader holistic perspective on the impact of risk factors on women's entire lives. In this regard, fortunately, many lifestyle factors associated

with lower breast cancer risk profiles are also habits that can be promoted to reduce the risk of many non-communicable diseases (NCDs). Notably, increasing levels of physical activity, avoiding tobacco and alcohol, and maintaining healthy body weight at post-menopausal ages are all healthy habits with multiple health benefits for women, not only for breast cancer but for many cancers and other NCDs. The promotion of breastfeeding to reduce the breast cancer risk of mothers is also of benefit to their babies. It must be noted, however, that several habits that have protective effects on breast cancer risk are not promoted (i.e., high parity, young age at first birth, no use of estrogen+progesterone oral contraceptives) because they are associated with more significant negative impacts across a woman's life – impeding her health, life-expectancy, independence, personal development and contribution to society. Thus, with the globalizing patterns of less and later childbearing, the promotion of acceptable healthy lifestyles to curtail the magnitude of increases in breast cancer incidence rates continues to be necessary. At the same time, it is likely that breast cancer will remain a common cancer thus, the need for breast awareness, early detection, and timely appropriate treatment will continue.

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Chapter 5

Breast History and Clinical Evaluation

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Keywords: clinical breast exam, resource stratification, breast mass, nipple discharge, breast pain, skin changes

Clinical Scenario

In low-income and middle-income countries (LMICs), women often present with advanced-stage breast cancer, and screening programs are not available. Five-year survival outcomes are 40-60% in LMICs; thus, early detection is needed in this vulnerable population [1]. Education for these women regarding the symptoms of breast cancer and the need for early evaluation can increase the detection and diagnosis of early-stage cancers.

Breast History

As breast cancer screening programs are difficult and costly to implement in LMICs, a thorough evaluation of breast abnormalities and education of the population can aid in early detection. Important information to collect regarding risk factors for breast cancer includes age, menopausal status, number of pregnancies and age at first delivery, and family history of breast cancer. Women identified as high risk can be educated and have regular clinical breast exams and/or mammograms where resources are available. Breast self-examination is the systematic assessment of the breasts by oneself to identify abnormalities. However, data has shown that

formal training on breast self-examination does not improve outcomes and can increase the number of biopsies on benign lesions [2]. Therefore, breast cancer awareness education is recommended and will aid women in seeking early care for breast abnormalities.

Lack of education and awareness about breast cancer is often the largest barrier for women to seek care and early detection of breast cancer [3]. During the evaluation of a breast complaint, it is an opportune time to counsel women regarding breast awareness and self-examination. Breast awareness involves understanding how one's breast feels and reporting any abnormality as soon as it is found. Education on breast abnormalities to be aware of are lumps and skin changes such as retraction, dimpling, peau d'orange, redness, or nipple discharge. It is also essential to counsel on behaviors such as limiting alcohol intake, increasing physical activity, and maintaining a healthy diet can reduce breast cancer risk and other cancers. Decreased patient awareness leads to late presentation of breast masses, skin thickening, and advanced-stage disease. Encouraging women to seek evaluation as soon as possible for breast abnormalities will assist in early diagnosis.

Social and cultural barriers often also need to be addressed in LMICs, as cultural norms may lead women to hesitate to seek medical care. The importance of seeking care for women's health issues should be insisted for all women. Women should also be encouraged to discuss health issues and any cancer history among family members so they can determine if there is a higher risk for breast cancer in the family.

Women with breast symptoms will need to be evaluated on duration, location of the lesion, and severity of pain or discomfort from the lesion. Breast abnormalities can be benign conditions, infections, or malignancies. A detailed history of the breast abnormality can guide the provider

on the level of suspicion for malignancy and utilize limited resources based on the level of suspicion.

Clinical Evaluation

Women with breast complaints need to be evaluated thoroughly to assess the possibility of breast cancer. Evidence-based guidelines have been established in evaluating breast problems by various organizations, including the National Comprehensive Cancer Network (NCCN), which comprises 30 comprehensive cancer centers across the United States. NCCN has adapted the guidelines based on resources available in a specific area or country and can be utilized among all nations. LMICs with limited resources can use these adapted guidelines for their patients. NCCN has defined three framework categories (basic, core, and enhanced) based on available resources, which are discussed in **Table 1** [4]. These categories can assist in determining the applicable guidelines based on resources available in that area or country.

Framework	Definition	Resources
Basic	Essential Services to provide a basic minimal standard of care that improves disease-specific outcomes	• Clinical encounter • Excisional/Incisional biopsies
Core	Includes services under Basic Framework and additional services that provide major improvements in outcomes that are not cost-prohibitive.	• Ultrasound imaging • More frequent clinical encounters • Core Biopsy is an option
Enhanced	Includes services under Core Framework and additional services that provide improvements in outcomes but are cost-prohibitive in lower resource settings	• Diagnostic mammography • Screening mammography for high-risk women

Table 1. Framework Categories Adapted with permission from the NCCN Guidelines® for Breast Cancer Screening and Diagnosis V.3.2018. © 2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form.

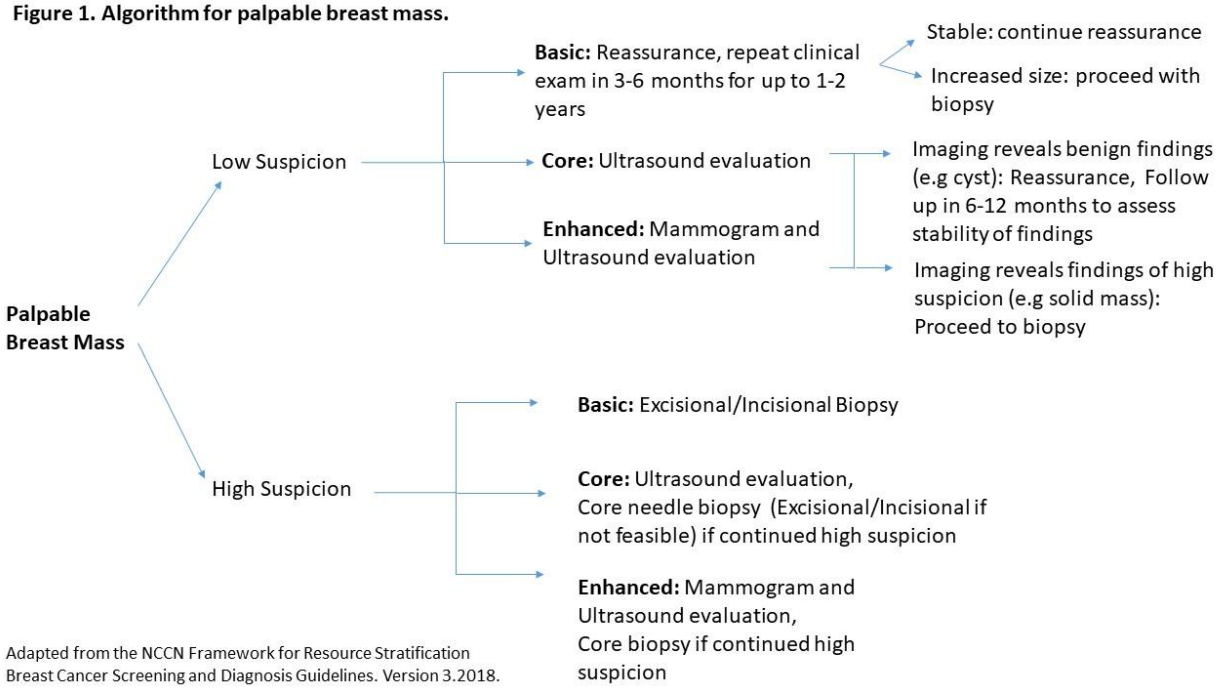
All women evaluated by a provider should be asked about their breast history and any breast complaints. In asymptomatic patients, it is recommended to use the opportunity to do a clinical breast exam for breast cancer screening and discuss healthy behaviors to prevent breast cancer. The breast exam should be completed in the upright and supine positions for inspection and palpation of all quadrants of the breast, axilla, and clavicular lymph node basins. Sensitivity for clinical breast exams is low (54%), but specificity is high (94%) and cost-effective [5]. Data shows a correlation between the amount of time spent on palpation of the breast with increased detection of abnormalities [6]. Upon palpation of an abnormality, document the location and distance from the nipple to assess the correlation with imaging findings. Further evaluation is recommended based on the type of breast abnormality or symptom.

Palpable Mass

Patients may report a breast lump or a mass may be palpated during a clinical breast exam. Smaller masses, mobile and smooth, are suggestive of a benign etiology. Larger masses that are fixed, hard, and heterogeneous in texture have a higher suspicion of a malignancy [7]. In areas with essential resources, cases where the palpated mass has low suspicion for malignancy, observation can be recommended with repeat clinical breast exams every 3-6 months for up to 1-2 years and monitoring for stability. If there is an increase in the size of the mass, an excisional or incisional biopsy is recommended for further evaluation. In cases of moderate or high suspicion, excisional/incisional biopsy is recommended. In situations where there is difficulty in establishing a level of concern or follow-up is not feasible, a biopsy is recommended.

In LMICs that have ultrasound imaging capabilities, ultrasound imaging is recommended for further evaluation of the palpable mass. Ultrasound evaluation can assist in determining if it is a solid mass versus a benign cyst (see Chapter 9). Also, a targeted core biopsy can be completed with ultrasound guidance. In areas with enhanced framework resources, a diagnostic mammogram can also be obtained (Figure 1).

Figure 1. Algorithm for palpable breast mass.



Adapted from the NCCN Framework for Resource Stratification Breast Cancer Screening and Diagnosis Guidelines. Version 3.2018.

Palpated axillary masses are concerning for breast cancer and metastatic disease. Further evaluation for systemic disease should be completed by a thorough review of symptoms and evaluation of any reported symptoms. Excisional biopsy is recommended of the axillary mass as well as a clinical breast exam to identify a primary breast mass. Further management is recommended based on pathologic findings. Areas or countries with available imaging capabilities should evaluate the axillary region by ultrasound and utilize other imaging modalities based on the patient's symptoms to evaluate for metastatic disease.

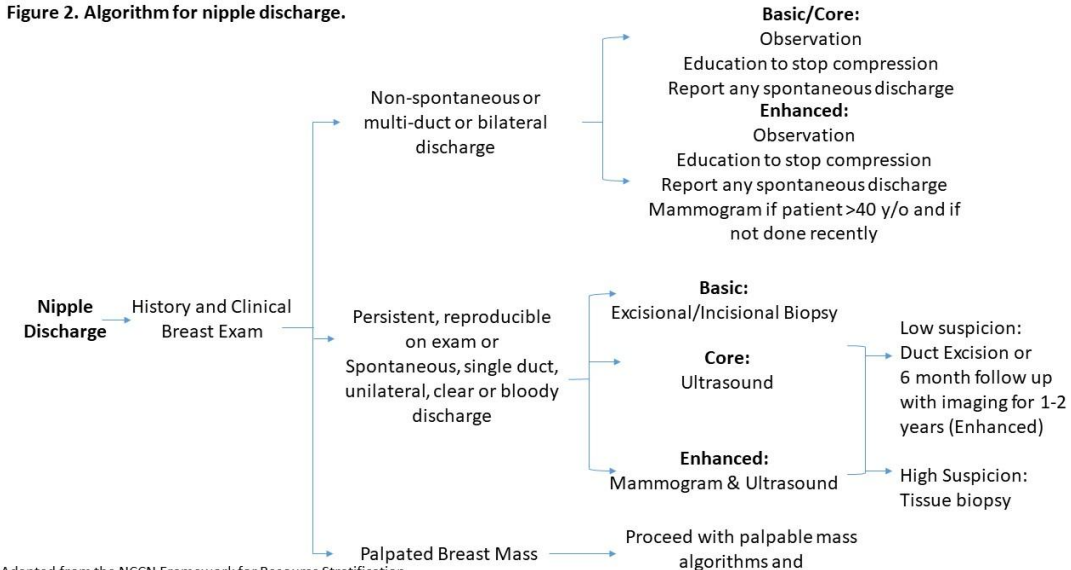
Nipple Discharge

Nipple discharge can be a benign process and a sign of malignancy. Evaluation of the discharge can be completed by a thorough history, noting the color and spontaneity of the discharge, frequency, and if it is single duct or multi-duct. Skin changes or breast lumps that are palpated with the nipple discharge should also be considered during the evaluation. A clinical breast exam

should be completed as described in all patients reporting nipple discharge. Expression of discharge should be completed to note the color and production from single or multiple ducts.

Physiologic nipple discharge is usually bilateral, multi-duct, non-spontaneous, and without blood. Non-spontaneous or multi-duct discharge can be observed, and patients can be educated to stop compression and report if spontaneous discharge occurs. In areas with enhanced resources, mammograms can be completed if not done recently for further evaluation. Persistent symptoms or spontaneous, unilateral discharge can be pathologic, and data reveals that 21% of patients may have a breast malignancy [8]. These individuals should proceed with excisional or incisional biopsy in areas with essential resources. LMICs with core or enhanced resources should consider breast imaging and proceed with duct excision if the imaging is benign and tissue biopsy if there is a suspicious mass (**Figure 2**).

Figure 2. Algorithm for nipple discharge.



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Skin Changes

Skin changes of the breast or nipple can suggest malignancy and need to be evaluated by clinical breast exam. Women need to be educated on findings such as changes to the nipple such as inversion or retraction, skin dimpling or retraction, breast erythema, or peau d'orange changes in the breast as they need to be evaluated as soon as possible for underlying malignancy.

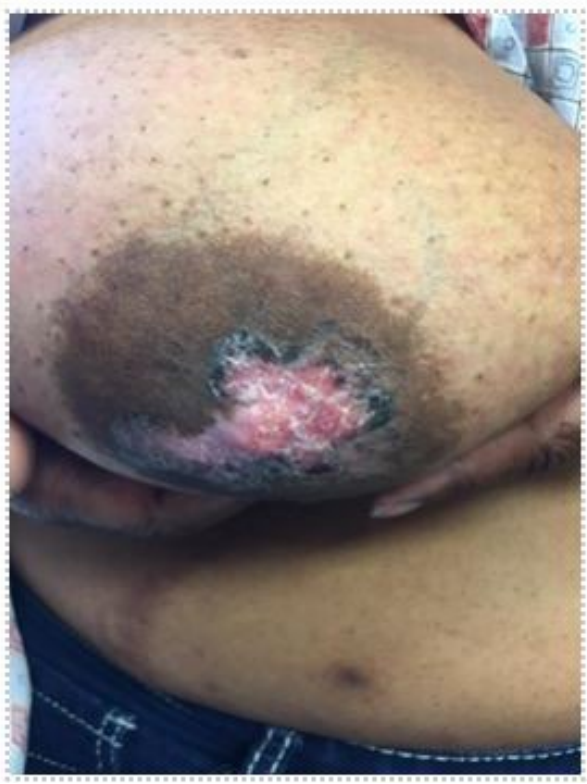


Figure 3 Ulcerated nipple with Paget's Disease

Nipple inversion can be congenital, and a thorough history of the duration of symptoms will aid in determining chronicity versus a new finding. Nipple retraction can be suspicious for a retroareolar mass and malignancy. Paget's disease of the breast is a rare disorder that is often associated with underlying malignancy that affects the nipple-areola complex and is accompanied by eczematous changes in the nipple. Ulceration, crusting, or scaling can be seen

on the nipple and areola and will often occur unilaterally, and the patient may experience pain, burning, and itching [9] (**Figure 3**).

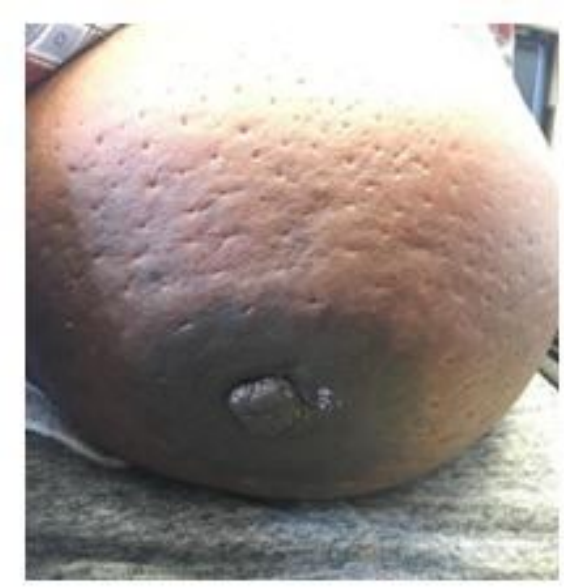


Figure 4 Peau d'Orange with Inflammatory Breast Cancer

Inflammatory breast cancer is an aggressive form of breast cancer and can often present with skin changes to the breast, such as skin thickening, erythema, and peau d'orange. Peau d'orange is when the breast skin is edematous and has a pitted or dimpled presentation similar to the appearance of an orange peel **(Figure 4)** Infections such as mastitis or cellulitis and

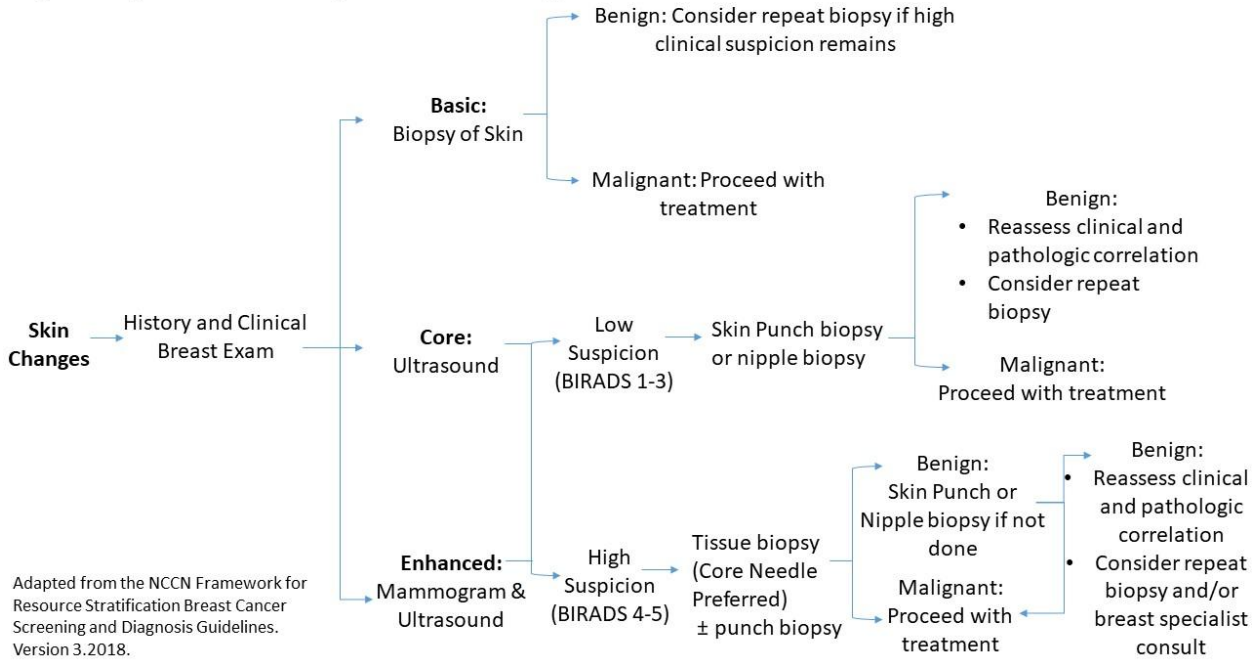
inflammatory conditions can also lead to skin changes in the breast, and the level of suspicion needs to be evaluated by the provider (See Chapter 8). Antibiotics for possible infection or a short course of topical steroids for eczema can be given based on history and symptoms. Close follow-up is recommended to assess for resolution and biopsy if symptoms persist. Women with findings suspicious of malignancy in LMICs with essential resources should be biopsied for definitive diagnosis and repeat biopsy if high suspicion remains and the initial biopsy is negative.

In areas with core or enhanced resources, imaging should be completed to assess for underlying abnormalities and tissue biopsy if a mass is noted. If imaging findings are benign, a skin punch biopsy is recommended. **Figure 5** illustrates the algorithm of how to approach a patient with skin changes of the breast or nipple by resource stratification.

Breast Pain

Breast pain is a common breast complaint, and 11% of women report severe pain that affects quality of life [10]. Over 60% of cases are secondary to cyclic mastalgia and occur in women in their 20s and 30s [11]. Cyclic mastalgia often occurs bilaterally, non-focal, and occurs in association with a woman's menstrual cycle. Hormonal stimulation of the breast parenchyma during the luteal phase is thought to induce pain. Non-cyclic pain, unrelated to the menstrual cycle, can be associated with medication use such as oral contraceptives, hormone replacement therapy, psychotropic, and cardiovascular medications. Other causes for non-cyclical pain include breast trauma, infection, benign breast masses, and ligamentous pain from heavy breasts.

Figure 5. Algorithm for skin changes of the breast or nipple.



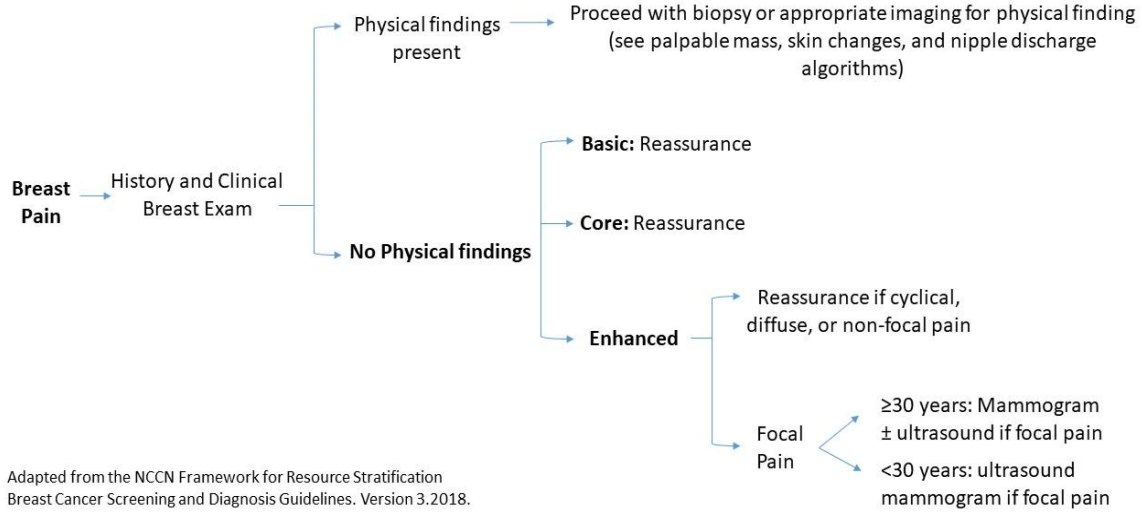
Adapted from the NCCN Framework for Resource Stratification Breast Cancer Screening and Diagnosis Guidelines. Version 3.2018.

A thorough history of the patient's breast pain should be obtained and assess severity as well as location, laterality, relation to menses, medication history, and any recent trauma. Any other associated breast symptoms with breast pain should be assessed and evaluated. The majority of cases of breast pain are from benign causes [12] (See Chapter 6).

Education and reassurance are recommended for cyclical, diffuse pain in all LMICs. Breast pain not associated with findings of palpable breast mass, skin changes, or nipple discharge is often benign and, therefore, areas with basic or core resources are recommended to give reassurance and education on breast awareness. In LMICs with enhanced resources, ultrasound and possibly a mammogram are recommended for pain that is focal and non-cyclical (**Figure 6**).

Focal breast pain has an occasional association with malignancy, and therefore imaging for this complaint should be completed if resources are available [13]. Otherwise, education should be given to the women regarding breast concerns and follow-up exams if possible.

Figure 6. Algorithm for breast pain.



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Conclusion

Detailed history and clinical breast exam can be completed by all providers to determine suspicion for malignancy. The level of suspicion can guide them to proceed with further evaluation with surgery or imaging if resources are available. Breast awareness and education concerning breast symptoms are key for the early detection of breast cancer and can lead to improvement in survival rates in these areas.

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Chapter 6

Breast Pain and Pain Management

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Epidemiology

Mastalgia, or breast pain, is, by far, the most common reason for a woman to seek counseling in a breast clinic. Seventy percent of women will experience breast pain during their lifetime. However, breast pain alone is rarely a presenting symptom of cancer (7%), and therefore, it alone is not a reason to obtain imaging. Rather, imaging studies should be reserved for women who fall within the usual screening guidelines (mammography yearly above 40 years of age) or those with associated abnormal physical exams. The two most common concerns for patients are breast cancer and its impact on their lifestyle and quality of life.

Cyclic mastalgia occurs in premenopausal women normally due to the cyclical effects of hormones during their menstrual cycle. This type of mastalgia occurs most prominently in the second half of the menstrual cycle and resolves with the onset of menstruation. Mild symptoms can occur up to 5 days prior to the start of the menstrual cycle. Noncyclic mastalgia is unrelated to the menstrual cycle and may be related to conditions such as breast infection, mastitis, breast masses such as fibroadenomas, or hematoma from breast trauma. Thrombophlebitis of the breast (Mondor's disease) is a rare disease that causes noncyclic breast pain and presents with firm

tender vessels along the surface of the breast. Some of the non-breast disease processes that are deep to the breast can give rise to breast pain, and these include costochondritis, scapulothoracic bursitis, radiculopathy, cardiac etiology, or gastroesophageal reflux disease (GERD).

An important fact that all clinicians should recognize is that as many as 22% of breast cancers are associated with pain, but only 7% of breast cancers present as pain alone. The old myth that breast cancer does not hurt is simply false. However, no study has reported an increased risk of breast cancer with cyclical mastalgia.

Although mastalgia is more common in pre-menopausal women, it can present in all age groups, from adolescents to the elderly. The relationship between the symptoms and the menstrual cycle suggests a possible hormonal etiology. Mild pain for less than five days prior to a woman's period is considered normal. Moderate or unusual pain for a more extended period is not. There are many non-hormonal etiologies of breast pain, and these include ill-fitting bras, puerperal infection, and neurogenic and musculoskeletal origins.

Fibrocystic Breast Changes as a Cause of Breast Pain

Fibrous tissue and cysts form in breast tissue in a cyclical manner with hormonal changes. Cysts are just dilated ducts in an area where the duct wall is weak. As the duct dilates, it puts pressure on the surrounding nerves and thus causes pain. The pain is intermittent in nature, and approximately half of women with breast pain have this type of pain.

Musculoskeletal and Post-Surgical Causes of Pain

Noncyclical and extramammary pain is usually caused by a problem outside of the breast, such as muscular or connective tissue, but can also include skin injury, chest wall, and spinal conditions. Noncyclical pain is more likely if it is described as soreness, burning, or tightness;

the pain is constant; it seems to affect one breast in a particular area and is more often present in postmenopausal women. Extramammary pain can have some relief with NSAIDs and cortisone injections.

Lack of adequate breast support is an issue for large, heavy breasts, and the pain is due to stretched ligaments and breast tissue. Such a condition can cause pain not only to the breasts but also to the shoulder, neck, and back. The surgical reduction can improve this pain. Noninvasive treatment includes a supportive bra and NSAIDs.

A frequently overlooked cause of breast pain is referred pain from inflammation of the shoulder bursa. This is due to chronic repetitive mechanical stress of the periscapular tissue due to trauma, overuse, and focal muscle weakness. Therefore, it is expected to have a right-handed individual present with right breast pain secondary to overuse of her right shoulder.

Costochondritis is an inflammatory reaction at the cartilage between the rib and sternum for which the pain can radiate laterally. It can occur with arthritis, injury, or physical strain. This usually causes burning pain and can mimic a breast or cardiac pathology.

Fibromyalgia is a disease that affects multiple musculoskeletal points as well as referred breast pain and has been thought to be another somatic symptom of the disease.

Mastitis

This condition is more common with breastfeeding due to clogged milk ducts. It can also happen at any age and is more common in patients who smoke, and in such a scenario, it can represent an underlying malignancy. Mastitis is easily distinguishable due to a significant tender mass that eventually progresses to erythema. It can be treated with continued breast-feeding,

pumping, and expression of clogged ducts with aid from warm compresses, antibiotics, ultrasound-guided aspiration of any abscesses, and surgical incision and drainage.

Surgery and Trauma

Trauma to a particular area of one's breast, such as breast surgery, placement of submuscular implants, or an accident to the breast, can cause breast pain. Sometimes an injury can cause a breast vein to swell and a blood clot to form (Mondor's disease). Mondor's is treated like any phlebitis, mainly with heat and analgesics.

Chronic breast pain after breast surgery is thought to affect up to 20-30% of patients. Risk factors include axillary node dissection, younger age, preoperative anxiety, depression, and higher BMI. The etiology is theorized to be due to scar tissue formation affecting the surrounding nerves. More commonly, chronic breast pain can result from scapulothoracic bursitis (shoulder), a condition that arises from positioning the patient at surgery. This type of chronic pain can be treated with trigger point injections (see below). Surgery to the breast can lead to the formation of scar tissue, localized nerve damage, and/or inflammation. This type of pain usually causes symptoms of increased sensitivity, pain to light touch, numbness, and/or difficulty with arm movement.

Evaluation of Breast Pain

Evaluation of breast pain, as with any patient, begins with a complete history and physical examination. Common descriptors include soreness, swelling, heaviness, shooting, and burning pain, and whether the pain is constant or cyclical. Therefore, the history should include the type and intensity of pain, location of the pain, relationship of the pain to the menstrual cycle, and number of days per month with pain.

Cyclic pain is the most common type of breast pain, accounting for 75% of all breast pain. It is usually bilateral but can be unilateral and is poorly localized. The pain tends to be chronic or intermittent. It is more likely to be achy and heavy or a shooting pain. A breast examination should be performed to exclude the presence of a breast mass. The breasts may swell or have benign masses. Although it usually resolves at the end of the menstrual cycle, it can persist throughout the month, with the luteal phase being the most intense. The prevalence of breast pain was found to be 21% lower in late menopause, indicating that there is a likely connection between hormones and breast pain. Of note, any type of pain, including musculoskeletal pain, can be cyclical as hormones affect pain receptors.

Anatomic Considerations

Breast skin is innervated by the lateral and anterior cutaneous branches of the second through sixth intercostal nerves. The third through the sixth branches of the lateral mammary branches supply the majority of the breast surface. The intercostobrachial nerve is a branch of the second intercostal nerve innervating the medial aspect of the arm and axilla. Referred pain is a potential source of breast pain, which is often overlooked. The scapulothoracic bursa is located near the origin of the nerves that supply the breast (T2-7). Thus, noncyclical breast pain could, in fact, be caused by scapulothoracic bursitis or even by radiculopathy.

Clinical Presentation

History: A detailed history and physical exam are essential components of the evaluation, which often guide treatment. Severity can be assessed by how much mastalgia affects the patient's daily activities, including work, sex, and sleep. In women and men, dietary intake of caffeine, fats, and medication should be ascertained. Cardiac and anti-hypertensive medications (digoxin, methyldopa, minoxidil, spironolactone, and other diuretics), hormone replacement therapy,

psychiatric medications (selective serotonin reuptake inhibitors, venlafaxine, haloperidol, and other antipsychotics), antimicrobials (ketoconazole, metronidazole), antacids (e.g., cimetidine and related medicines), cyclosporine, domperidone, penicillamine, and methadone are all associated with breast pain. Illicit drugs such as marijuana can also contribute to breast pain. A recent history of stress or trauma should lead one to consider the common cause of breast pain, shoulder bursitis. This is especially true in the postmenopausal patient, where endogenous hormones would not play as much of a factor.

Physical: Breast examination is essential to determine the exact location and character of the pain and whether there is an associated mass. In addition to a thorough breast exam, one needs to examine the entire chest wall to assess for parasternal pain; costochondritis versus pectoral muscle pain versus scapulothoracic bursitis presenting with or without trigger points along the medial scapular border should be evaluated as possible causes of breast pain.

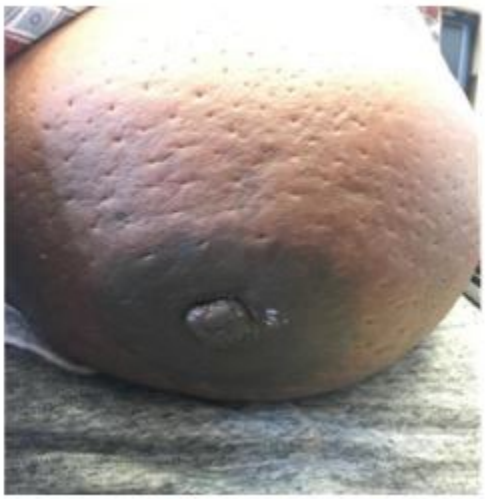

Figure 1: A patient with inflammatory breast cancer

Inflammatory Breast Cancer is unique in that the pain begins quickly as the disease progresses rapidly. The pain is caused by cancer cells blocking the lymphatic vessels, causing a backup of lymphatic fluid and stretching nearby nerve tissues. Typically, the rapid change in the inflammatory appearance of the breast occurs over several weeks, and pain will begin at this time. Like mastitis, erythema and *peau d'orange*

(skin of an orange) is present with tenderness, pain, or aching (Figure 1).

Imaging: As with a variety of breast conditions, including breast cancer, breast imaging is warranted for patients with a palpable breast or axillary abnormality or a focal breast pain to rule out an underlying cyst or mass as contributing to the symptom. Mammography and targeted ultrasound are reasonable for patients aged 30 years or older, whereas targeted breast ultrasound alone is reasonable for patients younger than 30. Breast cysts can be diagnosed with an ultrasound and treated with aspiration when they are small or with percutaneous excision when they are large.

Treatment

For all etiologies of breast pain, alternating over-the-counter analgesics have a beneficial effect on pain. However, it is essential to identify the underlying cause and remedy it to wean the patient off of any analgesics.

Supportive care/dietary modifications: Women with breast pain who have no breast/axillary abnormality on exam and imaging can be reassured and be told that no additional intervention is necessary. It is to be noted that stress itself can raise prolactin levels, which can give rise to breast pain. Mild cases of breast pain can be evaluated by obtaining a routine mammogram and reassuring the patient.

Lifestyle modification and the use of a well-fitted bra are often the first steps for symptomatic treatment. Dietary changes, including decreased caffeine ingestion and a low-fat diet, have been shown to reduce fibrocystic changes in the breast as well as breast pain. Physical activities such as running, gentle massages, and stretching exercises may also be practical. These interventions are safe, cheap, and reasonable to offer to all patients; however, no well-designed

research proves their effectiveness. There is something to be said that most interventions for breast pain lack prospective placebo-controlled trials, especially given that breast pain has a high spontaneous resolution rate as well as a high placebo effect.

Pharmacologic Intervention: Some prescribed medications can cause breast pain. These include hormonal medications, cardiac medications, and psychiatric drugs. Selective serotonin reuptake inhibitors are known to cause breast pain. Marijuana and anabolic steroids can cause gynecomastia in men, which can also be a cause of pain.

Non-hormonal agents- primrose, iodine, thyroid hormone, bromocriptine: Initial studies indicated that women with mastalgia have abnormally low blood levels of gamolenic acid, an essential fatty acid that can affect prolactin levels. Early clinical experience with evening primrose oil (EPO), a source of gamolenic acid, produced a good response rate. However, two recent multicenter randomized controlled trials have not supported or contradicted the efficacy of EPO or antioxidants in treating breast pain. A meta-analysis reviewing the data from all randomized controlled trials using EPO revealed no significant beneficial effect over placebo.

Thyroid replacement (73% effective) and molecular iodine (65% effective, 11% side effects) are other non-hormonal agents potentially effective for breast pain. Those agents may modulate the sensitivity of the terminal intralobular ducts and relieve symptoms. Bromocriptine is effective through an anti-prolactin mechanism and has been associated with a significant clinical response in patients with cyclic mastalgia. However, its use has been associated with seizure and death and is no longer recommended for mastalgia.

Hormonal Agent- danazol, luteinizing hormone-release hormone (LHRH), tamoxifen: Estrogen and progesterone play a causative role in premenopausal breast pain.

Although a variety of hormonal agents were investigated, the only medication that has been Food and Drug Administration (FDA) approved for breast pain is danazol (64% to 92% effective, 30% side effects). Danazol is an attenuated androgen with fewer side effects, which competitively inhibits estrogen and progesterone receptors in the breast, hypothalamus, and pituitary. Danazol is usually started at 200 to 400 mg/day in divided doses. To prevent androgen-related side effects, danazol is weaned within a few months or even given only in the second half of the menstrual cycleDanazol can be discontinued for those who had a complete response.

Endocrine Therapy: Many of these medications have a high side effect profile and must be used with caution. They include tamoxifen, testosterone, danazol, bromocriptine, thyroid hormone, gestrinone, and luteinizing hormone-releasing hormone (LHRH agonist to increase testosterone).

Psychiatric Approach: In states of acute emotional stress, it has been found that they account for prolactin release and cause a physiologic basis for mastalgia. It has been suggested that in patients with refractory breast pain, evaluation by a psychiatrist and a trial of antidepressants may be indicated.

Surgical Approach: Surgery is a possible treatment for breast pain when no identifiable pathology can be elicited. However, it should be considered as a last resort and rarely, only after the patient's request and considerable counseling.

Strategies to Reduce Surgical and Postoperative Pain

Minimize the Use of Needle Localization Breast Biopsy (NLBB)

Nonpalpable breast abnormalities are increasingly being diagnosed via mammography. While core needle breast biopsy (CNB) is often utilized for diagnostic purposes, needle localization breast biopsy (NLBB) is currently, by far, the most common technique for removing nonpalpable breast lesions. However, this technique not only imposes discomfort for the patient but also causes vasovagal reactions, which have been reported to occur in 10-20% of patients. NLBB also requires coordination between the surgeon and radiologist, which can lead to scheduling difficulties and subsequent delays in treatment. Thus, reducing its use has significant benefits for the patient. Other alternatives to address nonpalpable breast abnormalities are available, and a modern breast surgeon needs to be familiar with the emerging techniques of intraoperative image-guided breast surgery.

Intraoperative Ultrasound-guided Breast-Conserving Surgery

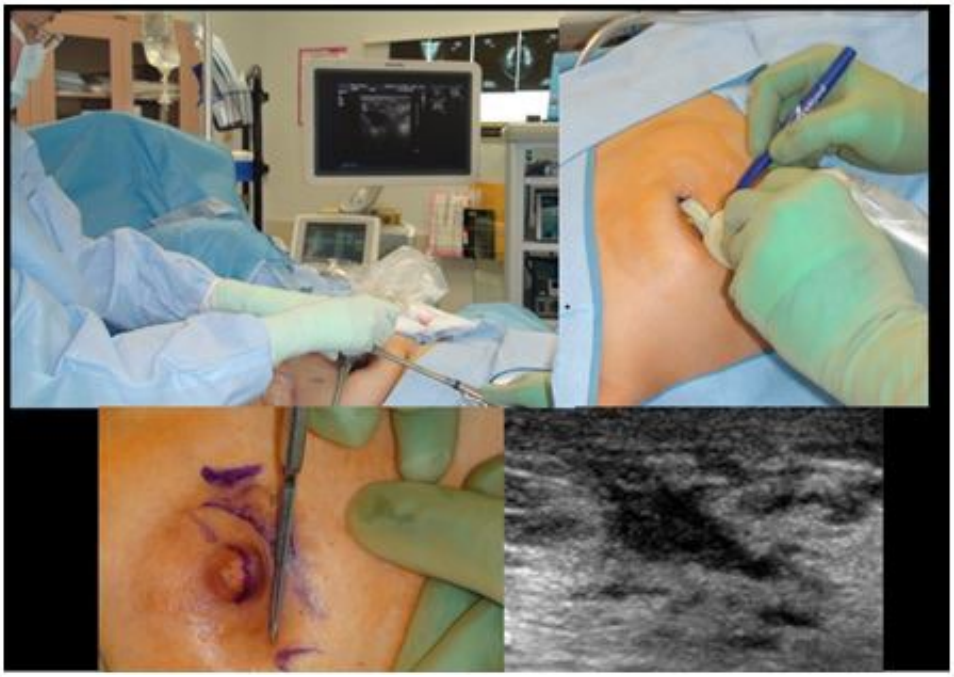

Figure 2: Set-up of ultrasound across the table and drape sterilely into the field, locate the lesion, and incise directly over the located lesion.

Since intraoperative US-assisted breast excision was first described in 1988 by Schwartz, its effectiveness has been widely investigated for nonpalpable breast lesions. (Figure 2) Several studies have reported the benefits of ultrasound-guided breast-conserving surgery over NLBB for surgical treatment of nonpalpable breast cancer. These benefits include fewer re-excision and smaller excision volumes. The same benefit of US-guided breast-conserving surgery was reported even for palpable cancers compared with standard palpation-guided surgery.

Hematoma-Directed Ultrasound-Guided (HUG) Procedure

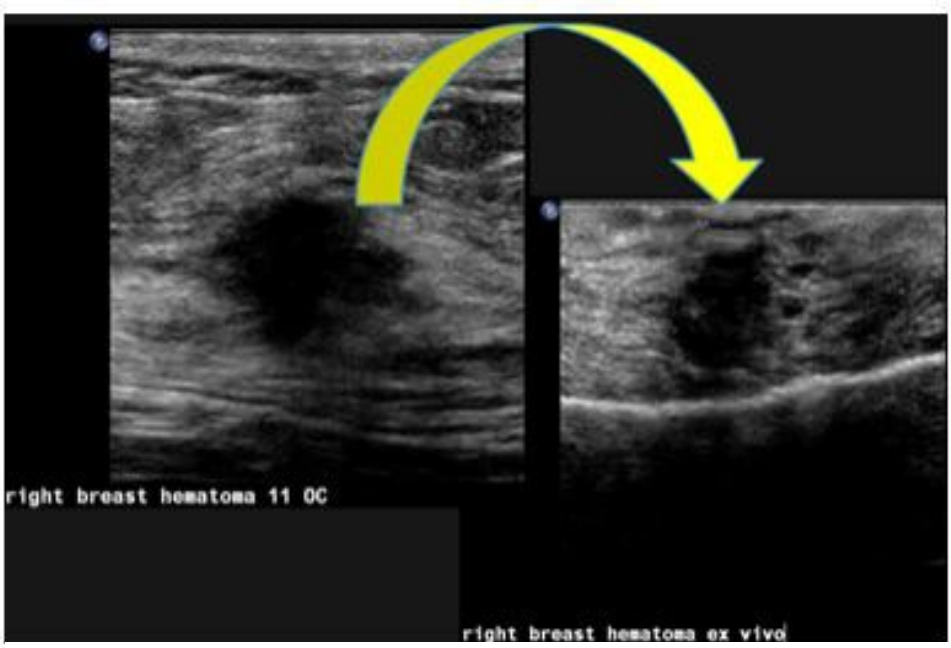

Figure 3. A core needle or stereotactic biopsy will leave a hematoma that can be localized by ultrasound and removed with confirmation of removal and assessment of margins ex vivo.

As opposed to palpable lesions, less than half of non-palpable lesions, including calcifications, are visible with ultrasound. The Hematoma-Directed Ultrasound-Guided (HUG) procedure was developed to resolve this problem. This technique utilizes the hematoma created

in almost all patients after a core needle biopsy (CNB) that lasts up to 5 weeks or more for most patients. At the time of surgery, intraoperative US is utilized to localize the hematoma in the breast. (Figure 3) The US location guides the site of the incision, and a block of tissue encompassing the hematoma is then excised while visualizing a 1-cm margin. Specimen US can also be performed *ex vivo* to confirm adequate resection. In the case the lesion or hematoma is not visible, the use of US-visible clips can be very useful, especially in the neoadjuvant setting.

Fluoroscopic Intraoperative Neoplasm and Node Detection (FIND) Procedure

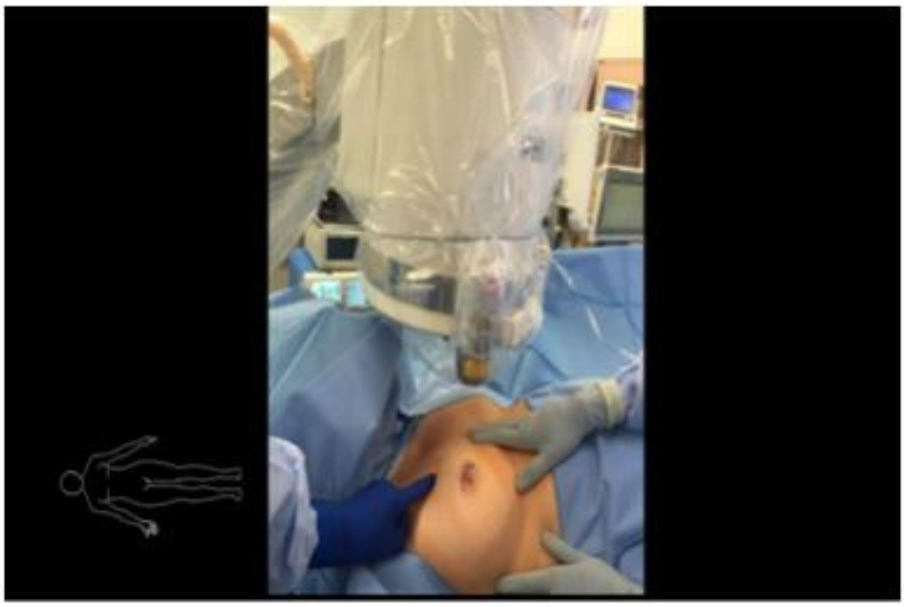

Figure 4. When a marker is left in place at the site of the lesion, most, but not all, can be seen with fluoroscopy.

Fluoroscopic Intraoperative Neoplasm and Node Detection (FIND) is another novel technique to reduce the use of NLBB for the excision of nonpalpable breast lesions. This technique utilizes a standard fluoroscopic C-arm to intraoperatively detect the clip that was placed with CNB, making CNB not only a diagnostic but a localizing procedure. The location of the fluoroscopically visible clip (bar, coil, or circular) is assessed by magnifying the image prior

to incision. (Figure 4) Marking the location of the clip and planned margin helps to guide adequate margins from the mass, which can be confirmed during excision by repeating a quick fluoroscopic shot. Taking a fluoroscopic picture of the excised specimen *ex vivo* is also helpful in verifying the presence of the clip and adequate margin. As most surgeons are familiar with the use of the C-arm, this simple technique can reduce time, cost, patient discomfort, and even radiation exposure. Newer technologies such as SAVI Scout and radioactive seed are limited in lower resource countries due to their expense and some because of the necessity for radioactive sources.

Intraoperative nerve block

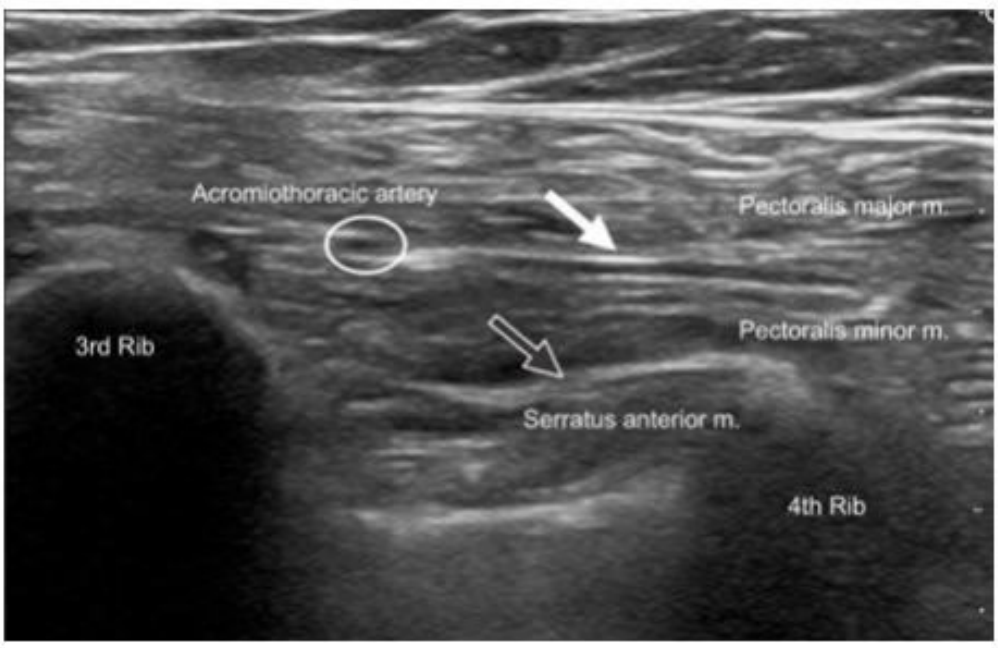

Figure 5: Pectoral Nerve Block identifying the two locations for injection.

Pectoral Block I & II: Complex nerves innervate the posterior chest wall. These nerves consist of (1) the medial and lateral pectoral nerves that lie between the pectoralis major and

pectoralis minor, (2) the lateral branches of the second to the sixth intercostal nerves that lie between the pectoralis minor and serratus anterior, and (3) the long thoracic nerve and thoracodorsal nerve, which lie between the latissimus dorsi and serratus anterior in the posterior-lateral chest wall. Injecting local anesthetic in the plane between the pectoralis major and minor muscles at the level of the third rib (PECS I) and the plane between the pectoralis minor and serratus anterior at the level of the fourth rib (PECS II) reduces pain from a variety of breast procedures. This is accomplished by blocking these complex nerves innervating the chest wall. Both techniques are effective for reducing postoperative muscle spasms and myofascial pain from the pectoralis muscles. These nerve-blocking procedures are often performed by the surgeon with visualization with intraoperative ultrasound guidance. Figure 5 demonstrates the interpectoral space by US (Pec I block). Injection of at least 20cc of a solution of Marcaine will give long-lasting post-operative relief. Injection deep to the Pectoralis minor in the Serratus will give additional relief.

Intercostal Nerve block

The breast skin is innervated by lateral and anterior cutaneous branches of the second through seventh intercostal nerves. Among them, the third through the sixth branches are known as the lateral mammary branches supplying the majority of the breast surface. Intercostal

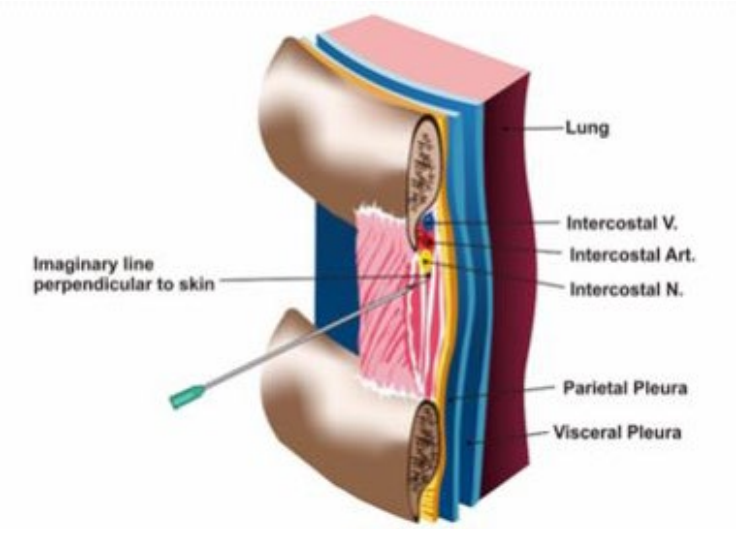

Figure 6: Intercostal Nerve Block

nerve block is performed by injecting local anesthetics to near intercostal nerves (Figure 6). This must be done at multiple levels (3-6) involving the disrupted tissue and lateral to it. Intercostal blocks should be combined with other approaches as this block does not anesthetize nerves derived from the brachial or cervical plexuses. This procedure can be modified to reduce the risk of pneumothorax by directly palpating the rib and injecting directly on the rib with enough volume to reach the nerve on the inferior surface of the rib.

Scapulothoracic trigger point injection

Referral pain from scapulothoracic bursitis is a common unrecognized cause of breast pain in the pre- and post-operative setting, and the pain can last for years. This type of pain responds well to trigger point injections.

Trigger Point Injections

Treatment of bursitis includes injection of a mixture of short-acting and long-acting anesthetics and steroids (Figures 7 & 8). According to a study by Boneti et al., 83.7% of women found complete relief with the treatment of pre- or post-operative pain via these injections. The injection should be a mixture of short-acting anesthesia (4.5 mL of xylocaine 1%), long-acting anesthesia (4.5 mL of bupivacaine 0.5%), and a corticosteroid (40 – 80 mg of methylprednisolone).

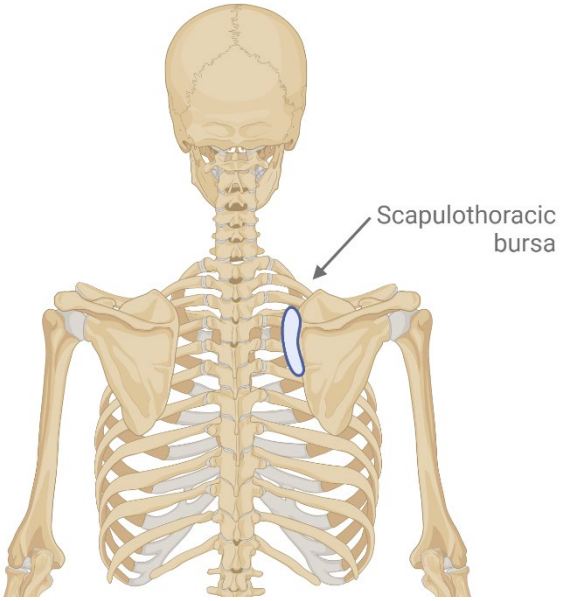

Figure 7: Scapulothoracic Bursa
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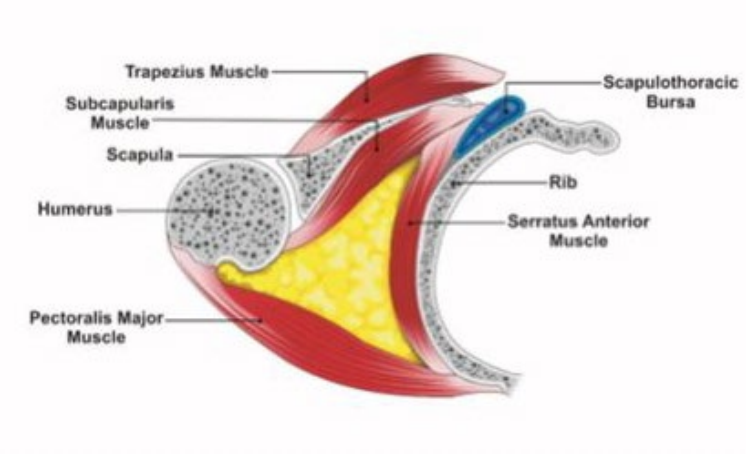

Figure 8: Scapulothoracic Bursa, coronal view.

It should be injected in the scapulothoracic bursa (upper and lower third of the scapula. See Figures 7 and 8). In our study, of the 461 patients with a presenting deep to scapula complaint of breast and/or chest pain, 103 were considered to have symptoms secondary to scapulothoracic bursitis, and 96 % of them showed a response to a trigger point injection. These injections are followed by daily heat (~1 hour) to the back and shoulder and the use of an analgesic. With this high prevalence and effectiveness of intervention, the clinician needs to be more aware of bursitis as a cause of breast pain.

Conclusion

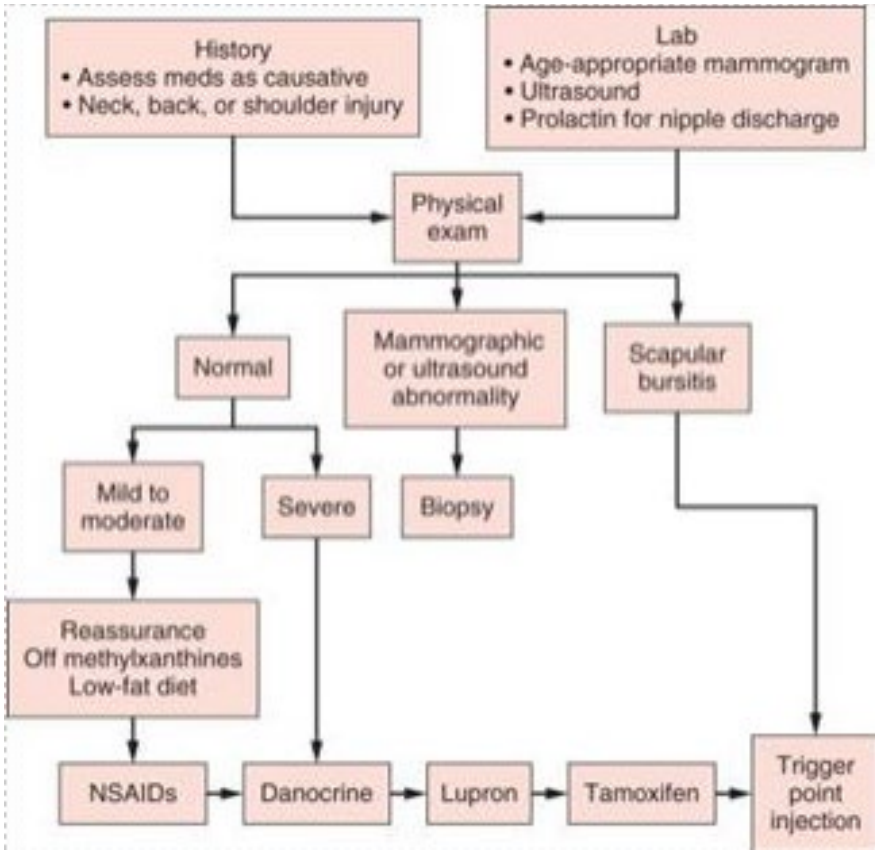

Figure 9: Algorithm for the treatment of breast pain.

The key to treating breast pain is to obtain a detailed history and physical examination, the findings of which will help direct therapy. Figure 9 demonstrates the suggested algorithm for treatment of breast pain.

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Chapter 7

Lactation and Complications of Breast Feeding

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Keywords: lactation; breast cancer; low-middle income countries; mastitis; galactocele; postpartum breast cancer

Clinical Case Scenario

A 39-year-old African-American woman presented six months postpartum with a right breast lump. She had no family history of breast cancer and had been breastfeeding her newborn. She never had a mammogram; her last breast examination was during her first prenatal visit.

On examination, she had a palpable 3cm mass in the right breast upper outer quadrant (UOQ). The mass was hard but not fixed to the overlying skin. She had a normal left breast examination; no axillary nodes were palpable. Ultrasound revealed a suspicious mass. Ultrasound-guided core biopsy was performed; pathology demonstrated a poorly differentiated invasive ductal cancer (IDC) (ER-/PR-/HER2-) with lactational changes present (Figure 1).

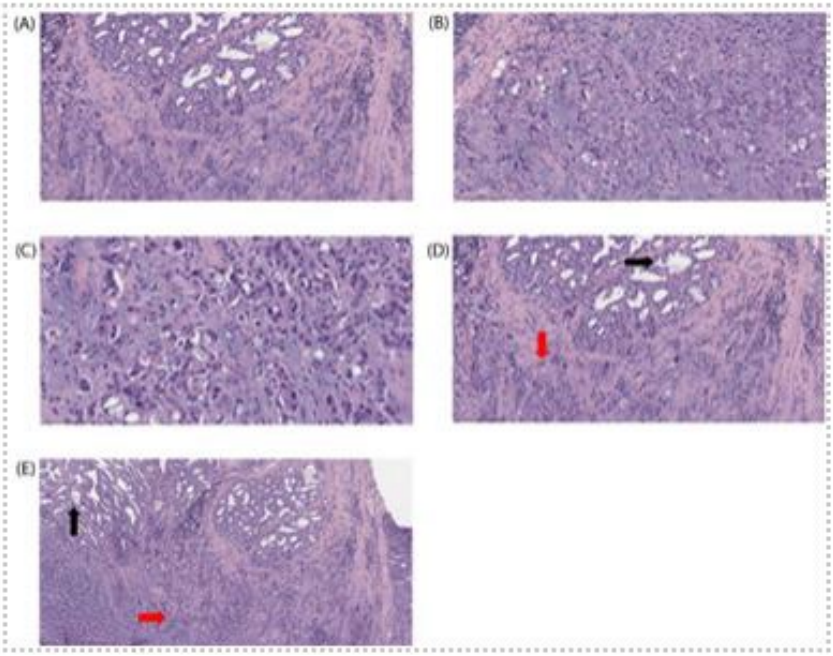

Figure 1: Pathology demonstrating a poorly differentiated invasive ductal carcinoma (estrogen receptor-negative/progesterone receptor-positive/HER2 negative) with lactational changes present. (A) 50x magnification. (B) 100X magnification showing the poorly differentiated carcinoma. (C) 200x magnification showing poorly differentiated carcinoma. (D) Invasive ductal carcinoma in the background of lactational change (H&E stain 100X magnification). Lactating mammary acini are shown by the black arrow. Invasive carcinoma, shown by the red arrow, is poorly differentiated. (E) Invasive ductal carcinoma in the background of lactational change (H&E stain 50X magnification). Lactating mammary acini are shown by the black arrow. The red arrow shows invasive carcinoma. H&E, hematoxylin, and eosin(Courtesy of Dr. Dilip D. Giri, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY.

Introduction

The World Bank defines low-middle-income countries (LMICs) as those with gross national incomes per capita between $1,026 and $3,995. Forty-seven countries are listed as meeting these criteria, with many countries located in Africa [1]. Breast cancer screening guidelines vary from country to country, and this may be influenced by the economic status of the country, among other variables. In Nigeria, a LMIC, according to the World Bank, there are no official national breast cancer screening guidelines. Screening recommendations are therefore based on international guidelines [2]. Data on screening practices are also not easily accessible.

Furthermore, Nigeria had the highest age-standardized mortality ratio in Africa, 29.5 per 100,000 [3]. A 2015 review comparing Nigeria's breast cancer screening practices to other countries reports that Nigeria has been encouraging asymptomatic women between 40-70 years of age to have mammographic screening done biennially [4]. However, access and knowledge of mammography there is limited. A questionnaire report of approximately 2000 women in 2 different regions of Nigeria showed that in both, more than 90% of women had heard of breast cancer, but only 11% had heard of mammography. Mammogram uptake in these two regions was about 2-3% based on the results of this questionnaire [2]. This low compliance with mammography is likely due to geographic and/or financial access. Some reports state that out-of-pocket mammography costs are about $50-70 and unaffordable, as a large portion of the population lives on less than one United States dollar per day [2, 4].

Lactation and duration of breastfeeding are variable around the world. The World Health Organization (WHO) recommends initiation of breastfeeding within the first hour of birth and for infants to be exclusively breastfed for their first six months of life [5]. A systematic review of 24 cross-sectional studies (1979-2014) on breastfeeding practices in Nigeria demonstrated significant geographical variation there, likely reflecting different sociocultural practices across that country. The rate of "any breastfeeding" in infants at six months ranged from 58-97.8%, with a mean of 81.6%. Any breastfeeding was defined as feeding on breast milk or from a wet nurse, with any liquids or foods added, including formula or non-human milk. The mean duration of breastfeeding in Nigeria showed an increasing trend—from 10 months in 1979 to 13 months in 2014.

Additionally, longer breastfeeding duration was noted among women with lower education levels and income. However, a declining rate of exclusive breastfeeding was noted,

from 42% in 2000 to about 29% in 2014. The demands of work and maternal illness were reported to be the most common reason for breastfeeding discontinuation [6].

In this review, we will discuss how lactation affects breast cancer detection, particularly in LMICs with limited resources for routine breast imaging for screening.

Pregnancy and Lactation Effects on the Breast and its Imaging

Pregnancy and lactation cause changes to the breast that play an important role in its physical examination and imaging. The breasts undergo physiologic alterations and proliferative changes of the breast parenchyma in response to high hormone levels of pregnancy and preparation for lactation [7]. In the later months of pregnancy, the breast weight will approximately double, and blood flow to the breasts increases by about 200% [8]. Engorgement of the breasts makes the detection of masses more difficult. Because of these physiologic changes to the breast, physical examination, as well as breast imaging, is more challenging.

Ultrasound is the first-line imaging modality for pregnant or lactating patients with a palpable breast mass [9]. Lactation affects ultrasound imaging because as more milk is synthesized and stored, the echogenicity of the glandular tissue of the breast becomes more marked. A breast filled with milk becomes more tense and limits both breast compression and adequate penetration of the ultrasound beam. Hence, current recommendations for lactating mothers undergoing breast imaging are to nurse or express milk prior to imaging [10].

The sensitivity of mammograms is reduced during pregnancy and lactation and is thought to be due to hormonal changes causing increased parenchymal density [9]. The radiation dose from a bilateral 2-view mammographic exam is less than three mGy, and a dose less than 0.03 μGy is delivered to the uterus [9]. The threshold for known teratogenic fetal effects is about 50-mGy [11]. A lead shield may be placed over the maternal abdomen and pelvis for additional

reduction of fetal dose but is not required [12]. Despite the relative safety, mammograms are less sensitive for detection but can be useful in certain situations. For example, if a highly suspicious mass or underlying malignancy is suspected, mammography should be considered, as it may be useful to determine the extent of the disease, including multifocality and multicentricity [7, 9].

Lactating patients are recommended to nurse or pump prior to imaging, and in asymptomatic women who are having routine breast mammography for screening (age ≥ 40 years), mammography should be delayed until 3 months after cessation of lactation to allow the breast parenchyma to involute [9] fully. Once breastfeeding is stopped for a few days, milk production decreases rapidly, and the involution of the breast follows [8].

Contrast-enhanced breast MRI may safely be performed in lactating patients due to negligible excretion of gadolinium in breast milk [9, 11]. However, hypervascularity and increased aqueous composition of milk during lactation can cause increased enhancement and difficulty with differentiation of lactational change from suspicious findings [9, 13]. The American College of Radiology does not require patients to discontinue breastfeeding after MRI; however, patients may choose to pump and discard milk for 24 hours after MRI to avoid any gadolinium ingestion by the infant [9].

Biopsies of lactating breasts have risks of hematomas and infection [14] and have, on occasion, been shown to cause milk fistulas [15]. The increased vascularity of the breast calls for meticulous hemostasis during surgical biopsies. Milk is a good culture medium and therefore predisposes the lactating breast to infection [14]. A milk duct fistula is a communication tract between the skin of the lactating breast and a milk duct. It can occur after biopsies, especially with larger-gauge needles and deeper lesions or masses. The recommended treatment for a milk

duct fistula is cessation of lactation [13]. Risks of milk duct fistula formation can be minimized by cessation of breastfeeding prior to the biopsy.

Benign Breast Conditions in Pregnant and Postpartum Women

A few days after delivery, there is a rapid increase in milk production that can cause tense breasts until effective nursing is initiated. This engorgement of the breasts can sometimes cause them to become tense and lead to compromised milk supply or even mastitis. On ultrasound, there is an increase in echogenicity and sometimes skin thickening and increased vascularity, which is seen in mastitis [10]. *Puerperal* or *lactational mastitis* is associated with pregnancy or lactation. It is typically caused by pathogen transmission from the infant's nose or mouth through a cracked nipple or skin abrasion, causing damage to the epithelial cells of the nipple-areolar complex. This leads to milk stasis and ductal dilation, and disruption causing focal inflammation [13]. Cellulitis of the interlobular connective tissue within the mammary gland characterizes lactational mastitis [16]. *Staphylococcus aureus* is the most common organism, followed by *Streptococcus*. Early treatment with antibiotics is usually sufficient [13]. Continuation of breastfeeding during antibiotic treatment can be safely performed [17]. A complication of mastitis can be abscess formation. If an abscess is present, drainage is necessary for adequate treatment in addition to antibiotics. If there is no resolution of the infection after continued antibiotics, a skin biopsy may be indicated, as inflammatory carcinomas can mimic mastitis [14].

Galactoceles are milk-filled cysts or proximal cystic dilations of milk ducts due to a distal obstruction by either a lesion or inflammation. Fibrous capsules typically surround them and tend to have a well-defined, thin echogenic wall [10, 13]. Patients may present with a tender mass that is sometimes associated with abrupt termination of breastfeeding [14]. On ultrasound, internal echogenicity may be homogenous or heterogenous, depending on the internal

composition. They contain varying concentrations of milk sugars, proteins, fats, and, often, associated inflammatory or necrotic debris [10]. On ultrasound, they may appear as benign-appearing cystic lesions or have characteristics of malignant lesions, such as solid internal echoes, a taller-than-wide shape, and poorly circumscribed margins [13]. Ultrasound-guided aspiration is typically diagnostic and therapeutic for large galactoceles [10]. If there is re-accumulation, surgical excision may be required to avoid infection [14].

Adenomas are well-circumscribed tumors composed of benign epithelial cells with minimal intervening stroma compared to fibroadenomas, in which the stroma is an integral part of the tumor. Lactating adenomas occur during pregnancy, generally in the third trimester or postpartum, as a freely mobile mass [14]. They are usually slow growing and rarely reach greater than 3 cm in size [18]. On histopathology, they show lobular expansion with enlarged acini separated by connected tissue. With ultrasound, a lactational adenoma is often a homogenous circumcised mass with gentle lobulations. If they infarct, they can sometimes mimic malignancy with irregular margins, heterogeneity, and posterior shadowing [13, 19]. On a mammogram, a circumscribed mass with no associated calcifications is often seen. Management varies from biopsy based on suspicious imaging appearance to conservative follow-up since they generally regress following cessation of breastfeeding [19].

Obstructed milk ducts commonly present as a tender, pea-size lump to a large wedge-shaped lump. They are not typically associated with erythema or fevers. Causes include mechanical obstruction, changes to infant feeding pattern, incomplete drainage of milk, scarring from previous breast surgery, or infection. Ultrasound imaging ranges from a discrete non-compressible mass to a diffuse echogenic area with a hypoechoic rim. Blocked milk ducts are typically managed with warm compresses, massaging of the area, and frequent milk expression.

Direct aspiration of the duct can be performed for symptom relief and diagnosis. If symptoms do not improve or for recurrent blocked ducts, an obstructive lesion should be excluded [10, 19].

Breast Cancer During Pregnancy and the Postpartum Period

The incidence of breast cancer during pregnancy is about 1 in 3000 [19]. Some reports state that breast cancer diagnosed during the gestational period or within one year of pregnancy is defined as pregnancy-associated breast cancer (PABC) [7, 19-21]. There is considerable variation in the definition of the postpartum period, ranging from 6 months to 2 years [21]. Other publications define postpartum breast cancer (PPBC) as breast cancer diagnosis within five years of the last childbirth [22]. A 2012 meta-analysis of 30 studies showed that women diagnosed with PABC had significantly worse overall survival (OS) compared to breast cancer control patients (pooled hazard ratio, 1.44). Patients diagnosed in the 1-year postpartum period had an even worse OS than those diagnosed during pregnancy. This study highlighted the need to consider separate definitions of PABC versus PPBC [23].

A Swedish study in 2011 showed women with PABC, defined as breast cancer diagnosis during or within two years after pregnancy, had higher mortality than non-PABC women diagnosed at the same age and calendar period. The highest peak for mortality occurred in women diagnosed 4-6 months after delivery, who had a 3.8-fold increased mortality rate compared with non-PABC patients at two years after diagnosis [24]. The increased mortality in the postpartum period seen in this study highlights an important needed distinction between PABC and PPBC.

More recently, studies focusing on breast cancer during the lactational period have defined PPBC as its own entity. A 2013 cohort study of 619 women aged ≤ 45 years looked to identify an expanded definition of PABC. Patients were grouped according to time (between

giving birth and diagnosis) as follows: nulliparous, pregnant, < 5 years postpartum, > 5 to <10 years postpartum, and ≥ 10 years postpartum. The study found that breast cancer cases within five years postpartum had a 2.8-fold increased risk of distant recurrence and a 2.65-fold increased risk of death compared to nulliparous cases after adjustment for biologic subtype, stage, and year of diagnosis [25]. A recent 2019 cohort study of 701 women 45 years of age or younger looked at PPBC as a breast cancer diagnosis within ten years of parturition. PPBC patients had an elevated risk for metastasis, increased lymphovascular invasion, and lymph node involvement compared to nulliparous patients [22].

The cause of this increased risk of metastasis in PPBC patients has not been proven, but several hypotheses exist. In the postpartum period, the breasts involute and undergo a cell death-mediated process that is characterized by tissue remodeling. The lactation component of the breast remodels to a non-secretory state. The breast exhibits immune cell influx, lymphangiogenesis, and a wound-healing extracellular matrix pattern that some theories associate with tumor progression or may increase metastatic efficiency. If an existing malignancy is superimposed with this robust involution microenvironment, it could be promoted, resulting in increased metastasis [22, 26, 27]. In addition, older age at first birth correlates with an increased risk of PPBC. As more women delay childbearing for personal or professional reasons, there may be an associated potential increase in the incidence of PPBC [22].

Effect of Lactation on Breast Cancer Detection in LMICs

The potential impact of breastfeeding in LMICs on the detection of breast cancer is not quantifiable. Coupled with the fact that access to medical care and breast imaging is limited in these countries, lactation and its physiological impact on the breast may adversely contribute to the detection of breast cancer. The majority of women in LMICs present with advanced breast

cancer, as well as more aggressive molecular subtypes such as triple-negative breast cancer, as seen in sub-Saharan Africa [28]. The 5-year breast cancer survival rates for Nigeria are reported to be 11-25% [2].

It is important to increase awareness of breast cancer in LMICs by increasing education on the signs and symptoms associated with breast cancer. Lack of awareness of breast cancer and screening has been shown to play an important role in low breast cancer survival rates. Some reports have focused on alternative methods of detection in LMICs with limited resources for mammographic screening. Evidence of clinical breast exam (CBE) efficacy is variable, especially based on the resources available [29]. In the United States, the American Cancer Society does not recommend CBEs for breast cancer screening of average-risk women at any age. This is assuming that women have access to and are undergoing mammographic screening [30]. However, in LMICs, where mammography-based screening programs are limited because of poor infrastructure, poverty, and inadequate manpower, CBEs may play a crucial role in breast cancer screening and detection [29-31].

A cross-sectional analysis of 113 patient interviews in Peru showed that previous clinical breast exams were associated with shorter patient delay and earlier-stage at breast cancer diagnosis [30]. A pilot study of a volunteer-based awareness and screening program in Sudan trained volunteers to visit households, screened women by completing clinical breast exams (CBEs), and obtained socio-demographic and medical histories. Women with suspected breast abnormalities were referred for further evaluation. The study showed increased detection of breast cancer in asymptomatic women who had volunteer-based screening in comparison to communities where no intervention was implemented [32].

Conclusion

Breastfeeding is an important component of the postpartum period and has been shown to have many benefits to the well-being of newborn infants. However, a lactating breast poses challenges to breast cancer detection for both the patient and the clinician. Benign breast conditions such as mastitis, galactoceles, adenomas, and obstructed milk ducts can make breast cancer detection difficult. In LMICs, where resources are limited, and combined with the changes to the breast associated with breastfeeding, decreased detection of breast cancer may result.

Prolonged lactation, whether exclusive or intermittent, makes the period of time associated with breast lactational changes persistent. These prolonged physiologic breast changes, coupled with limited screening and imaging, potentially contribute to poor detection of breast cancer and poor breast cancer survival in LMICs. In addition, breast cancer diagnosis during the postpartum period has shown to be more aggressive, with the potential for increased metastatic risk; further study is necessary.

Figure 2: Algorithm of Managing Women With Complaints of Breast Lump During Breastfeeding

CBEs may play a crucial role where resources and mammography-based screening are limited. Educational and grassroots efforts are an important component of educating young women and increasing breast cancer awareness in the LMIC setting. Figure 2 is our algorithm for managing women with complaints of breast lump during breastfeeding.

Clinical Scenario Conclusion Salient Key Points

- Pregnancy and lactation cause physiologic and proliferative changes to the breast that make physical examination as well as breast imaging more challenging

- Ultrasound is the first-line imaging modality for pregnant or lactating patients with a palpable breast mass
- Mammogram and MRI are safe to perform in lactating patients
- Lactating mothers who need breast imaging should either feed or express milk prior to imaging
- Biopsies of lactating breasts have risks of hematomas, and infection, and have rarely been shown to cause milk duct fistulas
- A breast mass detected during lactation should be evaluated by a clinician, and an ultrasound should be performed. If suspicious, a biopsy should be performed
- Benign breast conditions such as mastitis, galactoceles, adenomas, and obstructed milk ducts can complicate breast cancer detection
- Postpartum breast cancer has been associated with an increased risk of metastasis and mortality and should be considered a separate entity from pregnancy-associated breast cancer
- Clinical breast exams may play a crucial role in breast cancer screening and detection where mammography-based screening is limited

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Chapter 8

Management of Breast Infections

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Introduction

Infections of the breast are a common breast pathology seen in many outpatient settings. Knowledge of the presentation and the timely management of these frequently acute breast concerns is critical to minimizing complications. Though benign, breast infections can be a significant source of distress and anxiety among patients, especially if they become chronic. Prompt recognition and timely management of these conditions could prevent further morbidity.

Classification of Breast Infections

Acute Breast Infections

Acute breast infections are a common cause of concern among women. Acute breast infections frequently affect women in reproductive age groups but can also affect extremes of age. These infections constitute a spectrum of pathology ranging from mild resolving concerns to considerable causes of long-term morbidity. Acute breast infections can be broadly divided into lactational and non-lactational infections.

Lactational mastitis

The puerperal period may have common breast infections—these range from superficial infections like mastitis to deeper infections with collections of pus (abscess formation). Timely recognition and appropriate treatment may prevent breast infections from developing complications.

Etiology

Theories around the etiology of infection hold that skin breaches occur when patients develop sore or cracked nipples. This could result in colonization by pathogenic bacteria from the suckling infant. (1) Bacteria are able to gain entry into the breast tissue and ductal system. The milk in the engorged breast provides a rich culture media through which the bacteria are able to multiply, and the infection is able to spread along the ductal system. (1,2) Once the skin's normal defenses are breached, bacteria are able to gain access to the ductal system.

Presentation

Patients may typically give a history of acute onset breast pain and skin change. They may also give a history of pain when breastfeeding and painful, sore, or cracked nipples. They may also have constitutional signs like fever, chills, or malaise. Patients will present with a thickened, erythematous swelling of the breast. An examination may reveal a focal tender area and cracked nipples.

Treatment

Early use of antibiotics may prevent the progression to an abscess. The frequent cause is typically gram-positive organisms, and a good *Staphylococcus Aureus* cover should be adequate. Other organisms may include other staphylococci and streptococci. (3) First-line cloxacillin-containing agents like flucloxacillin typically have a good response. For patients with

penicillin allergies, consider cephalosporins, erythromycin, or clarithromycin. Fluoroquinolones or tetracyclines should be avoided as they have adverse effects on the infant and can be transferred to the baby through breast milk.

Advice to mothers

Mothers should be encouraged to continue breastfeeding as engorgement with stasis may encourage the infection to progress. (4) If the mother is unable to breastfeed on the affected side, manual expression or a breast pump may be used to remove the milk on the affected side. Rarely, the patient may require lactation suppressors such as cabergoline or bromocriptine to relieve engorgement and provide symptomatic relief.

Prevention of future infections

Counseling of mothers is critical in order to prevent recurrent breast abscesses. Care of the nipple-areolar area must be emphasized to new mothers. Making sure the nipple-areolar area is well lubricated when breastfeeding could help to minimize cracks. The use of lanolin ointment or other emollients can assist with this. Simple instructions, such as drying the nipple before returning it into the bra, will avoid skin maceration and minimize the chances of developing cracked nipples.

Breast abscess

Some breast infections, if not treated effectively, may progress to abscess formation and development of breast collections. Encouraging mothers to continue breastfeeding may prevent the progression of mastitis to breast abscesses (4). Although they occur more frequently in the setting of lactation, breast abscesses can still occur in the presence of other factors in non-

lactating women. Patients with breast abscesses in the non-lactational setting should be investigated for other conditions that may lead to relative immunosuppression.

Presentation

The location of an abscess may change based on location. More superficial abscesses may present as a fluctuant, tender mass. Deep-seated abscesses may present as a focal area of tenderness. Patients with abscess collections tend to be sicker and may have constitutional symptoms like fever. If an abscess is suspected but not clinically apparent, imaging through ultrasound may be done to confirm the diagnosis.

Treatment

In addition to empirical antibiotic therapy, drainage of the abscess is critical to get resolution and healing of the infection. Abscesses could be drained by ultrasound-guided aspiration where these facilities and skill sets exist or by an incision and drainage of the abscess.

Ultrasound-guided aspiration

The aspiration can be performed under local anesthetic, either injected or topical analgesic. The pus is drained under ultrasound guidance, and the empty cavity is confirmed. The pus is sent to microbiology for culture and sensitivity testing. Aspiration is a less invasive technique and should be considered for drainage of abscesses where resources are available. A

number of abscesses could re-accumulate, and a repeat aspiration can be performed for these patients. (Figure 1)

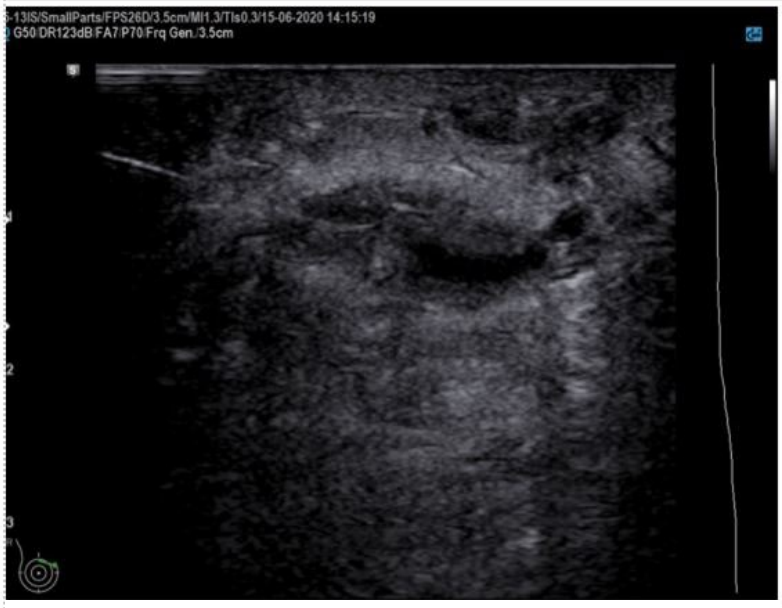
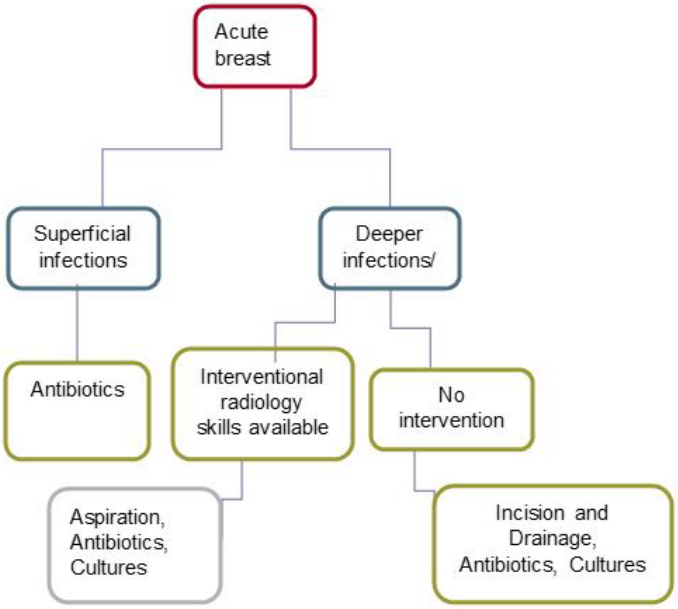


Figure 1: Aspiration of breast abscess with the collapse of the cavity.

Incision and drainage

Incision and drainage can be performed by placing an incision over the most fluctuant area of the wound. An inframammary incision has also been described to provide a more cosmetically acceptable outcome. Avoid incisions in the periductal area to lessen the chances of developing a milk fistula after surgery. The wound should be left open after the procedure to have cleaning and dressing until the wound heals. This typically takes 2-4 weeks. It is not necessary to pack the wound or leave drains in situ. These may be considered only in cases where there is a very large cavity. A wick with cleaning and dressing of the wound should be adequate. The following management algorithm should be considered. *(Algorithm 1)*



Algorithm 1: Management of breast infections.

Advice to the mother

As with mastitis, post-operative /procedural breastfeeding should be encouraged. Manual expressing of milk or a breast pump may be used to decompress the breast. Suppression of milk production may be done only when necessary with cabergoline or bromocriptine.

Non-lactational mastitis

Most breast infections frequently occur in the setting of lactation. Breast infections can, however, occur in the non-lactational setting. Breast infections in non-lactating women should prompt a search for underlying factors that may cause relative immunosuppression. Patients with immunosuppression, such as diabetes, HIV, or chronic steroid therapy, may be susceptible to infections.

Non-lactational abscesses could be either peripheral or centrally located in the peri-areolar.

Periductal mastitis

This refers to breast infections around the peri-areolar region. These infections typically follow a chronic course with recurrent infections, mastitis, recurrent abscesses, and in some cases, fistula formation. The majority of periductal mastitis occurs in individuals who have a history of smoking. Theories around periductal mastitis point to the deposition of compounds in the periductal vessels causing vasospasm and relative ischemia in the periductal region leading to an increased risk of infections.

Chronic inflammation in the periductal area can lead to recurrent fistulas, nipple changes like nipple retraction, or thickening of the periareolar area.

The presenting complaint should govern treatments of periductal mastitis. Mastitis should be treated with antibiotics. Abscesses will require some form of drainage. Periductal abscesses tend to be recurrent, and in patients with chronic recurrent infections and abscesses, more aggressive surgery may be warranted. Patients who smoke are counseled to reduce their habit in order to minimize recurrences. Excision of the fistula may be done through a Hadfield procedure. In recurrent infections with unresolved infections, nipple-areolar excision has been described.

Peripheral Non-lactational Infections

These infections occur in the absence of lactation and should prompt a search for any underlying factors. Systemic illnesses like diabetes or HIV may cause recurrent infections to develop. Immunosuppressants such as chronic steroid use may also lead to increased susceptibility to breast infections. Treatment is still the same as for other non-lactational infections involving antibiotics and drainage where necessary.

Special considerations

If an infection does not resolve on antibiotic treatment or on radiological imaging, a biopsy should be performed to rule out other causes of persistent inflammation. Tissue should be submitted for both culture and histology. Although rare, inflammatory breast cancers may present as a breast infection. In addition, malignancies may appear to have a cellulitis-like appearance. The *peau d'orange* appearance of cancers due to infiltration of lymphatics could sometimes have a similar appearance to breast inflammatory conditions. One should always consider a biopsy in the face of unresolved infections. Biopsies taken should be examined for granuloma formation and alcohol and acid-fast bacilli. Cultures should include TB and fungal cultures, depending on the level of suspicion.

Chronic Infections of the breast

Chronic infections of the breast are rare but may involve a few organisms found in tropical environments. Though rare, tuberculosis may be a significant finding in chronic breast infections in sub-Saharan Africa. In addition, tuberculosis may mimic other conditions, including malignancy, necessitating biopsies.

Tuberculosis of the breast

Tuberculosis (TB) is a contagious, infectious disease caused by *Mycobacterium tuberculosis* (MT). (5) It is estimated that the common ancestor of modern strains of MT might have appeared for the first time 20.000-15.000 years ago. (6) The first case of breast tuberculosis was documented in 1829 by Sir Astley Cooper, who described it as "scrofulous swelling in the bosom of a young woman." (7) TB currently infects nearly 2 billion people worldwide, with around 7-10 million new cases of TB each year.(6,8)

Incidence

Pulmonary TB accounts for most worldwide TB cases, with breast TB only making up a small percentage of the total TB burden. Breast TB has an incidence of around 0.1% of all breast cases, rising to 3% in endemic countries like India, East Asia, and Sub-Saharan Africa. (9,10) There is currently a re-emergence of TB in the West which can be attributed to the increased prevalence of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), the emergence of multi-medication-resistant strains of TB and the increased movement of people. (11)

Pathophysiology

The underlying reason breast TB is such a rare occurrence, even in TB endemic areas, is that breast tissue is thought to be resistant to the development of TB because it provides an infertile environment for the survival and multiplication of the TB bacilli.(12) Breast TB can be described as either primary breast TB, where no other focus of TB can be detected, or secondary TB, from the spread of a TB focus elsewhere in the body. The TB bacilli can reach the breast in one of the following proposed pathways:

1. *Lymphatic spread:* Centripetal lymphatic spread is thought to be the most common route of spread of the organism to the breast. Spread can be traced from the lungs to the breast

via tracheobronchial, paratracheal, mediastinal, internal mammary, and axillary nodes. According to Cooper's theory, communication exists between axillary lymph nodes and the breast resulting in secondary involvement of the breast by retrograde lymphatic extension. Axillary lymphadenopathy is present in 50-75% of cases with breast TB which supports this theory. Whether the concomitant lymphadenopathy is a primary source for the tuberculous breast infection or is secondary to breast involvement is unknown. Still, axillary lymphadenopathy occasionally precedes the appearance of a breast mass, thus implicating retrograde spread. (11,13,14)

2. *Hematogenous spread:* The hematogenous spread to the breast can potentially occur in miliary tuberculosis. Spread via this route is thought to be extremely rare because breast tissue appears to be resistant to the hematogenous spread of TB. In an autopsy series of 34 patients who had died of miliary TB, TB was demonstrated in almost all organs except the breast.(12,15)
3. *Neighborhood spread*: Direct spread can occur from a tuberculous infection in the vicinity of the breast. Examples would be a costal or sternal bone lesion (tuberculous osteitis), the shoulder joint (tuberculous arthritis), or the pleural space (tuberculous pleurisy). (13,15)
4. *Transcutaneous spread:* Exceptionally, transcutaneous penetration can occur through a cutaneous abrasion resulting from trauma to the breast. (16)
5. *Direct spread:* Penetration from the nipple by the milk ducts: expanded ducts during pregnancy and lactation are particularly susceptible to tuberculous infection. (11)

Risk Factors

Several risk factors have been identified, leading to the increased likelihood of developing breast TB. These are:

1. *Multiparity:* Breast tuberculosis is more common in multiparous women. (10,17,18)
2. *Pregnancy and breastfeeding:* Lactation, thought to protect the breast from carcinoma, increases susceptibility to tuberculosis, especially in the presence of poor general health and the stress of child-bearing. This period leads to increased vascularization of the mammary gland, which explains its susceptibility to tuberculosis. (19) Interestingly, increased organ vascularity during lactation facilitates the dissemination of the organism. During lactation, the mammary ducts are ectatic, encouraging canalicular contamination. (20)
3. *Immunosuppression:* The current rate of breast tuberculosis and HIV coinfection is not known, but there is a high rate of TB and HIV coinfection in general. John et.al. (21) reported a 95% HIV and TB coinfection rate in a South African hospital.
4. *Previous suppurative mastitis (22)*
5. *Trauma (19,22)*

Classification of Breast Tuberculosis

Breast tuberculosis was first classified into five different types by Mckeown and Wilkinson (23): (i) nodular tubercular mastitis, (ii) disseminated or confluent tubercular mastitis, (iii) sclerosing tubercular mastitis, (iv) tuberculous mastitis obliterans, and (v) acute miliary tubercular mastitis. Hamit and Ragsdale (24) in 1982 proposed using only three different types to classify the disease: (i) the nodular form, (ii) sclerosing form (iii) disseminated tuberculosis mastitis. The latter classification is most commonly used in recent publications and will be described in more detail.

1. *Nodular tuberculous mastitis:* The nodular form of breast tuberculosis presents as a well-circumscribed, slowly growing, painless mass. The overlying skin may be involved as the disease progresses, with ultimately the formation of sinuses opening on the skin surface. In the early stages, it might be difficult to differentiate from other breast lumps like a fibroadenoma, while in later stages, it resembles a carcinoma.
2. *Sclerosing tuberculous mastitis:* This type is characterized by extensive fibrosis rather than caseation. The clinical features are a hard, painless lump that grows slowly and may cause nipple retraction. Often the whole breast is involved in the fibrotic process. Sclerosing tuberculous mastitis is associated with involuting breasts in older females and may also be mistaken for carcinoma breasts.
3. *Disseminated tuberculosis mastitis:* The disseminated form is characterized by multiple lesions associated with sinus formation. This form mimics inflammatory breast cancer. (25)

Clinical Presentation

Constitutional symptoms of tuberculosis (fever, weight loss, and night sweats) are not a common finding on history and only occur in 16-21% of cases. (13,20,26)

The most common clinical presentation is that of a solitary, well-defined mass in the central or upper outer quadrant of the breast. (16,20) This could be explained due to frequent extension of tuberculosis from axillary nodes to the breast. The mass may mimic breast cancer, being hard, irregular, and fixed to the surrounding breast tissue, the chest wall, or the skin. Multiple lumps or bilateral disease is uncommon presenting in only 3% of individuals. (18,20) Axillary lymphadenopathy is a common finding and is present in 35-80% of cases. (11,16,27,28) The lump is usually painless with or without breast nodularity. In the later stages of tuberculous

mastitis, it may progress to skin induration, skin ulceration, a fluctuant mass representing a breast abscess, and multiple draining sinuses. 16,20) Da Silva et al. (28) found sinus formation as a presenting feature in 75% of their patients. Nipple and skin retraction can also occur. (29) Peau d'orange is often seen in patients with extensive axillary nodal tuberculosis, impairing lymphatic drainage and leading to diffuse swelling of the breast. (11) Purulent nipple discharge or persistent discharging sinus may be the rare presenting feature. Rarely cases may even present with erythema nodosum. (30)

Diagnostic strategies

The current delay in diagnosis of between 3-8 months reported in the literature could most likely be attributed to the very low incidence and, therefore, low index of suspicion of breast tuberculosis. (14,28,31) To prevent a delayed diagnosis, a high index of suspicion is warranted when performing a clinical examination or being confronted with an atypical breast infection.

Imaging

Chest X-ray: A chest X-ray should be done to look for evidence of an active or healed tuberculous lesion in the lungs. An extramammary source is identified in less than 15% of cases, but if features of TB are seen on CXR, it may expedite the diagnosis. (32)

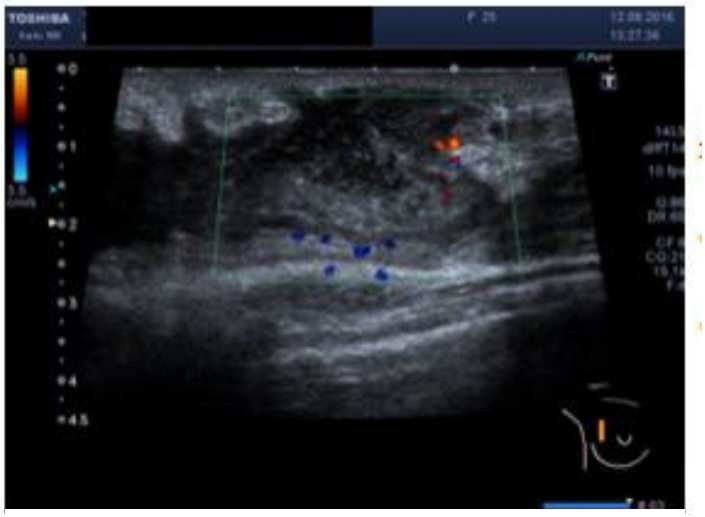


Figure 2: Large complex collection measuring, with non-dependent echogenic debris, skin thickening and increased vascularity peripherally.

Ultrasound of the breast and axilla: In nodular TB, the ultrasound often reveal a well-defined oval hypoechoic mass with posterior acoustic enhancement. (Figure 2)

The ultrasound picture can resemble that of a fibroadenoma. The difference is these hypoechoic lesions demonstrate no vascularity but rather a fluid collection containing debris. Lesions in the axillary tail can appear very similar to necrotic lymph nodes. (Figure 3)

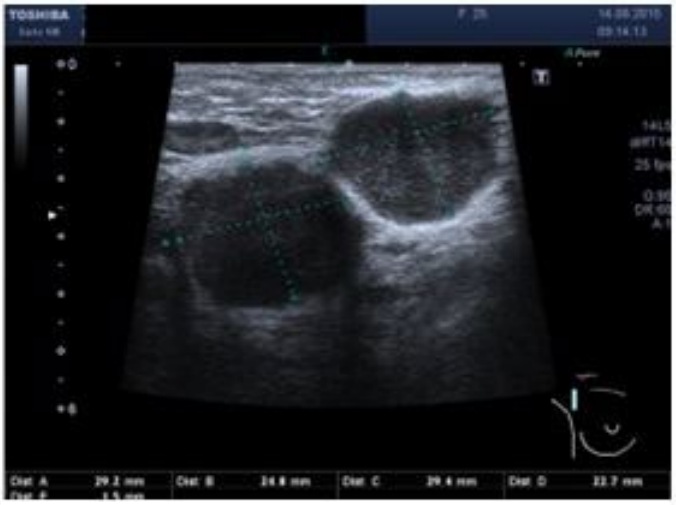


Figure 3: Large necrotic axillary nodes.

Ultrasound-guided aspiration of purulent fluid distinguishes these lesions from solid breast masses. In the sclerosing form, textural change with no visible fluid mimicking inflammatory carcinoma can be seen. (Figure 4) The disseminated form is associated with multiple anechoic collections, with and without debris, scattered throughout the breast with or without associated fistulation of the skin. (27,31)

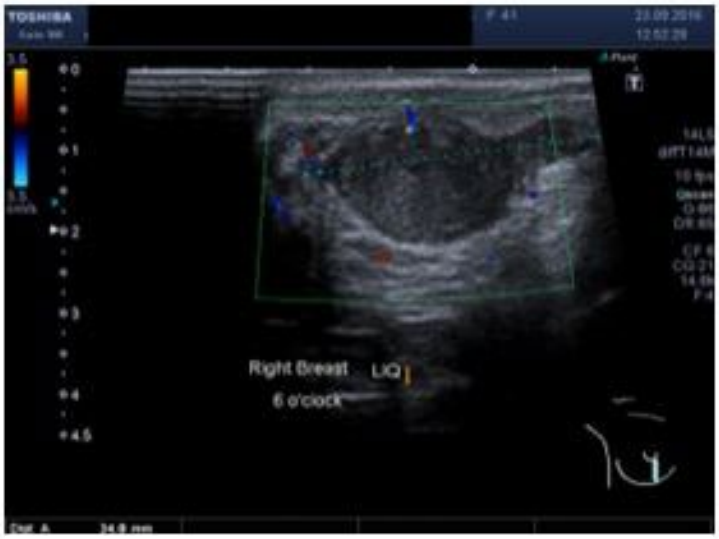


Figure 4: Ill-defined irregularly dense opacity in the right breast, reported as very suspicious of breast cancer.

Mammogram: The mammogram may show increased density consistent with a mass lesion in the nodular type breast TB to subtle increased density in the sclerosing type of disease. (Figure 5) Skin thickening and axillary adenopathy are other common findings. (27)

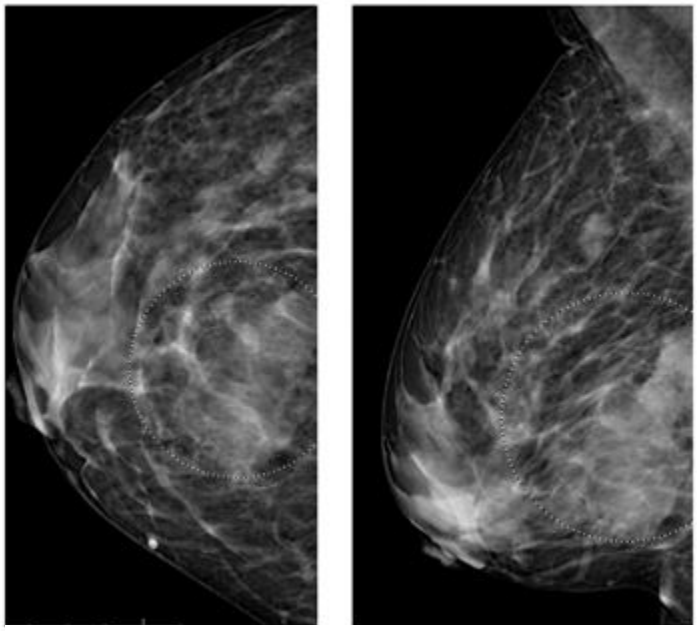


Figure 5: CC and MLO view of the right breast showing an irregular increased density in the lower inner quadrant.

CT Scan and MRI: CT and MRI are not universally available in developing countries, and there have been few reports on CT and MRI findings in individuals with breast tuberculosis. The main place of both these imaging modalities is complementary to mammograms and ultrasound, especially in documenting the extramammary extent of the disease. (11,33)

Tissue diagnosis

Various tests are used in the diagnosis and further evaluation of patients with breast tuberculosis. The available tests are; (i) Mantoux testing, (ii) Aspiration, and culture, (iii) Fine needle aspiration cytology (FNAC), (iv) Fine needle aspiration and Ziehl–Neelsen stain (ZN) for Acid-fast bacteria (AFB) (iv) Core needle biopsy and histopathology, (v) Polymerase chain reaction (PCR), (vi) Xpert® MTB/RIF. Any of these tests can be used in insolation, or multiple tests can be combined to improve sensitivity and specificity.

Mantoux testing does not offer a definitive diagnosis but confirms the exposure of the patient to the tuberculous bacilli. In endemic TB areas, the Mantoux test is of questionable value and likely to be positive because of previous exposure, and neither confirms nor rules out the diagnosis. The gold standard for the diagnosis of breast tuberculosis is the detection of *M. tuberculosis* by ZN staining or by culture, performed on fine needle aspirate specimens. The main drawback of culture for *M. tuberculosis* is a delay in obtaining the final result and the possibility of false-negative results in paucibacillary samples. In the largest systematic review on Breast TB done by Quaglio et. at. [30] they found the most common diagnostic techniques used were FNAC and tissue biopsy, used in 32% and 27% of cases, with a positive result in approximately 64% and 93% of cases, respectively. The main question regarding the diagnosis of breast TB is whether it requires the detection of the AFB, on ZN stain or culture, in extrapulmonary sites to make the diagnosis or whether morphologic features of necrotizing

granulomatous inflammation on cytology or histopathology are enough. In a study by Baily (35), 12 of 15 cases with cytologic features of necrosis and granulomas were culture positive for *M. tuberculosis*, but AFB had been demonstrated in only four cases. This is well explained by the fact that extrapulmonary sites usually contain only a few organisms. Detection of AFB is preferable, but when not present, necrotizing granulomas suggestive of TB on cytomorphology should be carefully evaluated, and a decision made to treat could be based on cytomorphology alone in some cases. (36) What needs to be kept in mind is that TB is not the only condition that can lead to granulomatous inflammation. (Table 1)

Infectious
• Mycobacterium tuberculosis
• Blastomycosis
• Cryptococcosis
• Histoplasmosis
• Actinomycosis
• Filarial infection
• Corynebacterium
Autoimmune process
• Wegener granulomatosis
• Giant cell arteritis
• Foreign body reaction
Duct ectasia
• Plasma cell mastitis
• Subareolar granuloma
• Periductal mastitis
Diabetes mellitus
Sarcoidosis
Fat necrosis
Idiopathic granulomatous mastitis

Table 1: Etiologic differential diagnosis in granulomatous lesions of the breast. (37).

PCR is not frequently used in low- and middle-income countries in the diagnosis of breast tuberculosis, mainly because of availability and cost. It was used in only 2% of cases, with

a positive diagnosis in 58% of cases, as reported by Quaglio et al. (34) Xpert® MTB/RIF (Xpert) is an automated diagnostic test for the detection of *Mycobacterium tuberculosis* complex. It is a DNA-based test that detects the *M. tuberculosis rpoB* gene. Xpert also detects mutations in *rpoB* that may cause rifampicin resistance. Results are available after two hours with minimal hands-on technical time. When available, it offers an attractive option of both producing a quick diagnostic turnaround time and the presence of multidrug-resistant TB. It has not been evaluated on breast TB but is effective on lymph node specimens. (38,39)

Treatment

Breast TB has a good prognosis, with medical therapy forming the cornerstone of treatment. No specific guidelines are available for medical therapy of breast TB, and the most common approach is the standard anti-tuberculous regimes used for pulmonary TB with two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months of isoniazid and rifampicin. Extension of treatment to a 9-month regimen, consisting of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, and seven months of isoniazid and rifampicin might be needed if the breast is not healed after six months of treatment. (20,40) The continuation phase may even be extended to 12-18 months in cases with slow clinical response. In general, complete resolution is obtained in most patients. (13,20) Primary Infection of the breast with multidrug-resistant (MDR) TB has been reported but is extremely rare. (41,42) The possibility of multidrug-resistant MDR TB needs to be considered if there was no initial culture done to confirm sensitivity and the infection fails to respond to standard or extended treatment. The treatment of MDR TB is with a combination of first-line and second-line drugs that include kanamycin, ofloxacin, ethionamide, para-aminosalicylic acid, pyrazinamide, and isoniazid. (41)

Surgery might be necessary in combination with anti-tuberculous medication in the treatment of breast TB. Less than 5% of the cases require radical surgical treatment in the form of subtotal or total mastectomy. Radical surgery might be an option in individuals not responding to medical treatment who have large painful, ulcerative lesions involving the entire breast. [16] Other surgical interventions that might be needed include; excision of a lump (to exclude malignancy), incision and drainage and cold abscess aspiration, and resection of sinus formation or necrotic tissue. In the review done by Quaglio et al. (34), excision was performed in 39% of cases, incision and drainage in 23%, and 11% had cold abscess aspiration and resection of sinus formation or necrotic tissue.

Summary

1. Tuberculosis of the breast is extremely rare, even in endemic areas
2. A high index of suspicion should be kept in atypical breast infections
3. Necrotizing granulomatous infection on FNAB or histopathology should trigger a clinician to exclude breast TB as a cause
4. Standard anti-tuberculous drugs are used for breast TB treatment
5. Surgery should rarely be necessary and is mostly confined to the excision of suspicious lesions to exclude cancer and aspirations of collections.

Infections in special circumstances

Infections in the neonate

Though rare, neonatal infections of the breast may occur. An infection of the breast can occur in the neonatal period (mastitis neonatorum) and is typically caused by gram-positive bacteria and occasionally. Treatment is with antibiotics. If a collection forms, it should be

drained. Care should be taken not to injure the breast bud. Consider the aspiration of the collection where possible. If incision and drainage are considered, the incisions should avoid the nipple-areolar complex in order to minimize the chances of damaging the breast bud.

Postoperative Breast Infections

Though considered clean surgery, there is still a small possibility of developing post-operative infections. The incidence of wound breakdown and infection is increased in patients with a history of smoking. Other factors that may increase the risk of wound infections include obesity, systemic illnesses like diabetes, and chronic steroid use.

Superficial infections can be treated with antibiotics. Deeper wounds /collections may require drainage and wound care.

Radiation-Induced Infections

Irradiation of the breast may result in infections due to tissue breakdown and vascular compromise of the tissues. Patients may develop pain, swelling, and erythema after undergoing radiation therapy. The treatment would be aspiration if possible. Aggressive incision and drainage in already compromised tissue may delay wound healing

Peri-prosthetic Infections

Due to the formation of a biofilm, patients may develop subclinical infections. Some theories suggest that there might be a link between infection, capsular formation, with contracture development. In low-grade infections with prostheses, intravenous antibiotics may be attempted with close monitoring of the infection and progression. More severe infections may warrant removal of the implant and deferring replacement for at least six months. An alternative is to have autologous reconstruction in lieu of a new implant.

Skin infections

Hidradenitis Suppurativa

Hidradenitis suppurativa, a recurrent suppurative skin disease, which typically involves the apocrine glands. It affects the axilla and inguinal areas frequently and presents with recurrent abscesses, sinuses, and fistulae. It may occasionally involve the inframammary fold of the breast or the Montgomery tubercles on the breast. The mainstay of treatment is mainly medical and will frequently involve follow-up by dermatology and administration of retinol-containing compounds and clindamycin. In severe recurrent infections, excision of the involved areas with skin grafting may be performed. Wide excision with secondary granulation can also be considered.

Fungal infections

Fungal infections are rare but may occur in the setting of immunosuppression, such as diabetes or HIV. Infection with Candida may occur in moist areas like the inframammary folds. Local management with topical antifungals is sufficient to treat the infections.

Inflammatory conditions of the breast

Idiopathic Granulomatous mastitis (GM) is a rare inflammatory disease of the breast, affecting mainly women of childbearing age. Originally described by *Kessler and Wolloch* in 1972, the condition can mimic carcinoma of the breast. (43) The diagnosis of GM can only be confirmed by histopathology, which is characterized by the presence of multinucleated giant cell granulomas with microabscesses. (43) The diagnosis is made after excluding inflammatory breast carcinoma and other infective and non-infective causes of granulomatous inflammation,

such as tuberculosis, parasitic and fungal infections, sarcoidosis, Wegener's granulomatosis, giant cell arteritis, polyarteritis nodosum, and foreign-body reaction (Table 2). (43)

Differential diagnosis
Idiopathic
Sarcoidosis
Parasitic infection
Fungal infection
Mycobacterium infection
Wegener's granulomatosis
Giant cell arteritis
Polyarteritis nodosum
Foreign-body reaction

Table 2: Chronic granulomatous mastitis.

The etiology of idiopathic GM is still unknown, and its treatment remains controversial. (43) Uses of antibiotics, corticosteroids, and surgery have been reported as treatment options. (43) The disease may be locally aggressive and has a tendency to relapse in up to 50% of cases.

Clinical Presentation

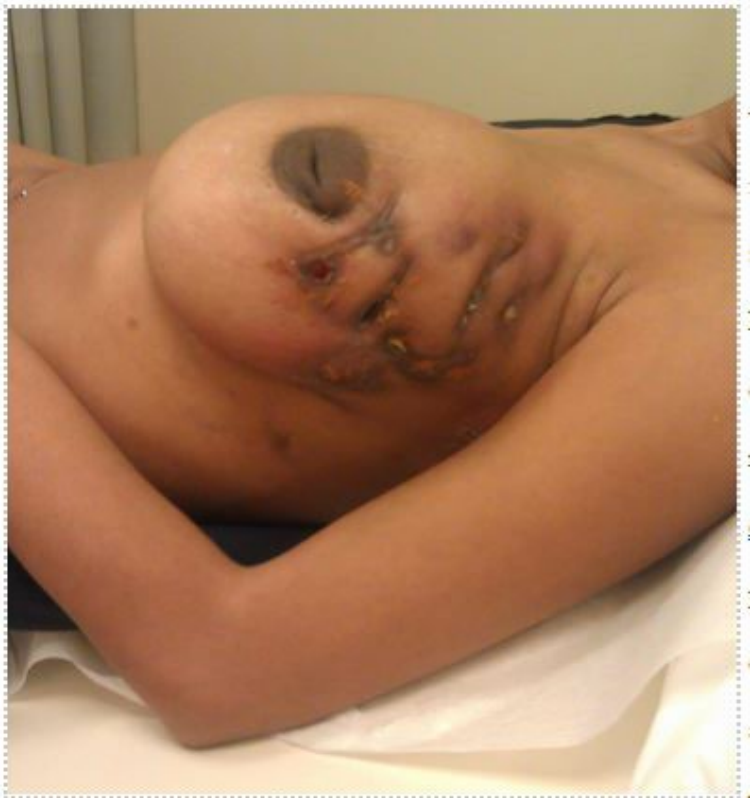


Figure 6: Patient with a severe case of GM treated at an outside hospital with multiple I&D leading to recurrent fistulae.

Patients generally present with painful palpable breast masses in the absence of constitutional symptoms. Thirty-three percent may have purulent ulcerative discharge on presentation. Half of the patients may present with overlying that is erythematous and warm. These patients fail to respond to multiple courses of oral antibiotics. The average number of lesions at presentation is 1.7 (range 1 - 4) but can be more. (Figure 6)

While most patients generally present with unilateral lesions, these patients can go on to develop lesions in the contralateral breast. Thirteen percent of the patients had axillary lymphadenopathy. Few patients show cutaneous manifestations of erythema nodusum in the lower extremity. The rest of the physical exam was unremarkable in all patients.

A small number of patients have demonstrated an elevated prolactin level for unclear reasons, but lab results tend to be unremarkable in these patients. (44) It is important that a lab workup, including a blood test for tuberculosis, prolactin levels, and angiotensin converting-enzyme be performed. (44)

Radiological investigations

All patients should have a chest x-ray, mammogram, ultrasound, and core biopsies of the lesion in question. Bacterial, fungal, and viral cultures are sent from the core biopsies. (44) Ultrasonographic examinations of the breast show hypoechoic masses with irregular margins, fluid collections, and parenchymal mixed echogenicity, all consistent with abscesses. Mammographic examinations of the breast show irregular masses with indistinct margins, measured from 1.6 cm to 4.0 cm in diameter. Complex cysts, fluid collections, and skin involvement was identified in all patients.

Histopathological evaluation

All patients were diagnosed with GM based on histopathologic findings. The granulomatous formation was identified in 80% of patients. In 60% of the biopsies, the lesions were necrotizing, while 20% were not. The immature granulomatous formation was identified in 20% of cases. Variable numbers of multinucleated giant cells, neutrophils, polymorphs, lymphocytes, plasma cells, and eosinophils were frequently seen. Microabscesses formation was

commonly recorded. Special stains for microorganisms (Gram), tuberculosis (Ziehl-Neelsen), and fungal infections (periodic acid-Schiff) were all negative. Mycobacteria cultures were negative after six weeks of incubation. (43)

Treatment

There are multiple medical approaches to the treatment of GM. One approach consists of needle aspiration of any abscess formation along with oral prednisone (1.0 mg/kg) for three weeks, followed by gradual tapering over the course of an additional two weeks. (43) Eighty percent of patients treated with prednisone had complete resolution of their inflammatory findings, with the remaining having incomplete but significant improvement. For patients who have a second flare-up, a second course of prednisone is given in combination with low-dose methotrexate (15mg/week). (44)

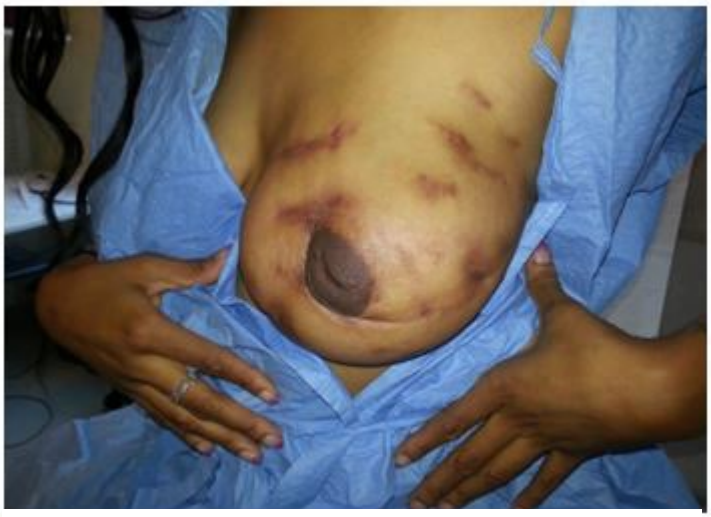


Figure 7. Six months post-treatment with medical treatment only. The patient's cosmetic appearance gradually improved with time.

A second approach is to initiate treatment with doxycycline 100mg orally, bid, and ibuprofen 600 mg orally. Doxycycline has anti-inflammatory properties and is started after all biopsies are performed, and ibuprofen is given promptly to alleviate the pain that almost all GM patients have on presentation. The average duration of treatment with doxycycline is 4.6 months. For those patients who fail doxycycline, methotrexate would be the next line of treatment. Surgery should

be considered a last resort and, in the authors' experience, has never been used in the management of GM. In most cases, GM, when diagnosed and with proper treatment, can be self-limited and respond promptly to treatment. (Figure 7)

Other Inflammatory Disorders of the Breast

Mastitis is an inflammation of the breast usually caused by an infection. It is commonly seen in postpartum women, diabetics, or in conditions where bacteria is able to enter the breast through the nipple or skin. Most cases are treated with oral antibiotics. However, more severe cases may require IV antibiotics and surgery.

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Chapter 9

Imaging Algorithms for Solving Breast Problems

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Imaging Workup of a Palpable Mass

Women < 30 years old

Start with targeted ultrasound of the palpable region. The immature breast (breast tissue in a woman who has not carried a fetus to the end of the third term) is more sensitive to DNA damage from ionizing radiation.

Women >= 30 years old (or a female who has carried an infant to the late third trimester)

Start with a mammogram. Her breast tissue is considered fully differentiated.

The following ultrasounds of palpable masses demonstrate various characteristics that can help determine the source of the palpable mass.

Figure 1 demonstrates breast cancer with angular and fuzzy margins, hypoechoic to anechoic internal echos.

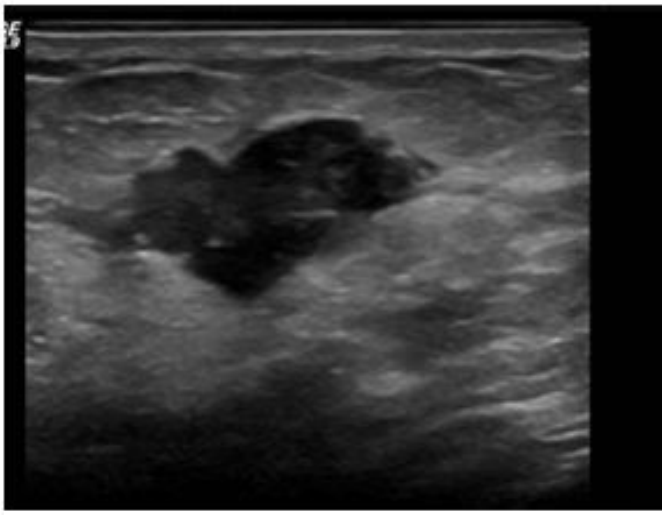

Figure 1: Targeted ultrasound of palpable breast mass: (Biopsy-proven invasive ductal carcinoma-mucinous type) "angular margins" are frequently seen in IDC-mucinous type.

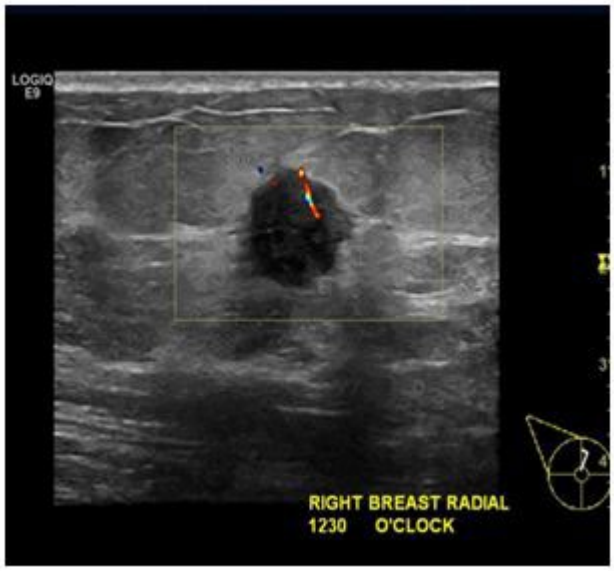

Figure 2: This mass demonstrates microlobulated borders (long arrows) and "edge vascularity" or abnormal vascularity seen by US Doppler interrogation at the margin of the mass (short arrow). Both are suspicious for cancer.

Figure 2 shows cancer growing across the natural planes of the breast with microlobulated borders and fuzzy margins and irregular shadowing.

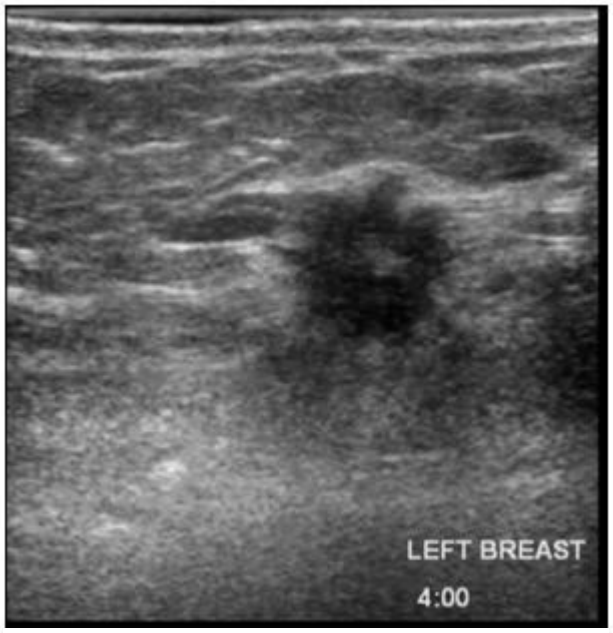

Figure 3: Spiculated borders highly suspicious for cancer.

Figure 3 is hypo- to anechoic with spiculated margins which mirror the spiculations in the mammogram (Figure 4) and in the gross specimen (Figure 5)

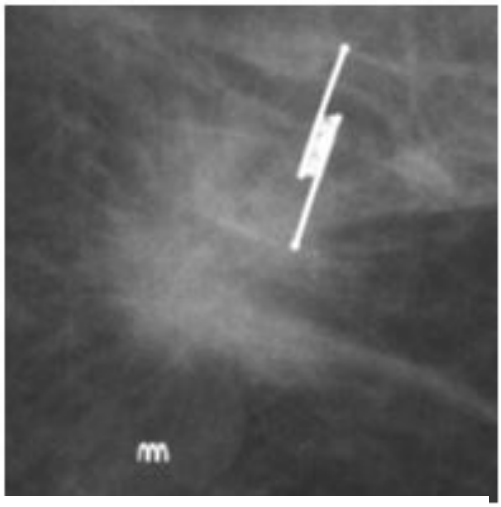

Figure 4: Spiculated borders were also seen on the radiograph of the operative specimen (same patient as Fig 3). The metallic "spring" is a marker placed after percutaneous core needle biopsy and the "two-armed" device is a SAVI electromagnetic reflector used for pre-operative localization of the target mass.

Figure 5: Target mass with spiculations in the operative specimen from Fig 4.

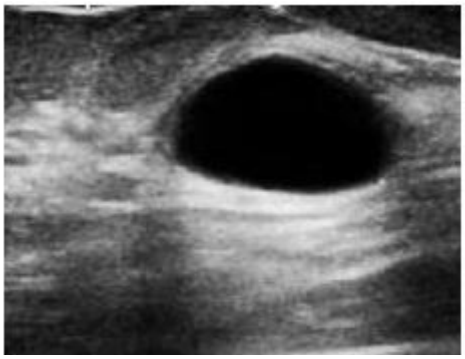

Figure 6: Simple cyst, which presented as a palpable mass.

Benign lesions present very differently, with the edges being very sharply defined. The long axis of the mass is parallel to the skin surface. The mass itself is uniformly black on ultrasound (anechoic). The tissues posterior to the mass are fairly uniformly bright (posterior acoustic enhancement). These are all signs of a benign mass (Figure 6). Figure 6 is a simple cyst and can simply be aspirated if big or painful to the patient. (Figure 7) Note the sharply circumscribed margins in Figure 7. It has perfectly anechoic echotexture, round to ellipsoid shape, and exuberant posterior acoustic enhancement. No mural nodules nor thick septations (>2mm) are present. The walls of the cyst may gently undulate due to mild inflammation around the cyst. No angular, spiculated nor micro-lobulated margins should be present. It was drained using a 19g 3.5" needle under ultrasound guidance due to tenderness. It collapsed completely with no residual mass. Encouraging the patient to wear a tight-fitting sports bra for 48hrs after drainage may help the cyst walls to adhere to each other and prevent reaccumulation of fluid.

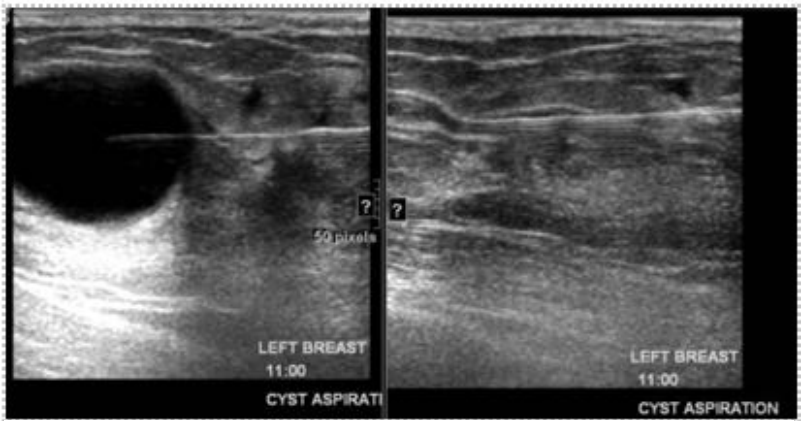

Figure 7: This simple unilocular cyst presented as a tender, palpable mass.

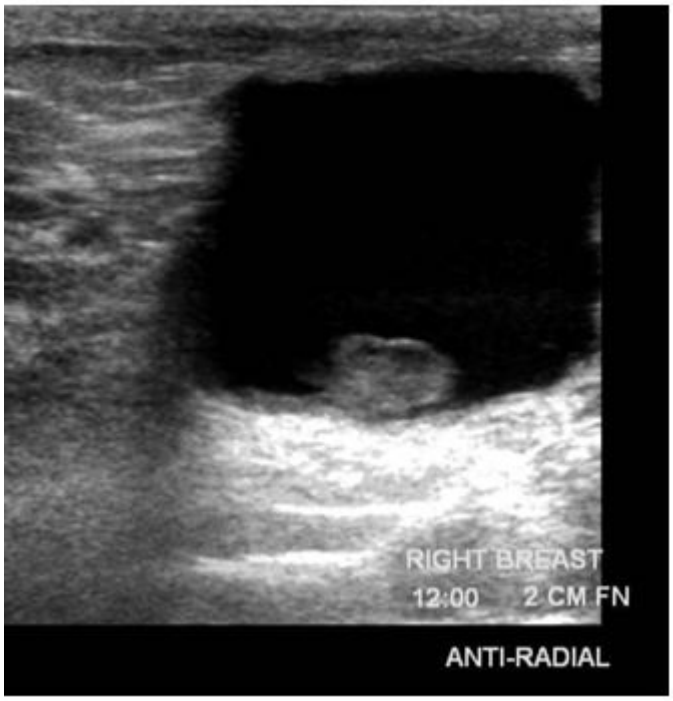

Figure 8: Mural nodule in a cyst.

Figure 8 demonstrates a complicated cyst. The walls appear smooth, but there is an obvious internal mass within the cyst. Ultrasound can be used to remove the mass and the cyst percutaneously. In this way, a preoperative diagnosis can be made. If not available, then intraoperative ultrasound can be used to localize the area if non-palpable.

This ***does not*** meet the criteria for a simple cyst. If the nodule is stable, it can be biopsied under the US. Alternatively, the mural nodule can be localized under the US for excisional biopsy.

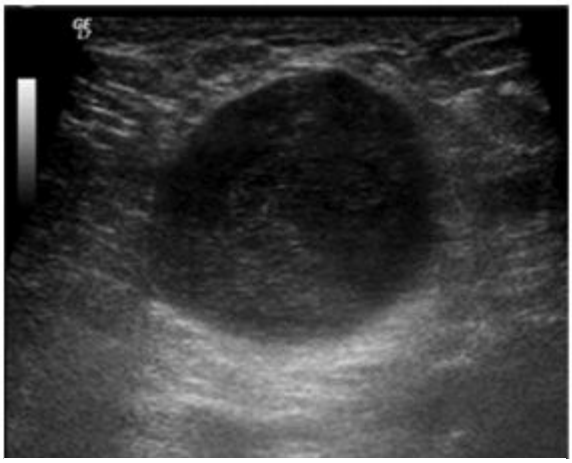

Figure 9: Galactocele, which presented as a palpable mass. Seen in lactating women, the echogenic material is mobile (can be seen to move or swirl with changes in patient position) at real-time ultrasound. There is no vascular flow seen within the mass on Doppler interrogation.

Internal echos, if mobile, can represent sludge within a cyst which is a dilated duct. (Figure 9) These can be aspirated to completion. This is a common characteristic of galactoceles. These can often be massaged and expressed through the nipple, aspirated, or left alone if not painful.

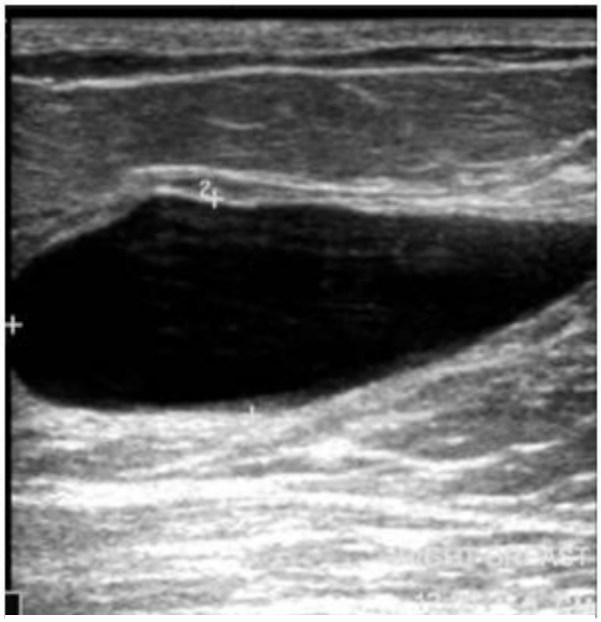

Fig 10- Biopsy proven phyllodes tumor (phyllodes tumor or cystosarcoma phyllodes). This mass is sharply circumscribed, uniformly hypoechoic with posterior through enhancement, and parallel to the skin surface. If you see a mass that meets most ultrasound criteria for a fibroadenoma but exceeds 3 cm in length, it should be sampled to exclude phyllodes.

When a mass is solid with uniform hypoechoic a solid component and smooth margins, a needle biopsy can confirm it is benign and most likely a fibroadenoma. When growing rapidly or beyond 3cm, it is recommended to remove the lesion as a needle biopsy is only a sample of the lesion and may miss a phyllodes tumor. (Figure 10).

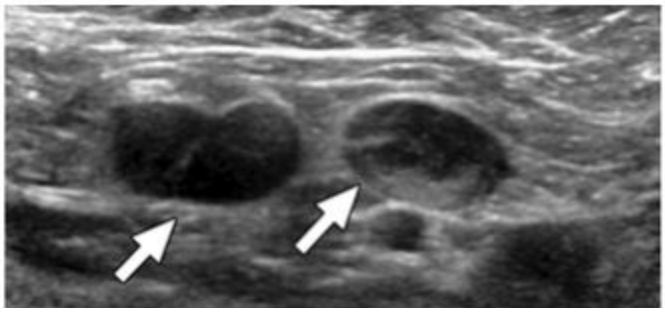

Figure 11: Palpable mass in the axilla. These abnormal lymph nodes are more "rounded" (rather than being oval or reniform), have lost their normal fatty hilum (which should be echogenic compared with the hypoechoic cortex), and may demonstrate abnormal vascularity at the periphery of the capsule (rather than entering the hilum).

Ultrasound can also be used to examine the regional lymph nodes (axillary, internal mammary, and supraclavicular) in a patient with known cancer or one with palpable lymphadenopathy to determine metastases. (Figure 11, 12)

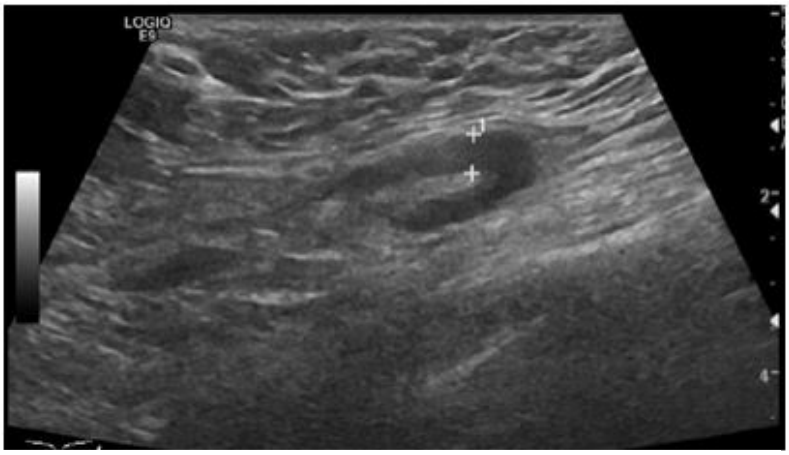

Figure 12: palpable mass in the axilla corresponded to an enlarged lymph node with an abnormally thickened (>4mm) cortex.

The US can then also be used to biopsy any suspicious nodes (Figure 13). Lymph nodes can be biopsied under ultrasound using an 18 gauge needle, Doppler can help you identify/avoid the surrounding vascular structures.

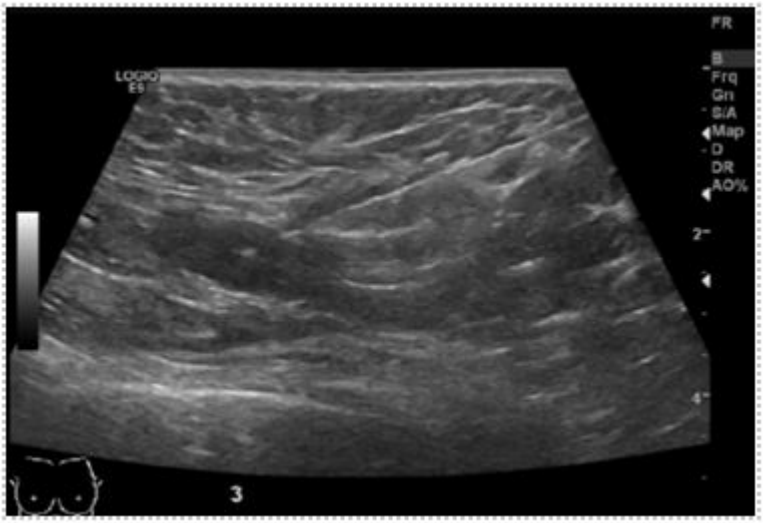

Figure 13: Ultrasound-guided bx of an abnormal lymph node with nodular cortex.

If a patient presents with a non-palpable mass on screening mammography, the next step is to perform an ultrasound over the area of concern. If suspicious on US then one can proceed with an US-directed needle core biopsy. (Figures 14, 15, 16) Ultrasound is particularly useful in a male as mammograms can often be difficult. Ultrasound-guided biopsies are far easier on the patient than stereotactic (mammogram-guided) biopsies. It will facilitate a needle biopsy. Any mass in a male should be considered cancer until proven otherwis

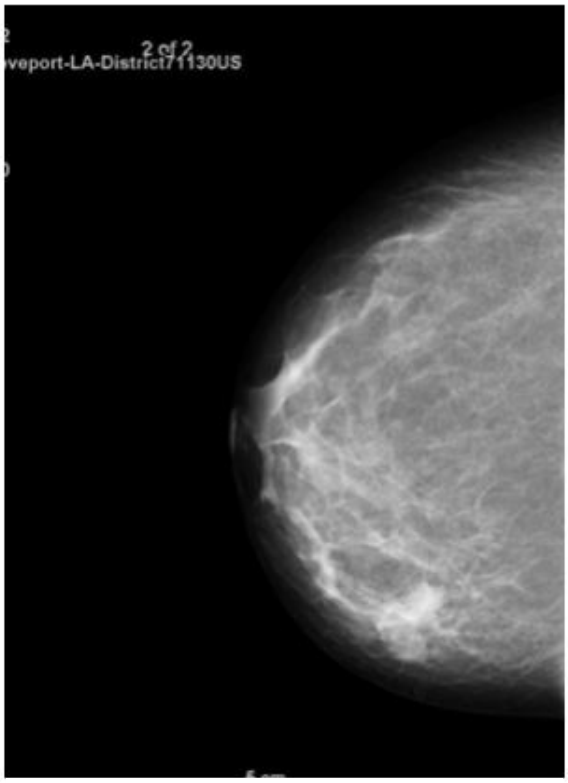

Figure 14: Mammogram of a palpable mass. The next step is ultrasound to see if the characteristics are benign or malignant at ultrasound. If malignant, looking at ultrasound, proceed to percutaneous biopsy under ultrasound guidance. (biopsy-proven IDC-mucinous type, same patient as in Fig 1).

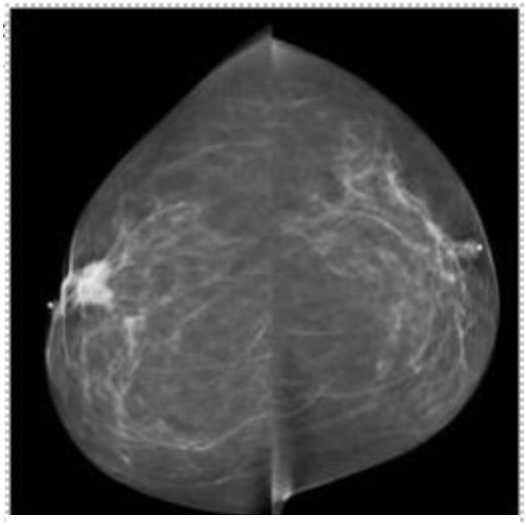

Figure 15: Suspicious mass on mammogram, next step is ultrasound. (Biopsy proven tubular carcinoma).

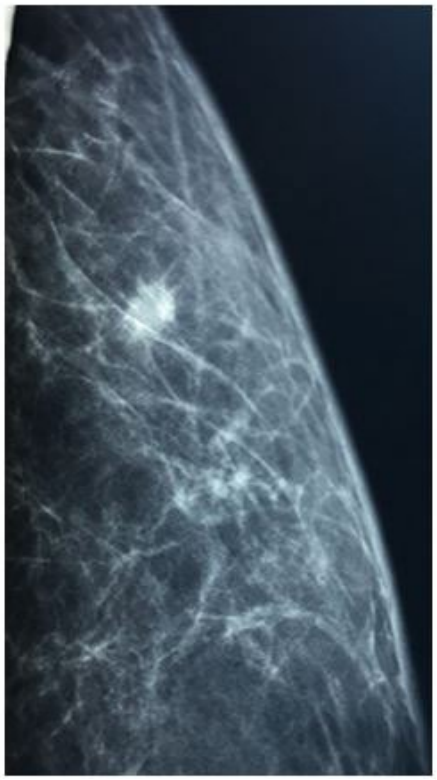

Figure 16: Palpable mass in a male breast. (Biopsy proven 4mm invasive ductal carcinoma).

Imaging workup of a mammographic abnormality

Mammographic abnormalities that require further work-up include microcalcifications, architectural distortion, a focal mass, or focal asymmetry.

Suspicious findings include pointed, hooked, triangular-shaped, or branching calcifications which are linear or grouped and vary in size and shape. (Figure 17-19)

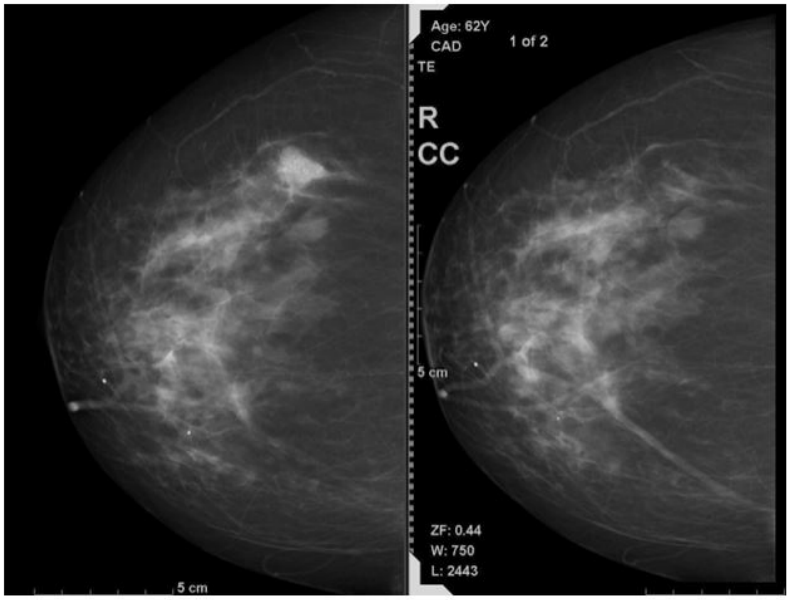

Figure 17: Suspicious microcalcifications are seen on a screening mammogram

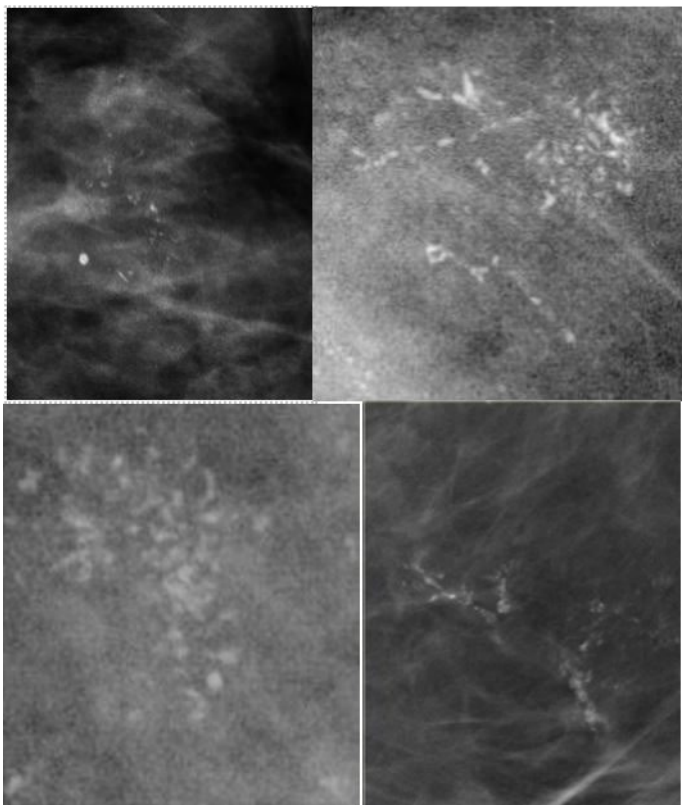

Figure 18: Magnification views of microcalcifications for better evaluation.

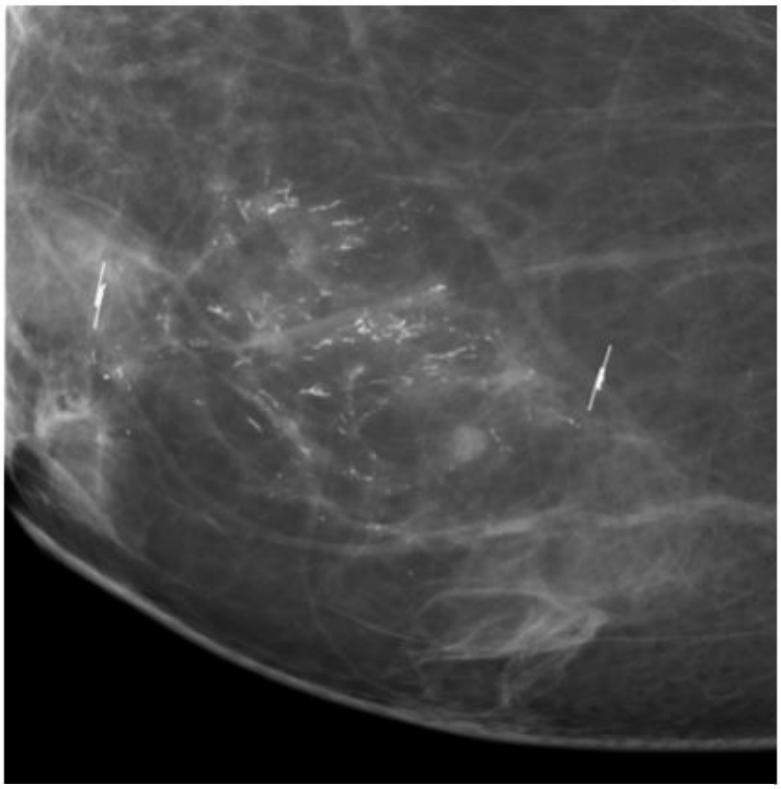

Figure 19: If you have a large focus of suspicious calcifications to remove, placing markers at each end of the worrisome focus ("bracketing") prior to surgery may be helpful.

When architectural distortions are seen, rolled views are preferred to spot compression views to differentiate *true architectural distortion* (due to cicatrization of tissue secondary to cancer) from *summation artifact* (overlapping of normal fibroglandular tissue). (Figure 20-23)

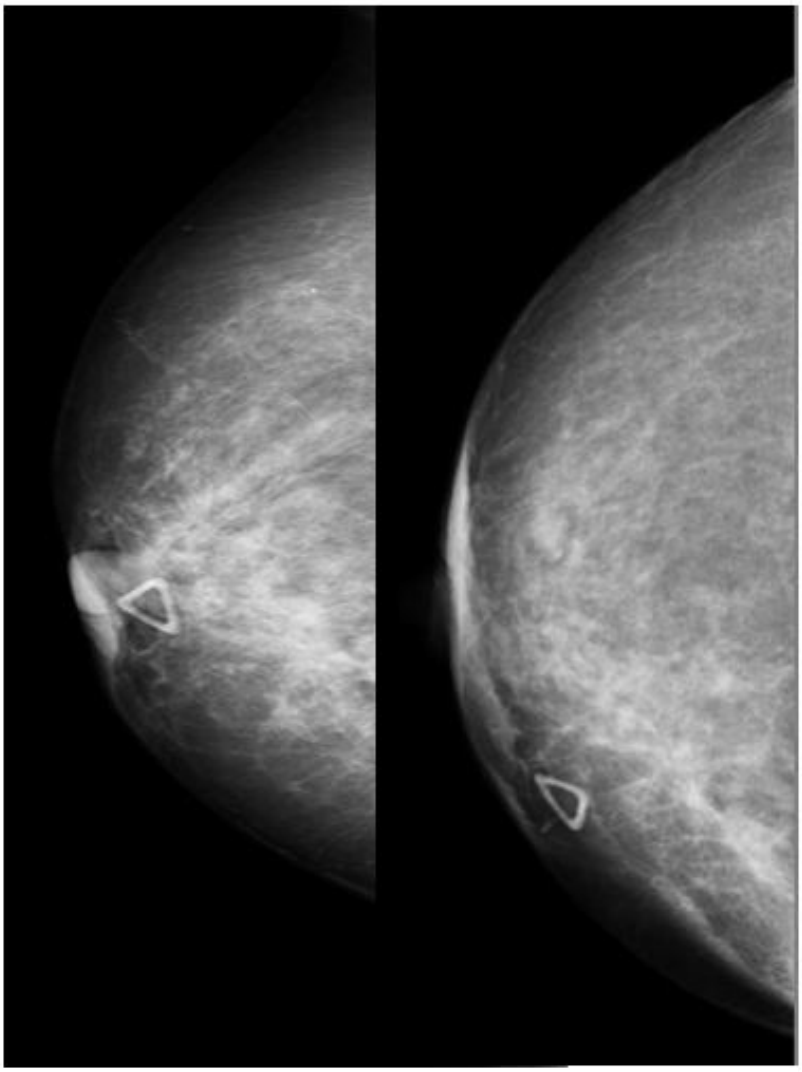

Figure 20: Area of architectural distortion. Triangular-shaped metallic marker indicates a palpable abnormality. (Biopsy proven invasive lobular carcinoma).

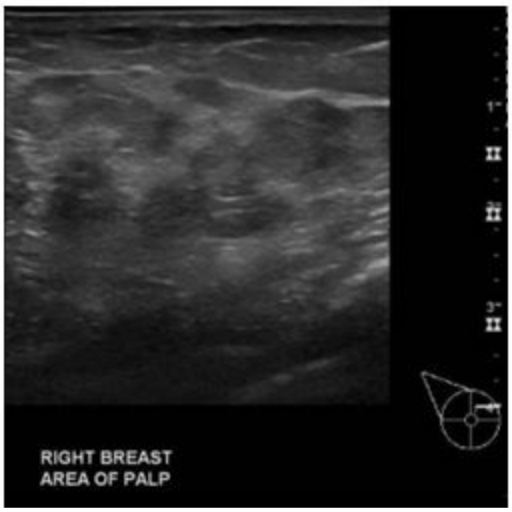

Figure 21: Same patient as Fig 19, biopsy-proven invasive lobular carcinoma. Invasive lobular carcinoma can be more subtle on imaging than ductal carcinoma.

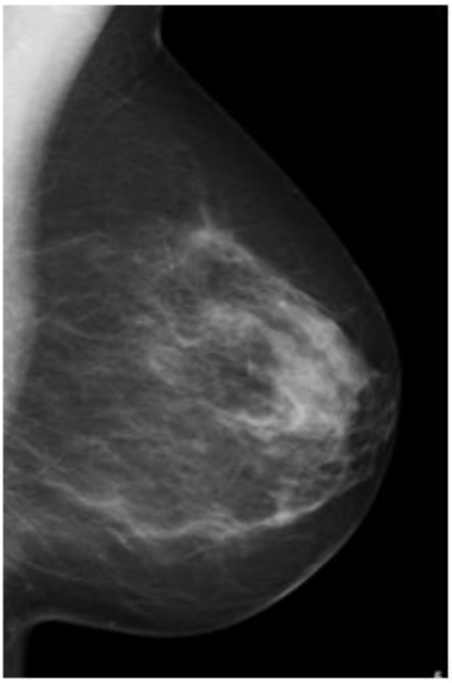

Fig 22- Area of apparent architectural distortion seen on a screening mammogram.

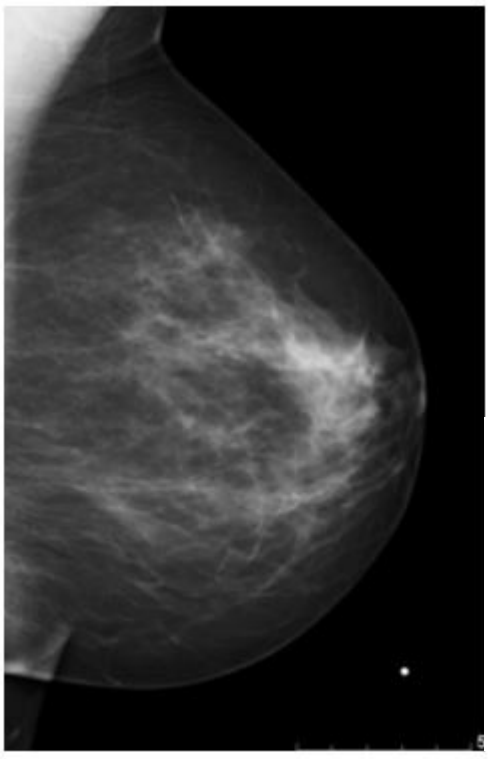

Fig 23- Diagnostic "call back" mammogram (same patient as in Fig 22). MLO repeated at a different angle, and the "architectural distortion" resolves. Overlapping normal fibroglandular tissue created a summation artifact.

When a Focal mass/focal asymmetry is demonstrated on a mammogram, localize the mammographic abnormality to one quadrant of the breast (Figure 24-28), then interrogate that quadrant of the breast ("targeted" ultrasound) to see if there is a lesion on ultrasound which corresponds in size and position to the mammographic abnormality.

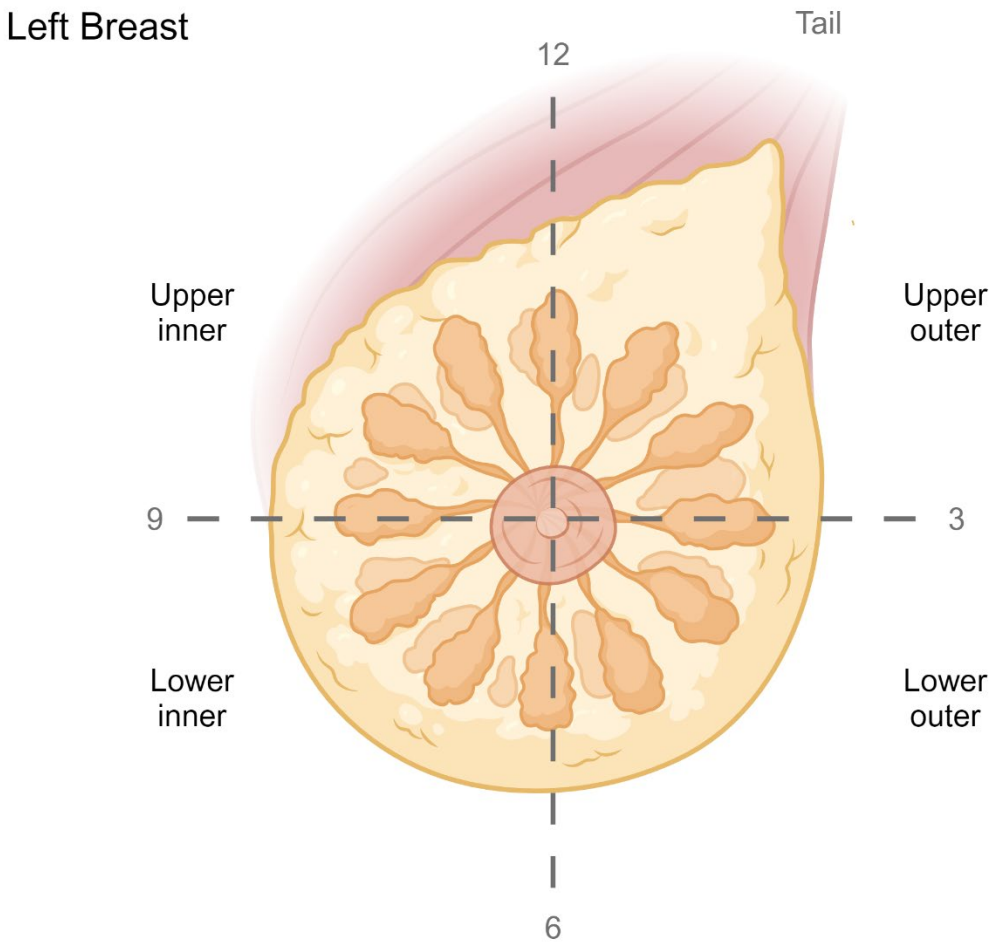

Figure 24: Quadrants of the breast
Created with BioRender.com

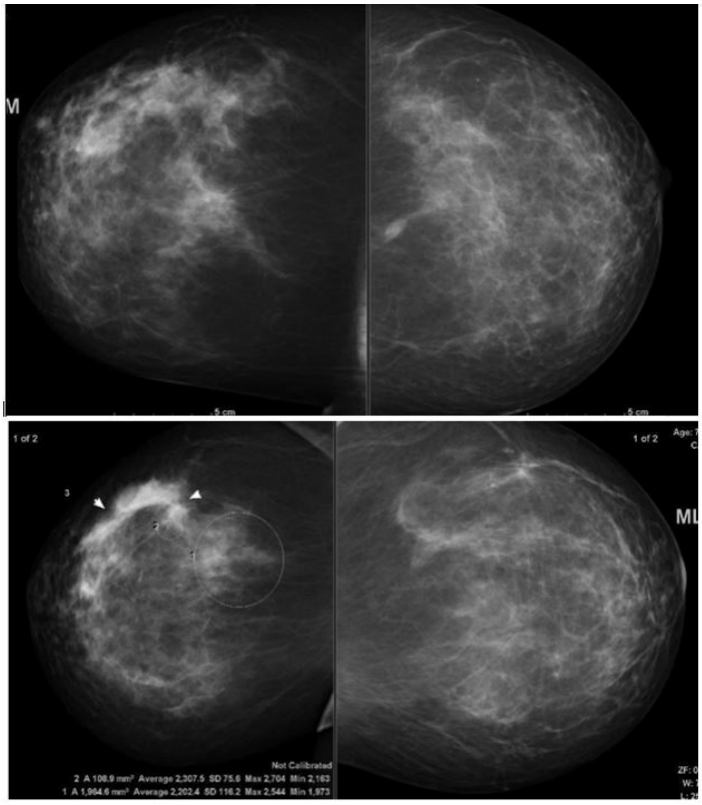

Figure 25: Focal asymmetry in the upper outer quadrant (UOQ) of the right breast seen on a screening mammogram.

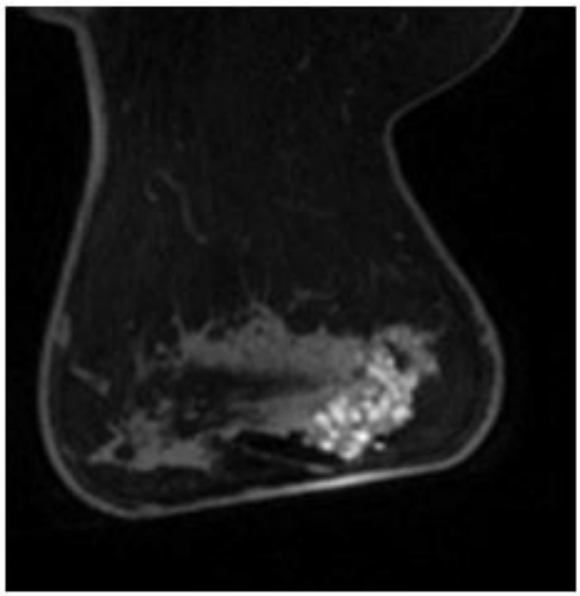

Figure 26: "clumped" area of Gadolinium contrast enhancement on MRI corresponding to the focal asymmetry seen on mammogram. (Biopsy proven invasive ductal carcinoma).

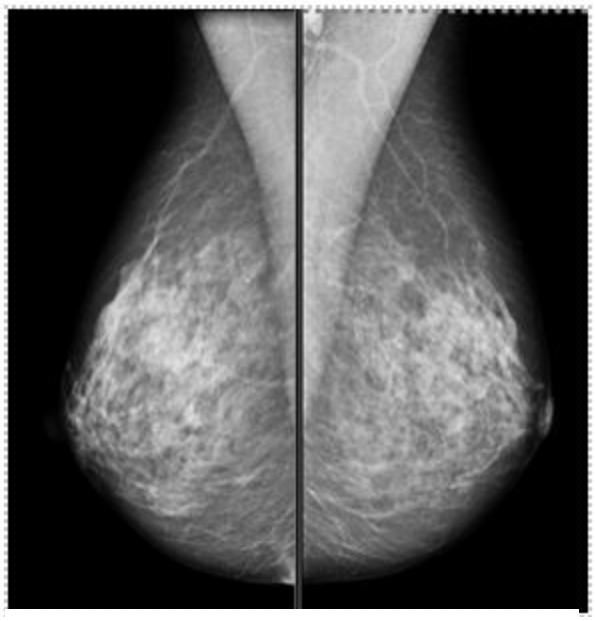

Figure 27: spiculated mass with surrounding architectural distortion.

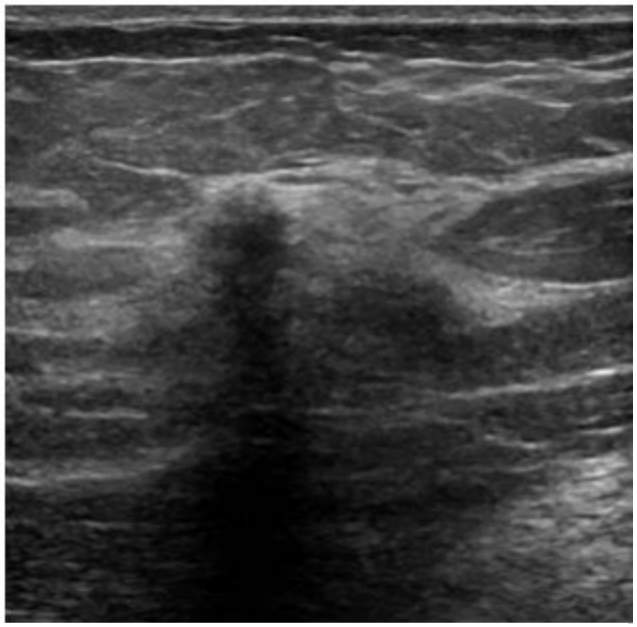

Fig 28 - ultrasound of the spiculated mass (same patient as in Fig 27).

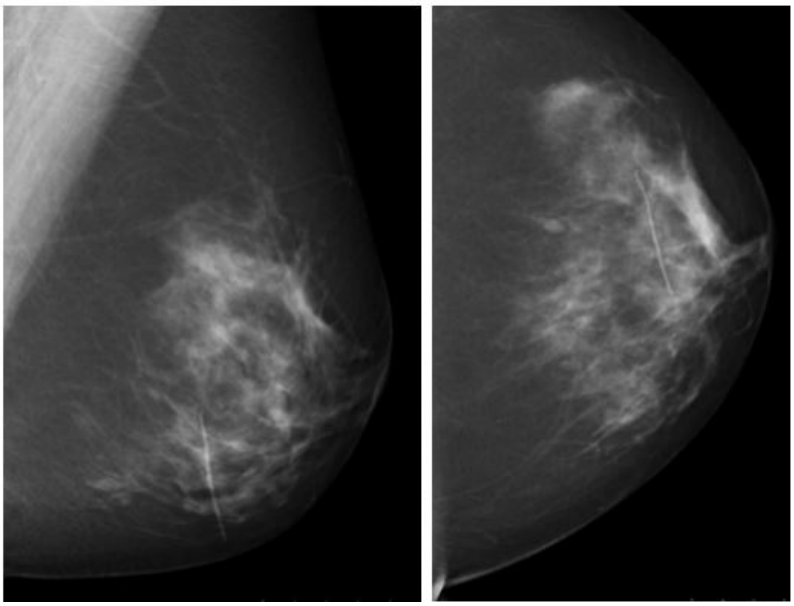

Figure 29: Mass only seen on CC view from screening mammogram.

If you cannot see the mass on two (orthogonal) views, you can use “rolled views” of the breast to localize the mass to one quadrant of the breast. (Fig 29-31)

Use “rolled views” to localize the mass:

- Place the breast in CC position.
- Roll the upper part of the breast, medial or lateral, and observe which way the mass rolls. If the mass follows the upper breast (moves laterally when the upper breast is rolled laterally), the mass is in the upper breast. If the mass moves medially when the upper part of the breast moves laterally, the mass is in the lower breast.

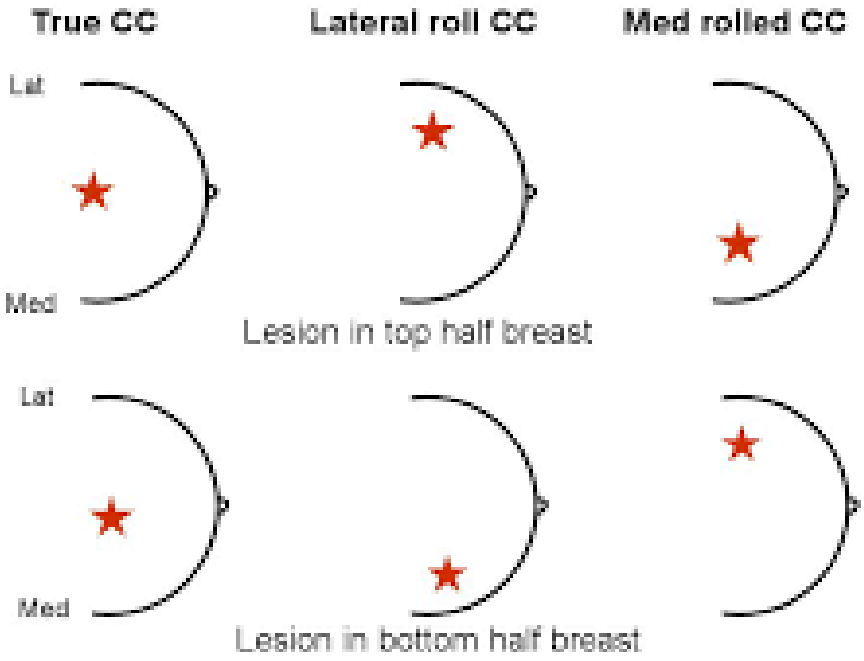

Figure 30: “CC rolled laterally” refers to the top half of the breast being rolled laterally and the bottom half of the breast subsequently rolling medially. To localize the lesion, observe which half of the breast the lesion follows. An Effective Way to Solve Equivocal Mammography Findings: The Rolled Views Alimoglua, E. Breast Care 2010;5:241–245

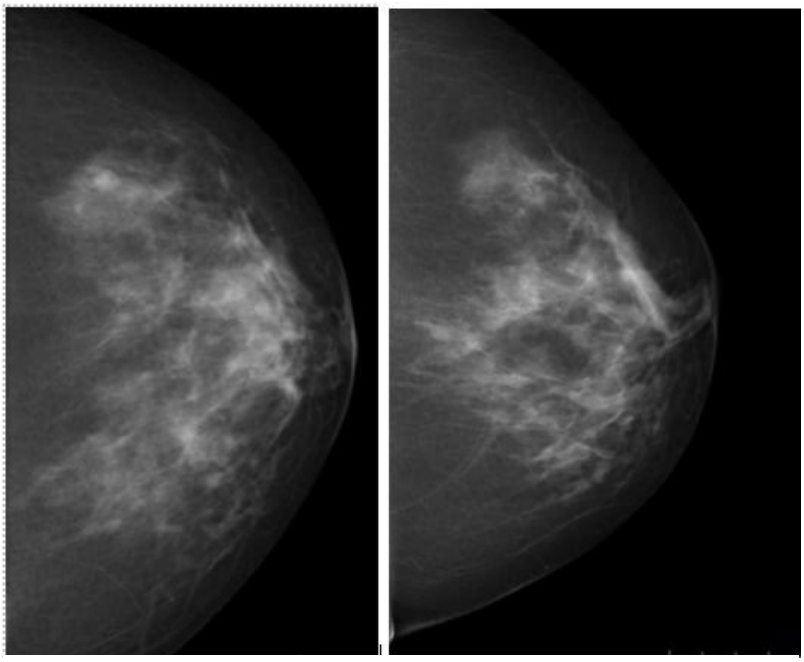

Figure 31: The mass seen on the CC view in Fig 29 moved in the opposite direction from the upper half of the breast when rolled views were obtained; thus the mass is in the lower breast.

Once the quadrant of the breast is determined, then the US can be used to locate the lesion and perform an US-guided biopsy with a needle core biopsy. (Figure 32-35)

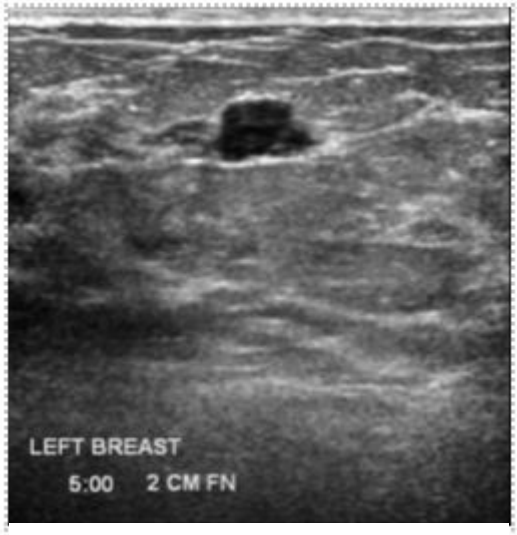

Figure 32: The mass was localized to the 5:00 position of the left breast (the lower outer quadrant) and interrogated using a linear 12 MHz transducer. It demonstrates angular margins and microlobular margins. It does not have a benign appearance at ultrasound and will require a biopsy.

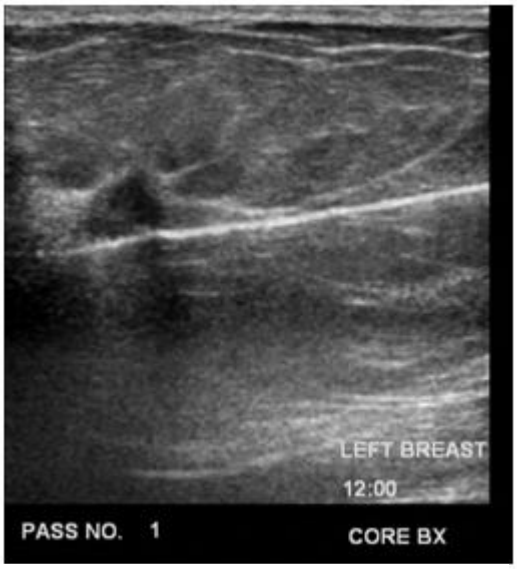

Figure 33: percutaneous biopsy under direct ultrasound visualization using a vacuum-assisted 13g cutting needle. Although 18g and 20g needles are useful to biopsy many other areas of the body, they are insufficient for accurate sampling of breast lesions. Use a 14g needle or larger!!!

Figure 34: The Mammotome Elite 13g directional vacuum-assisted needle is one example of a needle biopsy device that works well for this purpose

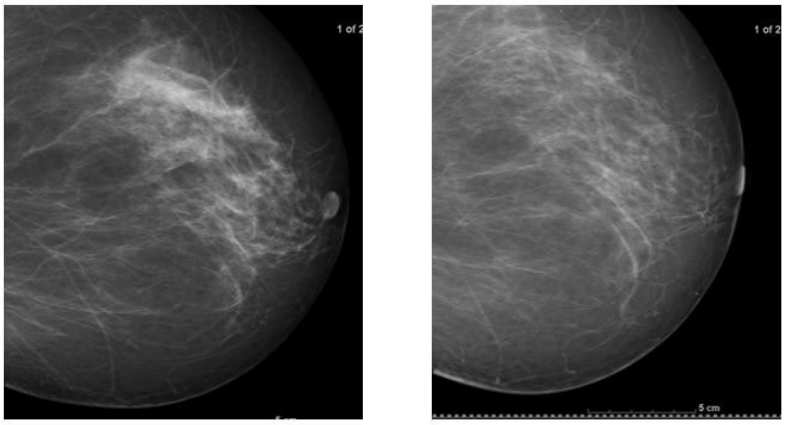

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Figure 35: Developing density. Lobular carcinoma can present as a subtle developing density that gradually increases in conspicuity on subsequent mammograms. Localize to one quadrant, ultrasound that quadrant, and biopsy any suspicious mass identified. If no ultrasound correlate can be identified, you can target the abnormal area on a stereotactic biopsy machine.

Workup of Nipple Discharge

Nipple discharge can be from duct ectasia, fibrocystic change, papilloma, DCIS, or papillary carcinoma. Nipple discharge which is unilateral, spontaneous, bloody, and from a single duct is the most worrisome for cancer.

Frankly bloody, rusty brown, or serous discharge from a single pore on the surface of the nipple is an indicator that the duct system drained by that pore may harbor a papilloma or papillary CA.

Cannulation of the pore using a 30g blunt tip sialogram needle with an injection of 1-3cc of non-ionic iodinated contrast and subsequent mammogram in CC followed by ML projections may be helpful in identifying a causative lesion.

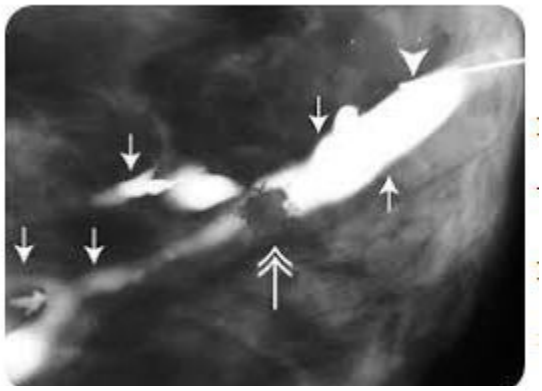

Figure 36: Multiple segmental duct narrowings and duct amputations. The filling defect is suspicious for papilloma/papillary carcinoma.

Mixing contrast with methylene blue (50:50) prior to injection can facilitate complete dissection of the ductal system of interest as well as facilitate pathologic identification of the (sometimes tiny) lesion in the surgical specimen. (Figure 36)

If there is no abnormal mass identified by ultrasound (Figure 37, 38) at the site that is abnormal on the ductogram ("ultrasound correlate"), the filling defect can be localized for surgical excision using the mammographic grid localization technique.

Notice that the duct between the papilloma and the nipple is dilated because the papilloma/papillary carcinoma produces serous or bloody fluid that distends the duct.

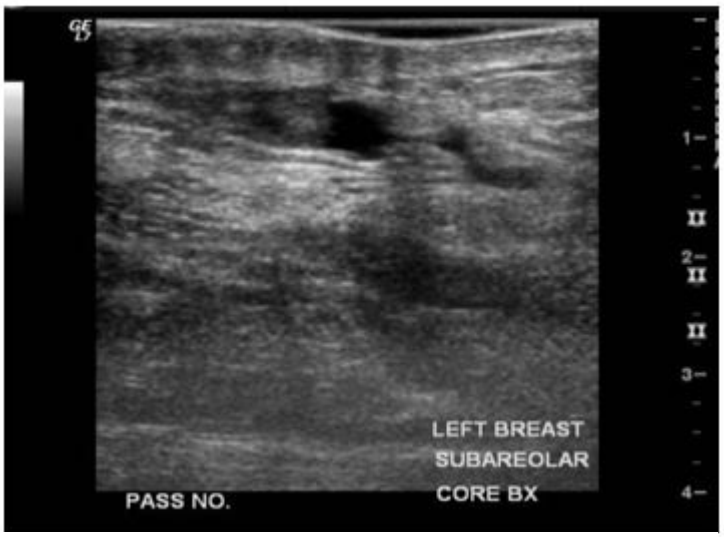

Figure 37: Intraductal mass seen on ultrasound of the area of the breast demonstrated to be abnormal on ductography. This mass was biopsied under ultrasound guidance

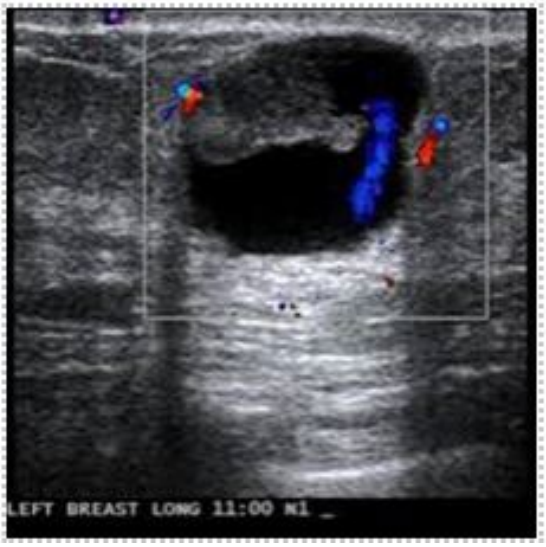

Figure 38: Biopsy proven intraductal papilloma. The distinction between papilloma and papillary carcinoma cannot be made at imaging. Either core needle biopsy or excisional biopsy is necessary.

Figures 39 and 40 demonstrate the appearance of DCIS on ductogram and ultrasound.

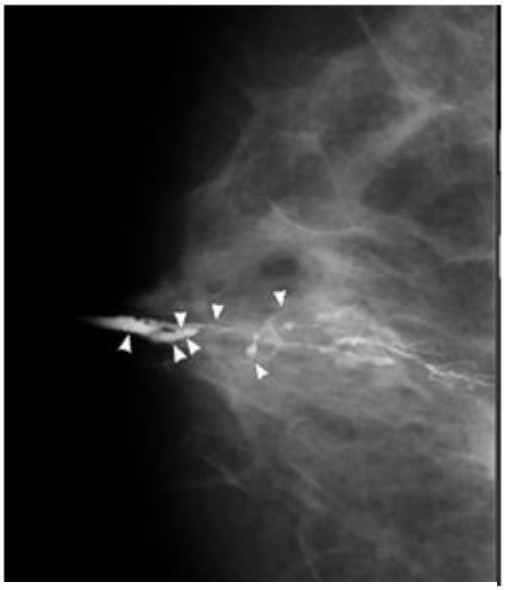

Figure 39: Ductogram demonstrates multiple duct amputations, segmental ductal narrowings, and filling defects. (Biopsy-proven DCIS).

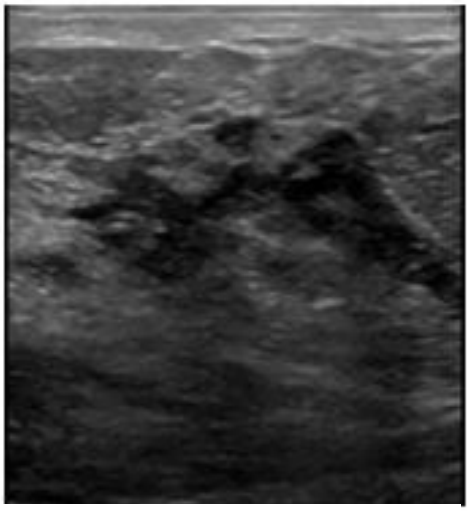

Figure 40: Ultrasound of the abnormal region identified on the ductogram in Fig 39. Dilated ducts with no focal target mass were identified. A hookwire, an electromagnetic reflector (such as the SAVI device) or a tiny pellet containing a small quantity of technetium 99-m radioactive material can be placed at the site of the filling defect/duct amputation seen on the ductogram using the mammographic grid localization technique.

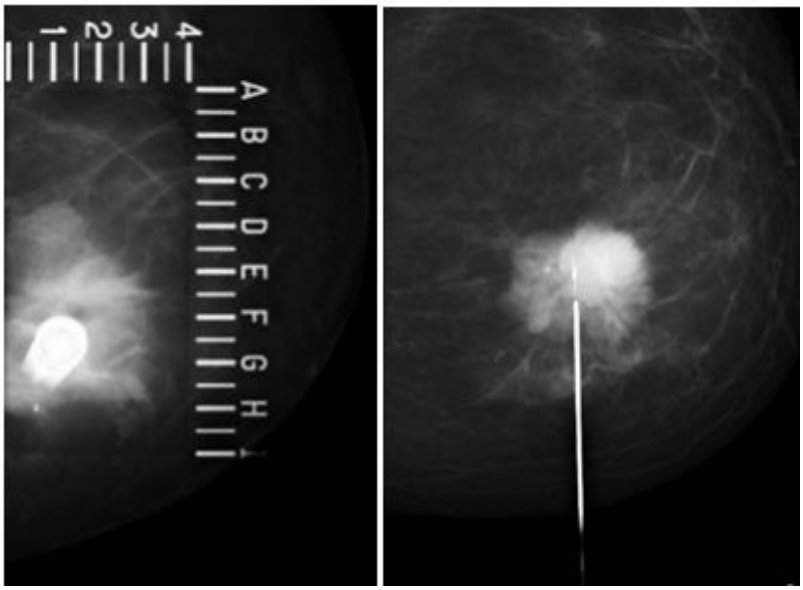

Figure 41: Preoperative localization of a mass under mammographic grid localization using an electromagnetic reflector (SAVI).

The breast was placed in ML compression initially, and the hub of the needle was kept projected over the tip as the needle was advanced into the breast. (Figure 41) The breast was then placed in CC compression, needle depth adjusted, and the device deployed in target mass. This mass (in a very large pendulous breast) only became palpable once it reached 5cm in the greatest dimension. ***Imaging can help detect cancers in very large breasts before they become palpable***.

Tips for successful ductography

If there is no active discharge on the day of the study, the pore will likely not be dilated enough to "take" the needle. Ask the patient to refrain from expressing the material from her breast in the morning (patients often do this to prevent soiling their clothing) and return to the clinic when active discharge is noted.

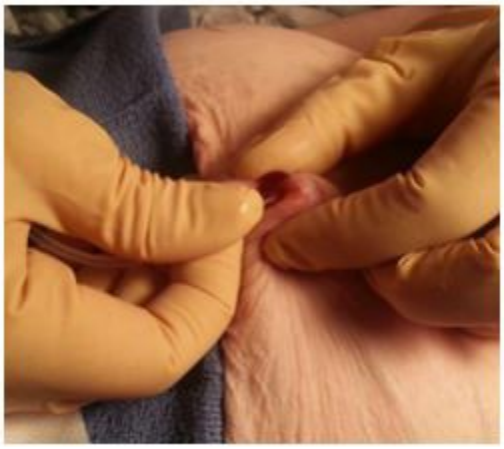

Figure 42: Successful cannulation of a discharging pore using a 30g blunt tip curved sialogram needle.

Use moistened cotton gauze to remove keratin debris from the crevices on the nipple. The pores lie in the base of these crevices. Use a bright light source to visualize the discharging pore. Repeated blotting of the surface of the nipple will help to identify the pore, as the discharged material will not cover the nipple and obscure the target opening. Take a deep breath… if you are patient, you ***can*** successfully cannulate the pore. Do not force the needle, when it is in the correct pore, it will "drop in". Grasping the nipple on the sides and gently elevating it can help straighten the lactiferous sinus and prevent the needle from "side-walling." (Figure 42)

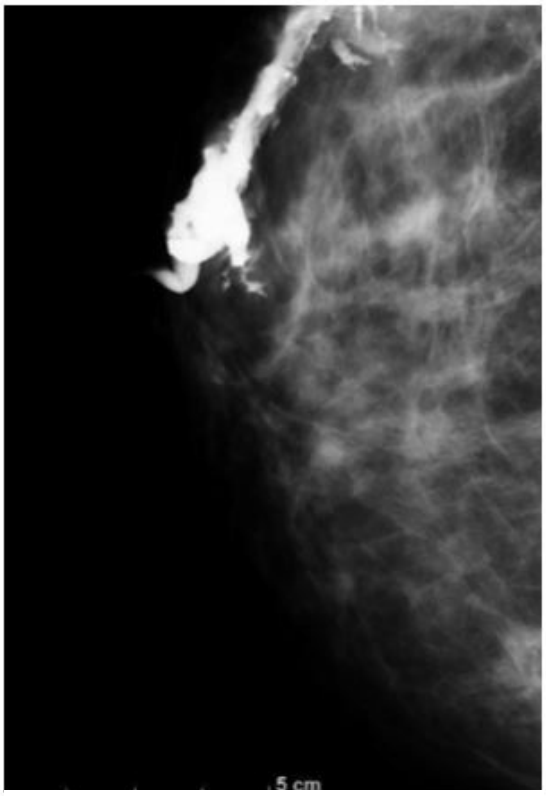

Figure 43: Multiple duct amputations, DCIS.

Ensure all bubbles are removed from the syringe and tubing prior to injection. These can create filling defects which can be difficult to differentiate from small papillomas. You should inject at least 1-2 cc of contrast before imaging. A 3cc syringe works best. It generates sufficient forward pressure. Injection with a 5cc or 10cc syringe is more difficult. Image in CC projection first, followed by ML. (Figures 43, 44)

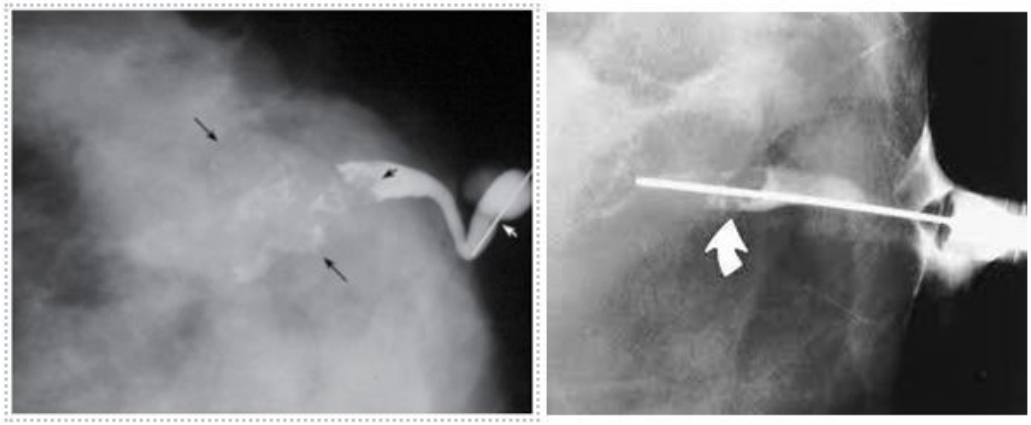

Figure 44: If you have trouble injecting, it may be because your needle is "sidewalling" or lodged in a lesion. Gently grasping the sides of the nipple and elevating can relieve resistance to flow from "sidewalling". (credit: Plastic Surgery Key online credit: RSNA pub online).

Slightly withdrawing the needle and again attempting to inject may relieve resistance to flow if the needle has impaled a lesion.

Warm tender erythematous breast

A warm tender erythematous breast can be postpartum engorgement, mastitis, abscess, or inflammatory breast cancer. Ultrasound the area of maximum fluctuance to determine if an abscess is present. (Figure 45)

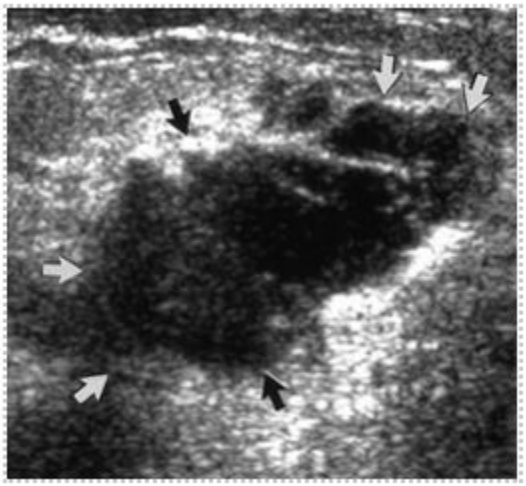

Fig 45- Ultrasound of an abscess demonstrating septations and loculations.

US-guided drainage of an abscess using a large gauge vacuum-assisted cutting needle, taking care to thoroughly interrupt all loculations under direct ultrasound visualization, can be helpful.(1,2) Installation of antibiotics may also be helpful.[3] Gram stain and culture of recovered material recommended. A recurrent abscess will likely require open I&D with healing by secondary intention. Non-lactational abscesses in diabetics and smokers are more likely to recur. Large abscesses and abscesses with significant retained fluid are also at greater risk for recurrence.

Place the patient on an antibiotic with coverage for staph and examine again in approximately ten days. Breast infections caused by community-acquired MRSA are becoming increasingly common. [4] A high index of suspicion is essential to avoid delay in the clinical response as these patients may benefit from an early change of antibiotics.

Oral anti-inflammatory medicine is useful for the control of pain. Chilled green cabbage leaves to the affected area may also provide some relief.[5,6] If there has been no improvement, a skin punch may be necessary to exclude inflammatory breast cancer.

Non-specific breast pain is usually related to unrecognized trauma (scapulothoracic bursitis) or hormonal fluctuations and can be exacerbated by caffeine intake. We usually ultrasound the breast in the region of concern and provide reassurance that breast pain not associated with warmth, erythema, or nipple changes is rarely due to cancer or infection.

Artifacts and benign findings

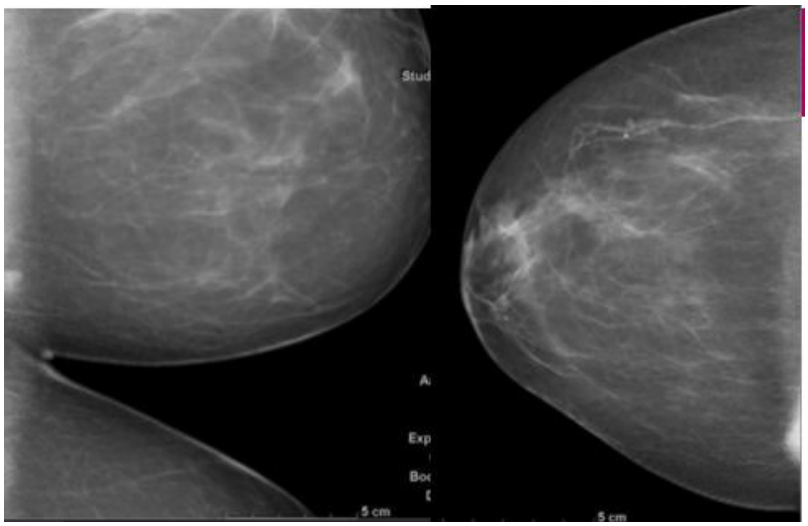

Figure 46: Sternalis muscle (rounded or triangular posterior density seen only on CC view).

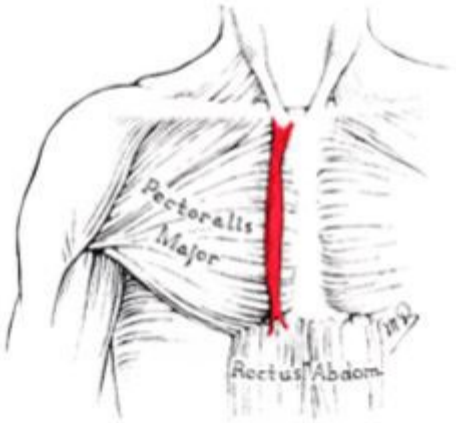

Figure 47: from Gray's Anatomy

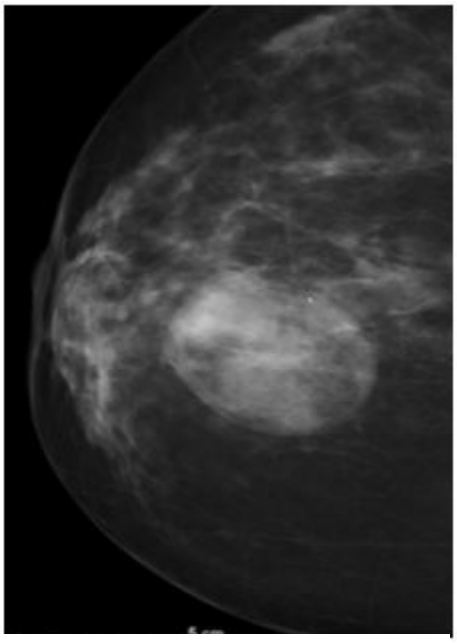

Figure 48: Fibroadenolipoma (breast hamartoma) thin capsule surrounding a sequestered focus of otherwise normal breast tissue. Breast cancer can develop in a fibroadenolipoma at baseline rate. There is no increased risk of cancer developing in a fibroadenolipoma.

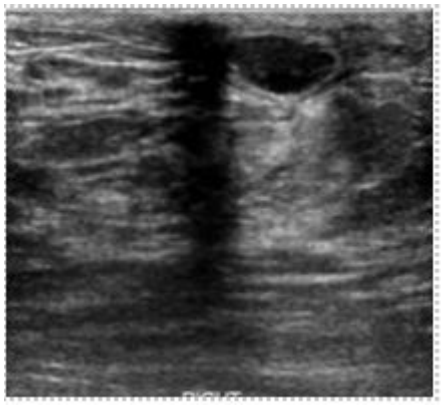

Figure 49: Epidermal inclusion cyst (uniformly hypoechoic sharply circumscribed parallel mass closely related to skin dermis on US).

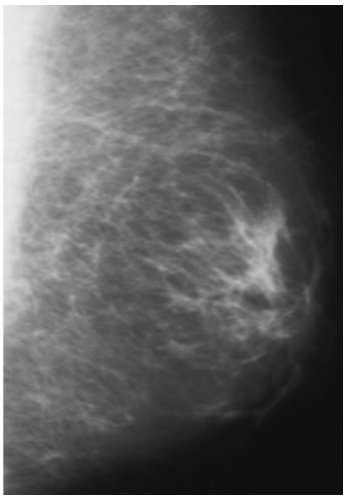

Figure 50: Typical appearance of dendritic gynecomastia in a male breast. “Flame-shaped” fibroglandular tissue in the immediate subareolar region which fades imperceptibly into normal tissue. Can present as a palpable mass, usually asymmetric. Associated with proton pump inhibitors, spironolactone, marijuana use, and other drugs.

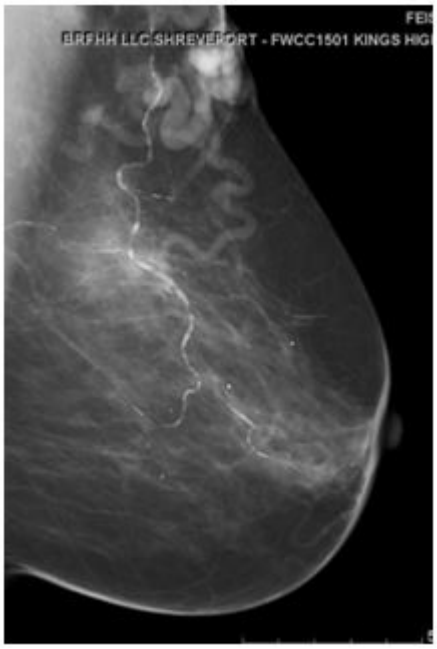

Figure 51: Dilated blood vessels due to central venous occlusion from long term hemodialysis. Atherosclerotic calcifications are not associated with breast cancer but are a marker for coronary atherosclerosis.

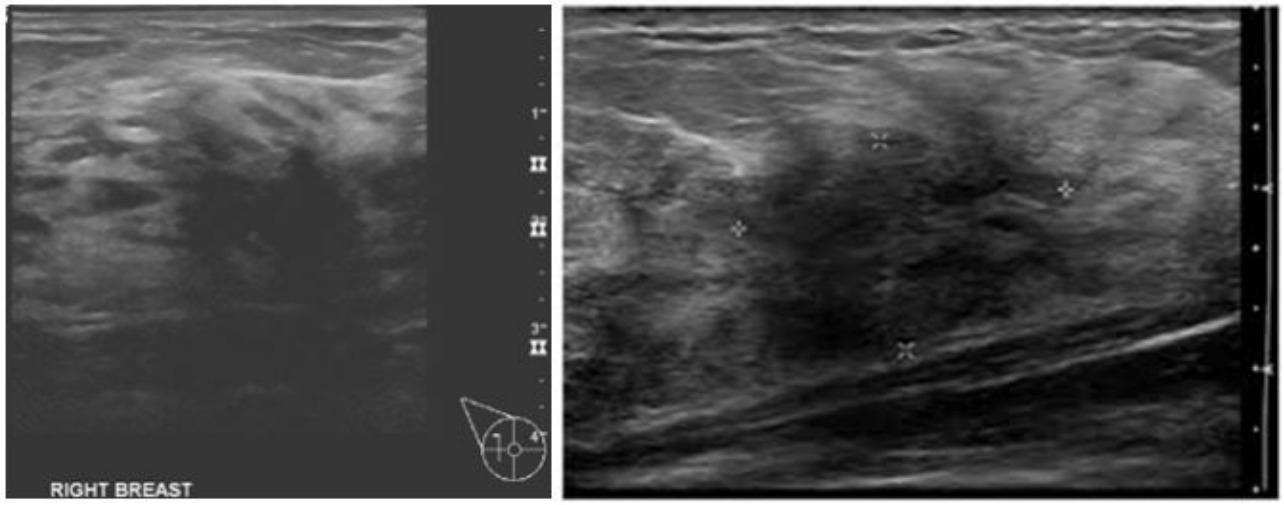

Figure 52: Diabetic mastopathy can appear mass-like. This is only seen in women with a significant history of insulin-dependent diabetes mellitus. It may require biopsy.

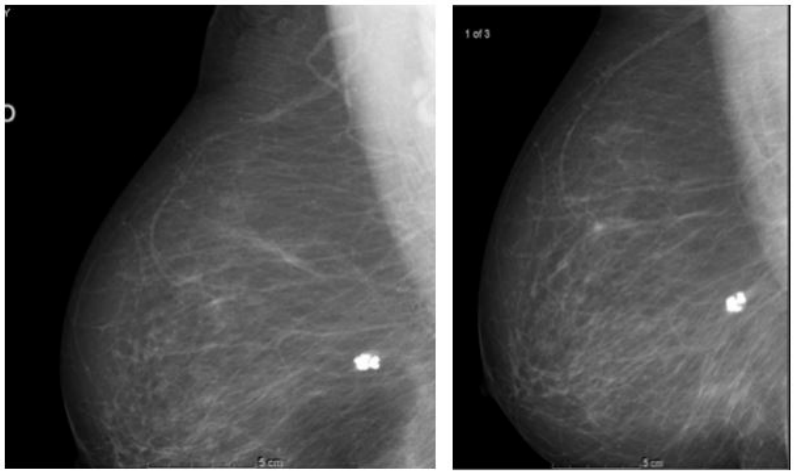

Figure 53: Deodorant artifact can simulate calcifications. Cleanse axillae and repeat images.

Ultrasound technique

The quality of images you obtain is very dependent on careful technique.

- Use a linear high frequency transducer (try your vascular probe).
- Position the patient so that her breast "flattens" out on the chest wall as much as possible. This can be challenging with the large or pendulous breast.

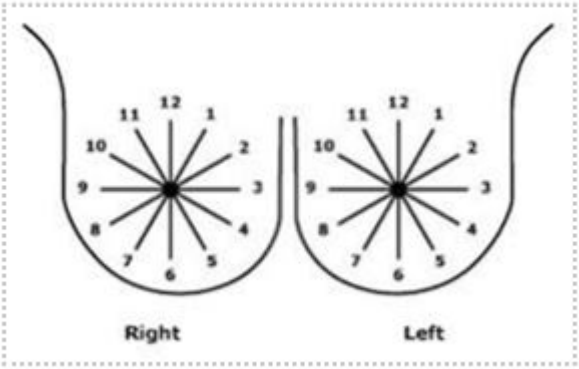

Figure 54: "clockface" system for documenting breast position.

- Carefully scan in radial fashion, starting at the nipple and scanning outward at each "hour of the clock" (Figure 54).
- Keep the transducer in orthogonal relationship to the skin as much as possible.
- When you see what you think is a mass, stop and see if you can turn the probe 90 degrees while maintaining the "mass" in your field of view. If it elongates out into a spindle shaped form, it is likely a fat lobule. If it appears to be a discrete mass in orthogonal planes, it is likely a real finding. Look for border spiculations/lobulations, dark shadowing deep to the mass, abnormal blood flow in or surrounding the mass (Figures 55 & 56)
- Findings are recorded as:
    - size of the mass
    - position in the breast tissue (anterior depth/middle depth/posterior depth)
    - echogenicity of the mass (hypoechoic/hyperechoic)
    - borders (sharply circumscribed, angular, microlobulated, spiculated)
    - posterior acoustic features
    - abnormal blood flow within or at the edges of the mass

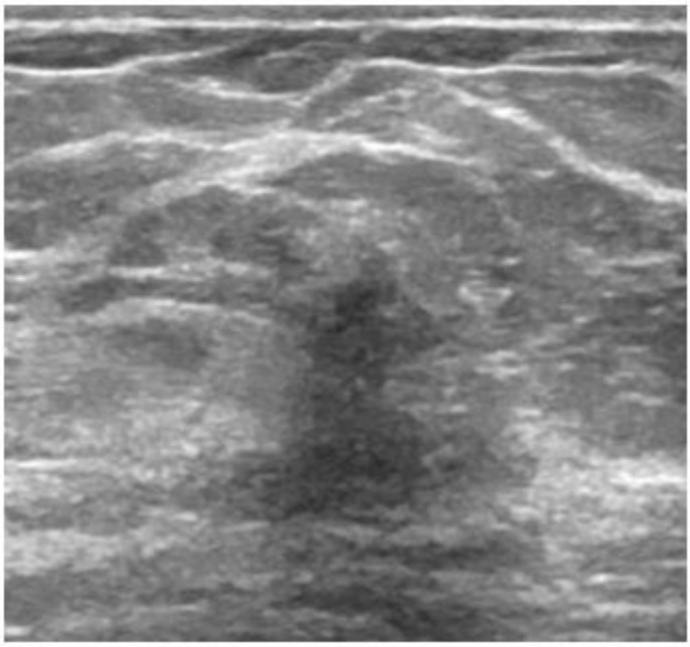

Figure 55: Insufficient pressure, margins of the mass are indistinct.

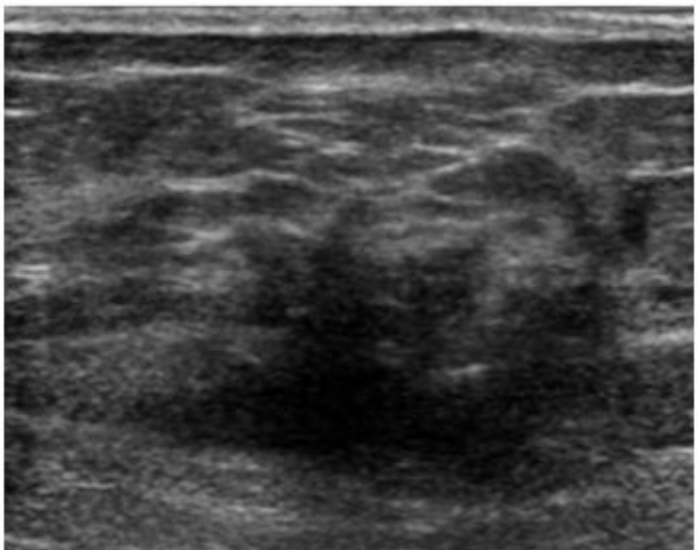

Figure 56: with sufficient pressure, margins of the mass and posterior acoustic features are better demonstrated (same mass as in Fig 55).

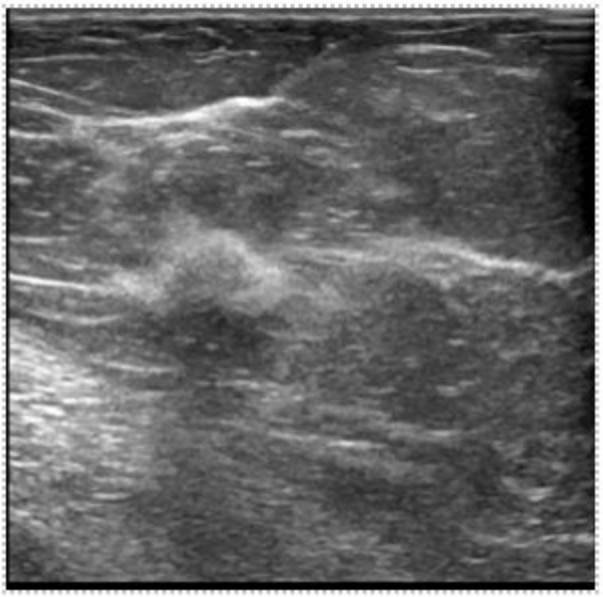

Figure 57: Insufficient pressure with US probe.

When insufficient pressure is applied the ultrasonographer may not see the mass (Figure 57 and 58)

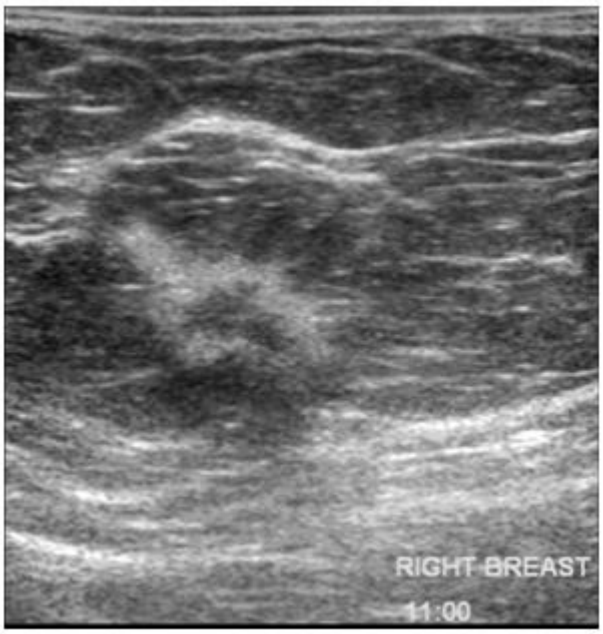

Figure 58: Adequate pressure demonstrates spiculations. (Same mass as in Fig 57).

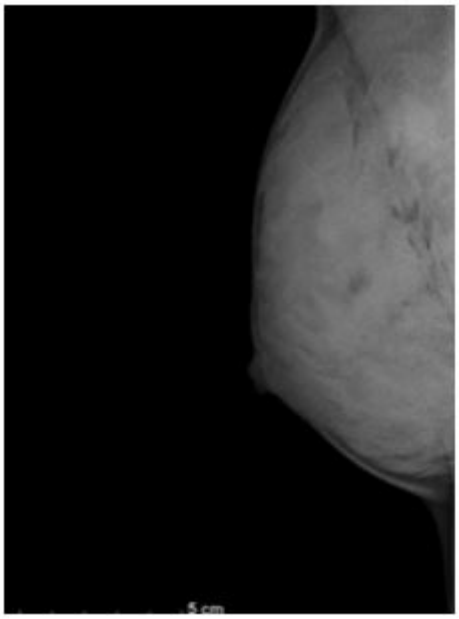

Figure 59: Extremely dense breast tissue.

Extremely dense breast tissue significantly reduces the sensitivity of mammography for the detection of early cancer (Figures 59-61).

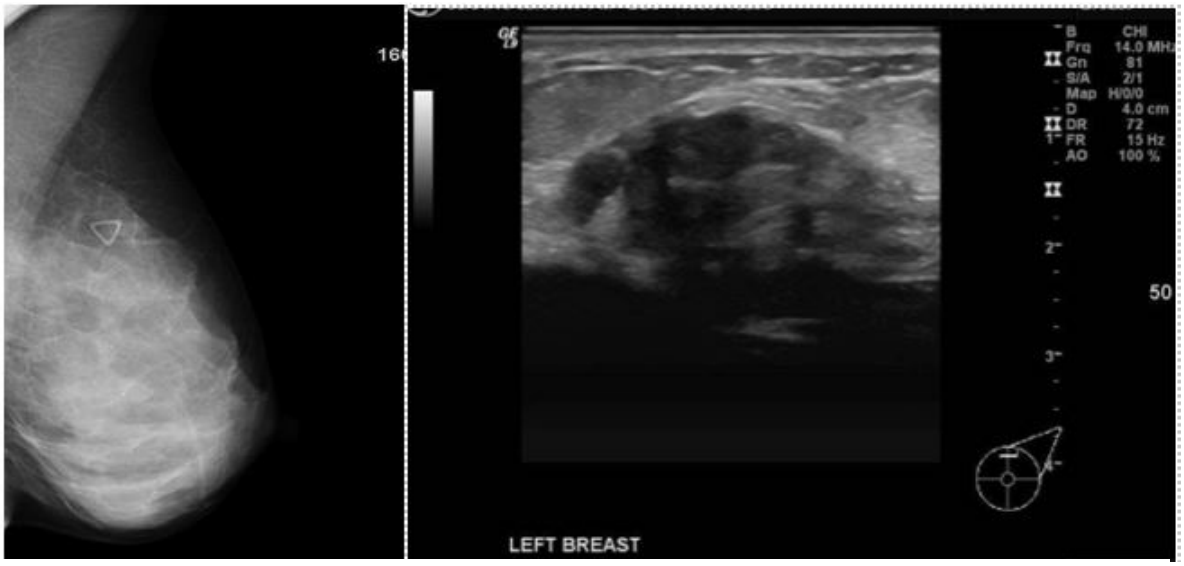

Figure 60: This mass was identified by ultrasound at the area of the palpable abnormality (marked with the triangular-shaped metallic marker on the mammogram obtained same day as ultrasound). It is completely obscured by dense breast tissue on the mammogram. Dense breast tissue obscures small masses and delays diagnosis.

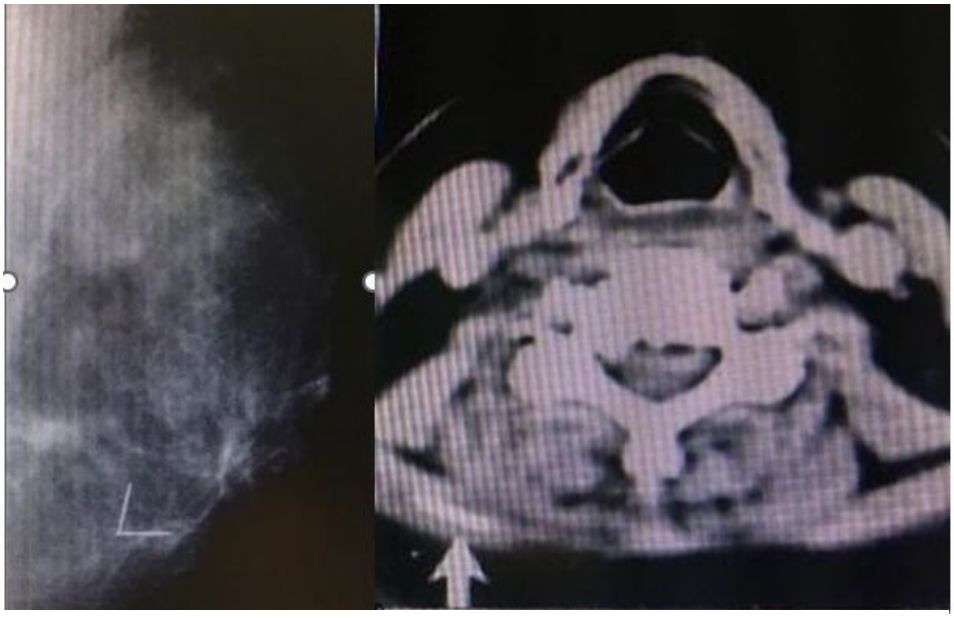

Figure 61: CAUTION: be sure to remove the entire hook wire used to localize a non-palpable lesion. If the tip is divided and retained, it can migrate, resulting in injury to other organs (e.g. pneumothorax).

References

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Chapter 10

Role of Mammography in Limited Resource Settings

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Clinical Scenario

An 81-year-old woman presents with an abnormal CT Chest, which was performed to evaluate for a parathyroid soft tissue mass. Incidentally, soft tissue masses were noted in each breast (Figure 1), for which a mammographic evaluation was recommended (Figure 2).

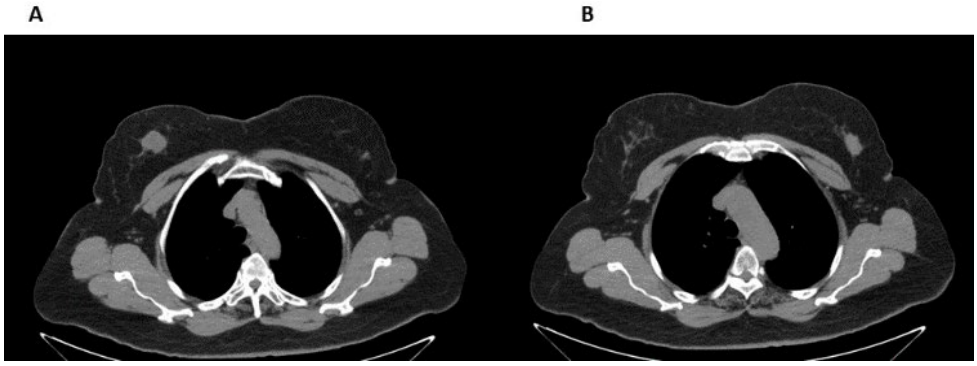

Figure 1: CT chest that was done for a parathyroid mass had discovered incidental masses on the right breast (A) and left breast (B).

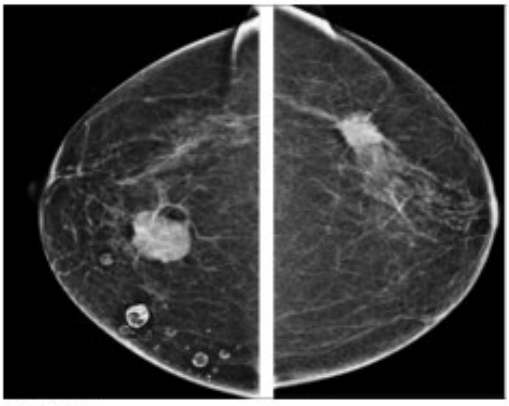

Figure 2A

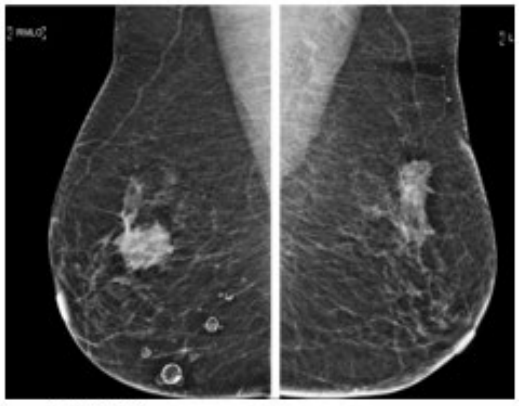

Figure 2B

Figure 2: Diagnostic Mammogram. CC views (Figure 2A) MLO views (Figure 2B). The right breast had a 3 cm oval, high-density mass with partially obscured margins in the upper inner right breast at approximately 1:00, 4.1 cm from the nipple at mid-depth. The left breast had a 2.5 cm irregular, high-density mass with spiculated margins in the upper outer quadrant of the left breast at approximately 12:30/1:00 at mid-depth, 6.6 cm from the nipple.

The patient had not been participating in routine screening mammography. The patient also had bilateral ultrasound (Figure3) and breast MRI (Figure 4). More than two million new cases of breast cancer were diagnosed worldwide in 2018 and 626,700 women died from breast cancer in 2018 (1). Breast cancer is the second most common cancer in the world. Early detection is a key component in decreasing breast cancer-related deaths. Screening mammography, through randomized clinical trials has been shown to increase early detection of breast cancer and lead to decreased breast cancer mortality (2).

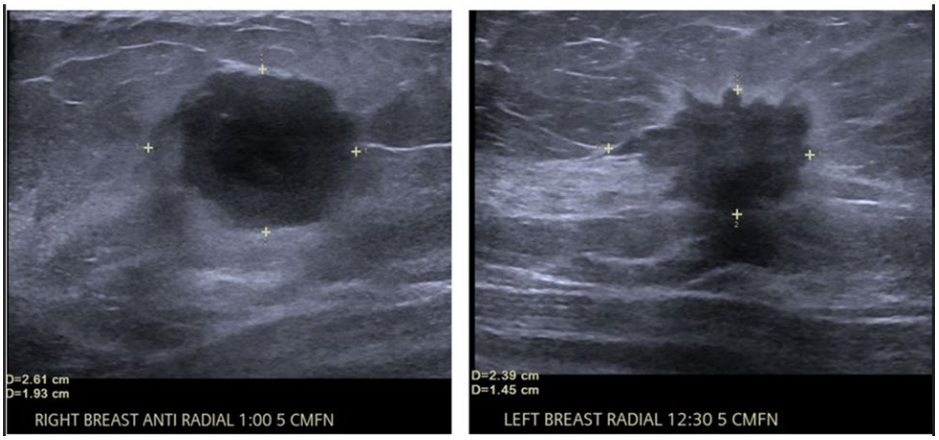

Figure 3: US on Right Breast Mass
(A) Right breast ultrasound: A 2.7 cm x 2.6 cm x 2 cm round hypoechoic mass with a few angular margins. (B) Left breast ultrasound: A 2.4 cm x 1.5 cm x 1.5 cm irregular, anti-parallel, hypoechoic mass with irregular and angular margins with the left breast at 12:30 5 cm from the nipple.

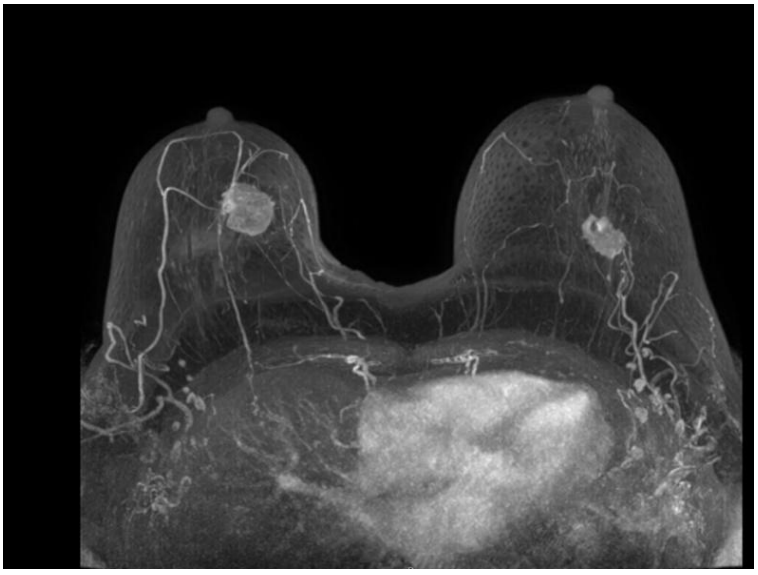

Figure 4: MRI showing bilateral breast masses.
***Breast MRI Maximum Intensity Projection:** Right breast MRI: Unifocal 3.0 cm heterogeneously enhancing mass in the upper inner right breast. Left breast MRI: Unifocal 2.5 cm irregular, heterogeneously enhancing mass in the upper outer left breast.*

Tabar et al. demonstrated a 47% greater reduction in risk of death in those screened with mammography compared to those

who were not screened (2). Data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program (SEER) demonstrates a 43% decrease in breast cancer deaths since the 1980s when regular mammography screening programs began (3). Screening mammography is an important tool in decreasing breast cancer mortality when utilized. However, late-stage breast cancer is still a common occurrence, especially in limited-resource settings where mammography equipment is not widely available.

Breast cancer incidence is increasing worldwide, and lower-income countries are experiencing more breast cancer-related deaths. Asia, Africa, and Latin America are among the countries with the largest breast cancer mortality rates (4). Increasing rates of breast cancer are thought to be due to changes in lifestyle as well as genetic and biological factors that differ among groups. Breast cancer risk factors include increasing age, a significant family history,

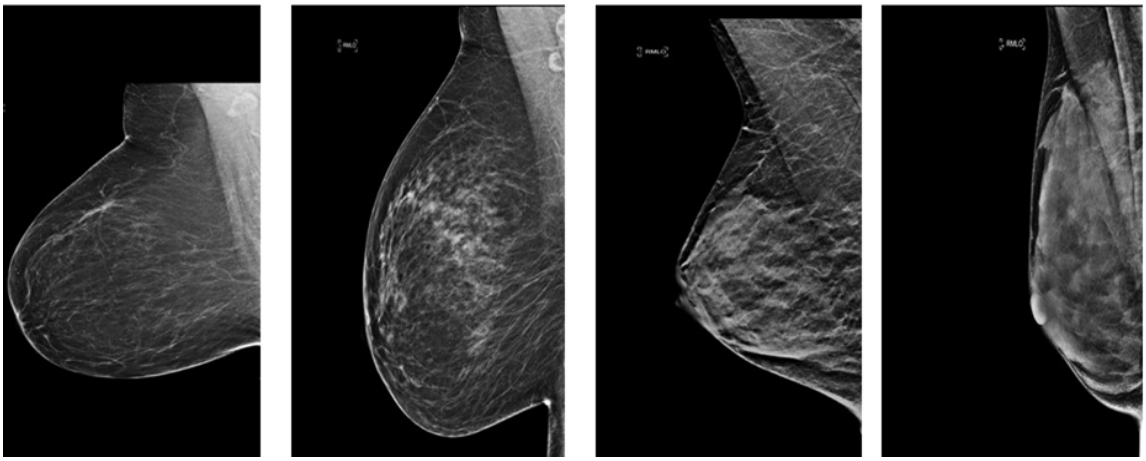

Figure 5: Mammogram showing increasing density from left to right.
Breast Densities by the Breast Imaging Reporting and Data System (BIRADS Classification)
A: The breasts are almost entirely fatty.
B: There are scattered areas of fibroglandular density.
C: The breasts are heterogeneously dense, which may obscure small masses.
D: The breasts are extremely dense, which may lower the sensitivity of mammography.
Breast cancer risk increases as the density increases. The masking effect of the dense white tissue also causes the mammogram to be less sensitive as density increases as cancers are white.

genetic mutations, hormonal stimulation, late reproduction after age 30 or nulliparity, and increasing mammographic breast density (Figure 5).

Mammography uses low-energy X-rays to evaluate the breast for screening and diagnosis. Early detection of breast cancer is the objective of mammography. Breast cancer can present as a mass, an asymmetry, architectural distortion, or microcalcifications. (Figures 6-9)

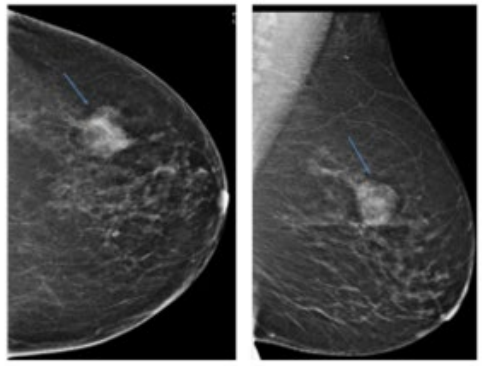

Figure 6

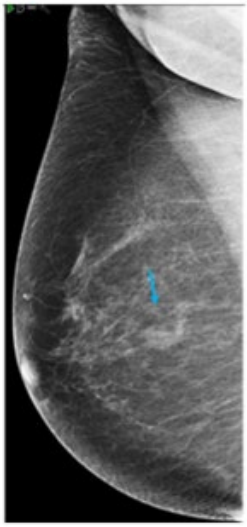

Figure 7

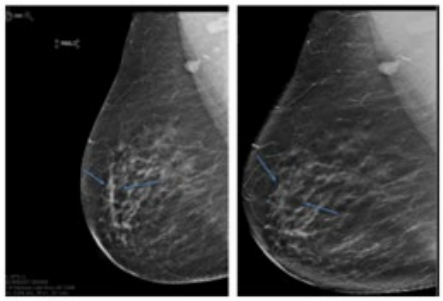

Figure 8

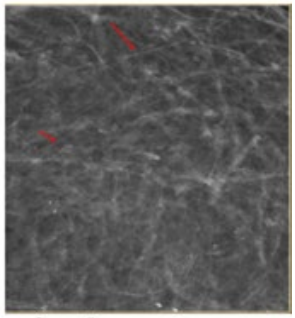

Figure 9

Figure 6-9: Mammograms demonstrating a mass (6), an asymmetry (7), an architectural distortion (8), and suspicious microcalcifications (9)

What is the difference between a screening mammography program and a diagnostic mammography program? Screening mammography programs focus on asymptomatic women. Women present for health screenings at defined intervals with the goal of detecting breast cancer at the earliest stage possible. Two standard views of each breast, a mediolateral oblique (MLO) and a craniocaudal view (CC), are performed (Figure 10,11).

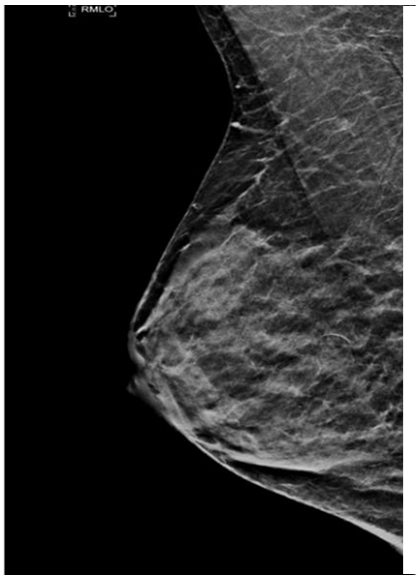

Figure 10: MLO Mammographic View of Right Breast

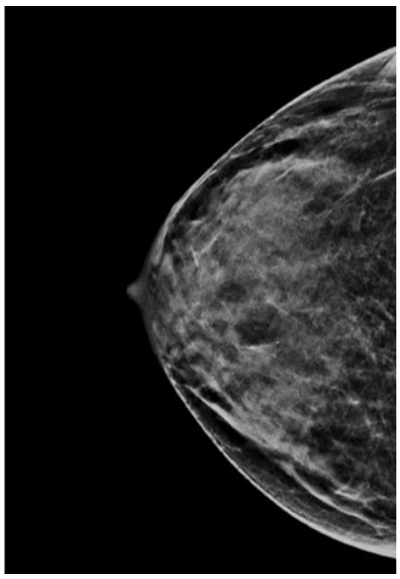

Figure 11: Right CC View of Mammogram

A diagnostic mammography program focuses on symptomatic patients with palpable lumps, skin changes, pain, and pathologic nipple discharge. Each breast's initial MLO and CC views are performed as in the screening regimen. Still, additional images are performed in the same visit if needed for a diagnostic evaluation. Diagnostic patients are evaluated to find the source of their complaints. If cancer is found, further treatment can be initiated.

Mammography practices vary around the world. Screening mammography programs require a significant commitment from communities, and some communities are not equipped to adequately provide mammography for their population. Well-resourced settings have sufficient mammography equipment, highly trained personnel, biopsy capabilities, surgical capabilities, adequate treatment protocols, research programs, and proper follow-up.

The World Health Organization (WHO) recommends organized population-based mammography screening programs for well-resourced settings. The recommendation is screening mammography for women 50-69 every two years. Mammography screening for women 40-49 and 70-75 in well-resourced settings is only recommended by WHO in the setting of rigorous research, monitoring, and evaluation (5).

The recommendations for screening mammography in well-resourced settings is very controversial in the United States. The American College of Radiology, the Society of Breast Imaging, the American Society of Breast Surgeons, and the National Comprehensive Cancer Network recommend that average-risk women begin annual mammography screening at age 40 years (7). The American Cancer Society (ACS) recommends that average-risk women have the choice to start annual screening with mammography at age 40 if they wish to do so. It also recommends annual mammography screening for average-risk women from 45-54 years and biennial screening for women 55 and older. The ACS supports the continuation of mammography screening as long as a woman is in good health and is expected to live ten more years or longer (1). The United States Preventive Services Task Force (USPSTF) recommends biennial screening mammography for women 50-74 years. The USPSTF states that a decision to start before the age of 50 years should be an individual one (8).

Limited resource settings face very different challenges compared to well-resourced settings. There are very few mammography guidelines for limited resource environments. WHO recommends organized population-based mammography screening programs for women 50-69 years every two years for limited resource settings with relatively strong health systems. WHO recommends against mammography screening for women 40-49 years of age and 70-75 years of age in this limited resource setting, whether a strong health system exists or not (5).

A strong health system is defined as one with financial resources to sustain a screening program. The program must assure diagnosis and treatment, have appropriate equipment, infrastructure, an appropriately trained workforce, quality assurance, and a monitoring process. There must also be appropriate communication. In the United States, these conditions are mandated by law.

The Mammography Quality Standards Act (MQSA), enacted by Congress on October 1, 1994, requires all sites performing mammography in the United States to assure timely diagnosis and treatment, have appropriate high-functioning equipment, a well-developed infrastructure, a trained workforce committed to lifelong learning and maintenance of certifications, quality assurance, and a monitoring process. MQSA continues to evolve and is enforced by the United States Food and Drug Administration with annual inspections.

WHO recognizes that organized population-based mammography screening programs may not be cost-effective nor possible in limited resource settings with weak health systems (5). Therefore, the focus in these populations should be early diagnosis of breast cancer in symptomatic women with prompt treatment. A clinical breast exam is an important initial screening method in low-resource communities. Clinical breast exam has not been proven to have a mortality benefit. However, it does find tumors at an earlier stage. A diagnostic mammography program is likely more effective than a screening program in this setting if mammography units are available.

Breast cancer rates continue to increase in low-resource settings secondary to lifestyle changes. In 2018, there were only 55 mammogram machines in Peru's Public hospitals, and only four were located in rural areas. 305,229 women were older than 50 years old in Peru during this time (9). The demand for mammography exceeded the supply of equipment. High mortality rates in low-resource settings are, in part, secondary to a lack of mammography access and a lack of breast cancer education. The lack of access to screening mammography and poor education lead to a late stage in diagnosis.

The five-year breast cancer survival rate in India is 52%, 46% in Uganda, and 12% in The Gambai. Tumor sizes are routinely 4-6 cm when discovered in the Middle East, Africa, and India (9). Fifty percent of breast cancers in Egypt are discovered when larger than 4-5 cm. Fifty-seven percent of women in Peru are diagnosed with breast cancer at stage three or four (9). In contrast, most cancers in the United States are discovered at less than 1 cm.

Common themes in low-resourced settings are poor program infrastructure, low capacity, and no national or regional data collection. Low-resource settings often do not have appropriate equipment, appropriate staffing, appropriate training, or accreditation. Lack of community awareness that breast cancer is treatable is also one of the major challenges for low-resource settings (11). Many low-resource communities believe cancer is a death sentence and cannot be treated. Proper education of these communities is a necessity to encourage self-evaluation and to seek and undergo treatment when a breast problem is discovered.

The Breast Health Global Initiative (BHGI) summits in 2002, 2005, 2007, and 2010 addressed breast cancer mortality disparities in low-resource settings. Resource-sensitive guidelines were discussed at these summits. The consensus conference included 150 experts from 43 countries and six continents.

Several implementation strategies were recommended. First is the formation of a data collection system or process that will assess the breast cancer burden in the community. Data, including stage and tumor size, should be collected. Monitoring of survival by stage should be performed and recorded regularly, as well as constant monitoring of the quality of treatment.

Second is the implementation of program organization. Interdisciplinary coordination of care is crucial to define a standard for the country. Outreach into rural and surrounding areas is

another important step. Patients in low-resource settings have been reported not to see screening as a priority. Breast cancer survivor groups are necessary for the emotional support of newly diagnosed patients. Survivors are also important to the outreach effort as they are able to communicate more effectively the positive effect of early detection.

Training is the next key step in optimizing mammography in limited resource settings. Healthcare systems must decide how the training will occur with physicians and non-physician staff, onsite or off-site, with each having advantages and disadvantages. This requires government financial support and focus (11).

Diagnosis and Diagnostic Mammography

Most low resourced communities do not have the infrastructure for mammography screening. Therefore, clinical breast exams should be highly promoted and utilized. A diagnostic mammography program rather than a screening program may be helpful in this setting if there are a limited number of mammogram machines.

The Breast Health Global Initiative Summit in 2007 focused on areas of prevention, early detection, diagnosis, and treatment in an effort to improve breast cancer mortality in low resource settings. In these settings, diagnostic mammography is helpful but not mandatory. Ultrasound is often the initial first imaging step in diagnosis after obtaining a detailed patient history (11). Prior to imaging with ultrasound, a focused clinical breast exam is performed. In a higher resource area, diagnostic mammography would precede ultrasound. However, in these low-resource settings, an ultrasound with fine needle biopsy, if a mass is detected, might be an appropriate first step (Figure 12 Ultrasound with Cancer).

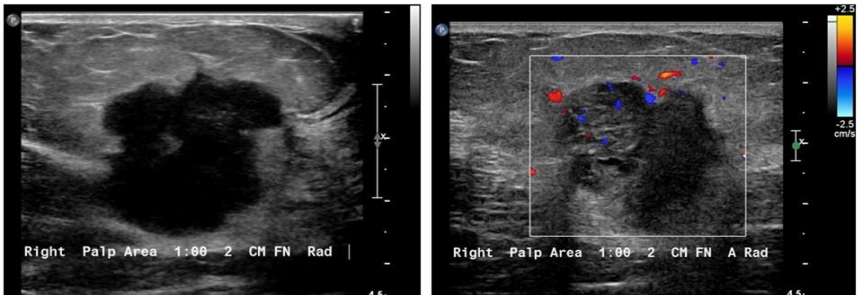

Figure 12: US of Right breast with Doppler of Cancer. Breast ultrasound images revealing an irregular, anti-parallel, hypoechoic mass with angular margins and internal vascularity—biopsy-proven invasive ductal carcinoma

In many low-resource settings, mammography is unavailable, and breast self-examination (BSE) has not proven very effective. However, clinical breast exams (CBE) through randomized trials has been shown to help discover cancers at an earlier stage. Specifically, a trial in Mumbai, India, which studied screening for cervical and breast cancers, showed that CBE was effective (13).

In the Mumbai study, breast cancer screening was performed by CBE. Women in the community with a 10th-grade education were trained for four weeks to perform CBE. Standard health education was given by women with a graduate degree in social work who were also trained over four weeks. There were significant differences found between the ever-screened group and the never-screened group. These differences included age, education, occupation, income, language, previous history of consultation for breast-related complaints, and family history of breast cancer. Rates for CBE positivity were 0.46%, 0.77%, and 0.94% for the first three rounds, respectively. Rates of compliance for diagnostic confirmation if a CBE was positive were shown to increase with subsequent rounds 68%, 70.60%, and 78.06% for the first three rounds. The average age of breast cancer diagnosis utilizing the CBE screening method was 49.80 years. 125 breast cancers were recorded in the study; 32 breast cancers were found in the first round, 24 in the second round, and 25 in the third round. There were 22 deaths that resulted from the CBE discovered breast cancers (13). In this study, 35% of the patients

presenting for screening were illiterate and were educated on screening for the first time. This study again reiterates the need for breast education in these communities as part of the strategy to reduce breast cancer mortality.

A study in the Philippines used a survey to evaluate the knowledge and practices of breast cancer screening in the population (14). Breast self-examination (BSE), clinical breast examination (CBE), and screening mammography knowledge were surveyed among the population. 1043 women were hosted in the program. 979 met eligibility, and 944 women completed the survey. 51% of the population had heard of BSE, according to the survey. However, only 33% had heard of CBE, and 29 % had heard of mammography. 80% of the population studied had not ever had a CBE. Only 8% had ever had a mammogram, and most had the mammogram three or more years prior. Breast cancer education must be a priority in low-resource settings.

A level of mammography awareness was studied in Ibadan, South-West Nigeria. 818 randomly selected Nigerian women were included in a hospital-based study. Only five percent of these women had heard of mammography (15). Female doctors' attitudes and practices in screening mammography were studied in Sana'a, Yemen. One hundred five female physicians were included in a survey. 36.6% did not refer asymptomatic patients for screening mammography due to high cost, unavailable instrumentation, high risk of radiation, or availability of other methods. 26.9% referred patients consistently for annual mammography screening if the patient had a family history or personal history of breast cancer. 24.7% referred patients for screening mammography annually. Seventy-seven physicians did say that they would refer patients for screening mammography if they requested the exam. The major limitation for screening mammography referral in this study was related to the high exam cost (16).

In sub-Saharan Africa, healthcare resources are primarily devoted to HIV/AIDS, tuberculosis, and malaria. This leaves very little for breast cancer education, detection, and treatment. Breast cancer is the highest female cancer in this population, and globally the mortality rates are the highest from this cancer in this group. Studies are ongoing in Africa to use ultrasound for screening (17).

Costs of breast imaging equipment continue to increase and are a major barrier. Ultrasound imaging equipment is significantly less expensive compared to mammography units. A typical ultrasound unit is approximately 100,000-150,000 U.S. dollars. A mammography unit is approximately 350,000-450,000 U.S. dollars.

Conclusions

Breast cancer incidence and breast cancer mortality in low-resourced settings continue to increase. Increased breast cancer education in these settings is crucial in reducing late-stage disease. Access to mammography remains limited in these populations. Therefore, other tools must be utilized. Clinical breast examination and breast ultrasound with fine needle biopsy may be the best solutions when diagnostic mammography is not an option. In order for the education efforts to make an impact, communities must be willing to provide time, money, and resources.

Clinical Scenario Conclusion

An ultrasound-guided core biopsy was performed for the hypoechoic masses in each breast. The right breast mass revealed an invasive mammary carcinoma with prominent basal-like features and extensive necrosis, Nottingham grade 3 with associated ductal carcinoma in situ, nuclear grade 3, solid pattern with comedo necrosis. Perineural invasion and

lymphovascular invasion were noted. One lymph node was negative for metastatic carcinoma. The left breast mass revealed invasive ductal carcinoma, Nottingham grade 2, with associated ductal carcinoma in situ. Perineural invasion and lymphovascular invasion were noted. Metastatic carcinoma is present in one of thirteen lymph nodes.

Key Points

- Screening mammography should be performed to identify cancers at an earlier stage and grade.
- When screening mammography is not an option, diagnostic mammography should be considered to direct further patient management and care.
- If diagnostic mammography is not available, breast ultrasound and clinical breast exam should be considered
- In high-resourced settings, breast MRI can further direct surgical management in patients with newly diagnosed breast cancers.

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Chapter 11

Breast Biopsy Techniques

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Case Scenario

45 y/o female presents with a palpable right breast mass for several months. She has no risk factors. Mammography shows asymmetric parenchymal distortion, and U/S shows a well-circumscribed 4 cm mass.

Introduction

Breast cancer is a disease of global concern, regardless of economic status. There is, therefore, a need to address the diagnosis and treatment of breast cancer in countries with varying healthcare resources and capabilities. By virtue of asset limitations in low- to middle-income countries (LMICs), clinicians are restricted in their diagnostic and therapeutic approaches. They may not be able to offer treatments that are commonplace and conventional in high-income countries (HICs). Nonetheless, it is essential that women with breast cancer, even

in LMICs, receive appropriate care. The challenge is finding the balance between cost and efficacy of care in this setting.

Unlike HICs, where screening mammography is widely adopted, it is not routinely performed in less affluent countries. While continued improvement in technology has been seen in HICs in the past two decades, with the adoption of 3D tomo-mammography overriding digital mammography in many centers [1], screening programs are rudimentary in LMICs. This has naturally led to different clinical presentations of breast cancer in these countries. In countries without organized screening programs, the majority of women present with palpable breast cancers. [2] In contrast, women in HICs present with image-detected lesions. Hence, clinical strategies for diagnosis and treatment necessarily differ.

Where image-detected breast lesions are commonplace, as in communities with mammographic screening, there is an opportunity for a non-interventional approach using short-interval monitoring. This is a reasonable management strategy for mammographically low-risk non-palpable lesions. In contrast, where screening is not readily available, women present with symptomatic lesions, the most common of which is a palpable breast lump. Population screening is associated with a survival benefit of 40%. [1] It follows, therefore, that a lesion large enough to be palpable, if malignant, would bear a 40% poorer survival for the patient. The diagnostic process, hence, should be escalated, and additional information may be reasonably attained through the use of the "triple test" assessment: abnormal exam, abnormal imaging, and abnormal pathology. In the diagnostic management of breast lesions, when all three are concordant, the accuracy of diagnosis for breast lesions is reliable and optimal.

Thus, the contemporary universal principle of minimally invasive breast biopsy (MIBB) for preoperative percutaneous diagnosis can still be achieved in a reliable, expeditious, and cost-effective manner in LMICs. This may require the regular use of techniques that have fallen out of favor in HICs for various reasons. Prior to a surgical biopsy, fine needle aspiration cytological biopsy (FNAC) and core needle biopsy (CNB), relatively inexpensive diagnostic procedures, may be employed routinely. More expensive instruments that offer greater accuracy, like vacuum-assisted breast biopsy techniques, may or may not be available when there are cost constraints. Prudent use of resources entails a 'pyramid' approach, where the great majority of diagnostic procedures applied are the least expensive, with careful triage and selection of cases that require procedures of incremental cost. This necessarily takes into account the potential for harm at each level of the diagnostic process as well.

Despite the availability of a complete range of percutaneous biopsy devices, there might still be a need for surgical biopsies, particularly when the position of the lesion is not amenable to image-guided biopsy or where there is radiologic-pathologic discordance. In such cases, one may perform an excisional biopsy or empirical lumpectomy with clear margins. The latter can be performed if ductal carcinoma in situ (DCIS) or cancer is suspected, with the objective of avoiding the cost of a second operation. A diagnostic excision biopsy should be performed only if percutaneous means have been exhausted, as the majority of biopsies will yield benign histology. For example, in the United States of America (USA), just over 2 million breast biopsies are performed yearly to diagnose 240,000 cancers. In contrast, in some large prospective series in Europe, 95% of all breast lesions biopsied are benign.[3] The cost to sustain such a volume of diagnostic procedures can be considerable. In the setting of LMICs, a reappraisal of

the triple test can optimize conservative care, control costs, and rely on surgical biopsy only when rarely warranted.

Percutaneous Breast Biopsy

The use of percutaneous breast biopsies for diagnostic purposes in favor of open surgical procedures is well established. [4] It allows better surgical planning and a reduction in the need for multiple surgical episodes for cost-effective treatment. This principle should be upheld as much as possible, even in cost constraints. The frequent use of FNAC as a first diagnostic procedure, followed by a core biopsy where necessary, would be consistent with this philosophy. Where possible, image guidance for these biopsies would be ideal. However, trained clinicians may perform these percutaneous biopsies with the help of clinical and tactile cues to achieve a reliably accurate diagnosis. Employing imaging-directed vacuum-assisted instruments, which may be routine in referral centers, may be a luxury and impractical where cost is an issue. The ensuing discussion keeps these tenets in mind.

Fine needle aspiration cytology (FNAC)

When applied appropriately, FNAC is an extremely useful diagnostic procedure.

FNAC for palpable breast lesions is most efficacious when performed in a multidisciplinary team. Clinicians working with trained cytopathologists can produce sensitivity levels of 99.7%, with associated low false negative rates. [2,6] These high accuracy rates allow the establishment of same-day tissue diagnosis within multidisciplinary breast clinics. Cytopathologists collaborate closely with clinicians to offer ‘on the spot’ interpretation of the adequacy of smears and cytological diagnosis. Such a workflow, as organized by the authors (ESL & SM) in a high-volume academic center, may be easily replicated in low-middle-

income countries where women must travel significant distances for medical care. [2] The minimal turnover time may be advantageous for triaging treatment. In the context of a concordant triple test for a palpable lesion based on clinical examination, imaging findings, and adequate cytology, benign lesions may be managed conservatively with follow-up. Where inconclusive or discordant, further testing with core biopsy is indicated. When all the elements of the triple test indicate malignancy, treatment decisions may be expedited depending on the circumstances of tumor presentation and resource availability.

Although FNAC, as a component of the triple test, is an accurate and cost-effective means of cytological diagnosis for palpable lesions, its use was much more prevalent in the US and Europe previously and has been increasingly replaced by CNB over the past few decades. [4,9] There may be several reasons for this. With the advent of screening, a higher proportion of women now present with image-detected, non-palpable lesions. This required the expertise of the radiologist for image-guided biopsy. In the case of calcifications, stereotactic-guided FNAC was associated with poor yield and unacceptable false negative results and served as the driving force for the development of larger core percutaneous needles. Once available, its use could be extrapolated to palpable lesions. Despite the fact that FNAC has been reported to have similar sensitivity (97% vs. 97%), specificity (94% vs. 96%), diagnostic accuracy (95% vs. 96%), and negative predictive value (98% vs. 96%) as core biopsy, with lower complications, [6] it seems to have been superseded by the latter. [9] It is likely that with the introduction of core biopsy for palpable lesions, there was little impetus for the clinician to be well trained in the use of FNAC, nor for cytopathologists to develop confidence in interpreting smears. Since the technique is an important component of the adequacy of cytological yield, this diminution of skill may have led to poorer quality smears and hence lower accuracy rates, leading to a vicious cycle of decreased

use and perhaps abandonment. There may be a case for revisiting the diminished use of FNAC and perhaps reviving its routine use, especially for palpable breast lesions, in light of increasing concerns about cost containment in the USA and other high-income countries. [4] Appropriate selection of patients for FNAC can yield significant cost savings and may be an advantageous approach not only for LMICs but for HICs as well.

While FNAC has the advantages of lower cost and rapid turnover, cytology is limited in its ability to confirm invasive disease. Therefore, when malignancy is diagnosed, a follow-up core biopsy may be indicated. This is especially true for women who elect to undergo mastectomy directly or for whom neoadjuvant chemotherapy is planned. Not only does the additional test differentiate invasive disease from DCIS, but it also affords immunohistochemistry (IHC) assessment, as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) status are predicated on the presence or absence of documented invasion and the ability to identify them in the invasive component.

Axillary status is an important prognostic factor, and its preoperative assessment should necessarily form part of the initial diagnostic work-up. FNAC would be the ideal approach for the evaluation of palpable lymphadenopathy. For impalpable suspicious lymph nodes, FNAC can be performed under ultrasound guidance where available. When malignant cells are detected in the cytological examination of the lymph nodes in patients with breast malignancies, invasion is assumed, and treatment planning may commence. Should IHC be required for this purpose, it may be possible to obtain a generous amount of cellular material through FNAC (see Section 4), which, if handled appropriately, can provide an adequate interpretation of ER/PR and Her-2 status of the invasive component. This technique would be useful if core biopsy facilities are not accessible.

Diagnostic techniques which routinely employ cytology require the presence of a trained cytopathologist on-site. This requirement has not prevented reports of high accuracy rates with FNAC in a low-middle-income country, indicating that good diagnostic outcomes are possible under such circumstances. [5, 6] As long as the treating team recognizes the need to integrate clinical information in the form of a triple test, FNAC can offer a cost-effective, expeditious, and accurate method of diagnosis.

Core needle biopsy (CNB)

The higher proportion of women presenting with image-detected lesions and the need for preoperative assessment of invasive disease likely served as the impetus for the increased use of CNB in HICs with organized breast screening programs. The larger needles, in comparison with FNAC, can obtain tissue samples with parenchymal elements rather than cellular preparations, which are submitted for standard histological processing. Paraffin processing, unlike FNAC, cannot be performed within the same day, and turnover is longer. However, it has the advantage of being able to distinguish invasive from non-invasive disease and provide ER, PR, and HER-2 status using the same tissue cores sent for diagnosis.

Due to the larger dimension of the core biopsy needles, the procedure is performed under local anesthesia, and a small incision is required. Multiple passes are necessary, coupled with a rapid-fire mechanism, which may be uncomfortable for the patient. In addition, there is a higher incidence of complications like hematoma formation post-procedure in comparison with FNAC. Due to the construction of these needles, early versions had difficulty penetrating schirrous tumors, precluding adequate tissue yield. Later versions incorporated features that overcame these issues. Even so, all forms of CNB, like FNAC, may be subject to sampling error.

Although CNB was developed for handling screen-detected lesions and hence image-guided procedures, CNB may also be used for palpable lesions. Due to the device mechanism, if performed without image guidance and limited experience, the needle tip, when deployed through the rapid-fire sequence, can result in inadvertent trauma to surrounding thoracic structures resulting in serious complications requiring costly treatment. Once again, there needs to be a balance between the additional information that CNB provides, the availability of ancillary services for image guidance as a safety measure and the increased cost that these diagnostic modalities would entail.

Despite the acquisition of larger tissue samples, false negative results of 3-7% have been reported with CNB. In addition, lesions such as atypical ductal hyperplasia (ADH) and DCIS may be upstaged on excision biopsy. [7] CNB may be used as a confirmatory test in low-middle-income countries when cytology results are inconclusive or inadequate. Furthermore, it may be performed on cytologically proven malignancies when either mastectomy or neoadjuvant chemotherapy is planned. If cytology were reported as a carcinoma for a palpable lesion which is amenable to breast-conserving surgery based on tumor-to-breast volume ratio, it would be reasonable to proceed with lumpectomy and sentinel lymph node biopsy (BCS) rather than perform an additional CNB. This may be a cost-effective approach since palpable DCIS is a risk factor for invasion and possible sentinel node metastasis.

The components of the triple test apply to the use of CNB as well as FNAC. Concordant findings with CNB harbor a low risk of false negatives, and patients with such findings can undergo interval follow-up with imaging and clinical review. This approach does allow considerable cost savings for the patients who are true negatives in low-middle income countries.

Vacuum-assisted Breast Biopsy Devices

While CNB was an improvement in tissue acquisition over FNAC, the multiple passes required to achieve adequate samples were an unsatisfactory element in the process. To surmount this, vacuum-assisted breast biopsy devices were developed, which allowed multiple tissue cores to be removed under direct visualization with a single pass. For smaller lesions, a minimally invasive, percutaneous excision can be performed. Conceptually attractive, it can reduce false negative results to a minimum, but it is still unable to eliminate the underestimation of high-risk benign lesions. [8] Notwithstanding, there may be cost advantages in using this device to excise small lesions for a definitive diagnosis. Since it has excisional capabilities that address the issue of discordance for small lesions (<5 mm) with an eventual benign diagnosis, [9] it reduces the need for excisional biopsy and follow-up. The challenge is to achieve financial equipoise in terms of the cost of investment for the equipment and optimum care for the patient with indeterminate image-detected lesions for which percutaneous excision is possible.

Surgical biopsy

Although, from a pathology standpoint, a surgical biopsy provides the best material for a complete evaluation, it is neither the most cost-effective nor clinically expedient approach to adopt on a wide scale. Among the diagnostic biopsy modalities mentioned, FNAC, CNB, and surgical biopsy, it is the general consensus that surgical biopsy should be seldom utilized. The financial burden of a surgical biopsy is significant. It would expose most women to unwarranted harm since the majority of palpable lesions are benign and do not require surgical excision. Many are self-limiting and often resolve with time.

Moreover, current management of locally advanced breast cancers offers the option of pre-operative chemotherapy or estrogen ablation undertaken with the tumor in situ. A favorable

clinical response with tumor downstaging in this setting may reduce the need for a deforming mastectomy. Complete clinical and pathologic resolution of the palpable cancer is accepted as a reliable prognostic sign which predicts long disease-free survival. Understanding the therapeutic strategies that necessarily follow a diagnosis of breast cancer, surgical excision as the primary diagnostic procedure should only be undertaken in exceptional circumstances.

Excisional Biopsy

In the case where the mammary lesion is screen-detected, there are very few situations where, due to technical reasons, localization and excision biopsy is warranted. These may include posteriorly sited lesions detected on mammography or those close to the skin, where using stereotactic needle biopsies would be technically challenging. In the past, women with breast compression thickness of less than 30 mm were deemed unsuitable for stereotactic vacuum-assisted biopsies. However, there are devices available now that enable a reduced aperture size of the instrument to surmount this issue. Despite these modifications, a small number of these women would still need to undergo image localization with excision biopsy for diagnosis.

In the event that a patient presents with a palpable lesion that has an incomplete or indeterminate triple test after initial FNAC and CNB, a few considerations need to be taken into account. Since contemporary data suggests that breast conservation treatment (BCT) results in superior survival outcomes compared to mastectomy, BCT would be the eventual goal if resources allow. With this in mind, where a mass is small enough to be resected as part of an attempt at breast-conserving surgery, an excision biopsy should be performed to achieve clear margins if possible. This is the preferred option to avoid a return to the operating room for margin re-excision if the lesion is diagnosed to be malignant or (DCIS) Careful incision

planning and placement and repair of the ensuing defect will minimize the impact on cosmetic outcome whether the lesion is diagnosed to be benign or malignant. The excision specimen, as well as the tumor bed, should be carefully oriented with either sutures, clips, or ink according to availability and the preference of the treating team. While this offers a single surgical procedure, a cost-effective approach for high-risk lesions like ADH and DCIS, it does not preclude the need for axillary staging for a possible invasive tumor.

Incisional Biopsy

In LMIC countries, some women may present with locally advanced breast cancers, which are too large to undergo BCT at the time of diagnosis. In the rare instances when FNAC and CNB fail to provide a definitive diagnosis, an incisional biopsy for pathologic assessment may be needed. Likewise, for those with large, ulcerative or fungating tumors with or without distant metastasis, tissue diagnosis may be obtained at the outset with incisional biopsy under local anesthesia. Often, the next therapeutic step would be the initiation of neoadjuvant chemotherapy. (NAC) Decision-making regarding surgery would depend on the response to NAC. Historically, local surgical therapy was not indicated for de novo Stage IV disease unless it was a palliative operation ("toilet mastectomy"). However, recent data appears to support improved control with loco-regional treatment if distant disease has responded well to NAC. Hence, prognostic and predictive information at the point of diagnosis is critical for optimal therapy. So the presence of fungating malignancy is one of the uncommon situations where a surgical incisional biopsy is recommended when MIBB is inconclusive or impractical to expedite appropriate, cost-effective treatment.

Handing of tissue samples

Tissue samples from each biopsy technique have unique handling requirements to optimize histologic interpretation. If they can be reasonably achieved within the scope of available funding, due attention should be given to these specific nuances.

Cytology

FNAC is a very simple procedure but requires significant practice to obtain diagnostic specimens reliably. The technique is best executed with a 23 or 25-gauge needle using quick repeated passes through the lesion with minor directional changes with each pass. The tiny disengaged cored fragments are compacted into the needle under negative pressure using a ten cc syringe to increase yield while keeping the aspirated material in the needle and hub. The material obtained is dislodged onto a glass slide, smeared, and spread out with a second slide, then either air-dried or placed in alcohol as the cytopathologist would prefer. The air-dried slides are then immediately stained using a Diff Quick stain and reviewed on-site. The slide smears fixed immediately in 95% ethanol are taken to the laboratory and stained with a traditional Pap Stain. This process requires at least 60 minutes and is usually done in addition to the preparation of the additional cell block (24-hour turnaround). Every attempt is made to avoid introducing the contents, particularly blood or fluid, into the syringe as it would significantly dilute the cellular specimen risking an inadequate cellular smear. If the specimen gets into the syringe, it is best removed by rinsing with saline or RPMI for cell block preparation. For cystic lesions or suspected abscesses, a larger gauge needle may be used to further aspirate the fluid contents within the breast. For bloody aspirates or infectious concerns, this can be sent for cytology and/or culture and sensitivity.

Cell block preparation:

The needle passes from the tumor rinsed directly into normal buffered saline or RPMI solution (cell culture media) are taken to the laboratory where they are centrifuged. The fragments are concentrated into a cellular pellet. The supernatant fluid is removed, and the pellet is resuspended in a small amount of pooled patient plasma. Thrombin is added, and the subsequent clot containing the tissue fragments is placed into formalin. This is fixed for at least 6 hours but not longer than 72 hours before being paraffin-embedded, sectioned, and stained with Hematoxylin and Eosin. These sections can be utilized for immunohistochemistry, including ER/PR and Her-2 receptor assessment.

The issues of specimen adequacy for breast cytology are not standardized as in the case of thyroid FNAC. However, there are "common sense" approaches to this somewhat vexing problem. In the ideal circumstance of the pathologist performing the FNA and reviewing the smears on site, adequacy is determined by the interpretation of the smear. Malignant cells are diagnostic, regardless of number. A defined pattern of benign findings (bipolar naked nuclei) that indicate a diagnosis such as fibroadenoma or similar benign entities (apocrine metaplasia, fibrocystic changes, mastitis) would be considered adequate, particularly if it is concordant with the triple test. Any acellular smears or normal structures (fat or histiocytes) in the presence of a palpable mass would not offer a definitive diagnosis and are considered unsatisfactory regardless of volume. These cases would require either CNB or excisional biopsy as an alternative means of assessment.

Cases identified as "malignant C5" by FNAC (see Discussion) would be significantly enhanced by the acquisition of tissue for ER/PR and Her-2 receptor evaluation. FNAC can reliably predict the presence of invasion in palpable lesions when the characteristic lesion

desmoplasia perceived by the needle resistance ("gritty feel") is best appreciated by the operator. However, this is not uniformly reliable as some DCIS can present with a palpable lesion. Since the subsequent management of the patient will be predicated on this distinction (need for sentinel lymph node biopsy) and because the determination of Her-2 status is necessarily performed on the invasive component, the patient should undergo a CNB for the purpose of assessing (see algorithm) frank invasion and more accurately determining Her-2 status. In patients with triple-negative breast cancers and Her-2 positive cancers, the treatment decisions may favor pre-surgical neoadjuvant chemotherapy. Given the expense and potential morbidity of these treatments, the CNB is preferred.

Core biopsy specimens

Tissue handling in the instance of a core needle biopsy is critical to the outcome of the determination of ER/PR and Her-2 evaluation. The core needle biopsy should be directly collected into formalin (cold ischemic time less than 1 hour). The needle biopsy, once in formalin, should be fixed for at least 6 hours and no more than 72 hours before being embedded in paraffin and sectioned and Hematoxylin and Eosin stained. These sections can be utilized for immunohistochemistry, including ER/PR and Her-2 receptor assessment.

Excisional biopsy specimens

Finally, there exists another problem with a diagnostic excisional biopsy. For reliable pathologic assessment, strict tissue handling requirements demand appropriate tissue fixation (time to fixation or "cold ischemic time") and duration of fixation, which in a large specimen can result in errors in the assessment of ER/PR and Her-2 receptor status. These larger tissue specimens contain considerable amounts of fat and connective tissue. The size of the specimen also poses problems for adequate formalin penetration. Also, the time between obtaining the

specimen and its addition to formalin is more difficult to control again, depending on the size of the specimen. These should be added to formalin no more than one hour after excision from the patient. The tissue should be sliced once directly through the tumor prior to introducing the specimen into formalin. This assures better tumor penetration by the formalin. The tumor should be fixed at least 6 hours and not longer than 72 hours before sections are paraffin-embedded and hematoxylin and eosin stained. Thin sections of this paraffin-embedded tissue are suitable for immunohistochemistry and ER/PR and Her-2 receptor analysis.

Excisional specimens also comprise another challenge for the pathologist, which is accurate tissue orientation. Ideally, the excised tissue sample should be oriented by the surgeon. The orientation should, at a minimum, allow for reporting all six margin faces of the tissue with a distance of the tumor to each of these margins. Most pathologists prefer the surgeon to ink each of the six faces of the specimen with colored inks. This reduces the potential for the pathologist to misorient the specimen in the laboratory. Many surgeons utilize a sequence of suture labels for orientation. This, while less desirable, is sufficient.

Discussion

Treatment selection and customization

All the treatment approaches discussed above must be tailored for the best applicability and cost-effectiveness with limited resources. Recent cost estimates for breast cancer diagnosis in the setting of palpable disease in the USA favor using FNAC over all other more technically advanced approaches. [4] Since there is a preponderance of patients with palpable disease in low and middle-income countries, the use of FNAC merits closer scrutiny with appropriate recognition of the issues described in detail above.

Where possible, percutaneous MIBB should be performed to allow appropriate treatment planning. However, we have shown that percutaneous biopsies are still inherently associated with a real, albeit low, false negative result. Furthermore, there is the issue of benign high-risk lesions and atypia on MIBB, which carry a modest risk of upgrade when an excision biopsy is performed. Therefore, in any algorithm designed to handle the best approaches for the minimally invasive diagnosis of breast cancer using FNAC or CNB, it will be necessary to include an alternative for those cases in which these two standard approaches may yield an indeterminate pathology report in the face of a worrisome triple test. In such a setting, a surgical biopsy may be required.

Important issues pertaining to tissue handling have been addressed above. Still, quality control requirements have been standardized worldwide to quantify the adequacy and reliability of the FNAC in the setting of a multidisciplinary approach. The most widely used system employs a five-tier assessment of the aspirate: C1-insufficient material, C2-benign, C3-atypical, C4-suspicious of malignancy, and C5-categorically malignant. This categorization remains instrumental for the clinician who, in concert with a skilled cytopathology team, may need to proceed to a CNB or excisional biopsy in such settings as described above. [10] Adequacy of the aspirate has been reported to offer the best results when both the aspiration and the interpretation are carried out by the same cytopathologist. Most reported series of palpable breast masses document that benign lesions account for as many as 75% of aspirates. [10] Although the sensitivity, specificity, and accuracy of FNAC have been reported to range between 77% and 100%, the potential for a false negative aspirate is very favorably described to be between 1.2% and 10.6%. False negative rates of 21% reported in small, impalpable lesions are less of a concern in a population where the main mode of presentation is palpable disease. Other common

reasons for false negatives are prevented by important quality assessment measures addressing sampling technique, adequate tumor cellularity, and proper localization. [10] However, in large populations of women with palpable disease in LMICs, the reliance on FNAC for the vast majority of cases is well established. The immediacy of the available results is often underestimated, particularly in settings where the patients have to travel significant distances to such a breast specialty clinic. A prompt FNAC diagnosis can address all the issues in a single visit for the majority of women with a benign aspirate in the context of a concordant triple test. These women can be safely discharged home without further intervention. Among those diagnosed with a malignant condition, prompt referral to surgical, medical, and radiation oncologist can proceed with subsequent assessment of their ER/PR and Her-2 status from appropriately collected aspirates or CNB obtained, preferably at the same sitting. [2] Thus, women with a malignant diagnosis are promptly identified in a same-day visit and are not likely to be lost to follow-up. In contrast, review appointments are usually required when tissue diagnosis solely depends on core biopsy as it entails a minimum 48-72 hour turnover. A multidisciplinary breast center may be robustly organized such that a small number of patients with non-diagnostic aspirates can be referred to undergo a CNB at the same visit. In order to reduce non-attendance at a second review visit due to travel and lodging concerns, appropriate education and counseling emphasizing the importance of follow-up may be imparted to the patient. Lastly, false positives in FNAC breast centers with experienced staff are less than 2% and are accounted for uniformly by small lesions with ADH or lobular hyperplasia. [10]

Centralized comprehensive breast diagnostic centers providing the above patient services can be established regionally in countries with limited resources, as shown by Kazi et al.[5], which can handle hundreds of patients with great accuracy. Furthermore, the high volume of

patients in these clinics serves to educate and hone the needed skills of expert cytopathologists, who can then help to set up more of these clinics without investment in expensive equipment. The same capabilities could easily be supplemented with relatively inexpensive ultra-sonographic and mammographic equipment useful to employ the triple test in the setting of non-palpable disease as screening programs begin to take shape in these countries.

Diagnostic Approach to Case Scenario Using Proposed Algorithm

An algorithm that summarizes our recommendation is shown in Figure 1. The highlighted boxes can trace its application to the case scenario that opens this chapter.

Several considerations for diagnostic and therapeutic strategies need to be made for a patient presenting with a palpable breast mass in a resource-limited country. Ideally, multidisciplinary care combines radiology, surgery, pathology, medical oncology, and radiation oncology expertise. Plastic and reconstructive surgery, while good to have, may not be practicable where there are cost concerns. Rarely, radiology and radiotherapy services also may not be accessible. If so, the approach would need to be modified.

Where the medical resources are extremely limited without the benefit of radiology and radiotherapy facilities, FNAC is the primary diagnostic modality for women with palpable lesions. CNB should be performed as a confirmatory test if cytology is inconclusive or malignant. Even though BCT offers good survival outcomes, mastectomy may be the only practical surgical therapy if radiotherapy is unavailable.

If the entire suite of services for multidisciplinary care is available to a patient, then a staged diagnostic approach is undertaken, with mammogram and sonography being the first step. FNAC should not precede imaging as it may alter radiologic characteristics and confound

interpretation. In this case, FNAC should follow imaging. Rarely, for lesions with benign but highly cellular cytopathology aspirates, a CNB may be needed for further evaluation. These highly cellular benign lesions may require a wide excision, particularly if they present a history of a rapidly growing mass. If cytology yields malignant cells, CNB of the breast tumor with FNAC of any identified axillary lymph nodes with clip placements would be the next step for purposes of NAC for tumor downstaging. This allows an attempt at BCT once NAC is completed. Adjuvant radiotherapy is a standard part of BCT. As radiotherapy facilities have high initial costs, these may not be readily acquired in low-middle-income countries and must be considered when planning surgery.

Conclusion

Healthcare cost is a perennial issue in the management of complicated medical problems such as breast cancer. At one end of the spectrum, high-income countries have few issues with the availability of technology to offer optimum diagnostic strategies. Still, over-utilization and overconsumption of resources can spiral into uncontrolled spending, especially in the face of patient autonomy and litigation. Paradoxically, these can pose a significant barrier to proper healthcare delivery. In contrast, low-middle-income countries frequently encounter the challenge of inadequate funding to provide appropriate care. Perhaps the best way forward would be to tailor a rational approach for an equitable, sustainable, and efficacious diagnostic strategy for breast cancer-specific to a country's circumstance, which is the objective of the algorithm presented.

Key Points

1) FNAC is a cost-effective and accurate biopsy approach to exclude the majority of palpable lesions that are benign with no further workup.

2) FNAC can select very reliably those palpable lesions that are malignant in a single visit. It allows for the selective use of CNB for added histologic confirmation for lesions such as DCIS.

3) FNAC & CNB, when diagnostic of specific malignant disease, permit the triage of high-risk or locally advanced lesions to proceed to preoperative or neoadjuvant systemic chemo or endocrine ablative therapy

4) FNAC is ideally suited for the biopsy of metastatic axillary nodal disease or other metastatic foci, enabling the prompt treatment of women with locally advanced stage III disease or stage IV disease not amenable to curative surgical therapy

5) Indications for surgical biopsy include non-diagnostic cytology following FNAC and non-diagnostic CNB (Table 1).

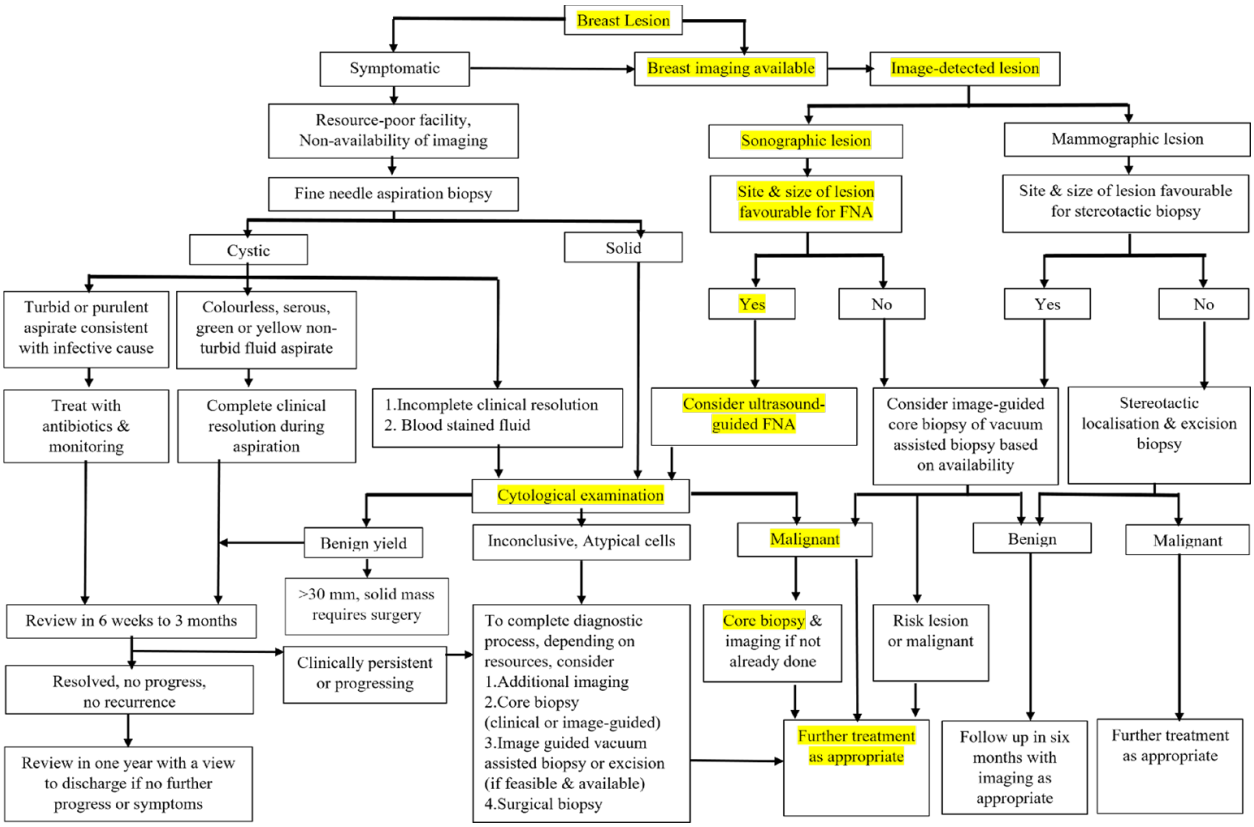

Table 1: Algorithm for Approach to Biopsy of Breast Lesions According to Resource Availability (yellow indicates malignant lesion pathway)

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Chapter 12

Basic Pathology of Breast Cancer

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Abstract

Breast cancer is one of the leading causes of cancer-related death in women worldwide. The diagnosis and management of breast cancer is a multidisciplinary endeavor. Optimal management decision is rendered upon integrating accurate diagnostic information, including pathological diagnosis and ancillary test results. This chapter highlights key features of most common breast lesions that may mimic carcinoma, contemporary classification and understanding of breast carcinomas, and effective interpretation of the pathology report. Benign breast diseases are selectively discussed from the perspective of mass-forming lesions that need to be differentiated from breast carcinomas. Basic breast cancer pathology with clinical correlation is presented and amply illustrated for a multidisciplinary audience. A standardized checklist pathology report according to international guidelines is presented to show how accurate interpretation of the pathology report can benefit the entire medical team.

Benign Breast Findings That Mimic Cancer

Although breast cancer is relatively common and remains the second leading cause of death in women, only about 5% of clinical abnormalities of the breast are breast cancer. The

majority of lesions discovered clinically and by imaging modalities are benign. Many benign conditions can present with clinical symptoms and physical examination findings, as well as abnormal mammography, ultrasound, or MRI findings that overlap with malignant processes. Close correlation of clinical findings and imaging characteristics aids in their recognition, although biopsy is necessary to confirm the diagnosis in many cases. Some of these lesions, though benign, require surgical removal. Others can be managed by clinical follow-up after diagnosis. Common benign conditions that may mimic breast cancer can be categorized as fibrocystic disease and various ductal and lobular proliferative processes, fibroepithelial lesions, papillary lesions, spindle cell lesions, and inflammatory conditions.

Fibrocystic Disease and Epithelial Proliferative Processes

Fibrocystic disease or fibrocystic change represents a variety of benign structural and histologic alterations that reflect exaggerated physiologic changes from baseline. These include cyst formation, apocrine differentiation of the duct and lobular cell6s, and stromal fibrosis. It is the most common breast disorder, accounting for 40% of women seeking evaluation. The significance of its recognition mainly resides in its differentiation from neoplastic processes and from other proliferative changes that are associated with increased risk for the subsequent development of malignancy. Fibrocystic disease predominantly occurs in premenopausal women between 20 and 50 years of age and is more commonly seen in women who are nulliparous or have menstrual abnormalities. The development of fibrocystic disease is associated with hormonal imbalance (1). Excess estrogen can be the result of anovulatory cycles, excess peripheral conversion of androstenedione to estrone in adipose tissue, exogenous hormones, or rarely functioning ovarian tumors. Elevated estrogen levels and relative progesterone deficiency induce hyperproliferation of epithelial elements and connective tissue, resulting in expanded

epithelial structure and stromal fibrosis. Oral contraceptive usually decreases the risk of fibrocystic change, perhaps due to a balanced supply of estrogen and progesterone.

Fibrocystic disease can be symptomatic and produces breast nodularity and mass. If a mass lesion is formed, differentiating it from a neoplastic process requires pathological examination of biopsied or excised tissue specimen. Grossly, fibrocystic disease is typified by subcentimeter clear or blue-domed cysts (due to retained semi-translucent, turbid fluid) distributed in soft white stromal tissue. Microscopically, these cysts are composed of cystically dilated ductules lined by cuboidal to flattened epithelial cells. Apocrine differentiation of the cyst lining cells is common. Apocrine metaplastic epithelial cells have large polygonal shape, large round nuclei and prominent nucleolus, and abundant granular eosinophilic cytoplasm due to the accumulation of mitochondria. There is often expanded and densely fibrotic stroma. Besides hormonal imbalance as a cause, fibrosis can also occur secondary to cyst rupture and inflammatory tissue reaction. In the absence of epithelial proliferation, fibrocystic disease does not increase the risk of subsequent development of breast cancer. In contrast, proliferative fibrocystic change shows adenosis and epithelial hyperplasia and a variably increased risk of developing breast cancer depending on the extent of epithelial proliferation and the presence or absence of cellular atypia.

Adenosis is a nodular proliferation of tubules in the terminal duct lobular unit, which is the basic functional unit of the breast. This process is characterized by a spherical expansion of lobules due to an increased number of acini secondary to hormonal stimulation. Conglomerate of adjacent areas of adenosis can result in clinically palpable mass (adenosis tumor). Adenosis with concurrent fibrosis and collagen deposition results in the compression of tubular architecture and formation of sclerosing adenosis (Fig. 1). Such change can mimic invasive carcinoma on gross and microscopic levels. Utilization of myoepithelial cell markers may be necessary since sclerosing adenosis retains an intact myoepithelial cell layer.

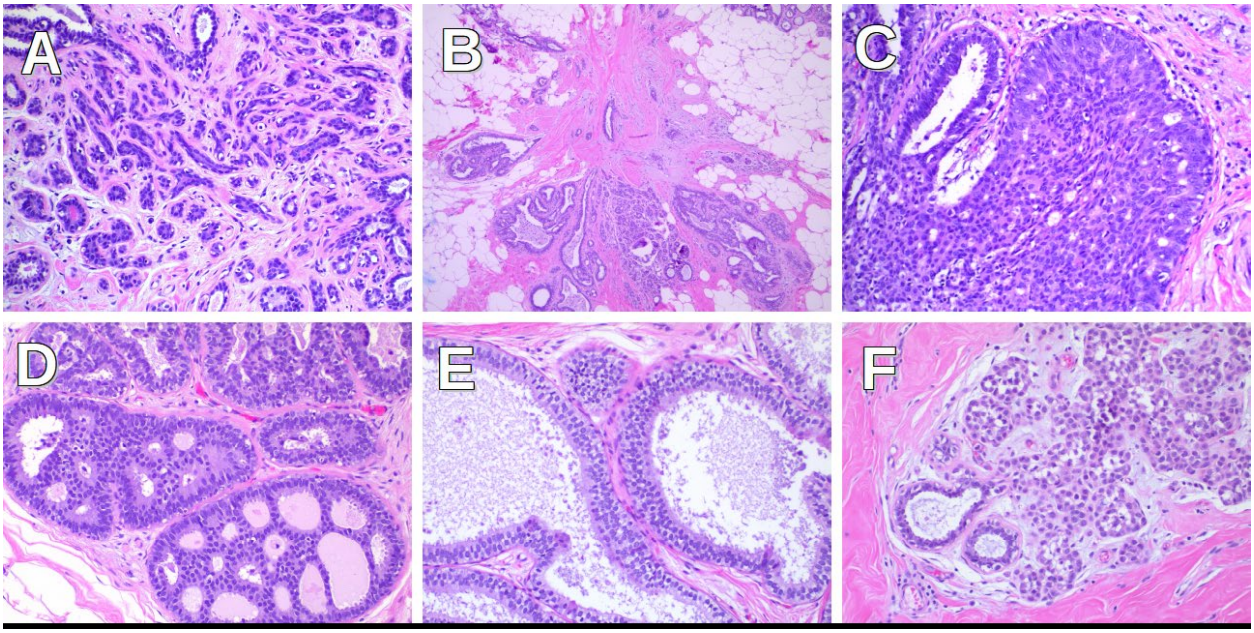

Figure 1: Benign breast diseases including epithelial proliferative processes. (A) Sclerosing adenosis is composed of expanded lobules composed of swirling glands separated by a fibrotic stroma. (B) Low-power image of stellate shaped radial scar shows a central fibrotic core and entrapped glands and peripheral proliferative ductal component. (C) Florid usual ductal hyperplasia is characterized by expanded ducts filled with heterogenous proliferative epithelial cells containing irregular luminal spaces. (D) In atypical ductal hyperplasia (ADH), proliferating epithelial cells have hyperchromatic, monomorphic nuclei and form rigid, cribriform architecture involving part of terminal duct lobular unit. (E) In flat epithelial atypia (FEA), the acini are lined by a few layers of columnar epithelial cells that show low-grade cytologic atypia, characterized by relatively round, monotonous nuclei. (F) Lobular carcinoma in situ (LCIS) shows dyshesive small cuboidal cells expanding more than half of the terminal duct lobular unit.

Another lesion closely mimics an invasive carcinoma radiographically and morphologically is a radial scar. Although this is usually an incidental finding in specimens obtained for other reasons, it can also be seen as a non-palpable lesion detected by screening mammography. Radial scar (or complex sclerosing lesion if the size is more than 1 cm) is a stellate-shaped lesion formed by proliferating ductal structures radiating from a fibroelastotic core containing entrapped and distorted tubules (Fig. 1). When only part of the radial scar is sampled as in a core biopsy specimen, immunohistochemical confirmation of myoepithelial cell layer in the central entrapped ducts may be necessary to differentiate it from a well-differentiated type of invasive carcinoma (tubular carcinoma). In addition, the radiating ducts may display a range of epithelial hyperplasia, including atypical ductal hyperplasia (see below). Surgical excision is generally recommended for larger radial scars (> 5 mm) and those associated with atypical ductal hyperplasia (2,3).

Ductal hyperplasia represents an increase in the cellularity of ductal epithelium. This results in the piling up of epithelial cells from a normal monolayer to two or more cell layers within a duct. When the epithelium is two to three cell layers thick, it is usually considered mild ductal hyperplasia. Mild hyperplasia is usually included in the non-proliferative fibrocystic change since it is not associated with an increased risk of developing breast cancer. When the epithelium is more than three cell layers thick, it is designated as moderate hyperplasia. Further ductal epithelial proliferation tends to fill most of the lumen and results in distension of the duct, a change considered severe or florid ductal hyperplasia. Thickened epithelium can form a micropapillary structure in the periphery of the duct, protrude into the lumen as strands to form a cribriform structure, or pile up as a solid cell group (Fig. 1). Such changes are referred to as

“usual” ductal hyperplasia to distinguish them from atypical ductal hyperplasia (see below). Common morphological characteristics of usual hyperplasia include overlapping of nuclei, swirling or streaming arrangement of nuclei, and irregular (non-rigid) cell bridges or fenestrated luminal spaces. The ductal epithelial cells show nuclear size and shape variation but no significant cellular atypia in the form of hyperchromatic nuclei, high nuclear-to-cytoplasmic ratio, and other cellular changes associated with intraductal carcinoma.

Atypical ductal hyperplasia (ADH) refers to abnormal ductal proliferation fulfilling some but not all criteria for a diagnosis of intraductal carcinoma. This can be in the form of structural or cytologic features of intraductal carcinoma intermixed with usual ductal hyperplasia, resulting in partial duct involvement. Alternatively, there is a complete involvement of only one duct or more than one duct involvement that measures less than 2 mm in aggregate (Fig. 1).

Another form of ductal epithelial atypia is flat epithelial atypia (FEA). It is characterized by a distended terminal duct lobular structure lined by usually multilayered monotonous epithelial cells that show features of low-grade cytologic atypia, including nuclear hyperchromasia and loss of nuclear polarity (Fig. 1). There are no secondary structures such as papillary projections, cellular bridging, or cribriform configuration as seen in ADH.

Benign breast diseases convey a variable degree of increased risk of developing breast cancer relative to the extent of ductal epithelial proliferation. There is no increased risk of non-proliferative fibrocystic change, such as cystic change, apocrine metaplasia, and stromal fibrosis. Proliferative fibrocystic change, including adenosis and usual ductal hyperplasia, carries a slight increase in the risk, in the order of 1.5- to 2-fold. ADH is associated with a moderately increased risk, in the order of 3- to 5-fold (3,4).

Lobular neoplasia represents a spectrum of abnormal proliferation of loosely cohesive epithelial cells in the terminal duct lobular unit. The proliferating cells are usually small and monomorphic in appearance, with round nuclei and inconspicuous nucleoli. There is a scanty rim of cytoplasm, with occasional formation of intracytoplasmic lumina. These cells have a dyshesive appearance and tend to create slit-like intercellular spaces. Such cellular proliferation usually expands acini (Fig. 1). If there is only partial involvement of a lobular unit, it is designated as atypical lobular hyperplasia (ALH). When more than half of a lobular unit is involved, a lobular carcinoma in situ (LCIS) is diagnosed. Pagetoid extension into the terminal duct frequently occurs. Besides classic LCIS, as described above, several variants of LCIS have been recognized. Florid LCIS describes an architectural growth pattern in which LCIS causes marked expansion of ducts and lobules. If the proliferating cells show marked nuclear enlargement and pleomorphism reminiscence of high-grade ductal carcinoma in situ (DCIS), the lesion is classified as pleomorphic LCIS. Mitotic figures, necrosis, and calcification can occur. Common to all lobular neoplasia is the lack of E-cadherin expression, a feature commonly employed for diagnostic confirmation of lobular differentiation. E-cadherin is a transmembrane glycoprotein that mediates cell-to-cell adhesion. Inactivation of E-cadherin leads to the loss of cellular cohesion, accounting for the morphological and biological characteristics of lobular neoplasia.

Lobular neoplasia is most often diagnosed in premenopausal women, with a mean age of about 45. Lobular neoplasia does not form a palpable mass or show any specific mammographic finding. Therefore, it is often an incidental finding in investigating other breast lesions, such as those containing mammographically evident calcifications. Recent reports indicate that LCIS can show certain imaging abnormalities, such as heterogeneous non-masslike enhancement with

persistent enhancement kinetics on MRI (5). Lobular neoplasia is frequently multicentric and more often involves bilateral breasts. LCIS is bilateral in 50~70% of women when both breasts are examined, compared with 10~20% in cases with DCIS (6). Lobular neoplasia has been established as a risk factor for the subsequent development of invasive carcinoma. Patients diagnosed with LCIS have an 8- to 11-fold increased lifetime risk of developing breast cancer, whereas ALH is associated with a 4- to 5-fold increase in risk (7). This increase in risk appears to apply nearly equally to both breasts. Therefore, LCIS has traditionally been regarded as a marker for an enhanced risk of developing breast cancer in both breasts (8,9). Recent studies indicate that there is a stronger propensity for the development of ipsilateral invasive carcinoma following a diagnosis of LCIS (10-12). These studies support a non-obligate precursor role of LCIS, in addition to being a risk factor, for the development of invasive carcinoma. Although morphologic variants of LCIS have seemingly more aggressive histologic features and are more often associated with invasive carcinoma at the time of diagnosis, there is insufficient data to show that such lesions are associated with a higher risk of subsequent cancer development compared with those with classic LCIS (13).

Lobular neoplasia is currently managed as a benign lesion and does not require complete removal or evaluation of margin status. A recent prospective multi-institutional trial reported a 1% upgrade rate to carcinoma when lobular neoplasia is diagnosed at core biopsy with concordant imaging findings (14). LCIS is considered a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition (15).

Fibroepithelial Lesions

Fibroepithelial lesions are a distinctive group of tumors characterized by biphasic proliferation of both epithelial and stromal elements that demonstrate widely variable clinical

behavior. Depending on differing degree of stromal proliferation in relation to the epithelial component, they are classified as fibroadenoma or phyllodes tumor. Fibroadenoma is the most common benign neoplasm of the female breast. It is the most common breast lesion in women younger than 25 years of age. Its frequent occurrence in younger ages indicates its likely association with the unopposed estrogen effect (16). The epithelial and stromal elements of fibroadenoma originate from the terminal duct lobular unit and intralobular stroma. Fibroadenoma usually presents as a painless, firm, freely movable mass. Increasingly encountered are fibroadenomas of smaller size detected by screening mammography. Grossly, it appears as a spherical, well-circumscribed rubbery mass with a fleshy white, bulging cut surface. Microscopically, the tumor is composed of a balanced proportion of biphasic epithelial and stromal components (Fig. 2). The epithelial component is in the form of oval (pericanalicular) or slit-like (intracanalicular) ducts. The stroma component is typically low in cellularity, shows no significant cellular atypia or mitotic activity, and does not significantly outgrow the epithelial component. Less commonly seen is myxoid fibroadenoma, characterized by a distinctive hypocellular, blue-gray colored myxoid stroma. Multiple and bilateral myxoid fibroadenomas may be associated with Carney syndrome, an inheritable, autosomal dominant condition most commonly caused by inactivating germline mutations of the PRKAR1A gene (17,18).

Phyllodes tumor is a rare breast tumor, accounting for less than 1% of all breast tumors. It occurs most often among women 45 to 49 years of age, about 15 to 20 years older than those with fibroadenoma. Phyllodes tumors have a microscopic resemblance to the intracanalicular growth pattern of fibroadenoma but with increased stromal cellularity and the presence of stromal overgrowth (Fig. 2). The latter usually protrudes into cystically dilated spaces, forming leaf-like architecture that can be recognized grossly. Phyllodes tumors are classified into benign,

borderline, and malignant grade categories based on the degree of stromal cellularity and atypia, mitotic count, and pushing versus permeative growth patterns. Benign phyllodes tumors have the potential to locally recur, while malignant phyllodes tumors have a high risk of metastatic spread.

The distinction of benign phyllodes tumors from cellular fibroadenoma with an exaggerated intracanalicular growth pattern can be difficult, particularly in a biopsy specimen. This is largely due to overlapping histologic features and the subjective nature of histologic criteria used in the diagnosis (19). Therefore, cellular fibroepithelial lesions diagnosed on core biopsy usually require complete removal. On a resection specimen, key diagnostic features of benign phyllodes tumors are the presence of increased stromal cellularity and leaf-like growth pattern. In the absence of a well-developed leaf-like structure, the presence of elongated branching ducts meandering through the cellular stroma may be a histologic clue to the diagnosis of benign phyllodes tumor. In difficult cases, the tumor can be designated as benign fibroepithelial neoplasm since both entities appear to have similar recurrence rates (20).

Papillary Lesions

Papillary lesions are characterized by arborizing finger-like structures formed by epithelial proliferation overlying fibrovascular cores. It is a diverse group of breast lesions that span the spectrum of hyperplastic and neoplastic processes. Multiple microscopic foci of papillary hyperplasia can occur in fibrocystic disease, which is usually referred to as papillomatosis. A common form of benign neoplastic papillary proliferation is intraductal papilloma. Solitary intraductal papilloma is located within the dilated lactiferous duct in the subareolar region, whereas those peripherally distributed tend to be multiple and located in small peripheral ducts. When intraductal papillomas are centrally located, nipple discharge, bloody or

non-bloody, can be the primary symptom. On microscopic evaluation, the papillary processes are composed of delicate or fibrotic fibrovascular cores covered by a double layer of epithelial cells and myoepithelial cells (Fig. 2). Calcification may occur in the stroma. The epithelial cell layer may show variable degrees of proliferation, manifested as usual ductal hyperplasia. The presence of intraductal papilloma is associated with a 2- to 3-fold increase in the risk of development of breast carcinomas (21). ADH and DCIS can also occur, with a corresponding further increase in cancer risk. In differentiating from papillary carcinoma, intraductal papilloma has a well-developed myoepithelial cell layer in its papillary structure, which can be confirmed by immunohistochemical stains for myoepithelial markers such as p63, calponin, CD10, and CK5/6 (22).

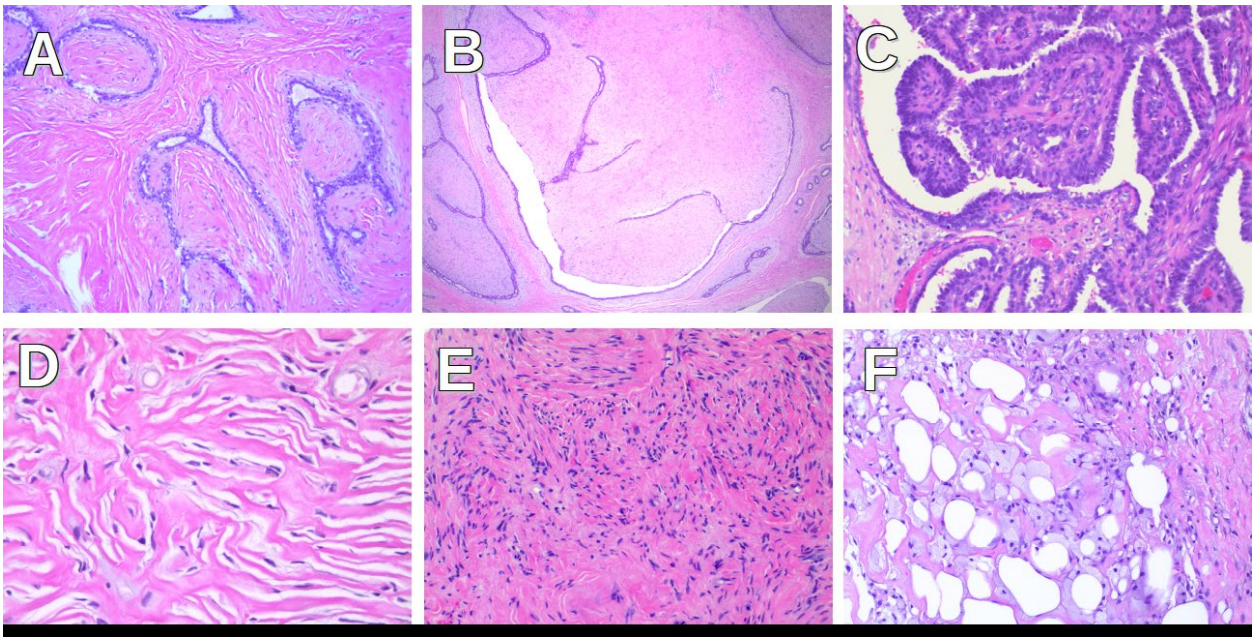

Figure 2: Fibroepithelial lesions, papillary lesions, and spindle cell lesions. (A) Fibroadenoma is composed of circumscribed proliferation of stromal tissue pushing epithelial component into elongated, slit-like structures. (B) Low-power image illustrates exaggerated stromal growth in benign phyllodes tumor, creating leaf-like configuration. (C) Intraductal papilloma has arborizing fibrovascular cores lined by a double layer of epithelial cells and myoepithelial cells. (D) In pseudoangiomatous stromal hyperplasia, there are prominent stromal clefts lined by bland stromal cells. (E) Myofibroblastoma is composed of fascicles of spindle cells in a collagenized stroma. (F) Fat necrosis is a histiocytic reaction to disrupted, degenerated adipose tissue showing here as irregular vesicular spaces.

Spindle Cell Lesions

Spindle cell lesions of the breast, which represent the proliferation of mesenchymal tissue with or without epithelial proliferation, are relatively uncommon. Many spindle cell lesions are derived from fibroblastic and myofibroblastic components of the specialized stroma of the terminal duct lobular unit. They encompass a diverse group of proliferative processes, ranging from reactive to neoplastic entities. Benign spindle cell tumor-like lesions are exuberant, reactive myofibroblastic proliferation. These include nodular fasciitis, pseudoangiomatous stromal hyperplasia (PASH), and fibromatosis. Among neoplastic proliferation, the most common one is myofibroblastoma, followed by benign fibroblastic spindle cell tumor, leiomyoma, schwannoma, solitary fibrous tumor, spindle cell lipoma, and myxoma.

Nodular fasciitis is a pseudoneoplastic myofibroblastic proliferation likely triggered by local injury. It usually presents as a rapidly growing, painless, firm nodule resembling a malignant neoplasm. The lesion is composed of a hypocellular central zone, reactive appearing fibroblasts arranged in short bundles in a prominent myxoid stroma, and lymphoid inflammatory cells and extravasated red blood cells at the periphery. Excisional biopsy is usually performed, both for diagnostic and therapeutic purposes (23).

Pseudoangiomatous stromal hyperplasia (PASH) is a benign growth of stromal cells most commonly found in premenopausal women. It can present with a palpable fibroadenoma-like lump. More commonly, it is discovered incidentally in imaging studies (PASH phenomenon). PASH is characterized by anastomosing slit-like clefts in the stroma separating dense collagen bands (Fig. 2). These slit-like spaces contain a discontinuous layer of spindle cells simulating vascular spaces, thus raising the differential diagnosis of low-grade angiosarcoma. The stromal cells in PASH are myofibroblasts, which do not express vascular endothelial markers such as

factor VIII and CD31. PASH represents the neoplastic proliferation of myofibroblasts contingent on endogenous or exogenous hormones in its development and progression (24). Enlarging lesion or inconclusive biopsy warrant0s surgical excision, although recurrence is not uncommon (25).

Mammary fibromatosis, also known as desmoid-type fibromatosis, is a locally infiltrative fibroblastic and myofibroblastic proliferation that arises either from the fascia of the pectoralis muscle or within the breast parenchyma. There is an association between previous trauma or breast augmentation with implants (26). It presents as a firm mass, sometimes associated with skin retraction or dimpling, clinically and radiographically mimicking an invasive carcinoma. Histologically, the lesion is composed of broad fascicles of spindle cells of uniform appearance separated by abundant collagen. The cellularity is variable, with cellular areas alternating with less cellular, hyalinized areas. Besides morphological features, the demonstration of nuclear expression for β-catenin is a useful adjunct in helping to establish a diagnosis. The lesion is infiltrative, with frequent extension into the surrounding tissue. Wide surgical excision is preferred, as inadequately excised lesions have a high recurrence rate.

Myofibroblastoma is a benign tumor of myofibroblasts that tends to affect older men and postmenopausal women (27). Clinically, it appears as a solitary, slow-growing nodule, mobile on palpation. The proliferating myofibroblastic cells are spindle-shaped cells arranged in short intersecting fascicles and interrupted by keloid-like dense collagen bands (Fig. 2). The tumor cells are immunoreactive for vimentin and CD34 and are variably positive for desmin, smooth muscle actin, estrogen, and progesterone receptors. Excision is the treatment of choice.

Inflammatory and Related Lesions

Inflammatory breast lesions have clinical and radiologic features that can mimic those of malignancy. Mastitis is a focal or diffuse breast infection seen in both puerperal and nonpuerperal states. Acute mastitis is usually a bacterial infection of the mammary duct system, most commonly occurring in the postpartum period (puerperal mastitis). Staphylococcus aureus is the most common causative agent. Patients with acute mastitis typically present with redness, swelling, and tenderness of the breast. Without prompt antibiotic treatment, the condition may progress to an abscess, forming a fluctuating mass in the affected breast. Ultrasound-guided fine needle aspiration can be used to drain a breast abscess for diagnostic and therapeutic purposes. The aspirate is purulent, composed of many neutrophils. Chronic mastitis commonly occurs in the non-lactational breast. It presents clinically with asymmetric breast thickening, lump, nipple discharge, and axillary lymphadenopathy. Treatment is antibiotics and percutaneous drainage if necessary, although surgical intervention is sometimes needed. A biopsy should be performed to exclude an inflammatory carcinoma if there is no clinical improvement on antibiotics.

Granulomatous mastitis is a rare chronic inflammatory condition commonly seen in young women and is associated with pregnancy and breastfeeding. Clinically, it presents as poorly defined areas of thickening and axillary lymphadenopathy, thus mimicking an inflammatory carcinoma. Biopsy shows non-necrotizing, non-infectious granulomas within the breast lobules. Most patients respond to treatment with corticosteroids, though some require surgical excision (28). A unique silicone-induced granuloma (“siliconoma”) is a foreign-body-type granulomatous response to exogenous silica particles. This usually occurs after direct injection of silicone into the breast for breast augmentation or after extracapsular rupture of a silicone implant (29). Histologically, there are many cystic spaces and vacuoles surrounded by

lymphocytes, macrophages, and foreign body giant cells. Fibrosis and contractions may lead to the formation of firm nodules.

Fat necrosis is a benign condition resulting from traumatic injury to the adipose tissue of the breast. Patients typically present with a superficially located, firm, painless mass, which may be discovered incidentally on imaging. It is more commonly seen following prior diagnostic intervention, breast-conserving surgery, or radiation therapy. Distinguishing fat necrosis from recurrent carcinoma in this setting can be difficult. Microscopically, fat necrosis is composed of various proportions of disrupted adipose tissue, histiocytes engulfing lipid (foamy histiocytes and multinucleated giant cells), and fibroblasts (Fig. 2). In later stage, dense fibrosis and dystrophic calcification can occur (30).

Carcinoma of the Breast

Breast cancer is the most frequently diagnosed cancer. It is the second leading cause of cancer-related death in women, accounting for 25% of cancer cases and 15% of cancer-related deaths worldwide (31). The etiology of breast cancer is multi-factorial. Established factors that increase breast cancer risk include genetic predisposition and environmental factors. A family history of the disease is a risk factor. About 5-10% of breast cancer cases have a strong hereditary component attributable to the inheritance of pathogenic genes. Two genes, BRCA1 and BRCA2, account for the majority of hereditary breast cancers (32,33). Increased breast cancer risk is related to reproductive factors that influence endogenous estrogen exposure (such as nulliparity, early age at menarche, later menopause, and later age at first full-term pregnancy), alcohol consumption, cigarette smoking, high-calorie diet rich in animal fat and proteins, excess body weight, use of exogenous hormones (oral contraceptives and menopausal hormone

replacement therapy), and high-dose radiation to the chest (34-46). Breast cancer incidence and death rates increase with age, and the median age at the time of breast cancer diagnosis is 62~63 years (37,38). There is an incremental increase in breast cancer risk in benign breast diseases depending on the extent of epithelial proliferation and the presence or absence of atypia. A recent study reported a 1.76-fold risk increase in proliferative fibrocystic change and related processes (sclerosing adenosis, moderate or florid usual ductal hyperplasia, intraductal papillomas). The presence of atypia in proliferative fibrocystic change has a 3.93-fold increased risk (3). Women with a family history of breast carcinoma have further increased risk in all categories.

Ductal Carcinoma in situ (DCIS)

Definition: DCIS is a non-invasive clonal proliferation of epithelial cells confined to the ductal-lobular system without evidence of invasion through the basement membrane into the surrounding stroma. DCIS originates from the terminal duct lobular unit as shown by the microdissection study (39).

Clinical and Gross Findings: About 80% of DCIS are detected by screening mammography due to microcalcifications. The rest are identified due to palpable mass (12%), nipple discharge (3%), and Paget's disease (3%) (40). DCIS accounts for about 30% of breast cancer detected at mammographic screening. Most cases of DCIS are not grossly evident, with the exception of comedo DCIS and some cases of papillary DCIS. Comedo DCIS has a tan-white appearance with pale yellow cylinders (comedos) extruding from the cut surface when compressed. The presence of microcalcifications imparts a gritty sensation on sectioning.

Microscopic Finding: DCIS represents the intraductal growth of tumor cells, usually accompanied by the expansion of the ductal structure. Nuclear grade is the most important

feature in classifying DCIS since it has a stronger predictive power of recurrence than architectural pattern (41-43). Nuclear features are used to separate DCIS into low, intermediate, and high grades (Table 1).

Table 1. Nuclear Grade of DCIS.

Feature	Low grade (grade I)	Intermediate grade (grade II)	High grade (grade III)
Pleomorphism	• Monotonous (monomorphic)	• Intermediate	• Markedly pleomorphic
Size	• Size of normal ductal epithelial nucleus or 1.5~2x size of normal red blood cell	• Intermediate	• >2.5x size of duct epithelial cell nucleus
Contour	• Round and smooth	• Intermediate	• Angular
Chromatin	• Diffuse, finely dispersed chromatin	• Intermediate	• Vesicular with coarse chromatin and irregular chromatin distribution
Nucleoli	• Indistinct	• Intermediate	• Prominent, often multiple
Mitoses	• Occasional	• Intermediate	• Usually frequent
Orientation	• Polarized toward luminal spaces	• Intermediate	• Not polarized toward the luminal space

Architecturally, DCIS can be divided into comedo, solid, cribriform, micropapillary, and papillary types (Fig. 3). Comedo DCIS shows solid growth of high nuclear grade neoplastic cells and central tumor cell necrosis with amorphous appearing dystrophic calcification. In solid DCIS, neoplastic cells of variable nuclear grade fill the entire duct. Secondary structures and necrosis are absent, but microcalcification may be present. Cribriform DCIS has an extension of cellular bridges within the duct space to create secondary lumina, imparting a fenestrated appearance. In contrast to cribriform hyperplasia, the intraductal spaces are evenly distributed and regular in shape. Cellular necrosis or punctate-type microcalcifications may be present. In micropapillary DCIS, neoplastic cells lining the duct protrude into the lumen, giving rise to papillary fronds. Adjacent papillary fronds can coalesce, forming so-called Roman bridge arches.

When papillary fronds are supported by fibrovascular stroma cores, the lesion is classified as papillary DCIS.

Clinical Correlation: DCIS is a precursor lesion, albeit not obligate, to invasive breast carcinoma since between 14 to 53% of them can become invasive carcinoma over a period of 10 years if left untreated (44). DCIS shares many of the same epidemiological and genetic risk factors as invasive breast cancer. Invasive carcinomas developed after a diagnosis of DCIS usually occur in the ipsilateral breast and the same quadrant as the original DCIS (45). The interval between a diagnosis of DCIS and subsequent development of invasive carcinoma varies between 3 to over 40 years, depending on the nuclear grade of DCIS (45-57). The prognosis of DCIS is excellent, with a 10-year cumulative breast cancer death rate of less than 3% (48). Estrogen receptor (ER) expression is determined by immunohistochemistry to help decision-making in hormonal therapy. Most cases of DCIS (>70%) are ER-positive. Elevated ER expression is likely the fundamental mechanism in promoting abnormal ductal epithelial proliferation and progression (49). Clinical trials have demonstrated an effective role for anti-estrogen therapy in recurrence prevention in women with ER-positive DCIS (48).

Paget Disease of the Nipple

Paget's disease of the nipple is the epidermal involvement by malignant glandular epithelial cells (Paget cells) in the nipple-alveolar complex. It is often associated with an underlying invasive ductal carcinoma and less commonly with DCIS. Rarely, it can occur without an underlying carcinoma. Most patients present with eczematoid, erythematous, crusted, or scaling lesions, simulating inflammatory and eczematous skin conditions. These may progress to fissure and ulceration, accompanied by nipple discharge. The Paget cells have large nuclei, prominent nucleoli, and abundant clear cytoplasm. They are found singly or in clusters in the

epidermis (Fig. 3). Histochemical and immunohistochemical stains can differentiate these cells from those of malignant melanoma or squamous cell carcinoma in situ (Bowen's disease). The intracytoplasmic mucin can be highlighted by mucicarmine stain. The tumor cells are usually positive for low molecular weight cytokeratin (CAM5.2 and CK7), CEA, EMA, and GCDFP-15. In 80~90% of the cases, the tumor cells also show HER2 over-expression (50,51). The prognosis of Paget's disease is related to the type of underlying ductal carcinoma. Patients with Paget disease and an accompanying invasive carcinoma appear to have a worse prognosis than those without Paget disease (52,53).

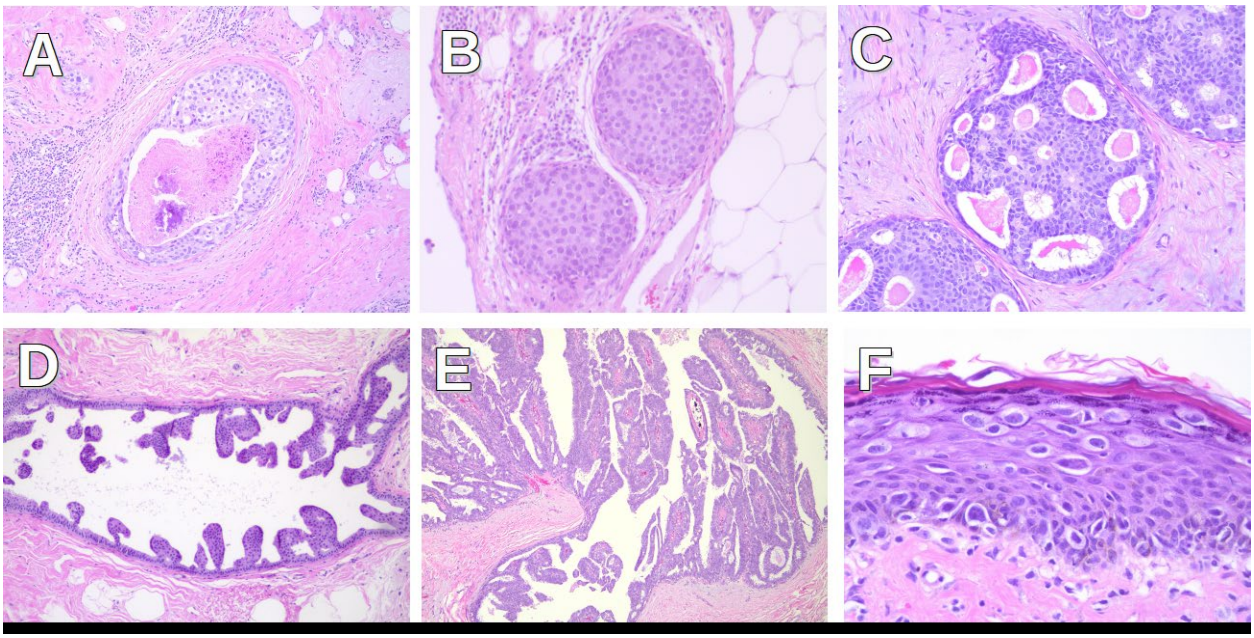

Figure 3: Ductal carcinoma in situ (DCIS). (A) Comedo DCIS is composed of high nuclear grade tumor cells with luminal necrosis and calcification. (B) Solid DCIS has expanded ducts filled with cohesive neoplastic ductal epithelial cells. (C) Cribriform DCIS has many punched out lumina. Punctate type calcification is also present. (D) Low-power image shows elongated papillary fronds projecting into duct lumen in micropapillary DCIS. (E) Papillary DCIS has fibrovascular core and absence of myoepithelial cells. (F) Clusters of large neoplastic cells with abundant, pale cytoplasm invades the epidermis in Paget's disease.

Invasive Carcinoma of No Special Type (IC, NST)

Definition: Also known as invasive ductal carcinoma of no special type (IDC, NST), this is the most common type of invasive carcinomas, comprising about 75% of invasive carcinomas (54,55). It encompasses a heterogeneous group of tumors that cannot be classified as a specific histologic type (see below). Any specific histologic type present should constitute no more than 10% of the total carcinoma. Since breast carcinomas arise from the terminal duct lobular unit, the term "duct" reflects the ductal resemblance of tumor cells and growth patterns rather than the tumor origin.

Clinical Findings: There is a gradual increase in breast cancer incidence with increasing age, and the incidence peaks between 50 and 69 years of age (54). About 7% of breast cancer cases are diagnosed among women younger than 40 years of age (56,57). Breast carcinomas in young women tend to be of high histologic grade and show a higher frequency of hormonal negative phenotype (58,59). The most common clinical sign of invasive breast carcinoma is a palpable mass, usually firm. Less commonly, breast cancer presents as skin retraction, nipple discharge, and nipple inversion. Since all of these symptoms and findings can also be caused by benign breast diseases, as discussed previously, imaging evaluation and tissue biopsy are required to establish an accurate diagnosis.

Gross Finding: The tumor is usually firm on palpation and has a gritty feel on sectioning due to fibroblastic stroma response (desmoplasia). Although the tumor can appear discoid in shape, closer inspection reveals irregular edges radiating into the surrounding tissue, creating a stellate configuration (Fig. 4).

Microscopic Finding: There are a variety of tumor cell cytomorphology and growth patterns. The tumor cell appearance ranges from bland and uniform to highly pleomorphic with the formation of tumor giant cells. The tumor cells grow in a sheet, cord, nest, or gland. Infiltrative growth is manifested as an irregular interphase between the tumor cell nest and stroma. There are variable degrees of deviation of tumor cell cytomorphology from its normal counterpart, described as tumor cell differentiation. Well-differentiated tumors closely resemble their tissue of origin and have a low proliferation activity, whereas poorly-differentiated tumors barely resemble their tissue of origin and have a high proliferation activity. Histologic grading is used as an estimate of differentiation and proliferation activity. Histologic grading not only describes morphologic characteristics but also provides important prognostic information since many studies have demonstrated a strong association between histologic grade and survival of patients with invasive breast carcinoma (60,61). Therefore, well-differentiated tumors are regarded as low grade, having comparably favorable prognosis, whereas poorly-differentiated tumors are regarded as high grade, having unfavorable prognosis. A semi-quantitative way incorporating key cytomorphologic and growth pattern characteristics is utilized to ensure uniformity in tumor grading. The most widely used histologic grading system is the Nottingham combined histologic grade (Nottingham modification of Scarff-Bloom-Richardson grading system) (62,63). This

grading system takes into account the extent of tubule formation, nuclear pleomorphism, and mitotic rate. Each of these three parameters is assigned a score on a scale of 1 (favorable) to 3

(unfavorable). The grade is determined by the sum of the scores. Scores of 3 to 5 are designated as low combined histologic grade (grade I); scores of 6 to 7, intermediate combined histologic grade (grade II); scores of 8 to 9 as high combined histologic grade (grade III) (Table

2 and Fig. 4).

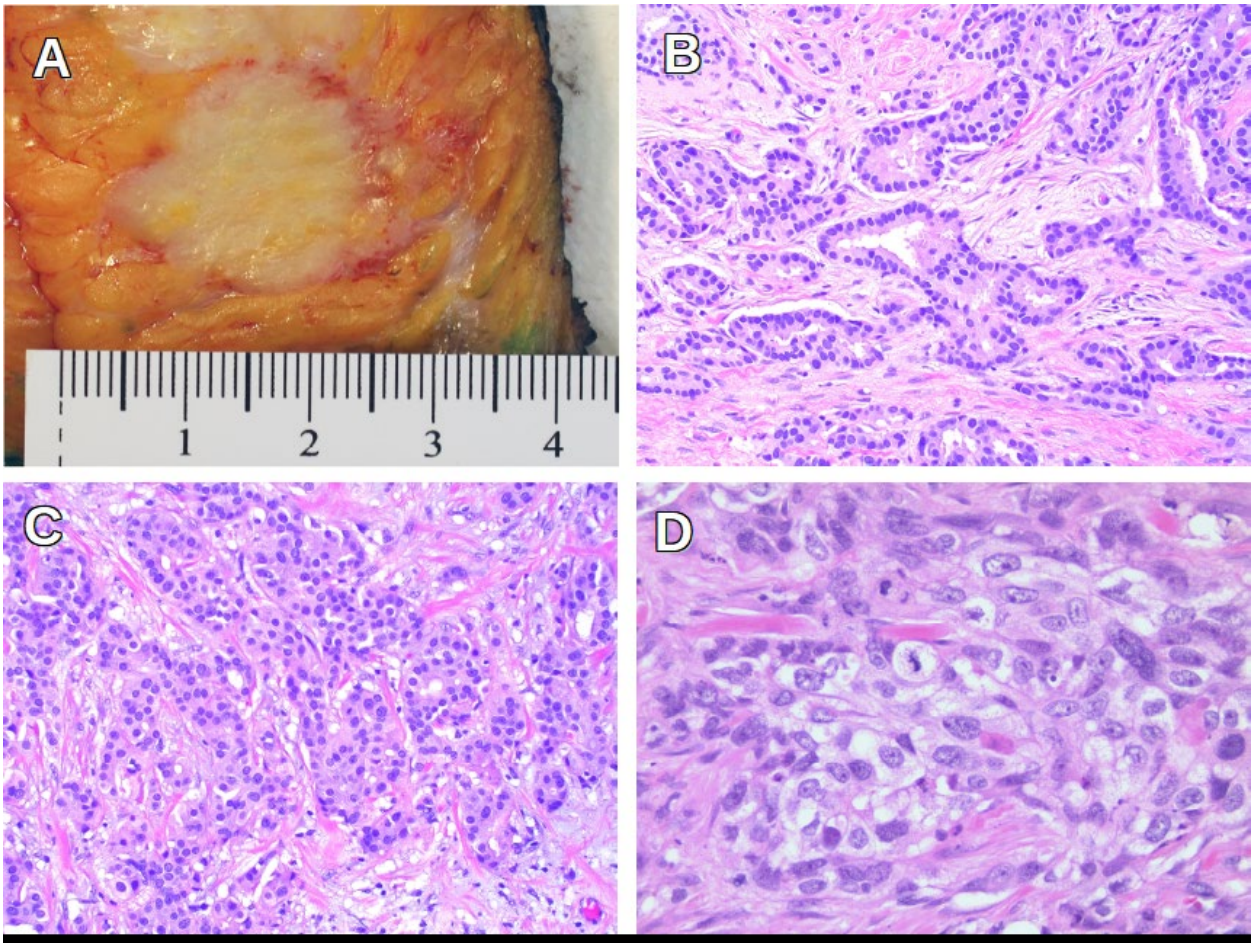

Figure 4: Invasive carcinoma of no special type (IC, NST). (A) Gross examination shows a solid mass with pale gray cut surface flecked with yellow chalky streaks. Note the ink-marked specimen margin on the right edge of the field. (B) Low grade invasive carcinoma generally has well-formed glandular structure, small and uniform nuclei, and rare or absent mitotic figures. (C) Intermediate grade invasive carcinoma. (D) High grade invasive carcinoma has solid growth pattern, large and pleomorphic nuclei, and frequent mitotic figures.

Tubule formation	
Score 1	• >75% of tumor has glandular/tubular structure
Score 2	• 10~75% of tumor has glandular/tubular structure
Score 3	• <10% of tumor has glandular/tubular structure
Nuclear Size	
Score 1	• Small regular nuclei, similar in size to normal ductal nuclei
Score 2	• Intermediate size nuclei, 1.5~2x size of normal ductal nuclei
Score 3	• Pleomorphic largest nuclei, >2x size of normal ductal nuclei
Mitotic count	
Score 1	• ≤3 mitoses per mm^2 or 0~7 mitoses per 10 high power microscopic fields
Score 2	• 4~7 mitoses per mm^2 or 8~14 mitoses per 10 high power microscopic fields
Score 3	• >8 mitoses per mm^2 or >15 mitoses per 10 high power microscopic fields
Nottingham combined histologic grade	
SBR score of 3~5 points	• Grade I (G1), low combined histologic grade (favorable)
SBR score of 6~7 points	• Grade II (G2), intermediate combined histologic grade (moderately favorable)
SBR score of 8~9 points	• Grade III (G3), high combined histologic grade (unfavorable)

Table 2. Modified Scarff-Bloom-Richardson (SBR) Histologic Grading

Clinical Correlation: IC, NST constitutes up to 80% of invasive breast carcinoma cases. Patient outcome is highly dependent on proper treatment. The average 10-year survival rate for breast cancer has increased from 55% in the 1980s to the current 83% (64,65). Reduction in the death rate is attributed to both early detection by screening and improvement in therapy.

Histologic analysis of breast cancer provides the first step in identifying individual tumor characteristics of prognostic and predictive significance. Tumor size, histologic type, histologic grade, lymphovascular invasion, and lymph node status are among the traditional prognostic factors that affect treatment choices. Biomarker testing helps to further identify therapeutic targets. Approximately 70~80% of IC, and NST cases are ER-positive, and approximately 15~20% of cases are HER2-positive (66,67). Molecular quantification technologies have been

developed to further aid in the risk stratification of early breast cancers. Gene expression profiling is now regarded as a powerful independent predictor in breast oncology (68).

Special Subtypes of Invasive Carcinoma

Breast cancer is a heterogeneous disease comprising many distinct entities. Besides tumor grade, tumor growth pattern creates histomorphological diversity that can be utilized to classify breast carcinomas into distinct histological types. These histological types are associated with distinct clinical presentations and outcomes. The most commonly seen invasive carcinoma of no special type (IC, NST) discussed previously is actually a diagnosis of exclusion, encompassing carcinomas that fail to exhibit sufficient characteristics to warrant their classification into one of the special subtypes. Breast cancer special subtypes account for up to 25% of all breast cancer cases. In the latest edition of the World Health Organization (WHO) classification of tumors recognizes more than two dozen distinct histological types (69). Special subtypes of invasive carcinoma commonly encountered in clinical practice are discussed below

Invasive Lobular Carcinoma (ILC): This is an invasive carcinoma composed of dyshesive tumor cells arranged in a single-file linear pattern or as dispersed individual cells. Disruption of cell adhesion molecule E-cadherin (most commonly due to loss of E-cadherin protein expression identifiable by negative E-cadherin immunohistochemical stain) accounts for the observed dyshesive phenotype. ILC is the most common special type of breast cancer, comprising up to 15% of invasive carcinomas. The tumor cells are typically small in size and monomorphic in appearance, with round to ovoid nuclei and a thin rim of cytoplasm. Some tumor cells have an intra-cytoplasmic mucin-containing vacuole or lumina. The classic growth pattern is dispersed cells or linear strings of cells infiltrating the stroma (Fig. 5).

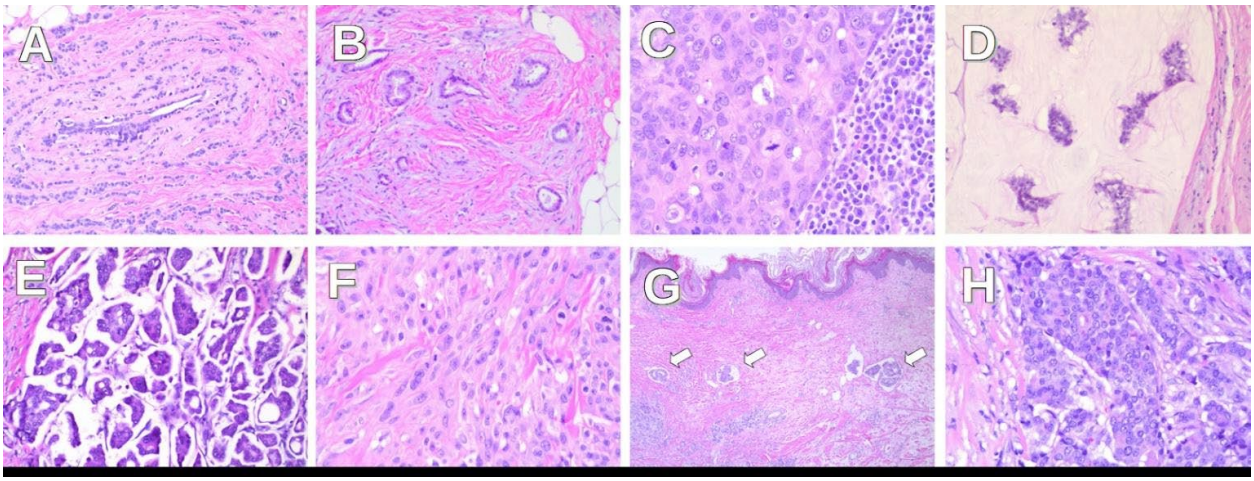

Figure 5: Special subtypes of invasive carcinoma. (A) Invasive lobular carcinoma is characterized by linear arrangement of discohesive tumor cells usually arranged in single file. (B) Tubular carcinoma consists of haphazard infiltration of glands lined by a single layer of low nuclear grade tumor cells. (C) In medullary carcinoma, the circumscribed tumor is composed of syncytial nests of high nuclear grade tumor cells with an intense lymphocytic host response in the stroma. (D) Mucinous carcinoma is characterized by clusters of low nuclear grade tumor cells floating in abundant extracellular mucin pool. (E) Invasive micropapillary carcinoma has many pseudopapillary clusters of tumor cells surrounded by hollow spaces. (F) This example of metaplastic carcinoma has a predominance of spindle cell carcinoma component. (G) The hallmark of inflammatory carcinoma is the extensive presence of dermal lymphovascular tumor invasion. Clumps of tumor emboli can be seen within dilated lymphatic channels in the dermis (arrows), illustrated here by a low-power image. (H) Most male breast carcinomas are high grade invasive carcinoma of no special type.

The tumor cells are frequently arranged in a concentric (targetoid) pattern encircling normal ducts. The tumor cell infiltration does not significantly disturb or destroy the preexisting tissue architecture compared to other types of breast carcinoma. A small portion of ILC shows marked nuclear pleomorphism and is classified as pleomorphic ILC. Pleomorphic ILC has a less favorable prognosis than classic ILC (70). Histologic grading is an important parameter, although it is a less powerful differentiating factor in predicting prognosis compared to other histological types since most ILCs have an intermediate combined histologic grade (grade II) (71,72). The monomorphic cytology, low mitotic rate, and highly infiltrative nature of ILC pose special challenges in clinical diagnosis. ILC is less frequently detected as a palpable mass or mammographically distinct abnormality owing to its usually non-destructive but extensive

infiltrative nature and rare association with calcifications. Compared to other types of invasive carcinoma, ILC is known to be more often multifocal, multicentric, and bilateral (73,74). Some studies suggest that despite lower grade appearance and good response to endocrine therapy, the long-term survival of ILC may be worse than IC, NST (72,75,76).

Tubular Carcinoma: This is a well-differentiated (grade I) invasive carcinoma composed of open lumina glands (tubules) lined by a single layer of monotonous tumor cells (Fig. 5). The tubules can be ovoid or angulated and are haphazardly distributed. Mitotic figures are rare. Due to its bland cytomorphology, a demonstration of a lack of myoepithelial cell layer by one or more myoepithelial markers may be necessary for its diagnosis, especially in a biopsy specimen. Pure tubular carcinoma appears to have a lower incidence of axillary lymph node metastasis and a more favorable prognosis compared to other breast cancer types (77-79). Larger tumor size and multifocal tumors, however, appear to be a predisposing factor in developing axillary lymph node metastases (59,80)

Medullary Carcinoma: Medullary carcinoma is characterized by a well-circumscribed growth pattern, composed of anastomosing sheets of tumor cells of high nuclear grade and dense lymphocytic infiltrate in the stroma (Fig. 5). There is no glandular formation, stromal fibrosis, or infiltrative margin. The tumor has a soft gross consistency due to a lack of desmoplastic stroma, hence the term “medullary,” which pertains to the softness of marrow. Medullary carcinomas consistently lack ER, PR, and HER2 expression (triple negative phenotype). Patients with pure medullary carcinoma have a good prognosis, with a 10-year survival rate of over 80% (81,82). Prominent lymphocytic inflammatory reaction may explain the better prognosis (83). It is of note that medullary carcinoma should be differentiated from carcinoma with medullary features, which do not share this favorable prognosis (84).

Mucinous Carcinoma: Mucinous carcinoma is a low-grade carcinoma characterized by neoplastic cells dispersed in the extracellular mucin pool. The age of presentation tends to be older than other types of invasive carcinoma, with a median age over 70 years (85). Microscopically, the tumor cells have low-grade nuclear features and form clusters and ribbons dispersed in acellular mucinous material (Fig. 5). The mucin forms a pushing border with the surrounding fibroadipose stroma. Pure mucinous carcinoma carries a significantly better prognosis and is rarely associated with axillary lymph node metastases compared to other types of breast carcinomas (85-87). It has been postulated that a combination of low tumor cell burden and abundant mucin acting as a barrier for stromal invasion may account for this less aggressive behavior (86).

Invasive Micropapillary Carcinoma: This rare type of breast carcinoma is composed of many small papillary-like nests of tumor cells surrounded by empty stromal spaces (Fig. 5). The papillary-like aggregates are devoid of fibrovascular cores. The clear space surrounding individual tumor cell nests is likely a fixation retraction artifact and does not represent lymphovascular invasion. Although tumor cells usually have low to intermediate nuclear grade, this particular tumor cell arrangement confers a significantly higher frequency of axillary lymph node metastasis, even if the micropapillary component is present in other more common types of breast carcinomas (88,89). There are conflicting reports regarding whether the micropapillary phenotype is an independent prognostic factor. Recent evidence suggests that the commonly observed adverse clinical characteristics (larger tumor size, higher frequency of lymphovascular invasion, and nodal metastasis) do not appear to negatively impact the overall survival rate (90-93).

Metaplastic Carcinoma: Metaplastic carcinoma shows diverse differentiation (through "metaplastic" transformation of adenocarcinoma component) and may contain squamous, spindle, chondroid, osseous, and rhabdomyoid cells (Fig. 5). Individual tumors can have one or more these elements, and should be designated by their corresponding descriptive terms (for instance, metaplastic carcinoma with squamous differentiation, metaplastic carcinoma with osteocartilaginous heterologous elements). Epithelial markers such as keratin and p63 may be necessary to identify epithelial differentiation. Tumor cells are usually negative for ER, PR, and HER2 expression (triple negative phenotype). Prognosis is variable contingent on the presence of specific metaplastic elements, although as a group, metaplastic carcinomas tend to have lower response rate to adjuvant chemotherapy, higher tumor recurrence rate, and lower patient survival rate than other forms of triple-negative breast carcinomas (82,94,95).

Inflammatory Carcinoma: Inflammatory carcinoma is the most aggressive form of breast carcinoma with a unique combination of clinical and pathologic findings. Clinically, there is a rapid onset of diffuse enlargement and firmness of the breast. The overlying skin tissue shows redness, edema, and dimple (peau d'orange appearance), resembling an acute inflammatory process such as acute mastitis and breast abscess. This clinical inflammatory appearing symptom is due to an underlying invasive carcinoma and the presence of numerous dermal lymphatic tumor emboli, causing dermal lymphatic obstruction and edema (Fig. 5). The use of a multimodal therapeutic approach, including neoadjuvant therapy, has improved survival rates, but survival outcomes for patients with inflammatory carcinoma are still very low, worse than those for patients with non-inflammatory locally advanced breast carcinomas (96-98).

Male Breast Carcinoma

Carcinoma of the male breast is very rare, accounting for less than 1% of all breast carcinomas (99). A high incidence is reported in several African countries and blacks in the United States. The development of male breast cancer is associated with estrogen-to-androgen imbalance. This likely explains the significantly increased breast cancer risk in patients with Klinefelter syndrome (100). Family history of breast cancer, both in the female and male first-degree relatives, is a risk factor. The presence of germline mutation in the BRCA2 gene confers a higher risk of developing breast cancer, though not as high as in females(32,101). There has not been an established link between gynecomastia and breast cancer (102). The median age at presentation (63~68 years) is older than that of female breast cancer (38). Typical clinical presentation is a self-detected unilateral, subareolar, painless mass. A full variety of breast carcinomas, as described previously, can occur in the male breast. As in female breast carcinomas, most male breast carcinomas are invasive carcinomas of no special type (invasive ductal carcinoma), comprising about 85% of the cases. Invasive carcinoma with neuroendocrine differentiation is more commonly seen in males (103). In comparison, invasive lobular carcinoma is extremely rare, which is likely related to the lack of lobular development in males (104). There is a higher frequency of nipple skin involvement (Paget's disease), likely due to the short length of the male mammary duct system (105). The percentage of male breast carcinomas with hormone receptor expression is higher than that of females (106). Male breast cancer presents at a comparably more advanced stage with larger tumor size and more frequent axillary nodal involvement than in females. As a consequence, overall survival rates are lower for men (104,110).

Breast Cancer Biomarkers:

The three biomarkers routinely tested for all invasive carcinomas are estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). They are both prognostic and predictive factors. Accurate assessment of their expression provides important prognostic information and also directs effective personalized therapeutic choices. The binding of estrogen with nuclear transcription factor ER stimulates the growth of breast epithelial cells. To counteract this growth-stimulating effect, steroid mimics such as tamoxifen have been utilized to competitively inhibit estrogenic signaling. In addition, enzyme inhibitors have been developed to block estrogen synthesis. Aromatase mediates the conversion of the steroidal precursors to estrogen. Selective compounds have been developed to block the aromatization process, thereby inhibiting estrogen synthesis (107). ER expression is determined in formalin-fixed paraffin-embedded tissue sections by immunohistochemistry (IHC) for all invasive breast carcinoma and DCIS (Fig. 6). The number of tumor cells staining positive for ER is determined semi-quantitatively. There is a direct correlation between the presence and level of ER expression and endocrine therapy response. Patients with higher hormone receptor levels have a higher probability of responding to hormonal therapy. Expression as low as 1% positive staining cells has been associated with clinical response (69). Therefore, ER-positive is defined as ≥1% tumor cells showing positive nuclear ER staining. About 70~80% of invasive breast carcinomas express ER (69). ER expression correlates with tumor type and differentiation. For instance, most invasive lobular carcinomas are ER-positive, while medullary and inflammatory carcinomas are predominantly ER-negative. PR expression, although not as important clinically as ER, can provide useful information. PR is less affected by fixation-related issues compared to

ER and can potentially help minimize the impact of sub-optimal fixation (108). Thus, PR expression is assessed and quantified concurrently with ER expression by IHC.

The HER2 gene encodes a transmembrane growth factor receptor tyrosine kinase on the surface of breast epithelial cells. HER2 is amplified and over-expressed in approximately 15~20% of invasive breast carcinomas (67). HER2 gene amplification and protein over-expression are more commonly seen in tumors of high nuclear grade than those of low nuclear grade. In general, HER2 is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality. Treatment with HER2-targeted therapy, such as trastuzumab and lapatinib, has led to significantly reduced recurrence and improved survival of HER2-positive breast cancer patients (109,110). HER2 status is determined either by IHC to assess the expression of the HER2 protein or by fluorescence in situ hybridization (FISH) to assess gene copy number on formalin-fixed paraffin-embedded specimens. Using IHC, HER2 expression is scored semi-quantitatively as 0, 1+, 2+, or 3+, depending on the percentage of cells with membrane staining and the intensity of the staining. If the tumor is 0 or 1+, it is considered HER2-negative. If the tumor is 2+, it is considered equivocal, and a reflex FISH test is performed. If the tumor is 3+, it is considered HER-2-positive (Fig. 6). Breast carcinomas with HER2 gene amplification usually show HER2-to-chromosome 17 centromere (CEP17) FISH ratio ≥ 2.0 and an average HER2 gene copy number of ≥ 4.0 per tumor cells (Fig. 6). HER2 testing and interpretation should follow the most recent American Society of Clinical Oncology and College of American Pathologists (ASCO-CAP) guideline (111).

A subset of breast carcinomas lacks expression of ER, PR, and HER2. This biomarker-defined group of so-called triple-negative breast cancer accounts for 10~20% of all breast cancers. They tend to occur in women of younger age, African descent, higher premenopausal

body mass index, earlier age at menarche, and higher parity (112). There is a higher prevalence of BRAC mutations in this patient population (113,114). Triple-negative breast cancers are generally more aggressive than the rest of the breast carcinomas. They have limited therapeutic targets when compared with endocrine-sensitive and HER-positive breast cancers and therefore are associated with an overall poor prognosis and a high incidence of early metastatic recurrence (115). Its aggressive clinical course demands innovative new therapeutic target identification and more effective treatment modalities.

Uncontrolled cellular proliferation is a hallmark of malignancy, and increased proliferative capacity is usually associated with more aggressive tumor behavior and poorer prognosis. The proliferative capacity of breast carcinomas can be assessed by a variety of methods, including counting mitotic figures in stained tissue sections (mitotic index), quantification of IHC staining for nuclear proteins expressed during the cell cycle, and flow cytometric measurement of the fraction of cells in S phase. Ki-67 is a nuclear marker expressed in all phases of the cell cycle except for the resting phase. It serves as a marker of cell proliferation and is the current assay of choice for measuring and monitoring tumor proliferation in standard pathology specimens (Fig. 6). Many studies have shown the clinical utility of Ki-67 as a prognostic marker in breast carcinomas (116). Therefore, the Ki-67 proliferation index is usually included in the biomarker testing panel. Ki-67 IHC assay is especially helpful as a cost-effective alternative where gene expression multiparameter molecular assays are not readily

available. With proper training, it is possible to achieve a high inter-observer agreement in scoring Ki67 using a conventional light microscope and manual field selection (117).

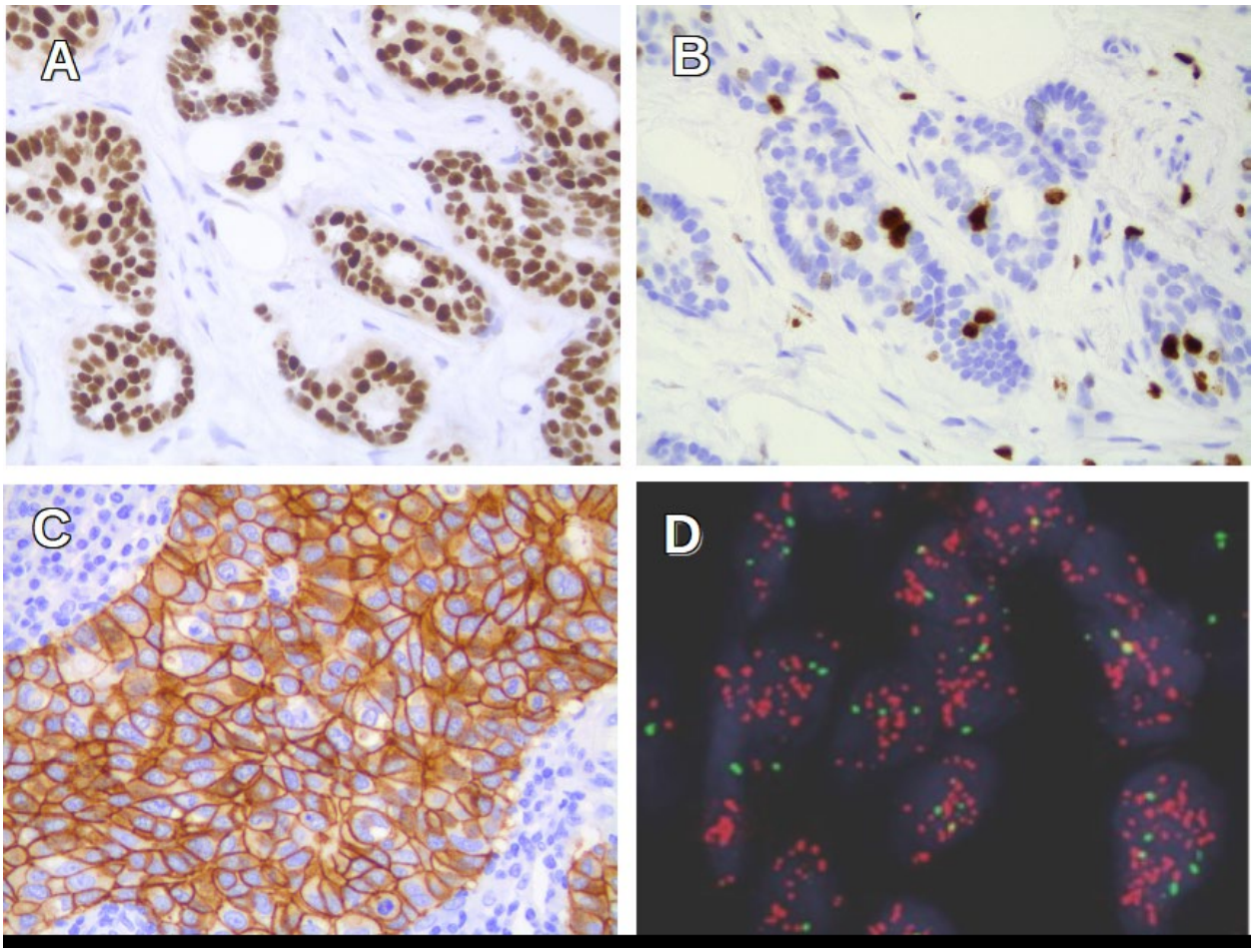

Figure 6: Breast cancer biomarkers. (A). This low-grade invasive carcinoma has strong nuclear expression of ER. (B) The same tumor has a low Ki67 labeling index (about 5%). (C) An example of intense and circumferential membranous staining for HER2 (3+ staining) indicates HER over-expression. (D) This is an image of breast carcinoma positive for HER2 amplification by FISH analysis. The ratio of HER2 (red signals) to centromere 17 (green signals) is more than 2 and there are on average more than 4 HER2 signals in each cell (silhouette of each cell can be seen against the black background).

A plethora of clinical parameters have been utilized to assess prognosis and therefore assist in the selection of endocrine therapy and adjuvant chemotherapy. Parameters such as patient age, tumor size, tumor grade, number of metastasized axillary lymph nodes, and others are strong factors to predict the risk of late recurrence. Newly introduced molecular tools

promise to provide additional information in assisting clinical decision-making, particularly in otherwise equivocal cases by routine analysis. In this approach, data generated by DNA microarrays and RNA sequencing are linked with clinical parameters and treatment outcomes. Differential gene expression profiles are weighed using bioinformatic tools. This allows the assembly of a smaller pool of pertinent gene alterations that are most informative for survival prediction. A mathematical equation is generated using this gene signature, which in turn produces a genomic assay recurrence score to predict the risk of recurrence. Major gene expression prognostic panels commercially available include OncotypeDX, Mammaprint, Prosigna, EndoPredict, and Breast Cancer Index (BCI). Some of these tests have already been approved by the FDA and recommended by guidelines set forth by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO). Oncotype Dx, a genomic test based on the assessment of 21 genes, is the multigene panel currently included in the AJCC staging system to classify the Prognostic Stage Group (15). Oncotype Dx testing is recommended for early-stage, ER-positive, HER2-negative breast cancer cases. A recurrence score of 11 is usually regarded as the most pertinent cutoff value to divide low versus medium to high risk of recurrence (118). Incorporating this information, the assigned Prognostic Stage Group is used to assist in the selection of appropriate endocrine and/or systemic chemotherapy strategies.

A number of studies have shown that a combination of histologic type, grade, and routine IHC biomarkers (ER, PR, HER2, and Ki-67) can be utilized to predict disease recurrence risk (119-121). When properly selected, such information closely parallels Oncotype DX recurrence scores in certain subtypes of breast carcinomas. Since these biomarkers are widely available, such an approach is cost-effective and can be utilized to approximate results from multigene

molecular tests in certain clinical settings. Several algorithm-based models are available (122-124). The Magee equations, for instance, utilize tumor size, grade, and semi-quantitative ER, PR, HER2, and Ki-67 staining results. They provide a reasonable estimate of the 21-gene recurrence score generated by Oncotype DX in the low to intermediate recurrence score range (122,125).

Pathology Report

Effective diagnosis and management of breast cancer require a multidisciplinary approach, as documented in other chapters of this book. An accurate and complete pathology report plays a pivotal role in bridging the clinical finding and ultimate therapeutic undertaking. A pathology report is a formal documentation of pathology findings based on gross, microscopic, and auxiliary testing of the specimen. A comprehensive pathology report is most effectively presented in a synoptic format, structured as a checklist. Diagnostic information is entered in a series of data element-response pairs and listed in individual lines to ensure visual clarity. Such a templated reporting format enables a speedy, thorough, and accurate comprehension of all the important diagnostic data by clinicians. Tabulated information also facilitates discrete field extraction by registrars and researchers for statistical analysis and medical research.

For breast cancer resection specimens from mastectomy or breast-conserving surgery, many international guidelines for pathology reporting have been developed, such as those from the College of American Pathologists (126), Royal College of Pathologists UK, and Royal College of Pathologists Australia. One of the most comprehensive breast cancer reporting protocols is provided by CAP. It is composed of a comprehensive checklist, incorporating key findings to delineate the type and extent of the tumor, biochemical characteristics of the tumor, adequacy of the tumor resection, and regional tumor spread. Together, they define the biological

nature and postsurgical tumor stage to guide further adjuvant treatment, estimate recurrence risk and prognosis, and help predict response to therapy and disease outcome. Essential components of a synoptic pathologic report for breast cancer are summarized in Table 3.

Summary finding: invasive carcinoma size/histologic type/grade, lymphovascular invasion, status of margin, lymph node metastasis	
Specimen identification	• Procedure: excision/mastectomy • Specimen laterality: right/left • Tumor site: quadrant/o'clock position
Invasive carcinoma	• Tumor size: x mm • Histologic type: invasive carcinoma of no special type/invasive lobular carcinoma, etc • Histologic grade (Nottingham modification of the SBR grading system): 1. Glandular (acinar)/tubular differentiation: score 1/2/3 2. Nuclear pleomorphism: score 1/2/3 3. Mitotic rate: score 1/2/3 4. Overall grade: grade 1/2/3 • Tumor focality: single focus/multiple foci
Ductal carcinoma in situ (DCIS): size, architectural pattern, nuclear grade, necrosis	
Tumor extension: involvement of skin, nipple, skeletal muscle	
Resection margins	• Invasive carcinoma: uninvolved - distance from closest margin (mm)/positive - extent of involvement • DCIS: uninvolved - distance from closest margin (mm)/positive - extent of involvement
Regional lymph nodes	• Number of sentinel lymph nodes • Number of total axillary lymph nodes • Number of lymph nodes with macrometastasis 1. Size of largest metastasis: x mm 2. Extranodal extension: yes/no • Number of lymph nodes with micrometastasis • Number of lymph nodes with isolated tumor cells
Treatment effect	• Treatment effect in the breast: complete response/probable or definitive response/no definitive response • Treatment effect in the lymph node: complete response/probable or definitive response/no definitive response
Lymphovascular invasion	• Absent/present
Pathologic stage classification (pTNM or Pathologic Prognostic Stage; AJCC 8th Edition)	
Additional pathologic findings	
Ancillary studies: ER/PR/HER-2 status and multigene assay	

Table 3: Example of synoptic pathologic report adapted from CAP guidelines

Summary Finding

At the beginning of the report, a paragraph summary can be presented, serving as an abstract for the entire report. Several key findings, such as tumor histologic type, grade, size, margins, lymphovascular invasion, and lymph node status, are listed. This allows clinicians to master key findings at a glance. More detailed information can be accessed in the standardized, templated synoptic report.

Specimen Identification

This section defines the surgical procedure performed (lumpectomy vs. mastectomy), specimen laterality (left vs. right breast), and tumor site (individual quadrant or central portion).

Tumor Information

This section provides information about tumor size (greatest dimension of the invasive carcinoma), histologic type (IC, NST, or special subtypes of invasive carcinoma), histologic grade (grade 1/2/3), and tumor focality (single focus vs. multiple foci). Tumor size is essential for the staging of breast carcinoma and thus affects the choice of postoperative treatment strategy. The greatest contiguous dimension of the invasive carcinoma is used for tumor size measurement. The tumor size is measured grossly and verified by microscopic analysis if the tumor is large. A small-sized tumor can be measured directly on glass slides. Often it is necessary to correlate gross, microscopic, and imaging findings to determine the best T category. The survival rate of women with breast cancer decreases as the mean size of the tumor increases (127-129). Tumor histologic type is based on the current WHO classification of breast tumors (72). Histologic grade is an important parameter of prognostic importance for overall survival, independent of other parameters such as tumor size and nodal status (130). High-grade or poorly

differentiated carcinomas have a significantly higher frequency of local and systemic recurrences compared to lower-grade tumors (61,131-133). Histologic grade is determined using the Nottingham combined histologic grade (Nottingham modification of Scarff-Bloom-Richardson grading system) (63). This system is based on the extent of tubular formation, nuclear pleomorphism, and mitotic index to assign a score of 1 to 3 and use the total score to stratify the tumor grade from 1 to 3 (see Table 1).

Breast cancer can present as multiple tumors, either as multifocal or multicentric disease. The latter is defined as at least two lesions more than 5 cm apart or in different quadrants. There is a reported link between multifocality and lymph node involvement, indicating an adverse impact on disease-free survival rate (134). The current Tumor-Node-Metastasis (TNM)-based staging of breast cancers by the American Joint Committee on Cancer (AJCC) and International Union for Cancer Control (UICC) staging system uses the size of the largest tumor focus, adding the suffix "m" to indicate multiplicity. The tumor size of the largest tumor focus shows the best correlation with overall survival and progression-free survival, whereas the aggregate diameter of multifocal tumors has a less robust correlation (135,136).

In Situ Component

This section lists the presence or absence of DCIS and LCIS. It is important to assess the presence of in situ components in analyzing invasive breast cancer since their presence increases the local recurrence rate and therefore influences the clinical selection of risk-reducing adjuvant therapies. DCIS, in association with invasive carcinoma, increases the risk of local recurrence for women undergoing breast-conserving surgery due to a higher incidence of positive surgical margins (137,148). The presence of LCIS is also associated with an increased recurrence rate for patients undergoing breast-conserving surgery (139,140). For DCIS, the following parameters

are documented: size, architecture pattern (such as comedo, cribriform, solid, and other patterns), nuclear grade (grade 1~3), and presence or absence of necrosis. If DCIS is a major component (approximately 25%) within the area of invasive carcinoma and DCIS is also present in the surrounding breast parenchyma, or there is extensive DCIS associated with a small (~10 mm or less) invasive carcinoma (i.e., the invasive carcinoma is too small for DCIS to comprise 25% of the area), this is reported as extensive intraductal component (EIC). EIC-positive carcinomas are associated with an increased risk of local recurrence after breast-conserving surgery (141,142). The presence of microcalcifications in the invasive carcinoma, DCIS, or non-neoplastic tissue is documented. This provides correlative information for imaging studies. Pathologic radiologic correlation is especially important in a mastectomy specimen, allowing informed mapping and effective sampling of the specimen.

Tumor Extension

If the skin, nipple, and skeletal muscle tissue are involved by the tumor, these should be documented in this section. Skin and nipple involvement can be in the form of direct tumor extension, dermal lymphovascular invasion, or in the form of Paget disease of the nipple. Locally advanced breast cancer usually shows breast skin and/or chest wall skeletal muscle involvement. The prognosis of patients with locally advanced breast cancer is poor, with a 5-year survival rate of less than 50% (143).

Margins

The resection specimen is oriented in the operating room to annotate its in vivo orientation in three dimensions. Orientation is usually accomplished by sutures, surgical clips, or dyes. The oriented specimen surface is differentially inked in the pathology laboratory. Margins are sampled with perpendicular sections, superior to on-face margin evaluation (144). The status

of six surface margins (superior, inferior, medial, lateral, anterior, and deep/posterior) is documented, including the distance from the tumor to the closest inked margin and, if involved (i.e., a distance of 0 mm), the extent of involvement. Surgical resection margin status is a crucial parameter to evaluate for the adequacy of the resection, estimate local recurrence risk, and formulate a postoperative management plan. Evaluation of margin is particularly important for breast-conserving surgery. The risk of local recurrence is increased if the tumor involves the surgical margin (145,146). Therefore, achieving a negative margin reduces the risk of local recurrence. Recent studies suggest that no ink directly present on tumor cells indicates a negative margin and adequate resection. The rationale for this is as follows: After tumor resection, additional microscopic tumor foci can usually be found in adjacent normal breast tissue in a substantial proportion of cases despite seemingly adequate surgical resection (147). Since breast-conserving therapy requires postoperative radiation therapy, a negative margin or "no tumor on ink" is sufficient to ensure that the residual tumor burden is minimal and is likely to be effectively controlled with post-surgical treatment. Re-excision to achieve more widely clear margins does not significantly further reduce the odds of local recurrence (148,49). Re-excision also carries operative risk and delays adjuvant therapy. Per recommendation by the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) consensus guideline, routine use of re-excision for more widely clear margins is not indicated (150). For DCIS, studies have shown that margins of at least 2 mm are associated with a reduced risk of local tumor recurrence relative to narrower negative margins. Again, per consensus guidelines, the routine practice of re-excision to obtain a wider negative margin prior to postsurgical irradiation is not encouraged. The precise reason for different margin requirements to achieve a low recurrence rate for invasive carcinoma and DCIS is not clear. This may be related to the

biological nature of the two diseases. DCIS tends to be multifocally distributed along the branching ductal tree, with gaps among the normal tissue (151). A comparison of the odds of local recurrence rate has shown that a negative margin width of 2 mm is significantly lower than 0 or 1 mm. No statistical association between increasing margin widths and a decreased rate of local recurrence is observed for margin widths beyond 2 mm (152).

Regional Lymph Node

Sampled lymph nodes include sentinel lymph nodes (SLN) and/or axillary dissected lymph nodes. Sentinel lymph nodes are identified intraoperatively by uptake of radiotracer or dye. All lymph nodes are thinly sliced and embedded in their entirety for microscopic evaluation. The number of lymph nodes examined and the number of lymph nodes with metastasis are documented. If present, the largest contiguous tumor deposit is measured and used for the pN category. Positive lymph nodes are further divided as macrometastases (tumor deposits >2 mm), micrometastases (>0.2 mm to 2 mm and/or >200 tumor cells), and isolated tumor cells (≤0.2 mm and ≤200 tumor cells). Axillary lymph node status is an important prognostic factor and determinant of further treatment. Disease-free survival rate inversely correlates with the presence and number of lymph nodes involved (132, 153-154). The number and size of axillary lymph node metastasis as well as extra capsular spread, inversely correlate with overall survival (132,155). A positive regional lymph node is a marker for an increased risk of distant metastasis. SLN evaluation is a safe method and equivalent in efficacy for staging the axilla as lymph node dissection. Complete removal of axillary lymph nodes after SLN biopsy has not been shown to affect the overall survival and recurrence-free survival (156,157). SLN is evaluated by entirely embedding the thinly sliced (2 mm thick) lymph node tissue and examining a single-level routinely stained slide for each slice. Attempts have been made for more extensive evaluation, by

step-level sections and cytokeratin IHC staining, to detect occult metastasis. Studies have shown that information on occult metastases is not a discriminatory predictor of cancer recurrence (158,159). Therefore, the College of American Pathologists (CAP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Carcinoma Network (NCCN) do not recommend the use of ancillary techniques such as cytokeratin IHC stain for the assessment of SLN.

Treatment Effect

Neoadjuvant systemic therapy is being increasingly used in breast cancer treatment for earlier-stage disease besides locally advanced and inflammatory breast cancers. If presurgical neoadjuvant therapy is performed, pathologic evaluation of the excised specimen determines the treatment efficacy of ongoing chemotherapy in the form of response rate. The treatment effect of breast tumor and nodal metastasis is graded as no residual tumor (complete response), probable or definitive response, and no definitive response (160). Pathologic complete response (pCR) is the absence of residual invasive cancer after evaluating the completely excised breast specimen and all sampled regional lymph nodes. If there is residual invasive carcinoma present, detailed quantification of residual disease, including residual tumor dimension, cellularity, proportion of in situ component, and the number of positive lymph nodes as well as the size of the largest metastasis, should be reported in order to accurately assess the residual cancer burden (161,162). Evaluation of treatment effects after neoadjuvant chemotherapy is an important prognostic indicator. Pathologic complete response is associated with increased disease-free survival and overall survival. No response or progression of the disease is associated with poor clinical outcomes (163,164). The treatment response of lymph nodal metastasis is documented separately from the breast tumor since the nodal response may have more prognostic importance than does

response in the breast (165). Reassessment of hormone receptor and HER2 status in residual cancer after neoadjuvant therapy should be considered in certain clinical settings (160).

Lymphovascular Invasion

Lymphovascular invasion (LVI) refers to the permeation of tumor cells into endothelium-lined lymphatic vessels and/or blood vessels in the breast tissue surrounding the invasive carcinoma. Peritumoral LVI is recognized in routinely stained slides as groups of tumor cells within an endothelium-lined space. Although not routinely employed, IHC markers for lymphatic and blood vessel endothelium (such as CD31, ERG, and D2-40) can be utilized to ascertain the presence of LVI and to differentiate it from tissue retraction artifact. LVI has been shown to be an adverse prognostic marker for local and distant recurrence (166,167). The presence of LVI is associated with an increased risk of axillary lymph node and distant metastases (168). It is used along with other clinical and pathologic parameters to assist clinical decision-making (169). LVI may also represent a treatment-resistant breast cancer component after neoadjuvant therapy, with residual tumor emboli in the lymphovascular space (170).

Pathologic Stage Classification

The most widely used system for staging breast carcinoma is the Tumor-Node-Metastasis (TNM)-based staging system developed by the American Joint Committee on Cancer (AJCC) in collaboration with the Union for International Cancer Control (UICC) (see Appendix). This system is based on the extent of the primary tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M). These are combined to create five stages (stages 0, I, II, III, and IV). It provides a standard nomenclature to define the anatomic extent of disease and disease progression risk assessment, which in turn facilitates clinical decision-making. This system is now in its 8th edition (15).

Pathologic staging (pTNM) captures information gathered after analyzing the surgically excised specimens. Following neoadjuvant therapy, post-therapy pathologic staging is recorded using the "yp" designator. The size of invasive carcinoma and the extent of local tumor invasion are used to generate a pT category. The number of positive regional lymph nodes and the size of the largest metastatic deposit are used to generate a pN category. The pathologic assignment of the presence of metastases (pM1) requires biopsy confirmation of the same tumor at the metastatic site. A major change in the AJCC Cancer Staging Manual 8th edition breast cancer staging is the addition of biological factor-based Prognostic Stage Groups in conjunction with the anatomic stage group. These include tumor grade, biomarker (HER2, ER, and PR) status, and multigene panel (such as Oncotype DX) status for selected subsets of breast cancer as elements required to assign stage in conjunction with anatomic information on the TNM categories. The incorporation of biomarkers and multigene prognostic panels allows for more refined tumor staging that reflects the prognostic and predictive significance of biologic factors.

Ancillary Studies

Biomarker testing should be performed on all primary invasive breast carcinomas and recurrent or metastatic tumors. Biomarker expression provides important information about prognosis and helps the selection of optimal combinations of locoregional treatments and systemic therapies. Commonly performed biomarkers include hormone receptors (ER, PR), HER2, a marker of proliferation (such as Ki-67), and for appropriate subgroups of breast cancers, a genomic prognostic panel if available. Hormone receptor status is determined to identify patients who may benefit from hormonal therapy and to provide additional prognostic information. About 70~80% of invasive breast cancers are positive for ER and PR, including almost all grade I and most grade II carcinomas. Studies have shown a substantial survival

benefit from targeted endocrine therapy for patients with ER-positive breast cancers (171). ER-negative, PR-positive carcinomas are rarely encountered. Patients with such tumors are also considered eligible for hormonal therapy. Quantification of positive cells is reported since the response rate to hormonal therapy directly correlates with hormonal receptor expression level. HER2 status is determined to identify patient eligibility for anti-HER2 therapy and to provide additional prognostic information. Approximately 15~20% of breast carcinomas are HER2-positive. HER2 gene amplification leads to its protein over-expression, which can be assessed by FISH and IHC tests, respectively. The percentage of Ki-67 positive tumor cells is determined to help stratify patients into good and poor prognostic groups, although the clinical utility of intermediate level of Ki-67 expression is rather limited (172). In recent years, multigene expression assays have been developed to help predict prognosis and the likelihood of response to specific treatment. Results of these proprietary assays, if available, are reported in this section.

In summary, this chapter presents essential information on the pathologic diagnosis of breast cancer, differential diagnosis from benign breast lesions, and interpretation of pathologic reports. The more commonly seen benign breast conditions can present clinical and radiographic findings that mimic breast cancer, requiring careful clinical and radiographic evaluation. In many cases, tissue biopsy is needed for definitive diagnosis. The majority of invasive carcinomas belong to invasive carcinoma of no special type (invasive ductal carcinoma). Several histologic subtypes are recognized since they confer distinct clinical characteristics. The pathologic characteristics of the tumor have prognostic significance. Important histologic prognostic parameters include tumor size, grade, lymphovascular invasion, and lymph node status. For Kiddbreast-conserving surgery, no invasive carcinoma on the inked surface is regarded as a negative margin, and a minimum of 2 mm from the inked surface is regarded as sufficient

resection for DCIS. Biomarker testing for ER, PR, and HER2 is routinely employed both as a prognostic *factor and as a predictive factor in identifying therapeutic targets. Besides standard biomarkers, multigene panels provide increasingly important prognostic information, particularly when clinical parameters and traditional prognostic parameters lead to equivocal prognostic prediction. The above prognostic and predictive information is summarized and effectively presented in a tabulated fashion in a pathology report, which in turn is utilized in the clinical decision-making process by a multidisciplinary team.

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Chapter 13

Principles of Breast Cancer Early Diagnosis

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WHO DECLARATION: Drs. Anderson and Ilbawi are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policies, or views of the World Health Organization.

Abstract

In most low- and middle-income countries (LMICs), breast cancer is diagnosed at a late stage, when treatment is generally less effective, more expensive, and more disabling. Two distinct approaches can be used to identify cancer early in its course – early diagnosis for symptomatic disease and screening of asymptomatic individuals in a target population. Early diagnosis programs are the priority for LMICs. Unfortunately, breast cancer patients in LMIC face many obstacles to achieving early diagnosis. Effective implementation of cancer early diagnosis programs should include community-based health promotion for cancer education and awareness, training, and deployment of health workers, and efficient patient navigation systems. Successful planning and implementation of such programs, along with robust monitoring and

evaluation, are necessary to effectively downstage breast cancer and ultimately improve mortality rates in LMICs.

Background

Breast cancer is the most common cancer globally and is the leading cause of cancer deaths among women worldwide, accounting for more disability-adjusted life-years lost by women globally than any other malignancy.[1] Breast cancer deaths disproportionately affect women living in low- and middle-income countries (LMIC), where the majority of deaths occur in women younger than 70 years old. Worldwide, 52% of the approximately 1.7 million breast cancer cases and 62% of breast cancer deaths occur in LMICs, [2] where the mortality is higher in LMICs compared to HICs.[3] Breast cancer 5-year survival exceeds 90% in HICs, compared to 66% in India and 40% in South Africa.[4] By 2040, 60% of the projected 3 million new breast cancer cases and 70% of the 1 million new deaths annually will occur in LMICs if current mortality trends remain unchecked.[5] The incidence of breast cancer is dramatically increasing in LMICs due to changing risk factors such as earlier age of menarche, late age at first birth, and lower rates of breastfeeding.[6, 7] Premature deaths and catastrophic health expenditures from breast cancer result in social disruption and generational impoverishment, orphaning children at devastating rates. In Sub-Saharan Africa, 100 cancer deaths in women under age 50 caused 210 children to become maternal orphans.[8] Additionally, maternal death from breast or cervical cancer in LMICs results in increased child mortality.[9]

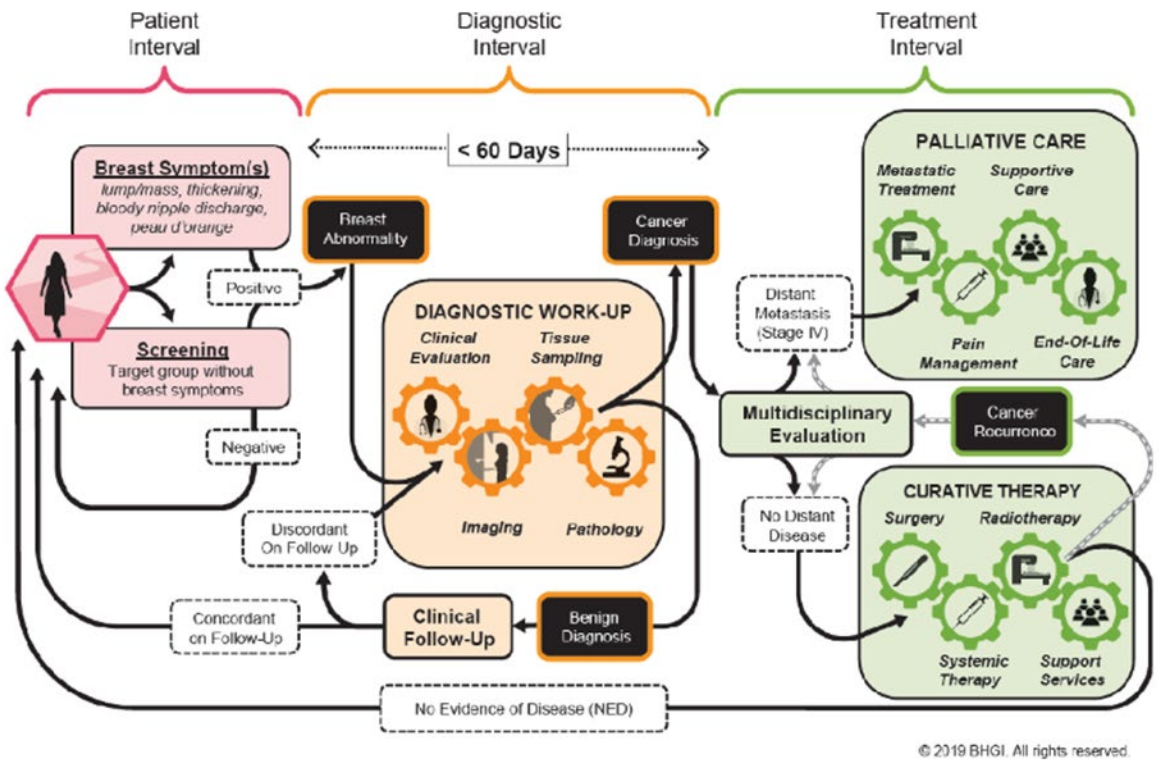
While breast cancer mortality dropped by 40% from 1989 to 2017 in HICs, minimal progress has been made in LMICs, a painful inequality marking a missed opportunity to improve women's lives globally through the reduction of premature mortality.[10] Higher mortality in

LMICs results from late-stage diagnosis and limited access to quality care, compounded by the lack of inclusion of breast cancer diagnosis and management as part of the universal health coverage commitment. In 2021, the World Health Organization (WHO) launched the Global Breast Cancer Initiative (GBCI).[11] The primary objective of GBCI is to reduce global breast cancer mortality by improving breast cancer early diagnosis rates and increasing access to prompt, comprehensive cancer management.

The Problem of Delayed Diagnosis

Breast cancer management requires that patients undergo an orderly process of initial presentation and accurate diagnosis followed by timely breast cancer treatment (Figure 1) .[12]

Figure 1. Universal Patient Pathway (reproduced with permission from the Breast Health Global Initiative)

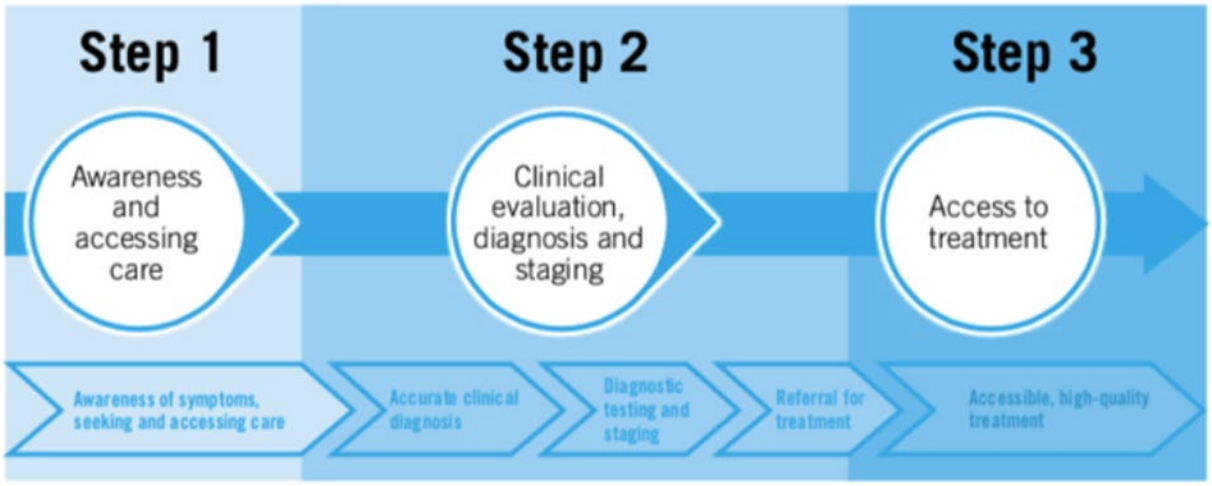


Significant delays of months or more than a year from the first presentation to the health system prior to the initiation of breast cancer treatment contribute to late-stage diagnosis and elevated

mortality rates in LMICs. A substantial proportion of women with breast cancer in LMICs are diagnosed at a late stage (AJCC stage III or IV), ranging from 30-50% in Latin America to 75% in Sub-Saharan Africa. [13, 14] Late-stage diagnosis markedly reduces survival, and treatment is both difficult and resource intensive. The great majority of these late-stage cancers are initially detected by the patient herself based on changes that she appreciates as a lump, thickening or other progressive change. [15, 16]

Effective early diagnosis of cancer involves three steps (Figure 2).[17]

Figure 2. Steps in early diagnosis of cancer (reproduced with permission from the World Health Organization).[14]



The first step, "presentation," requires awareness and ability of the general public to seek medical attention promptly when symptoms of suspected cancer arise. Many women in LMICs don't seek medical attention early. For example, Mody et al. reported that 85% of women in Rwanda presented more than 12 weeks after a breast abnormality was noted; 41% experienced a delay greater than one year.[18] In the second step, "diagnosis," healthcare providers must be able to recognize early signs and symptoms of cancer with accurate, accessible laboratory services and imaging devices. The Breast Health Global Initiative (BHGI) recommends that the

diagnostic interval that includes clinical evaluation, imaging, and biopsy be completed within 60 days.[12] Survival outcomes are worse if this interval is longer than three months.[19] Yet, few LMICs achieve a diagnostic interval within 60 days.[20] The final step, "treatment," requires timely access to high-quality, affordable health services to initiate cancer therapy. The capacity to effectively diagnose and treat clinically detectable breast cancer begins with a clinical breast assessment by taking a medical history and performing a focused physical examination, including a clinical breast exam (CBE). CBE is followed by diagnostic imaging, tissue sampling, and pathologic evaluation, the so-called "triple test" of breast diagnosis.[21] At the same time, education of primary care providers to recognize the early signs and symptoms of breast cancer is necessary for prompt referral through the healthcare system.

Barriers to Early Diagnosis

In order to decrease the proportion of patients with late-stage breast cancer, a better understanding of the causes of delay in care is critical to develop relevant and effective interventions. Prior studies have described several categories of barriers to early diagnosis including delays in patients seeking care, geography, and healthcare system disorganization. Delays in patients seeking care are a major contributor to late-stage diagnosis in LMICs. Patient misconceptions primarily revolve around fear, especially regarding treatment options and the social consequences of their diagnosis. Women from Ghana describe an intense fear of surgery causing death and disfigurement, as well as the side effects of chemotherapy. [22] Bangladeshi patients report stories of their husbands divorcing them when they find out their wives had breast cancer, casting them into social abandonment and even homelessness.[23] Many patients in Ethiopia believe that their breast cancer cannot be treated medically, and they lack trust in the medical system.[24] A systematic review identified that 88% of studies assessing barriers to breast

cancer care reported health literacy as a primary barrier.[20] Patients frequently mistakenly associate breast cancer symptoms with breastfeeding, menopause, or other normal changes.[22] In a study from Tanzania, only 31% of women correctly identified risk factors for breast cancer.[25] Using a qualitative study design, Taib et al. reported that fatalism and lack of individual decision-making were barriers to early breast cancer detection in Malaysia.[26] National health insurance funds covering cancer care are less common in LMIC [27], and the costs of breast cancer treatment can be catastrophic. Furthermore, the financial consequences of non-medical costs can be prohibitive to many patients seeking care. For example, at Hôpital Universitaire de Mirebalais in Haiti, patients receive free breast cancer medical treatment; however, O'Neill et al. reported that more than two-thirds of patients met conservative criteria for catastrophic medical expenses (defined as spending more than 40% of their potential household income on out-of-pocket payments), and 52% of patients were forced into debt.[28]

Geography often limits early breast cancer detection because many women in LMICs live great distances from the limited number of diagnostic centers. Additionally, transportation is often unreliable, and costs are high. In Sub-Saharan Africa, greater distance to diagnostic/treatment facilities resulted in a significant delay in diagnosis and a higher proportion of late-stage breast cancer.[29]

The greatest delays to breast cancer diagnosis in LMICs are not attributable to patients delaying care but rather occur after the first medical consultation has taken place.[30] Even when a patient seeks care soon after the onset of symptoms (i.e., "early presentation"), this does not always translate to early diagnosis and treatment. For example, if the first or subsequent providers do not have the appropriate training or knowledge to recognize early breast cancer and do not know where or how to refer for necessary diagnostic intervention(s), diagnostic delay will

result. In a study from Botswana, many healthcare providers at local clinics did not recognize cancer symptoms and misdiagnosed women as having other common health problems such as sexually transmitted diseases or tuberculosis.[31] Even if a breast symptom is recognized as suspicious by a healthcare worker, there may be failures within the healthcare system referral, lack of equipment, delay to biopsy, and prolonged laboratory turnover time that further delay breast cancer diagnosis.[32] For example, in a study from Rwanda, the median time from biopsy to pathology report was 23 days, which is almost half the entire diagnostic interval recommended by the BHGI.[33] Poor coordination and lack of patient navigation result in late-stage breast cancer and higher mortality rates.

Strategies to Improve Early Diagnosis

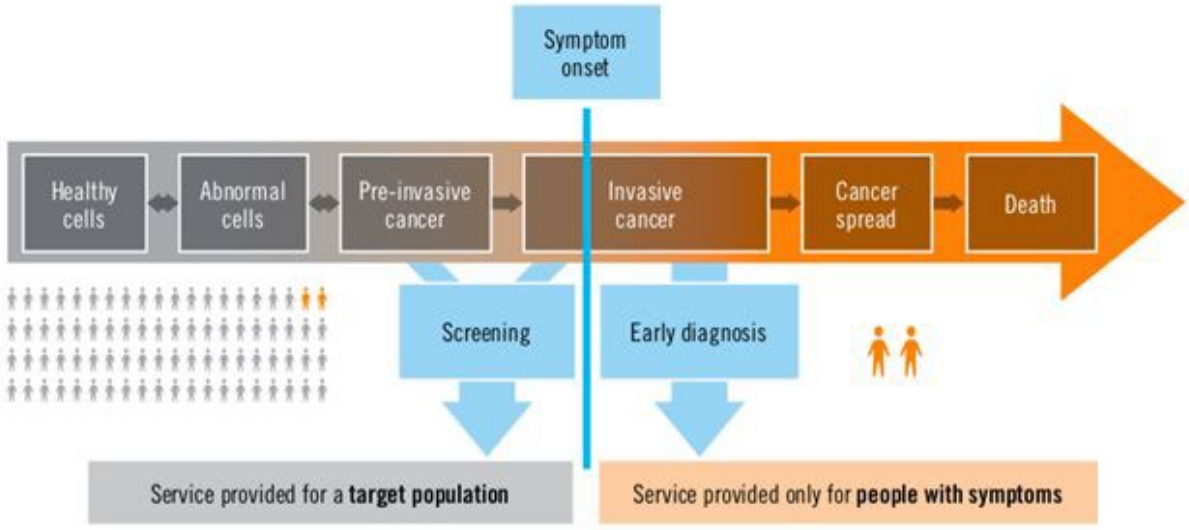


Figure 3: Distinguishing screening from early diagnosis according to symptom onset (reprodeuced with permission from the World Health Organization).[14]

Communities that have achieved annual mortality reductions have done so, in part, because of the reductions in the proportion of women who are diagnosed with late-stage disease.[34,35] Breast

cancer prevention through health promotion for risk-reduction strategies (encouraging lactation, avoiding obesity, limiting alcohol) are foundational steps for cancer control but must be implemented alongside early detection programs.[36] WHO has defined two distinct but related strategies to promote the early detection of cancer: i) early diagnosis, that is, the recognition of symptomatic cancer at an early stage, and ii) screening, that is, the identification of asymptomatic disease in a target population of apparently healthy individuals[37] (Figure 3). In such settings, efforts to promote early diagnosis are a *prerequisite* to population-based mammographic screening, which is not feasible in most LMICs. Health planners, policymakers, and other stakeholders, including clinicians, educators, community members, and advocates, should be aware of the health system requirements as well as the overall costs of these approaches to breast cancer early detection to make effective investments, plans, and policies. A common misconception is that mammographic screening is required to achieve this level of breast cancer downstaging. While population-based mammographic screening reduces breast cancer mortality by over 20%,[38] early diagnoses of breast cancer in the absence of mammographic screening have successfully downstaged disease to levels approaching those seen with mammographic screening.[39] However, CBE may be an effective alternative screening modality to mammography. In a prospective, cluster-randomized clinical trial in Mumbai, biennial CBE significantly downstaged breast cancer at diagnosis and led to a nearly 30% reduction in mortality in women $\geq$ 50 years. [34]

A primary challenge to the successful implementation of any breast cancer program is the ability to manage clinically detectable disease and to do so in an equitable manner for the target population, that is, for all adult women with signs and/or symptoms suggestive of breast cancer. Once she presents to the healthcare system with signs and/or symptoms in the breast, diagnostic

services need to be available such that a prompt and accurate diagnosis (benign versus malignant) can be provided. Thus, patient navigation programs and effective workflow pathways through local healthcare systems are necessary to overcome barriers to early diagnosis in LMICs. *Alerta Rosa* is a patient navigation program created in Nuevo Leon, Mexico, that seeks to break down medical care barriers to reduce delays and improve quality of care.[40] *Alerta Rosa* identifies and prioritizes patients with abnormal breast findings to accelerate their medical assessment and decrease health system delays. After initiating this program, the median time from alert activation to treatment initiation was only 33 days. In contrast, the median time between patients' identification of breast abnormalities and the beginning of treatment is seven months in Mexico.[30]

Training and adoption of breast ultrasonography is another strategy that may facilitate early breast cancer detection in some resource-limited areas. In contrast to diagnostic mammography, breast ultrasound is portable, less expensive, and widely available in LMICs for patients with breast symptoms. In a systematic review and meta-analysis, Sood et al. reported that breast ultrasound's pooled sensitivity and specificity in LMICs were 89.2% and 99.1%, respectively. [41] Additionally, breast ultrasound provides an ideal guide to biopsy any suspicious findings. Thus, the patient does not have to be referred to a surgeon for a surgical breast biopsy. Current point-of-care ultrasound probes can connect to cell phones, tablets, and various cloud services. Training general physicians to use such devices for women with breast symptoms can potentially shorten diagnostic intervals.

Patient education interventions may lead to earlier diagnosis and may downstage breast cancer in LMICs. In Indonesia, Setyowibowo et al. evaluated the effectiveness of a self-help intervention named PERANTARA, which is a culturally sensitive intervention that consists of

health education that uses testimonials and a narrative story. In a cluster randomized crossover design across four hospitals, the use of PERANTARA significantly reduced the time to definitive diagnosis in women with breast cancer symptoms.[42]

Implementation programs that focus on physician training may also improve rates of late-stage breast cancer. The Department of Radiotherapy and Oncology in Sarawak General Hospital in Malaysia instituted a low-cost early cancer surveillance program that consisted of i) training healthcare staff in hospital and rural clinics to improve their skills and ii) raising public awareness through pamphlets, posters, and sensitization.[35] Approximately 400 healthcare workers were trained in early diagnosis techniques, including clinical breast examination. Four years after implementation of this program, the proportion of stage III/IV breast cancer was reduced from 60% to 35% in Sarawak, Malaysia, in the absence of a population-based screening mammography program.

Conclusion

Early cancer diagnosis and prompt, appropriate treatment are widely applicable priorities in public health. Current disparities in breast cancer mortality rates between LMICs and HICs are reversible. Much more can and should be done to assure more equitable outcomes for marginalized women/communities in countries of all income levels. In many countries, significant delays before diagnosis and initiation of breast cancer treatment contribute to late-stage diagnosis and elevated mortality rates. While breast cancers do not change in days or weeks, breast cancer survival rates begin to erode with delays greater than three months.[19] For this reason, the establishment of accessible, rapid diagnosis systems (clinical evaluation, imaging, tissue sampling, pathology reporting) is needed. Diagnostic services can be technically

simple but often suffer from systemic disorganization. Effective implementation programs should include community-based health promotion for cancer education and awareness, training and deployment of health workers, and efficient patient navigation programs that facilitate earlier diagnosis, translating to resource conservation and lives saved.

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Chapter 14

Detection and Diagnosis of Metastatic Breast Cancer in Low- and Middle-Income Countries

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Introduction

The global burden of metastatic breast cancer (MBC)

Globally, breast cancer is the most commonly diagnosed female cancer and the leading cause of cancer-related mortality in women.[1] While the worldwide incidence of breast cancer is on the rise, the distribution of disease incidence is skewed, with the majority of new breast cancer diagnoses occurring in low- and middle-income countries (LMICs), while high-income countries (HICs) are collectively experiencing a decline in breast cancer incidence.[1] Similarly, breast cancer-specific mortality disproportionately affects LMICs. According to the most recent estimates, 5-year survival for women with breast cancer in LMICs is 40-66% compared to 90% for women with breast cancer in the United States (US).[2]

The higher mortality rates observed in LMICs can be attributed, in large part, to higher rates of advanced disease stage at presentation and limited access to care, leading to delays in diagnosis and treatment. Moreover, the average age at diagnosis of women in LMICs is 10-15 years younger than that of women in HICs, further underscoring the asymmetry of the disease burden in LMICs. A 2016 meta-analysis showed that over 75% of women with breast cancer in

sub-Saharan Africa presented with stage III or IV (i.e., metastatic) disease.[3] Across the globe, in most LMICs, 20-30% of patients present with metastatic breast cancer (MBC), compared to only 3-6% in the US.[4]

MBC is a heterogeneous disease with metastatic spread most commonly occurring in the bones, followed by the lungs, liver, and brain.[5,6] The heterogeneity of the disease is reflected in the median survival of women with MBC, which varies according to tumor biology, metastatic site, and access to treatment. Compared to all other metastatic sites, bone-only metastases have the highest 5-year survival rates at 21% compared to 11% for visceral metastases.[7] Furthermore, patients with hormone receptor-positive (HR+) breast cancer are more likely to develop bone metastases, whereas patients with tumors that overexpress human epidermal growth factor receptor-2 (HER2) have higher rates of brain and liver metastases.[8] Increasingly, women with MBC, especially those with HER2-positive (HER2+) and HR+ disease, are living longer in high-income countries as a result of improvements in systemic therapies for those breast cancer subtypes. Unfortunately, access to these new therapies is lacking in LMICs, where survival for women with MBC remains dismal, reflecting a disparity in treatment opportunity that translates directly into disparities in outcome.

Diagnosing MBC

Since the burden of breast cancer in LMICs is heavily skewed towards advanced-stage disease in young women, it is imperative that cancer care delivery be structured to include evaluation and management of MBC as well as early detection. The diagnosis and management of MBC are complex and should involve a multidisciplinary approach with the participation of all available treatment team members. Patients with MBC may be diagnosed as part of a work-up

for an asymptomatic new or recurrent breast cancer diagnosis or may present with a constellation of signs and symptoms that are largely dependent on the site of metastatic spread.

At the outset of any diagnostic evaluation of a patient with MBC, goals of care should be established based on a comprehensive and honest discussion about patient-related and healthcare system-related factors. MBC is an incurable disease, with a median survival measurable in months, and it is important to keep in mind that the goal for these patients is often to alleviate symptoms and prioritize quality of life. Prolongation of survival and quality of life are highly dependent on the availability of resource-intensive, expertly coordinated, and culturally sensitive care.

In the event that potentially metastatic lesions are detected and goals of care include systemic treatment, histologic confirmation of the diagnosis should be performed, if possible, with a tissue biopsy and assessment of estrogen receptor (ER), progesterone receptor (PR), and HER2 biomarkers should be performed.[9] This confirmation requires the availability of a physician capable of performing the biopsy and all the infrastructure required for pathologic assessment of the tissue. Diagnostic and treatment capacity is variable from country to country, and the recommendations highlighted in this chapter must be considered within the framework of the health care system in which a patient is being evaluated.

Detection of metastases in patients with newly diagnosed or prior history of breast cancer

Evaluation for MBC often begins when a patient is first diagnosed with breast cancer, is dictated by consensus guidelines, and follows a stage-based approach. In the US, approximately 75% of women with MBC are diagnosed subsequent to a primary diagnosis of breast cancer,

whereas an estimated 25% are diagnosed with de novo MBC.[10] This distribution is likely very different in LMICs, but accurate estimations from these countries are lacking.

The staging work-up of all patients with a new diagnosis of breast cancer should begin with a complete history and thorough physical exam. Specific attention should be placed on symptoms associated with MBC (**Table 1**). This initial evaluation should be used to triage patients since those with early-stage disease who have no symptoms of distant metastases do not need any further staging evaluation.[11] Notably, however, this recommendation is based on data from HICs, where the incidence of metastatic disease in asymptomatic patients with early-stage breast cancer (stage I-II) is < 1%.[12]

Site of metastasis	Symptoms
Bone	• Pain, fracture, decreased mobility
Brain/Central Nervous System	• Headache, confusion, weakness, seizures, cranial nerve palsies, speech impairment
Liver	• Abdominal pain, bloating, coagulopathy, decreased appetite, jaundice, pruritus, and other symptoms of liver failure
Lung	• Chest pain, dyspnea, hemoptysis, cough
Nonspecific/generalized	• Fatigue, malaise, decreased appetite, weight loss

Table 1. Symptoms of metastatic breast cancer by the site of metastasis

The definition of early-stage disease can be confusing as breast cancer staging has recently moved from an anatomic to a prognostic model that incorporates grade and biomarker status in the most recent edition of the American Joint Commission on Cancer (AJCC) staging manual,[13] a change based on emerging evidence that the biology of breast cancer drives metastatic potential more than the anatomic extent of disease does.[5,14] From a clinical perspective, early-stage breast cancer patients are those with operable disease and who would not derive significant benefit from neoadjuvant systemic therapy (tumors ≤ 2cm, clinically node-negative, HR+).[9,11,12] For these patients, in the absence of symptoms, care can proceed directly to

the locoregional treatment of the primary tumor. In patients with early breast cancer but with symptoms or signs suggestive of distant metastases, additional work-up can be selectively pursued based on the clinical presentation.

For patients with locally advanced disease at diagnosis (tumors > 5cm, clinically positive regional lymph nodes) or smaller tumors with aggressive biology (e.g., triple-negative, HER2+, high genomic risk) that may benefit from neoadjuvant systemic therapy (NST), routine staging is recommended even in the absence of symptoms.

Again, it is important to note that the vast majority of clinical practice guidelines were developed in resource-rich settings, and care should be taken when applying them to LMICs. For instance, if resource restrictions limit the availability of NST, patients should be spared unnecessary staging scans and lab tests that would be costly and delay surgical treatment. In the absence of advanced imaging, such as CT scans and nuclear medicine studies, less resource-intensive approaches to diagnosing potential metastases in patients with known breast cancer may be attempted using a combination of imaging and lab work. For example, abdominal ultrasound plus LFTs can be used to work up the patient with ascites and abdominal pain concerning symptomatic visceral metastases, while 2- and 3-view X-rays of symptomatic sites plus alkaline phosphatase could be used to evaluate patients with bone pain. If metastatic disease cannot be definitively confirmed or these alternative tests are not available, the choice to empirically treat likely metastatic disease must be made through a process of shared decision-making between physician and patient, taking into account the availability, costs, risks, and benefits of empiric treatment; the patient's baseline health; and her goals of care.

Staging studies for distant metastases in primary breast cancer

When indicated, the minimum recommendations for systemic staging of a patient with breast cancer include blood tests (complete blood count [CBC], complete metabolic panel [CMP] including electrolytes and liver function tests [LFTs]) and imaging studies of the chest, abdomen, and bony skeleton (**Table 2**). Due to the low prevalence of metastatic disease in patients with early-stage breast cancer, the yield of routine staging studies in this patient population is 1% for stage I and 1.9% for stage II disease and is not recommended in most international consensus guidelines.[9,11,12,15,16]

Society	Target population	Staging studies
NCCN	• T0-4, N1-3, M0 • T2-4, N0, M0	• Chest CT • Abdominal/pelvic CT or MRI • Bone scan or sodium fluoride PET/CT
ESMO	• Clinically positive nodes • T3-4 • Aggressive biology • Signs/symptoms of metastatic disease	• Chest CT • Abdominal US, CT, or MRI • Bone scan
CCO	• Stage III (as per AJCC 7th Ed.)	• Anatomic imaging: CXR, liver US, or chest/abdominal/pelvic CT • Functional imaging: PET/CT, bone scan

Table 2. Society Consensus Guidelines for Systemic Staging in Breast Cancer Patients

CCO: Cancer Care Ontario. CXR: chest X-ray. CT: computed tomography. ESMO: European Society of Medical Oncology. MRI: magnetic resonance imaging. PET: positron emission tomography. NCCN: National Comprehensive Cancer Network. US: ultrasound.

For patients with locally advanced breast cancer or for those who will receive NST, the most recent National Comprehensive Cancer Network (NCCN) guidelines recommend a diagnostic chest CT, abdominal/pelvic CT or MRI, and a bone scan or sodium fluoride PET/CT.[11] Similarly, the European Society of Medical Oncology (ESMO) recommends a CT scan of the chest; abdominal imaging with an ultrasound (US), CT, or MRI; and a bone scan.[9] The 2019

Canadian guidelines from Cancer Care Ontario (CCO) recommend anatomic (chest X-ray, liver ultrasound, chest/abdominal/pelvic CT scan) or functional imaging (PET/CT, bone scan).[12]

Diagnosing de novo MBC

Women with MBC can also present with de novo metastases. As with recurrent disease, clinical presentation and prognostication vary based not only on the site and burden of metastases but also on the biology of the disease. Given the burden of de novo MBC in LMICs, healthcare providers must have a high index of suspicion when evaluating these patients. Pre-treatment assessment of patients with suspected de novo MBC should proceed similarly to patients with early-stage disease with a thorough history and physical exam, and clinical signs and symptoms should guide metastatic work-up. If clinically indicated, the evaluation can begin with a CBC and CMP, including LFTs. As with patients found to have distant metastatic recurrence or progression after an initial diagnosis of operable breast cancer, imaging studies for the detection of metastases should be used judiciously and considered in the context of the therapeutic options available to the patients.

Metastatic disease by anatomic site

Bone metastases

Skeletal bones are the most common site for breast cancer metastases, with some studies reporting a prevalence of up to 80% in patients with MBC. Women with isolated bone metastases can have significantly prolonged survival as compared to patients with visceral or CNS metastases; in one study, median survival in women with solitary bone metastases was five times as long as for women with combined bone and visceral metastases (65 vs. 13 months).[17]

Patients with bone pain or elevated alkaline phosphatase should initially be evaluated with plain radiographs, keeping in mind that X-rays are the least sensitive of the imaging modalities for skeletal metastases (**Table 2**). If local capacity exists, bone scan, CT scan, and MRI can all be used to bolster the diagnostic evaluation. While PET/CT is often used for staging and to follow response to treatment, there is limited evidence to support its use for staging purposes due to its high false-negative rate for lesions < 1cm and its low sensitivity.[11]

Lung metastases

An analysis of the Surveillance Epidemiology and End Results (SEER) database showed that about 1/3 of patients with MBC had lung metastases across all biologic subtypes. Patients with HER2+ and triple-negative breast cancer (TNBC) subtypes were more likely to develop lung metastases as compared to HR+ breast cancer patients. The results of this study showed that the median survival of patients with isolated lung metastases was 25 months, which is comparable to the survival associated with other visceral metastases. In addition, median survival was the lowest for patients with TNBC at 11 months.[18] A chest X-ray or a chest CT can be considered in the patient presenting with a new onset of pulmonary symptoms (**Table 2**).

Liver metastases

According to evidence from high-resource settings, approximately 50% of women with MBC develop liver metastases, with a median survival of 3 to 22 months with appropriate systemic and ablative therapies.[19] Abdominal imaging such as an ultrasound or abdominal/pelvic CT can be obtained for a patient with abnormal liver enzymes or symptoms suggestive of liver metastases (**Table 2**).

Brain metastases

Breast cancer is the second most common cause of brain metastases after lung cancer, with the HER2+ and TNBC variants having higher rates of brain metastases compared to their HR+/HER2- counterparts. The true incidence of breast cancer-associated brain metastases, however, is unclear, and estimates are lacking in LMICs.

Since routine brain imaging is not recommended for patients with breast cancer, patients should be assessed for metastases when new neurological symptoms are present. A CT scan of the head or, if available, an MRI of the brain can be used to detect brain metastases, with MRI being the more sensitive study.

Challenges associated with treating MBC in LMICs

Caring for women with stage IV breast cancer in LMICs can be extremely challenging given the severe limitations in healthcare capacity faced by many oncologists in many of these countries. However, investment in healthcare capacity-building for patients with MBC in LMICs is fundamental from both a public health and economic perspective, especially in light of the young age at which many women are diagnosed in these areas. With increasing global incidence of the disease, MBC costs are also rising. The economic burden of stage IV breast cancer is comprised not only of the direct costs of management and treatment borne by the healthcare system and the patient but also the indirect costs of care associated with the broader impact of the disease on the patients, their families/caregivers, and society. The true cost of MBC is unclear and widely underestimated as most cost-of-illness studies examine direct costs alone and are limited to evidence from high-income countries. For example, the average direct cost of stage IV breast cancer is estimated to range from 30,000 to 48,000 euros per patient in Belgium,

France, and the United Kingdom, while the direct cost per MBC patient in the United States was significantly higher at $153,000.[20-22]

Although estimation of direct costs is an important health system baseline measure, cost comparison between countries is not always feasible due to variation in disease epidemiology and healthcare system financing and resource allocation. In addition, the unique nature of MBC as a disease experienced by young women in LMICs makes the indirect costs of the disease particularly significant to society. As previously mentioned, in LMICs, MBC affects women at a median age that is 10 to 15 years younger than women in HICs. Women in this age group play important roles within the economy and within the home, and the impact of their lost productivity can account for upwards of 50% of the total cost of their stage IV disease.[23] Since it is difficult to quantify the real costs using the available evidence, the societal impact of MBC is often overlooked by policymakers and other stakeholders. Furthermore, decision-makers need to recognize that local attitudes towards metastatic disease can exacerbate the isolation and distress experienced by women with MBC, further compounding the economic burden of the disease. Inaccurate, culturally informed perceptions and stigmatization of MBC contribute to the delayed presentation of some women.[24-26]

Addressing the challenges associated with treating MBC in LMICs requires a multifaceted approach, which includes increasing healthcare system capacity, establishing a system of data collection and evidence generation to inform health policy, and raising public awareness. There is evidence that successful policy interventions that prioritize cancer care on a national level can improve oncologic outcomes for all cancer patients.[27] Unfortunately, based on World Health Organization (WHO) data, almost 75% of countries in Africa lack any sort of national cancer plan. However, policymakers in LMICs can look to multilateral organizations for support in this

venture. For example, in 2013, the WHO prioritized cancer control as part of its Global Action Plan and committed to a goal of having 80% of essential medicines available across the globe. For MBC, this included chemotherapy, endocrine therapy, and HER2-targeted therapy.[28] Several organizations, such as the Breast Health Global Initiative (BHGI) and the Pan American Health Organization (PAHO), have developed resource-stratified guidelines for various income levels.[29] For the most part, these recommendations address early detection and locoregional management strategies for breast cancer, but the implementation framework proposed by these guidelines (baselining, identifying needs and barriers, goal setting, and costing) is still a valuable resource for local stakeholders involved in the care of patients with MBC.

Until screening programs and other early-detection strategies are successful at shifting the presenting stage of breast cancer at a population level, healthcare providers, researchers, and policymakers must work to ensure equitable access to cancer care in order to improve the lives of women living with MBC.

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Chapter 15

Principles of Neoadjuvant Therapy for Locally Advanced Disease

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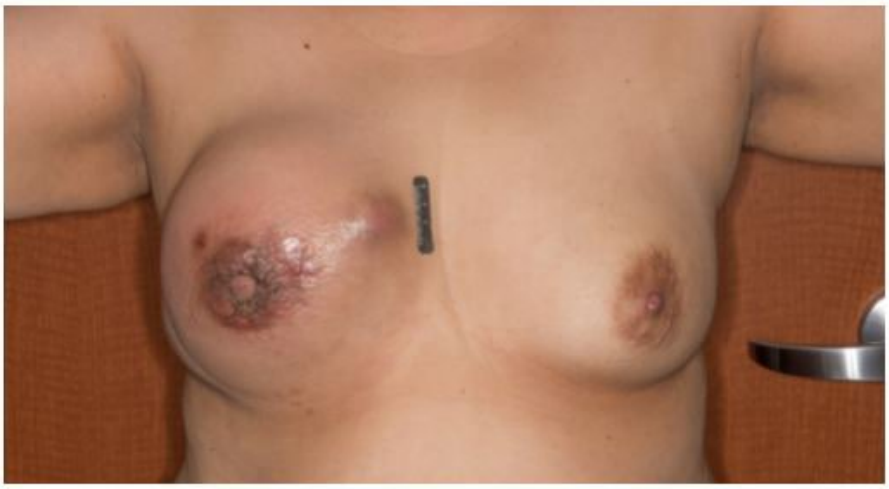
Keywords: Neoadjuvant chemotherapy, locally advanced breast cancer, low/middle-income counties, neoadjuvant endocrine therapy

Clinical Scenario



Locally advanced breast cancer of the right breast.

A 51-year-old female presents with a self-palpated right breast mass that has been present for 1 year. She states that the mass was the size of a golf ball but has recently increased in size. She also reports skin changes to her nipple-areolar complex within the past 2 weeks. On physical exam, the right breast is enlarged compared with the left. The entire breast is hardened on

palpation with diffuse skin thickening. Several enlarged lymph nodes are palpable in the right axilla.

Introduction

Locally advanced breast cancer describes a wide distribution of breast neoplasms. They include primary tumors greater than 5cm, tumors involving the skin or chest wall, and extensive disease within the regional lymph node basins. In countries with high rates of mammographic screening, a minority of patients present with locally advanced disease.[1] Due to various factors, including inadequate resources for early detection and stigma surrounding breast cancer, this is not the case in low and middle-income countries (LMC) where a more significant portion of patients present with stage 3 or stage 4 disease.[2-4] While surgery remains integral in the treatment of locally advanced breast cancer, multimodality therapy has been shown to have a favorable impact on overall and disease-free survival. Recently, the use of neoadjuvant systemic therapy has become more widespread and is now an integral part of the treatment algorithm for patients with locally advanced breast cancer. The National Comprehensive Cancer Network (NCCN) and the Breast Health Global Initiative (BHGI) have developed resource-stratified guidelines in the treatment of breast cancer and have both adapted neoadjuvant systemic therapy as the primary recommendation for patients presenting with locally advanced breast cancer.[5-7]

Systemic therapy presents one of the most significant challenges to breast cancer care in LMC due to a variety of factors. Although many chemotherapeutic agents have been included in the World Health Organization (WHO) Model List of Essential Medications, access barriers to cancer drugs remain problematic in LMC.[8] Additionally, healthcare infrastructure and providers trained in the delivery of systemic therapy are lacking. Despite these limitations, neoadjuvant

systemic therapy is the preferred initial treatment for patients with locally advanced breast cancer. This chapter will outline key, resource-stratified principles for neoadjuvant systemic therapy in the treatment of locally advanced breast cancer in LMC.

Diagnosis and Staging

When a patient presents with suspected locally advanced breast cancer, obtaining a tissue diagnosis and assessing the extent of the disease is key prior to initiating neoadjuvant systemic therapy. Initial evaluation should consist of a complete patient history and physical examination, including a comprehensive exam of the breasts and regional lymph node basins. This will allow the provider to identify the extent of local disease, assess for signs and symptoms of metastatic disease, and gain insight into the patient's ability to tolerate systemic therapy and surgery. The breasts should be examined with the patient in the upright and supine positions with arm-raising maneuvers, noting the presence of asymmetry between the bilateral breasts, nipple changes, and skin changes. If a palpable breast mass is present, it is essential to obtain a focused history from the patient, including the length of time the mass has been present and if there have been recent changes in size because a rapidly growing mass may alter treatment plans. Particular attention should be applied to evaluate for signs of chest wall involvement, such as a fixed, immobile breast mass or animation of the mass when flexing the pectoralis muscles. Palpation of all regional lymph node basins to assess for enlarged or matted nodes should be performed bilaterally to evaluate for clinical lymph node metastasis. Breast imaging

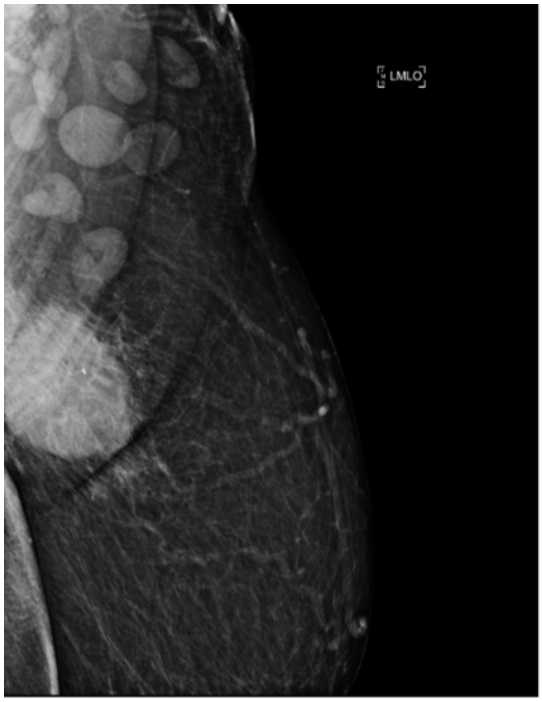


Figure 1: Bulky axillary adenopathy seen on mammogram

with ultrasound and, if resources allow, with mammogram will assist in evaluating the extent of local disease (Figure 1). The ultrasound exam should include not only the breast but also the regional lymph node basins, comprised of the axillary, infraclavicular, supraclavicular, and internal mammary basins. Breast imaging will also allow for imaged guided biopsy of the primary breast mass and abnormal appearing lymph nodes. If neoadjuvant systemic therapy is planned, photography should be used to document the scope of disease at presentation, especially if there is skin or nipple involvement, to monitor response to therapy and optimize surgical and radiation treatment planning.

Tissue sampling in order to confirm the presence of invasive cancer is essential prior to initiating treatment. If breast imaging is not readily available and a breast mass is present on the exam, palpation may be used to guide the needle biopsy. If skin changes are present or inflammatory breast cancer is suspected, a skin punch biopsy may also be considered. In cases where abnormal appearing lymph nodes are seen on ultrasound, fine needle aspiration or core biopsy of the node that has maximal impact on staging should be performed, for example, biopsy of an abnormal supraclavicular node should be prioritized over biopsy of an abnormal level 1 axillary node. Although systemic treatment can be given without known hormone receptor status, determining estrogen receptor (ER) and progesterone receptor (PR) status is important in optimizing medication selection in both the preoperative and adjuvant settings, therefore ER/PR testing is recommended at all resource levels by the NCCN and at limited resource level centers and above by the BHGI. ER status testing without PR testing is acceptable if cost-saving measures are needed.[9] Even though trastuzumab has led to improvements in survival for patients with HER2-positive breast cancer, routine testing for HER2 status is not recommended by either the NCCN

or BHGI. Because trastuzumab is cost-prohibitive in most low and middle-income countries, unless HER2 targeted therapy is available, HER2 status testing is not indicated.[6,7]

Patients presenting with locally advanced breast cancer are at high risk for *de novo* metastatic disease therefore, staging studies should be performed. Information obtained from the history and physical exam, such as bone pain, headache, shortness of breath, or abdominal pain, should be used to guide additional workup if resources allow. The NCCN recommends comprehensive blood counts for all resource level centers and comprehensive metabolic panels including liver function tests and alkaline phosphatase for core resource level centers. If resources allow, chest X-ray, abdominal ultrasound, and plain radiograph of symptomatic bony sites are also recommended. In centers with enhanced resources, a CT scan of the chest, abdomen, and pelvis is recommended for staging.[7](Figure 2)

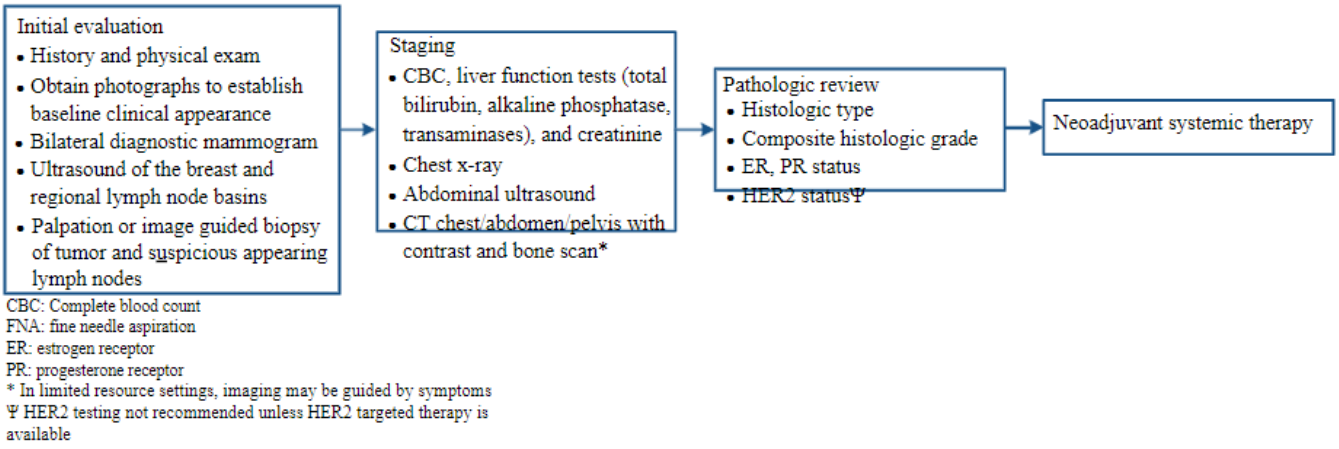


Figure 2: Pretreatment evaluation algorithm for locally advanced breast cancer

Systemic Therapy

Neoadjuvant systemic therapy is an integral part of the multidisciplinary treatment of locally advanced breast cancer. If resources allow, it is the best initial approach for patients with

inoperable or operable locally advanced breast cancer. There are several advantages to neoadjuvant systemic therapy. First, initially, inoperable cancers may be rendered operable after preoperative systemic treatment. Secondly, in centers where breast conservation is offered, neoadjuvant therapy may increase the rate of eligibility for breast conservation. Third, it allows for *in vivo* assessment of tumor response to therapy, which is predictive of long-term outcomes and allows for regimen adjustments if no response is seen or if there is disease progression. Lastly, the information gathered in the neoadjuvant setting can be used to guide adjuvant treatment. There are also drawbacks associated with neoadjuvant therapy, including the loss of pretherapy pathologic staging. While uncommon, it is also possible for tumor progression to occur during systemic therapy, which leads to delay in locoregional treatment.

Several randomized trials have shown no difference in long-term outcomes between preoperative and postoperative systemic therapy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 evaluated 1,523 women who were randomly assigned to receive doxorubicin and cyclophosphamide (AC) preoperatively or in the adjuvant setting and were followed for 9 years. The study showed that there were no statistically significant differences in overall or disease-free survival between the two groups. There was a slightly higher rate of ipsilateral breast tumor recurrence (IBTR) in the preoperative therapy group (10.7% vs. 7.6%) however, it was not statistically significant. More women in the neoadjuvant systemic therapy cohort received breast conservation when compared to those who had adjuvant systemic therapy, especially for patients with tumors larger than 5cm. The NSABP B-18 also showed that primary tumor response to neoadjuvant chemotherapy correlated with long-term outcomes. Overall survival for patients with pathologic complete response (pCR) was 85% compared to 73% for those with residual cancer on pathologic examination. Disease-free survival was also higher in the pCR group (75%

vs. 58%).[10] The NSABP B-27 evaluated the addition of docetaxel to preoperative AC. 2,411 women were randomly assigned to one of three groups 1) AC followed by surgery, 2) AC plus docetaxel followed by surgery, or 3) AC followed by surgery and adjuvant chemotherapy with docetaxel. The study showed the addition of docetaxel in the neoadjuvant or adjuvant setting had no impact on overall or disease-free survival however, the addition of preoperative docetaxel doubled the rate of pCR, which was associated with statistically significant longer disease-free and long-term survival. This confirmed that tumor response may be used as a surrogate predictor of long-term outcomes.[11] The 2008 update to the NSABP B-18 and B-27 trials confirmed the findings that there were no differences in long-term outcomes for patients receiving systemic therapy in the neoadjuvant or adjuvant setting and the addition of docetaxel led to significantly higher rates of pCR (26% vs. 13%, $p<0.0001$) which was associated with superior overall and disease-free survival.

Predictors of Response and Long-Term Outcomes

Response to neoadjuvant systemic therapy has been shown to vary dramatically depending on tumor subtype and treatment regimen. A large meta-analysis that included 11,695 patients across 30 studies showed that the rate of pCR was 8.3% for patients with ER/PR positive, HER2-negative tumors, 18.7% for those with ER/PR positive, HER2-positive tumors, and 31.1% for triple-negative breast cancer. Patients with ER/PR negative, HER2-positive cancers had the highest rate of pCR at 38.9%.[12] Tumors with a higher grade and Ki-67 scores were also associated with higher rates of pCR.[13,14]

In addition to the NSABP B-18 and B-27 trials discussed previously, several other studies have demonstrated the prognostic value of pCR. In 2012, von Minckwitz and colleagues evaluated the long-term outcomes of 6,377 patients receiving neoadjuvant anthracycline-taxane-based

chemotherapy from seven randomized trials. They showed that disease-free survival was significantly higher for patients with no residual invasive or in-situ disease in the breast and lymph nodes compared to those with residual disease within the breast or lymph nodes. The study also showed that while the correlation between pCR and improved disease-free survival was seen in luminal B/HER2-negative tumors, HER2-positive/nonluminal tumors, and triple-negative tumors, there was no statistically significant difference in pCR rate and disease-free survival for patients with luminal A or luminal B/HER2-positive breast cancer.[15] Similar findings were reported in the pooled analysis by Cortazar and colleagues in 2014, who found that the association between pCR and long-term outcomes was strongest for patients with triple-negative or hormone receptor-negative/HER2-positive breast cancer and least for those with hormone receptor-positive disease.[16] More recently, the I-SPY2 randomized trial evaluated women with stage 2 or 3 breast cancer who received standard neoadjuvant systemic therapy or one of several investigational regimens. The three-year follow-up analysis, published in 2020, showed 95% event-free survival and distant recurrence-free survival for patients who achieved pCR compared with 78% event-free survival and 81% distant recurrence-free survival for the non-pCR group. While the 3-year event-free survival did not differ significantly based on subtype for those with pCR (93%-97%), differences were seen in those who did not achieve pCR with 3-year event-free survival of 57% for hormone receptor-negative/HER2-positive tumors and 89% for hormone receptor-positive/HER2-positive tumors. The study also showed an approximate 80% reduction in the rate of recurrence associated with pCR regardless of tumor subtype or treatment regimen.[17] Because of the predictive value of therapy response, pCR has become a surrogate endpoint in neoadjuvant systemic therapy trials.

The NCCN has provided guidelines for optimal neoadjuvant chemotherapeutic regimens based on tumor subtype.[7] While most of these medications are included in the WHO Model List of Essential Medicines and have been shown to provide the best long-term outcomes, real-world availability and delivery of these treatments to patients with breast cancer in LMC are lacking. This is because many of these drugs are costly, associated with toxicities, and require the expertise of a treatment team and healthcare system to deliver the therapy and manage potential toxicities.

HER2-Nonamplified Breast Cancer

The optimal regimen for patients with HER2-negative disease has been extensively studied. However, none of the trials address issues related to low-resource countries. Bonadonna and colleagues first evaluated the efficacy of adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) in the treatment of node-positive breast cancer. The trial started in 1973 and showed significant improvement in relapse-free survival and overall survival in those who received adjuvant CMF after 20 years of follow-up.[18,19] Because of the ease of administration, rarity of severe toxicities, and relatively low cost, CMF remains a recommended neoadjuvant regimen by both the NCCN and BHGI.[7,20]

Randomized controlled trials have shown that anthracycline-based regimens are superior to CMF in terms of recurrence and survival in the adjuvant setting.[21,22] A meta-analysis by the Early Breast Cancer Trialists' Collaborate Group evaluated 11 studies that compared anthracycline-containing regimens to CMF alone. They reported a 12% decrease in recurrence and an 11% improvement in survival for the anthracycline group.[21] The NSABP B-28 trial evaluated the addition of paclitaxel after doxorubicin/cyclophosphamide postoperatively for women with node-positive breast cancer. The authors found that the addition of paclitaxel led to a 4%

increase in disease-free survival at five years; however, there were no significant differences seen in overall survival.[23] Extrapolating from the superior outcomes of anthracycline and taxane-containing regimens in the adjuvant setting, more recent studies evaluated similar therapies in the neoadjuvant setting.[11,24-27] The landmark NSABP B-27 trial showed that while the addition of docetaxel to doxorubicin and cyclophosphamide did not impact survival, the rate of pCR was doubled in patients who received preoperative docetaxel.[11,27] Dieras and colleagues randomized women with T2-3, N0-1 disease to preoperative doxorubicin plus paclitaxel or doxorubicin plus cyclophosphamide. The rate of pCR, defined as the eradication of invasive cancer in the breast and axillary lymph nodes, was higher in the paclitaxel arm (16% vs. 10%). The study also reported higher disease-free survival in patients who achieved a pCR compared to those who did not (91% vs. 70%).[24] Drawing from the results from these studies, the NCCN currently recommends doxorubicin and cyclophosphamide followed by paclitaxel as the preferred preoperative regimen for patients with locally advanced HER2-negative breast cancer.[7] However, toxicities and high drug costs limit the widespread use of anthracycline and taxane-based regimens in LMC.

A study performed at the MD Anderson Cancer Center comparing the efficacy of paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide (FAC) in the neoadjuvant setting also reported treatment toxicities associated with the two regimens.[28] Overall, a higher percentage of patients in the paclitaxel (delivered every three weeks) arm suffered from toxicities, the most common being myalgia (56%), followed by neutropenic fever (53%), and paresthesia (46%). In the FAC arm, 35% developed myalgia, 21% had neutropenic fever, 21% had nausea, and 16% had diarrhea. There were no episodes of clinically evident cardiac dysfunction in either group, however, transient arrhythmias were observed in a few patients but did not require intervention

or changes in therapy. Notably, 25% of patients in the FAC arm and 56% in the paclitaxel arm received myeloid growth factor support.[28] The need for myeloid growth factor with anthracycline and taxane-containing treatments presents another challenge that limits the use of these regimens in LMC. Depending on drug cost and availability, providers trained in the delivery and monitoring of treatment regimens, and the infrastructure available to provide neoadjuvant treatment, the recommended preoperative regimen for patients with locally advanced breast cancer is doxorubicin and cyclophosphamide followed by paclitaxel. If this is unavailable, other acceptable regimens include doxorubicin and cyclophosphamide followed by docetaxel, doxorubicin, and cyclophosphamide alone, anthracycline monotherapy, epirubicin, and cyclophosphamide, or CMF.[6,7] It is important for providers to monitor for toxicities throughout treatment with complete blood counts, chemistry levels, and cardiac function studies. (Table 1).

Table 1: HER2-negative or HER2 unknown disease[4,9]

Resource Level		Considerations
Basic	• If operable, proceed with modified radical mastectomy • If inoperable: neoadjuvant therapy (CMF; endocrine therapy; radiation)	Consider neoadjuvant endocrine therapy
Core	• AC every 3 weeks • CMF • AC followed by docetaxel every 3 weeks • AC followed by weekly paclitaxel • EC • FAC	
Enhanced	• Same as above • If available consider: Dose dense paclitaxel every 2 weeks followed by or preceded by dose dense AC every 2 weeks	

AC: doxorubicin and cyclophosphamide
CMF: cyclophosphamide, methotrexate, fluorouracil
EC: epirubicin and cyclophosphamide
FAC: fluorouracil, doxorubicin, cyclophosphamide
*Refer to NCCN Guidelines for specific doses and number of cycles

Neoadjuvant Endocrine Therapy

Endocrine therapy is an effective treatment for hormone receptor-positive breast cancer both in the neoadjuvant and adjuvant settings. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed through meta-analyses of randomized trials that adjuvant endocrine therapy reduced the rate of recurrence by 50% and breast cancer-specific mortality by 30% in women with estrogen receptor-positive disease irrespective of chemotherapy use and tumor characteristics.[29] If chemotherapy was given, the addition of endocrine therapy provided a further

reduction in recurrence and improvement in survival when compared with chemotherapy alone.[30] Reduction in contralateral breast cancer risk was also appreciated. Even though tamoxifen use is associated with small increases in thromboembolic events and uterine cancer, the EBCTCG showed no significant negative impact on survival.[29,30] Oral administration, low cost, and favorable toxicity profiles make endocrine therapy a valuable option for systemic treatment in LMC for patients with hormone receptor-positive disease. In resource-limited settings where neoadjuvant chemotherapy is not available or the patient is not medically fit to receive it, endocrine therapy should be considered, especially in older women with hormone receptor-positive disease. Spring and colleagues performed a systematic review and meta-analysis of 20 randomized clinical trials with 3,490 patients that compared neoadjuvant chemotherapy to neoadjuvant endocrine therapy.[31] While the regimens of neoadjuvant chemotherapy therapy differed between trials, the pooled results showed no significant differences in response and rate of breast conservation between the chemotherapy and endocrine therapy treatment groups. However, the rate of grade 3 and grade 4 toxicities was lower in the neoadjuvant endocrine cohort. The study also found aromatase inhibitors to be superior to tamoxifen in response rates and rates of breast conservation. It is important to note that most of the studies included only postmenopausal women. The STAGE study is the only trial that focused on premenopausal women in which patients were randomly assigned to receive goserelin plus either tamoxifen or anastrozole for 24 weeks before surgery.[32] More patients in the anastrozole group had favorable clinical and pathologic responses to therapy when compared with those who received tamoxifen with similar side effect profiles. The ACOSOG Z1031 trial compared outcomes between neoadjuvant letrozole, anastrozole, and exemestane in women with stage 2 and 3 estrogen receptor-rich breast cancer.[33] The study reported that letrozole was associated with the highest

rate of clinical response (74.8%) and that severe toxicities were observed in less than 5% of the study population. Additionally, 51% of patients who were recorded as only candidates for mastectomy before neoadjuvant endocrine therapy were able to undergo breast-conserving surgery. The authors also sought to identify which patients were most likely to benefit from neoadjuvant endocrine therapy. They found that while there were no differences in the rate of breast conservation and clinical response between Luminal A and Luminal B tumors, more patients with Luminal A tumors were found to have a preoperative endocrine prognostic index (PEPI) score of 0 at the time of surgery compared with those with Luminal B tumors (27.1% vs. 10.7%, p=0.004).[33] This suggests that patients with Luminal A type tumors are more likely to derive benefit from neoadjuvant endocrine therapy with increased likelihood of achieving PEPI-0 status, which in turn is associated with improved disease-free and disease-specific survival.[34] While aromatase inhibitors are preferred for neoadjuvant endocrine therapy, widespread use in LMC is cost-prohibitive, especially when breast conservation therapy is not available due to the lack of radiation treatment facilities. Therefore, tamoxifen alone for post-menopausal patients or in combination with ovarian ablation (i.e., surgical oophorectomy or radiation ablation) for premenopausal women are acceptable alternatives in LMC.[20] While long-term outcomes data are limited for neoadjuvant endocrine therapy, the low cost, ease of administration, low toxicity, and good response rates make it a reasonable alternative for use in the preoperative setting. Even though side effects associated with endocrine therapy are milder compared to those associated with cytotoxic chemotherapy, it is still important to monitor patients for toxicity while receiving endocrine therapy. The most common side effects associated with tamoxifen are hot flashes (40.9%), thromboembolic events (4.5%), and rarely endometrial cancer (0.8%).[35] Aromatase

inhibitors are most commonly associated with arthralgias (35.6%) and fractures due to decreased bone mineral density (11%).[35] (Table 2).

It is important to note that for women with hormone receptor-negative locally advanced breast cancer or those with unknown hormone receptor status, chemotherapy should be the first choice for neoadjuvant therapy. However, in older women with slower-growing, well-differentiated tumors that are likely hormone receptor-positive, neoadjuvant endocrine therapy is appropriate even with unknown hormone receptor status.[9] While most women with hormone receptor-positive locally advanced breast cancer will benefit from chemotherapy, this could be delivered in the adjuvant setting in patients who have residual disease following treatment with neoadjuvant endocrine therapy. Combining endocrine therapy with chemotherapy is generally not recommended due to the negative impact of endocrine therapy on chemotherapy by limiting the sensitivity of cancer cells to chemotherapy. The SWOG 8814 trial found that the addition of tamoxifen to adjuvant chemotherapy was associated with improved disease-free survival. However, the magnitude of benefit was greater when tamoxifen was given after chemotherapy than when it was given concurrently.[36] The current standard is to start endocrine therapy separately from chemotherapy and to avoid simultaneous use.

HER2-amplified Breast Cancer

Evaluating HER2 status and providing HER2-targeted treatment remains a challenge in LMC. The cost, need for specialized training, and laboratory capabilities limit the ability to assess

Table 2: Neoadjuvant endocrine therapy[7,19]

Resource Level	Premenopausal	Postmenopausal
Basic	• Tamoxifen with ovarian ablation (surgical oophorectomy or radiation)	• Tamoxifen
Core	• Tamoxifen with ovarian ablation (surgical oophorectomy or radiation) • Aromatase inhibitors with ovarian ablation	• Aromatase inhibitors • Tamoxifen if aromatase inhibitors unavailable or patient unable to take aromatase inhibitors
Enhanced	• Tamoxifen with ovarian suppression or ablation (surgical oophorectomy or radiation) • Aromatase inhibitors with ovarian suppression or ablation	• Aromatase inhibitors • Tamoxifen if aromatase inhibitors unavailable or patient unable to take aromatase inhibitors

HER2 status and HER2-targeted medications are often prohibitively expensive for the healthcare systems in LMC. Even though trastuzumab or an equivalent biosimilar has been added to the WHO Model List of Essential Medicines, accessibility of these medications in LMC remains problematic. Several trastuzumab biosimilars are in development, and a few have been approved by the Food and Drug Administration and the European Commission. However, significant price reductions are still necessary to increase access and decrease the burden on healthcare spending in LMC.[37] Because of this, routine HER2 status testing is not recommended by either the BHGI or the NCCN unless there is the ability to provide HER2-targeted medications.

In settings where HER2-targeted therapy is available, combination therapy is recommended for HER2-positive locally advanced disease in the neoadjuvant setting. The NOAH trial evaluated the addition of trastuzumab to neoadjuvant chemotherapy (doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil) in women with HER2-positive locally advanced or inflammatory breast cancer.[38,39] The study randomized 117 women to receive one year of trastuzumab given as neoadjuvant and adjuvant treatment and 118 to receive neoadjuvant chemotherapy alone. After a median follow-up time of 5.4 years, the trastuzumab group had lower rates of local, regional, and distant recurrences when compared with the chemotherapy-only cohort; event-free survival was 58% for the trastuzumab group and 43% for the chemotherapy group. While not statistically significant, the 5-year overall survival was also higher for the trastuzumab group at 74% vs. 63% for the chemotherapy group. Patients who received trastuzumab were also more likely to achieve a pCR (38% vs. 19%, p=0.001), which was associated with improved event-free and overall survival.[38,39] The non-cardiac side effect profiles were similar between the two groups however, 2% of patients who received trastuzumab experienced left ventricular dysfunction compared to 0% in the chemotherapy-only group.

Buzdar and colleagues evaluated the addition of trastuzumab to preoperative paclitaxel, fluorouracil, epirubicin, and cyclophosphamide. Similar to the findings from the NOAH trial, the rate of pCR was higher in patients who received trastuzumab compared to the chemotherapy alone cohort (65.2% vs. 26.3%, p=0.016). While no patients developed clinically evident congestive heart failure in either group, a greater than 10% decrease in ejection fraction was seen in five patients (26%) and seven patients (30%) in the chemotherapy-only and trastuzumab arms, respectively.[40,41]

More recently, the addition of pertuzumab to trastuzumab has been evaluated for dual anti-HER2 therapy in both adjuvant and neoadjuvant settings.[42-46] The APHINITY trial showed that pertuzumab was associated with improved disease-free survival when used in conjunction with trastuzumab and chemotherapy in the adjuvant setting.[42] The NeoSphere and TRYPHAENA studies evaluated the use of pertuzumab in the neoadjuvant setting. Both studies showed that the addition of pertuzumab led to higher rates of pCR, which in turn was associated with improved disease-free survival with similar rates of cardiac toxicity.[43-46]

In settings where HER2 targeted therapy is available but limited, studies have shown that there is still benefit, though slightly less, that can be gained from shorter durations of adjuvant trastuzumab treatment.[47-49] The Short-HER trial compared sequential anthracycline-taxane chemotherapy followed by the traditional 1-year course of adjuvant trastuzumab to 9 weeks of trastuzumab. The disease-free and overall survival between the two groups were similar (slightly lower in the 9-week cohort but not statistically significant) at five years of follow-up. However, the risk of severe cardiac toxicity was significantly lower in the short-course trastuzumab arm.[48] Due to the variation in resources in different LMCs, targeted therapy for HER2-positive locally

advanced breast cancer is an area where modifications in guidelines can be used to maximize the benefit to the largest number of patients based on available local resources. (Table 3).

Table 3: HER2-positive disease[7,19]

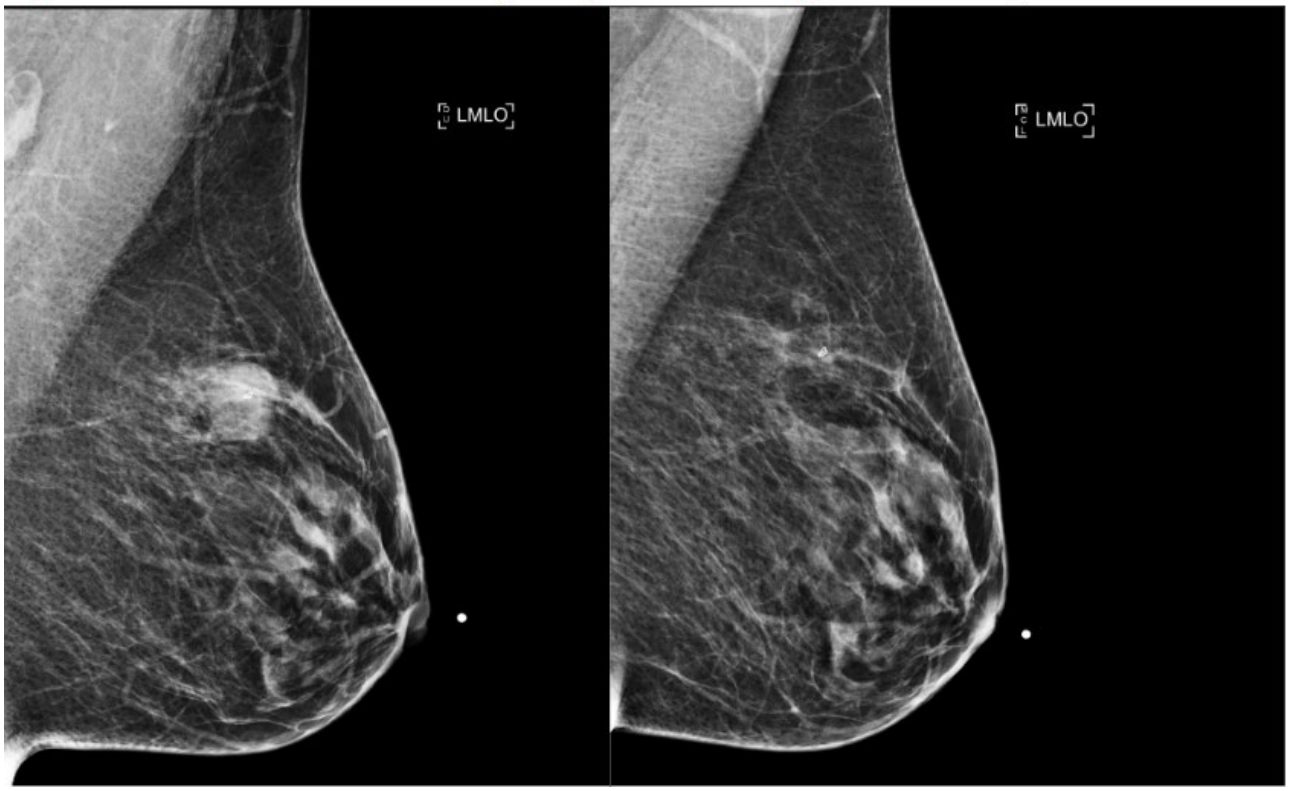
Resource Level		Considerations
Basic	• If operable, proceed with modified radical mastectomy • If inoperable: neoadjuvant therapy (CMF; endocrine therapy; radiation)	• HER2 testing not recommended unless HER2 targeted therapy is available • Consider neoadjuvant endocrine therapy if hormone receptor positive
Core	• AC every 3 weeks • CMF • AC followed by docetaxel every 3 weeks • AC followed by weekly paclitaxel • EC	
Enhanced	• AC followed by paclitaxel + trastuzumab • Docetaxel, carboplatin and trastuzumab • AC followed by docetaxel + trastuzumab • Docetaxel + cyclophosphamide + trastuzumab • Paclitaxel + trastuzumab	• Consider dual anti-HER2 therapy with the addition of pertuzumab if available • Shorter courses of anti-HER2 therapy still beneficial

AC: doxorubicin and cyclophosphamide
CMF: cyclophosphamide, methotrexate, fluorouracil
EC: epirubicin and cyclophosphamide
*Refer to NCCN Guidelines for specific doses and number of cycles

Assessment of Treatment Response

Assessment of response to treatment during and after completion of neoadjuvant systemic therapy is vital in clinical decision-making regarding local-regional management and adjuvant systemic treatment. The patient should be monitored with at least clinical exams at regular intervals during neoadjuvant treatment to evaluate for disease response or progression. Accurate documentation of the extent of disease with photography is a valuable tool to monitor disease status clinically. If disease progression is found and no acceptable alternative systemic therapy is available, the patient should proceed to surgery if the disease is operable or to radiation if inoperable. If imaging modalities are available, the combination of imaging (mammogram and/or ultrasound) and physical exam has been shown to improve accuracy in evaluating disease status during neoadjuvant therapy.[50-52] (Figure 3). Herrada and colleagues showed that physical exam is the best noninvasive predictor of breast tumor size in locally advanced breast cancer, whereas ultrasound improved the evaluation of axillary nodal status.[50] If resources allow, MRI is another modality to assess tumor response following neoadjuvant therapy. It has been shown to provide

Figure 3. Resolution of breast mass following neoadjuvant chemotherapy seen on mammogram



the highest accuracy for evaluating response to therapy. The ACRIN 6657 trial showed that MRI was able to predict final pathologic size with the highest accuracy when compared with mammography and clinical exams.[53] A meta-analysis that included 2,050 patients across 44 studies showed that MRI had the highest sensitivity at 83-87% when assessing for residual disease after neoadjuvant systemic therapy. However, specificity was lower and more heterogeneous at 54-83%.[54] The ability of MRI to estimate response to therapy varies with tumor subtype. Studies have shown that MRI is most accurate for triple-negative and hormone receptor-negative/HER2-positive cancers, while its ability to detect residual disease is least reliable for luminal tumors.[52]

Post-operative pathologic assessment of tumor response to neoadjuvant systemic therapy has been used as an indicator of prognosis. The American Joint Committee on Cancer (AJCC) provides a y designation when calculating the pathologic stage for patients who received neoadjuvant therapy. The residual cancer burden (RCB) index provides more granularity in treatment response and is a validated instrument that correlates with the risk for disease recurrence after neoadjuvant chemotherapy.[55,56] The index score is comprised of primary tumor size, cellularity of residual invasive cancer, the number of involved lymph nodes, and the size of the largest metastasis. RCB 0 corresponds to pCR in the breast and lymph nodes or ypT0N0. RCB-I is classified as a minimal residual disease, RCB-II is a moderate residual disease, and RCB-III is an extensive residual disease. Studies have found the RCB to be prognostic in patients with AJCC yp-stage II and stage III disease and across all receptor status subtypes.[56] Instructional materials, videos, and a calculator for the RBC index and class are available on a public website.[57]

For patients who receive neoadjuvant endocrine therapy, the preoperative endocrine prognostic index (PEPI) score was developed using surgical pathologic findings to predict long-term outcomes.[34] The score is calculated from the pathologic tumor size, nodal status, Ki-67 level, and ER status (Allred score). The scores are then classified into three groups: 0, 1-3, and ≥4. The PEPI score has been shown to be most useful in identifying patients with low risk for recurrence in the absence of adjuvant chemotherapy (group 1) and patients who are at high risk of recurrence (group 3). The heterogeneity associated with group 2 (PEPI score 1-3) limits its predictive value.[34] Using data from the ACOSOG Z1031 trial, Ellis and colleagues showed that the recurrence rate after 5.5 years for patients with PEPI score = 0 was 3.7% vs. 14.4% for those with PEPI >0. This suggests that the benefit derived from adjuvant chemotherapy is limited in

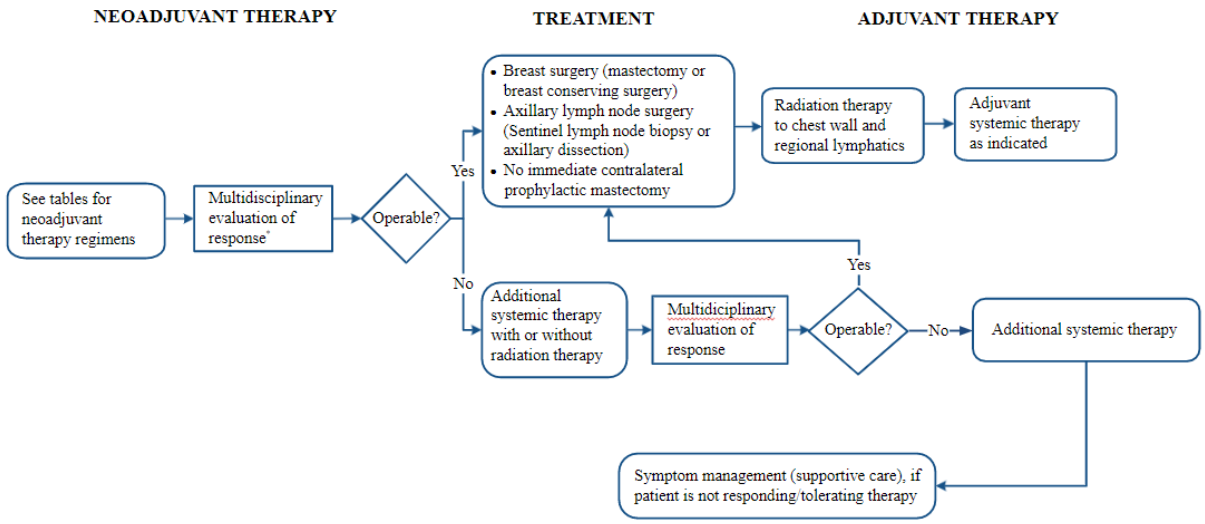
patients with PEPI=0 disease and supports the use of postoperative treatment with endocrine therapy without the need for chemotherapy.[58]

Conclusion

Management of locally advanced breast cancer remains clinically challenging even in resource-rich counties. Despite optimal multidisciplinary treatment, a large number of patients will experience recurrence. Marked heterogeneity exists among and within countries in terms of economic and healthcare development; therefore a tailored, resource-stratified approach to breast cancer care maximizes existing resources in order to improve outcomes for patients on a global scale. While current data supports the use of neoadjuvant systemic therapy for locally advanced breast cancer, access to first-line medications is often limited in LMC. In centers with enhanced or maximum resources, anthracycline, and taxane-based regimens have been shown to improve the chance of achieving a pCR, which is associated with improved long-term outcomes. In LMCs with constrained resources due to factors such as drug costs and limited health system infrastructure, alternative regimens, including traditional CMF, provide acceptable outcomes as well as ease of administration and lower toxicity. Neoadjuvant endocrine therapy is another well-tolerated treatment option, especially for older women with hormone receptor-positive tumors. Even though HER2-targeted therapy has been shown to improve outcomes for patients with HER2-positive breast cancer, the costs of receptor status testing and trastuzumab therapy remain prohibitively expensive. Therefore, routine HER2 testing is not recommended unless HER2-targeted therapy can be provided. Reduction in testing costs and development of less costly biosimilars are needed in order for HER2-targeted therapy to be widely available. Optimal treatment for locally advanced breast cancer requires a multidisciplinary approach from all

available specialists. Efforts should be made to assemble a multidisciplinary team at all resource levels. (Figure 4).

Figure 4. Neoadjuvant treatment algorithm for locally advanced breast cancer



*Evaluate breast and nodes at initial assessment and during therapy to assess for response to therapy with mammogram, ultrasound, and physical exam

Key Points

- Obtaining tissue diagnosis and evaluating the extent of disease is key prior to starting neoadjuvant systemic therapy.
- Determining estrogen and progesterone receptor status is important in optimizing the selection of treatment regimens.
- Routine testing for HER2 status is not recommended unless HER2-targeted therapy is available.
- Pathologic complete response to neoadjuvant systemic therapy is a predictor of long-term outcomes.
- Neoadjuvant endocrine therapy is an effective treatment option for hormone receptor-positive disease, especially in older women or if chemotherapy is not available.

- HER2 targeted therapy with either trastuzumab or a biosimilar is recommended for HER2-positive locally advanced breast cancer, even in shortened courses.
- Assessment of treatment response during and after neoadjuvant therapy is important for clinical decision-making. This can be achieved with the clinical exam in combination with a mammogram and/or ultrasound if available. MRI can also be considered if available.

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Chapter 16

Palliative Therapy for Metastatic Breast Cancer

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Clinical Scenario

- Scenario one: 48-year-old post-menopausal lady who presents to the clinic with a cT3N2, IDC III, ER 8/8, PR 8/8, Her2 positive 3+ and on metastatic work up has two lesions at D10 and D11 vertebra, multiple liver lesions in both lobes of the liver suggestive of metastasis

- Scenario two: 48-year-old post-menopausal lady who presents to the clinic with a cT3N2, IDC III, ER 8/8, PR 8/8, Her2 negative and on metastatic work up has two lesions at D10 and D11 vertebra suggestive of metastasis.

Denovo metastatic breast cancer (MBC) accounts for less than 10% of newly diagnosed breast cancer cases. (1) Traditionally, metastatic breast cancer has always brought to mind the image of debilitated patients with large, often fungating tumors in the breast and axilla and a poor performance score in whom the goal was to prolong survival and reduce morbidity. However with changing trends of increased awareness and advanced diagnostic techniques, stage 4 disease now varies from indolent low-burden metastatic disease to disseminated symptomatic cases. Evolutions and progress in systemic therapy have resulted in improved survival in patients with metastatic breast cancer.

A study (2) of 724 Denovo metastatic breast cancer patients treated in three French cancer centers between two time periods reported an overall 3yr survival of 27% for those treated between 1987-1993, which improved to 44% for those treated between 1994-2000, with comparable tumor characteristics. Indicating improving trends in treatment and possible stage migration with improved imagining used for staging breast cancer. A similar analysis by Giordano et al. on multivariate analysis showed a 1% reduction in risk of death with each increasing year (3).

Role of surgery of the primary tumor in metastatic breast cancer

RETROSPECTIVE EVIDENCE FOR IMPROVED SURVIVAL WITH SURGERY

Achieving local control in patients with stage I-III disease impacts overall survival, reduces the chance of local recurrence and distant disease, but the role of locoregional therapy (LRT) continues to be debated in metastatic breast cancer. There have been different concepts of breast cancer growth and metastasis that have been disputed against surgery in the metastatic setting. Fisher's animal model studies have shown that the removal of the primary tumor is not a local phenomenon devoid of biological consequences. It triggers the release of a series of growth factors and temporary immunosuppression (due to the impairment of natural killer cell cytotoxicity under surgical stress) (4), causing an increase in angiogenic factors like circulating angiostatin to partially neovascularize dormant metastatic disease (5). As per the angiogenesis concept, the presence of an intact primary tumor, suppresses the metastatic growth by a circulating angiogenesis inhibitor (6).

On the other hand, retrospective audits have shown the benefit of surgery in MBC. Khan et al. (7) analyzed data from 16,023 women with Denovo stage 4 disease from the National Cancer

Database between 1990 to 1993. They reported that 9,162 (57.2%) of these patients underwent partial (3513) or complete (5641) mastectomies for excision of the primary tumor and demonstrated an improvement in survival at three years of 26% in patients with positive margins and 35% in patients with negative margins vs. 17.3% in patients who had not undergone surgical excision($p<0.0001$), with a 39% reduction in the risk of death. Over the years, 19 retrospective studies have analyzed survival outcomes with respect to surgical resection in Denovo stage IV patients. Population-based studies provide data on 27,000 women, of whom 52% underwent surgical excision for primary tumor (Table 1) and demonstrate an improvement in survival. (7-12) Most of these retrospective studies showed that younger women with estrogen-receptor positive tumors, fewer sites of metastasis, more specifically bone-only metastasis, seemed to benefit significantly with local control but this could be viewed as either benefit from local therapy or a bias in patient selection. A meta-analysis by Petrelli et al. in 2012 showed a survival benefit with surgery when offered in a multimodality treatment setting [HR 0.69 95% CI 0.63-0.77, $p< 0.00001$] and in ER-positive breast cancer patients, which was independent of age, extent, site of the metastatic disease, and HER2 status (13). Another meta-analysis by Harris et al with data from ten studies of 28,693 patients with stage IV disease, of whom 52.8% underwent excision of the primary tumor, demonstrated a superior survival at three years (40% (surgery) vs 22% (no surgery) (OR 2.32, 95% confidence interval 2.08-2.6, $p<0.01$). Subgroup analysis favored lower metastatic burden ($p<0.01$) (14).

Study	Duration	Source	Sample Size	No. of patients who had undergone surgery	Survival with surgery (negative margins-positive margins)	Survival without surgery	Factors affecting OS on Multivariate analysis	HR for surgery (95% CI)
Khan et al. (7)	1990-1993	National Cancer Database Study	16,023	9,162 (57.2%)	27.7%-31.8% at 3 yrs	17.3% at 3 yrs	Margin status, number of metastatic sites, systemic therapy	0.61 (0.58-0.65)
Rapiti et al. (8)	1977-1996	Geneva Cancer Registry	300	127 (42.3%)	27%-16% at 5 yrs	17.3% at 3 yrs	Age, ER +, Margin status, bone only metastatic site, nodal burden, hormone treatment	0.6 (0.3-0.7)
Gnerlich et al. (9)	1988-2003	SEER	9,734	4,578 (47%)	36 median months	21 median months	Not known	0.63 (0.60-0.66)
Ruitercamp et al. (10)	1993-2004	Netherlands	728	288 (40%)	24.5% at 5 yrs	13.1% at 5 yrs	Age, tumour size, number of metastatic sites, hormone treatment	0.62 (0.51-0.76)
Cady et al. (11)	1970-2002	MGH and BWH tumour registries (matched pair analysis done)	622	234 (38%)	42% at 3 yrs	25% at 3 yrs	Age, bone only metastatic site	Not known
Dominici et al. (12)	1997-2007	NCCN breast cancer outcomes database	290	54 (18.6%)	3.5 median yrs	3.4 median yrs	Not known	0.94 (0.83-1.08)

Table 1: Population based retrospective studies analyzing the role of surgery for primary tumour in stage IV breast cancer

Prospective Evidence

The discrepancy between the results of Fisher animal model and the retrospective audits and meta-analysis meant the need for well-planned randomized controlled trials. Six prospective randomized control trials were designed to answer the role of local therapy in stage IV Denovo breast cancer patients, with the primary endpoint being overall survival. In a report from MDACC (15), better progression-free survival was observed in patients having surgery between 3-8.9 months or more than 9 months from the time of diagnosis than patients having surgery within three months after diagnosis, demonstrating that patients had better survival rates when surgery is done after primary systemic therapy. Two trials thus evaluated the role of LRT after systemic therapy in women with Denovo MBC.

The first of these trials to be published was from Tata Memorial Hospital in India (16). Three hundred and fifty women with stage IV Denovo metastatic breast cancer, with an estimated life expectancy of at least one year, were randomized either to LRT, which included surgery +/- radiation therapy (RT) of the breast primary including axillary dissection or no LRT. All patients received standard systemic therapy as per institutional protocol and post-chemotherapy, those that did not progress were randomized in the study. Patients with resectable tumors that could be treated with endocrine therapy were randomized upfront. The study reported a median overall survival of 19·2 months (95% CI 15·98–22·46) in the locoregional treatment arm versus 20·5 months (16·96–23·98) in the no locoregional treatment arm (HR 1·04, 95% CI 0·81–1·34; p=0·79) and 2-year overall survival was 41·9% (95% CI 33·9–49·7) in the locoregional treatment group and 43·0% (95% CI 35·2–50·8) in the no locoregional treatment group, showing no difference in overall survival. Locoregional treatment resulted in a significant improvement in locoregional progression-free survival compared with that in the no locoregional treatment group

(median not attained *vs* 18·2 months [95% CI 15·1–21·3]; HR 0·16, 95% CI 0·10–0·26; p<0·0001. While a significant detriment in distant progression-free survival was noted in the LRT arm compared to no LRT arm (median 11·3 months [95% CI 7·7–14·84] *vs* 19·8 months [10·26–29·0]; HR 1·42, 95% CI 1·08–1·85; p=0·012. Despite good local control with surgery, the significant detriment in distant progression-free survival was consistent with the results of preclinical studies suggesting the growth of a metastatic tumor subsequent to the removal of the primary tumor.

The Eastern Cooperative oncology group trial in the United States (E2108) (17) was a similar design to the first study, wherein 256 patients who had responded to systemic therapy were randomized to undergo locoregional treatment versus no locoregional treatment (continued systemic therapy). The preliminary results of this study were presented at ASCO 2020 and showed no difference in overall survival at three years between the two groups. Surgery (68.4%) and no surgery study arms (67.9%; hazard ratio [HR], 1.09; 90% CI, 0.80-1.49; log-rank *P* =.63). At a median follow-up of 53 months, median OS for the overall study population was 54 months. Furthermore, no progression-free survival benefit (PFS) was observed for early locoregional treatment with optimal systemic therapy compared with optimal systemic therapy alone (*P* =.40). The 3-year rate of recurrence/progression of locoregional disease was significantly lower in those who underwent early locoregional treatment (10.2%) compared with patients who did not (25.6%; HR, 0.37; 95% CI, 0.19-0.73). The E2108 trial also compared patient-reported quality of life (depression, anxiety, and well-being, for example) between the two groups. Despite better local control in the surgery arm there was no quality of life advantage with surgery in MBC.

Of the studies randomized that women with *de novo* MBC upfront to either surgery with systemic therapy or systemic therapy alone, ABSCG-28-POSYTIVE (18) stopped early due to

poor recruitment. They reported the analysis on 90 stage IV, with no difference in overall survival and no prognostic benefit for LRT. At a median follow-up of 37.5 months, median survival in the surgery arm was 34.6 months versus 54.8 months in the no-surgery arm [HR 0.691, 95% CI 0.358 – 1.333; P= 0.267]. Time to distant progression was 13.9 months in the surgery arm and 29.0 months in the no-surgery arm (HR 0.598, 95% CI 0.343–1.043; P= 0.0668). They, too, reported that surgery of the primary tumor does not improve nor alter the QoL of patients with *de novo* stage IV BC. (19)

The SUBMIT by the Danish Breast Cancer Trialists Group in 2012 (20) was also terminated due to slow accrual, wherein 258 MBC were planned for upfront randomization to either undergo surgery with systemic therapy or systemic therapy alone. Lastly, the Japan Clinical Oncology Group study (JCOG 1017) is designed to assess the superiority of locoregional therapy with systemic therapy versus only systemic therapy in stage for Denovo MBC and is one of the trials to look forward to (Table 2).

Study	Sample size	Survival with surgery	Survival without surgery	Results
Tata Memorial Hospital, India (16)	350	19.2 months OS at 2 yrs 41.9%	20.5 months OS at 2 yrs 43%	• No difference in overall survival • Despite good local control with surgery, significant detriment in distant progression-free survival.
Turkish MF 07-01 (22)	274	46 months	42 months	• No difference in overall survival • Median survival was 14 months longer in LRT vs ST for solitary bone metastasis
Danish Breast Cancer Trailists Group (SUBMIT) (20)	258	-	-	• Closed due to poor accrual
ECOG E2108 (17)	256	OS at 3 yrs 68.4%	OS at 3 yrs 67.9%	• No difference in overall survival • 2.5-fold higher risk of local disease progression without LRT • No difference in quality of life
ABCSG-28-POSYTIVE trial (18)	90	36 months	54.8 months	• Terminated early due to poor recruitment • In overall survival and no prognostic benefit for LRT • No QOL benefit

Table 2: Prospective randomized trials analyzing the role of surgery for primary tumour in stage IV breast cancer

There is no evidence that locoregional treatment of the primary tumor affects overall survival or quality of life in women with *de novo* MBC, and surgery should not be part of routine practice. It is reserved for palliation of symptoms like fungation and bleeding (21).

However, for scenario two with low-burden disease, the Turkish trial (MF07-01) (22) is an RCT with an accrual of 278 women who were randomized upfront to undergo surgery with systemic therapy (LRT) or systemic therapy alone (ST). With a median follow-up of 21 months, the study showed no difference in overall survival (46 vs. 42 months (p=0.20)), but a trend towards the benefit of LRT was observed in ER-positive [HR 0.64], Her-2 negative, below 55 yrs of age with solitary bone metastasis [HR 0.47] compared to multiple bone or visceral metastasis. The updated results showed an overall survival of 23% of patients in the LRT group and 8% of

patients in the ST group at ten years, with a median survival was 46 months for LRT and 35 months for ST [HR:0.71, 95%CI;0.59-0.86, p=0.0004]. Median survival was 14 months longer in the LRT group comparing the ST group [HR:0.55, 95%CI; 0.35-0.86, p=0.008] in patients with solitary bone metastasis (22)

Oligometastasis

In most developing countries due to limited access to cancer care, the patients presenting with advanced and metastatic disease outnumber those with early cancers. This, along with the limited availability and use of cross-sectional imaging/ PET scan, a smaller proportion of patients present with oligometastatic disease. Nevertheless, in future, with improvement in scanning capacity and breast cancer awareness, the number of OMBC patients is expected to rise. Throughout literature, there is significant heterogeneity in the definition of oligometastases which makes it difficult to compare the results and allow generalizability. The recent ESTRO-ASTRO consensus document now defines oligometastatic disease as 1-5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable. (23)

Singletary et al. (24) showed that surgery with adjuvant therapy provides better 5-year survival rates when compared to a single line of treatment alone in select patients with a single tumor or single site to the lung, liver, brain, or sternum- rendering them as Stage IV NED (no evidence of disease). Taking forward the results of the Turkish trial and the retrospective audits, we continue to explore the role of surgery in OMBC or low-burden MBC. The evidence favors the rationale of offering local control in low-burden metastatic disease or oligometastatic disease.

Role of radiation therapy

The role of RT varies dramatically with the intent of the treatment; where radical or ablative RT is used for the oligometastatic sites with the intent to cure, and simple single or multi-fraction RT is used in the palliative polymetastatic setting. Radiation therapy is recommended for symptom palliation or cancer-related complication prevention. Occasionally, urgent RT may be indicated for complications like spinal cord compression, superior vena cava obstruction, uncontrolled venous bleeding, or in some cases of brain metastases. It is recommended that all metastatic patients be seen in multi-disciplinary joint clinics so that palliative therapies are instituted early to prevent major cancer-related complications.

Breast primary and Nodal Metastases

Palliative intent RT should be considered for patients with pain that requires regular analgesics, bleeding from the lesion, or loss of function. Multi-fraction palliative radiation is preferred for patients expected to have longer survival for durable symptom control, especially in patients with unresectable disease. (25) An Alternative weekly hypofractionated RT regimen of 30-35Gy/5-7 fractions delivered once a week can be offered for patients living closer to the RT facility. In patients with oligometastatic disease being treated with radical intent, adjuvant locoregional RT should be considered.

Radiotherapy to the metastatic sites: This is planned based on the intent of therapy. In OMBC or low-burden disease where the intent is curative, radical RT is considered. The advances in treatment planning and delivery have enabled radiation oncologists to treat with ablative doses of RT called stereotactic body radiation therapy (SBRT). With SBRT, high doses of radiation are delivered precisely to the target while restricting the dose to the surrounding tissues due to the rapid dose falloff. This helps to minimize toxicities to adjacent critical normal tissues. [26]. With the prospective randomized phase-II studies reporting improved survival outcomes with the use

of SBRT for oligometastatic disease [27, 28], its use is expected to rise in the future. The SABR-COMET study included patients from various sites like breast, prostate, lung, and colorectal cancers. The results of NRG-BR002, a breast cancer-specific phase-III randomized study evaluating the role of SBRT for oligometastatic disease, are eagerly awaited.

Here, we describe the role of RT by site of metastasis, both for radical curative intent in OMBC and palliation in cases of disseminated MBC.

Bone Metastases

Bone is the most common site of metastases from breast cancer. All three types of bone metastases (lytic, sclerotic, and mixed) commonly occur with breast cancer. Palliative RT to the bones is indicated for symptoms like pain, prevention of impending fracture or painful fractured sites, and spinal cord compression. Palliative RT helps to control pain in about 60-80% of the patients to varying degrees [29]. Patients who present with pain or symptoms localized to a particular site are usually treated with localized palliative RT. However, patients with extensive bone metastases with generalized pain not controlled by medications can be treated with sequential upper and/ lower hemibody or radiopharmaceuticals [30]. Chemotherapy or any myelotoxic systemic therapy should be avoided for six weeks to allow recovery of myelosuppression after hemibody therapy and is therefore preferred in patients where such therapies are not recommended.

The most commonly used dose fractionation for the treatment of uncomplicated bone metastases is 8Gy in a single fraction. Several randomized studies[29] and meta-analyses [31] have shown that single-fraction treatments are equally efficacious and provide adequate pain relief and should be preferred over multi-fraction treatments to reduce hospital visits and treatment costs of

patients with painful metastases. Multiple fraction RT may be preferred for patients with epidural spinal cord compression with neuropathic pain or fractured bones with soft tissue mass. Surgical fixation of the long bones in an ambulatory patient should be recommended unless the patient is unfit for surgery.

If affordable, RANK ligand inhibitor Denosumab should be used rather than bisphosphonates like Zoledronate as it is more efficacious and has a better safety profile[32]. Both these agents can be given concurrently with palliative RT.

In patients with oligometastatic disease, SBRT can be considered for most sites of bone metastases. Among bones, the spine is one of the most common sites treated with SBRT, where vertebral compression fractures are among the main side effects of the single fraction treatments [33]. Radiation myelitis, though feared most, has rarely been reported, and thus the use of SBRT is considered safe [34].

Lung Metastases

In a patient with polymetastatic disease, lung metastases are treated with palliative RT only when a patient experiences obstructive symptoms or hemoptysis. However, in patients with oligometastases to the lung, SBRT should be used if not undergoing metastatectomy. The safety of lung SBRT is established with the experience of treating stage-I lung cancer[35]. Interestingly, similar dose fractionations as those used for treating stage-I lung cancers (3-10 fractions) have been found effective for treating lung metastases from breast cancer. The dose fractionation varies based on the tumors' proximity to 'central' structures like the tracheobronchial tree, esophagus, and heart. Radiation pneumonitis is rarely reported, unlike in lung cancer, mostly due to superior baseline lung functions.

Liver metastases

Non-surgical options like radio-frequency ablation (RFA) and trans-arterial chemoembolization have been successfully used to treat isolated liver metastases in cases of OMBC. SBRT is a non-invasive treatment option that is equally effective and tolerated well with ≤5% of patients with grade III toxicities [36]. It is especially preferred in the treatment of metastases larger than 3 cm or when the lesions are closer to the large vessels where the 'heat sink' effect is likely with RFA.

Brain Metastases

For patients that present with >4 intracranial metastases, it is pragmatic to offer whole brain RT rather than focal radiation therapy unless the cumulative volume of the metastatic sites is ≤ 15cc. Patients with single, large brain metastasis with peritumoral edema that is located in a surgically accessible part of the brain should be offered surgical excision followed by RT. Surgery followed by focal cavity RT or whole brain RT in such patients is known to result in significantly improved survival and intracranial local control [37]. For smaller metastases 1-4, all ≤ 3 cm in size can be treated with stereotactic radiosurgery (SRS) as it reduces the chances of neurocognitive and other acute and late toxicities of whole brain RT while producing similar [38] or better [39] survival despite the higher chances of distant intracranial failure [38,39]. When recommending SRS for brain metastases, emphasis should be laid on the requirement of frequent MRIs during follow-up due to high rates of distant intracranial progression. For patients who opt for whole brain RT instead of SRS, hippocampal sparing RT, along with simultaneous integrated boost with or without memantine, should be considered to reduce neurocognitive deficits [40].

ROLE OF SYSTEMIC THERAPY

In Oligo metastatic disease the systemic therapy planned is similar to that for stage 3, locally advanced disease. Systemic treatment for an MBC may include chemotherapy, endocrine therapy, targeted therapies, and novel therapies (CDK 4/6 inhibitors, PI3K inhibitors, PARP inhibitors) either alone or in combination based on the subtype. Determining the hormone receptor (HR) expression and HER2/neu status is one of the most pivotal steps in selecting an appropriate regimen. Whenever feasible, one should attempt to biopsy a metastatic lesion to determine the tumor phenotype, as up to 10-15% of these metastatic cancers may have discordant estrogen receptor (ER)/ progesterone receptor (PR) and HER2 status[41]. Essentially it is the receptor turning positive from negative that has more therapeutic relevance rather than the ones turning from positive to negative. Despite turning negative, there is a role of endocrine or targeted therapy owing to tumor heterogeneity and the possibility of benefit with the specific therapy. However, the sequence may differ, and we may consider offering chemotherapy first, followed by endocrine therapy.

Visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease[42]. It is not the mere presence of visceral metastases but implies organ compromise, warranting urgent intervention with the most rapidly efficacious therapy (usually cytotoxic chemotherapy). For example, *Liver visceral crisis* – rapidly increasing bilirubin > 1.5 ULN; *Lung visceral crisis* – rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion.

MBC is generally considered as incurable, but with the available treatment modalities and recent advances, it is certainly possible to

achieve meaningful improvements in survival while maintaining a socially acceptable quality of life. The general approach to treating a MBC is seen here (Figure 1).

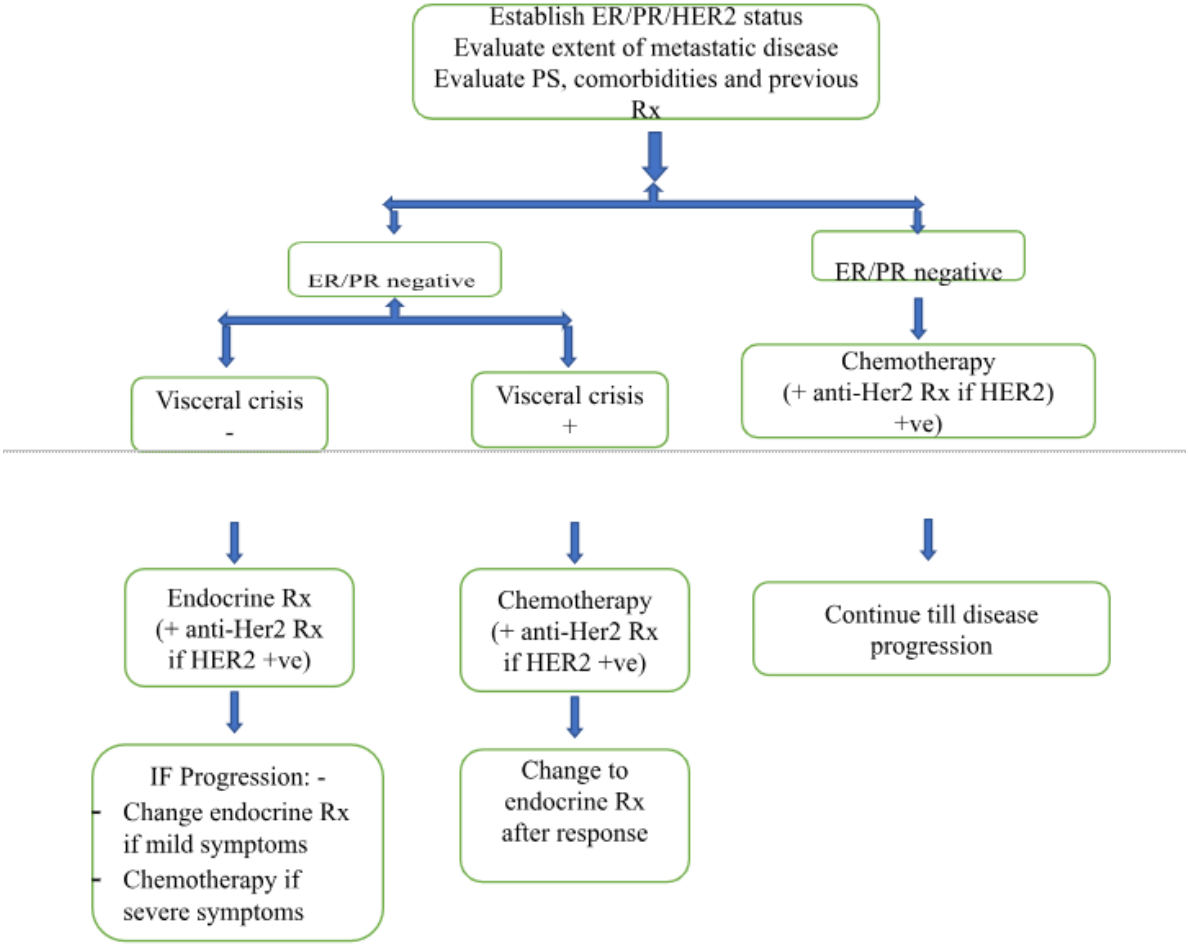

Figure 1: The general approach to treating an MBC

ENDOCRINE THERAPY (ET): - It is the therapy of choice for HR-positive/HER2-negative MBC patients not in visceral crisis. Selective estrogen receptor modulators (e.g. Tamoxifen) and Aromatase inhibitors (e.g. Letrozole, Anastrozole, and exemestane) remain the mainstay of ET. Another option in the ET of MBC is the selective ER downregulator fulvestrant. The first line of therapy (if feasible) is the addition of CDK4/6 inhibitor to ET plus ovarian ablation if premenopausal. Other acceptable options include single-agent fulvestrant or fulvestrant in combination with an AI or a CDK4/6 inhibitor.

CHEMOTHERAPY (CT): - Metastatic TNBC, metastatic HER2-positive breast cancers, and HR-positive MBC with recurrent/resistant disease to ET or rapid disease progression are the main indications for chemotherapy. A monotherapy should be preferred over a polychemotherapy regimen in patients with a limited tumor burden, as the latter is accompanied by an increased rate of treatment-associated toxicities. Combination chemotherapy regimens should be restricted to patients with severe symptoms and a high need for remission (eg, OMBC). A large number of agents (Table 3) are available for monotherapy regimens. Taxanes and anthracyclines are the most commonly used chemotherapeutic agents in breast cancer treatment.

Endocrine Therapy	Chemotherapy	Biologic Targeted Therapies	Newer Drugs
• Tamoxifen • Letrozole • Anastrazole • Exemestane • Fulvestrant	• Anthracyclines (*adriamycin, epirubicin*) • Taxanes (*paclitaxel, docetaxel*) • Capecitabine • Platinum agents (*carboplatin, cisplatin*) • Gemcitabine • Etoposide • Eribulin • Vinorelbine	Anti HER2 agents – • Trastuzumab • Lapatinib • Pertuzumab • TDM1 • Tucatinib • Trastuzumab-deruxtecan	• CDK 4/6 inhibitors (p*albociclib, ribociclib, abemaciclib*) • mTOR inhibitors (*everolimus*) • PI3K inhibitors (*alpelisib*) • PARP inhibitors (*olaparib, talazoparib*) • Immunotherapy (*atezolizumab, pembrolizumab*)

Table 3. Commonly available systemic therapy agents for treatment of MBC

Capecitabine, Vinorelbine and Gemcitabine (in combination with platinum agents) are the commonly used agents in later lines of therapy. The role of platinum salts (carboplatin and cisplatin) in the palliative therapy of patients with hereditary breast cancer (i.e., those carrying a BRCA1/2 mutation) and TNBC has increasingly been demonstrated by many studies. There is no predetermined duration of treatment except for anthracycline agents whose cumulative dose is limited by cardiotoxicity. For those who are responding to treatment, the chemotherapy is continued beyond best response. However, for patients who experience intolerable side effects, treatment discontinuation is reasonable. Patients with HR-positive disease who received

chemotherapy in the first line may consider switching to endocrine therapy for maintenance treatment.

BIOLOGICAL TARGETED THERAPIES: The treatment of HER2 positive MBC has undergone a paradigm shift with the availability of monoclonal HER2 targeted antibodies like trastuzumab. Trastuzumab is a humanized monoclonal antibody targeted against the extracellular domain of the HER2 receptor and has been shown to significantly improve OS in combination with monochemotherapy (usually a taxane). In addition to trastuzumab, Pertuzumab - a monoclonal antibody directed against the HER2/HER3 dimerization domain of the HER2 receptor and Trastuzumab emtansine (TDM-1) - an antibody-drug conjugate (ADC) of the cytotoxic DM-1 and trastuzumab are the other HER2 directed antibodies. Lapatinib (targeting both HER1/EGFR and HER2) is a small molecule HER2-targeted agent used in HER2-positive MBC frequently in combination with oral capecitabine.

For previously untreated patients, the combination of a taxane plus trastuzumab (+/- pertuzumab) is the most frequently used choice. However, patients with HR-positive and HER2-positive MBC may receive HER2-directed therapy in combination with ET, especially if their disease is not rapidly progressive or symptomatic.

IMMUNOTHERAPY: Immunotherapy with checkpoint inhibitors has been approved recently for use in metastatic TNBC patients whose tumors express PDL-1. Atezolizumab is the only approved drug for use in this setting, in combination with Nab-paclitaxel, for sporadic tumors with PD-L1 expression by immunohistochemistry of ≥1 percent.[43] Pembrolizumab is the other agent that has shown benefit in select patients of TNBC.[44]

METRONOMIC CHEMOTHERAPY: Metronomic chemotherapy refers to the regular administration of conventional chemotherapy drugs at low dose levels that are minimally toxic with the aim of stabilizing the effect on cancer growth.[45] They have the advantage of reduced hematological and gastrointestinal toxicities. They are especially useful against drug-resistant tumors by acting on the tumor microenvironment and microvasculature. Metronomic treatment is not a new drug rather conventional drugs at new dose and new schedule. Commonly used drugs are oral cyclophosphamide (50 mg PO OD), oral etoposide (50 mg PO OD), oral capecitabine (500 mg BD), and celecoxib (200 mg BD) in various combinations. Such metronomic combinations have been studied extensively in triple-negative breast cancers.

The recently reported trials exploring the role of systemic therapy in MBC with the aim of further improving survival have been enlisted in Table 4.

Patient population (trial name)	Type of study (n=)	Arms compared
Her2 +ve advanced breast cancer patients (KATE-2) previously treated with trastuzumab and taxane [46]	Phase-II RCT (n=202)	TDM1 with Atezolizumab or placebo
Metastatic HR+ve breast cancers [47]	Phase-II RCT (n=247)	Exemestane plus Enzalutamide or placebo
Endocrine refractory HR+ve MBC after chemotherapy [48]	Phase-II RCT (n=234)	Abemaciclib monotherapy or combination with Tamoxifen
Pretreated metastatic TNBC (ASCENT trial) [49]	Phase-II RCT (n=529)	Sacituzumab govitecan vs single agent chemotherapy
Pretreated metastatic TNBC (ENHANCE1 trial) [50]	Phase-IB/II RCT (n=167)	Eribulin plus Pembrolizumab
Metastatic TNBC (tnAcity trial) [51]	Phase-II RCT (n=191)	nab-paclitaxel plus carboplatin vs nab-paclitaxel plus gemcitabine vs gemcitabine plus carboplatin

Table 4: List of recent/ongoing important trials in MBC patients

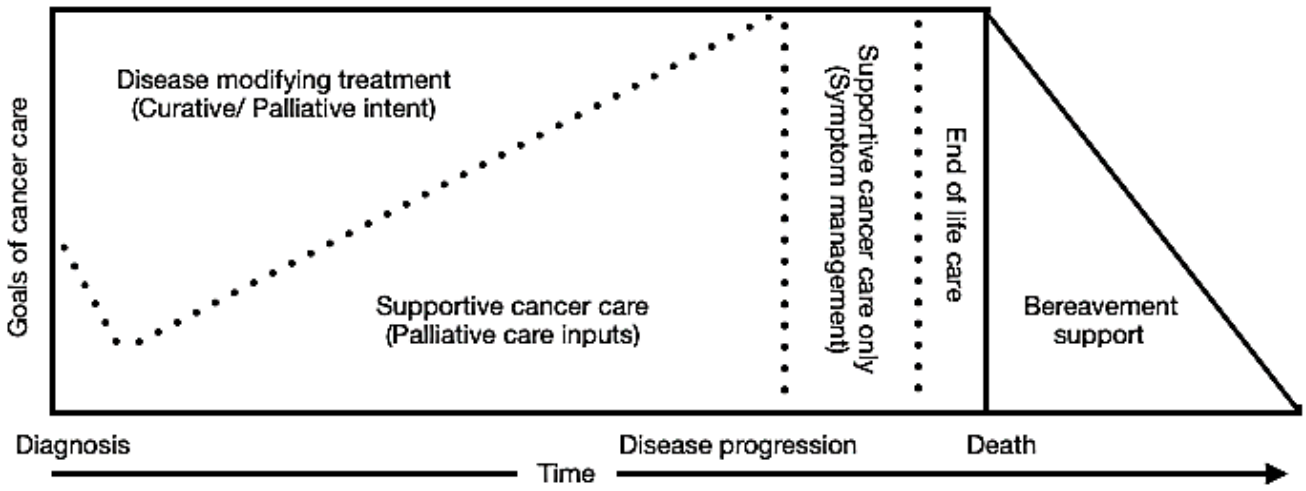

Figure 2: Integration of palliative care in MBC (56).

Palliative care (PC) is a patient and family centered approach to improve the quality of life (QoL) by identifying, preventing and relieving suffering and encourage shared decision making.(52) Provision of PC in metastatic breast cancers (MBC) is challenging due to the wide spectrum of disease-modifying treatments like surgical interventions, chemotherapy, radiation, biological and hormonal therapy, which can provide substantial benefits in terms of survival, disease, and symptom palliation. (53) Apart from symptom management, concurrent early PC referral in MBC can be largely focused on managing treatment-related side effects, counseling, reviewing goals of care, information provision, addressing psychosocial concerns, family support, rehabilitation, and advanced care planning (ACP). (54,55) The role of PC in MBC management may broaden as the disease progresses or disease-modifying treatments are no longer helpful, possess more risk rather than benefit and goals care are providing relief of symptoms and addressing suffering. (54,56) (Figure 2)

There is significant lack of access for PC provision in LMICs (Lower- and Middle-Income Countries). Hence, the models of PC delivery that fit better to the available settings and expertise should be adopted by LMICs (57). It is essential that cancer care specialists from all the core oncology disciplines undergo standard training for providing basic PC (generalist PC provision) in the form of routine symptom assessment, management, and basics of communication skills. Integration with specialist PC services (specialist PC provision) can be considered for complex symptom management, difficult communications and decision-making, failure of disease-modifying treatments, change in goals of care to supportive care, ACP or end-of-life care. This specialist care may need a good understanding and collaboration between oncologists and the PC team. (58)

Common palliative care issues include pain, fatigue, dyspnoea, wound care, lymphedema, psychological and neurological symptoms. (Table 5).

No.	Domain	Assessment issues
1	Physical	• Uncontrolled pain • Other symptoms – nausea, constipation, dyspnea, etc. • Complications secondary to the tumor metastasis • Nursing issues – wound care • Lymphedema management / exercises • Fatigue
2	Psychological	• Anxiety, depression, hopelessness • Body image issues • Anger, fear, uncertainty • Coping • Maintaining patient's dignity
3	Decision making	• Understanding about the illness and prognosis • Treatment options • Complications • Respecting patient's autonomy, exploring care preferences
4	Communication	• Discussing diagnosis and prognosis, addressing collusion/conflicts • Goals of care
5	Social	• Family situation, caregiver support • Place of care • Loss of income/identity/changing role in family • Social stigma
6	Spiritual	• Dwindling faith • Loss of meaning in life
7	Practical	• Rehabilitation measures – brace, spinal support • Assisting ADL (Activities of Daily Living) • Patient and caregiver training and education
8	Anticipatory	• Ensuring care coordination and continuity of care • Advanced care planning
9	Bereavement	• Supporting families/caregivers after death of patient

Table 5. Comprehensive PC plan for patients with MBC

Conclusion

Mounting evidence raising intriguing questions paired with newer biological concepts on cancer growth have definitely changed the outlook of managing stage IV metastatic breast cancer and helped identify a subgroup of patients where locoregional treatment can be offered with a curative intent.

Of the two scenarios described at the beginning of the chapter, the patient in scenario one is *de novo* metastatic breast cancer with metastasis at multiple sites not amenable to local treatment.

While scenario two is clinically locally advanced with two sites of bone metastasis making it an oligometastatic breast cancer that can be treated with curative intent. She should be offered aggressive multimodality treatment.

Summary and key points

- MBC patients have multiple and complex care needs
- Comprehensive and holistic management of patients requires a multidisciplinary team approach
- Oligometastatic breast cancers can be considered for curative intent by multidisciplinary approach.
- Mounting evidence raising intriguing questions paired with newer biological concepts on cancer growth have definitely changed the outlook of managing stage IV metastatic breast cancer and helped identify a sub group of patients where locoregional treatment can be offered with a curative intent. Several upcoming prospective trials will aid in answering further questions to improve outcomes with surgery in the metastatic setting.
- Specialist PC in MBC addresses suffering in terms of physical, emotional, psycho-socio-spiritual and communication needs and should be instituted early in the management of any patient with advanced breast cancer.

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Chapter 17

Radiation Therapy for Breast Cancer

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Clinical Scenario

A 45-year-old woman presents with a palpable right breast mass. She is otherwise healthy and has no family history of breast or ovarian cancers. She is gravida 2 para 2, first pregnancy at age 29, and breastfed each of her children for 1 year. She has a history of 10 years of oral contraceptive use. On physical exam, there is a 2cm palpable mass in the upper outer quadrant of the right breast. No adenopathy is palpable. Diagnostic mammogram and ultrasound are performed revealing a solid mass corresponding to the lump measuring 2.4cm in greatest dimension. A biopsy reveals grade 2 invasive ductal carcinoma, ER+, PR+, Her2-. She elects to proceed with lumpectomy and sentinel node biopsy. Final pathology demonstrates a grade 2 ER/PR+ Her2- IDC, with no in situ component, measuring 2.2cm. There is lymphovascular space invasion noted. The final surgical margins were negative with the closest being 2mm posteriorly. There were 2/3 sentinel nodes involved, with the largest deposit measuring 1.3cm without extracapsular extension. She is staged as pT2N1a. She is a prognostic stage group IIA.

Introduction and rationale for radiation therapy in breast cancer

Radiation therapy is a critical component of multidisciplinary care for most patients with breast cancer. Its purpose is to eradicate residual microscopic disease following surgery. Early studies demonstrated that lumpectomy plus radiation is equivalent to mastectomy for patients with early breast cancer.[1] This has spared hundreds of thousands of women the physical and psychological morbidity of mastectomy. Since that time, radiation techniques have improved and the role of radiation therapy has been expanded and refined. This chapter will outline the indications for radiation therapy; timing and logistics; treatment fields and techniques; and acute and long-term side effects and management.

Whom to treat

A. After breast-conserving surgery

For invasive cancer, the addition of radiation to lumpectomy reduces the rate of recurrence by half, with an associated reduction in breast cancer death.[2] Thus, all women who have had breast-conserving surgery should have a consultation to discuss the risks and benefits of radiation therapy. For some women, the risk of recurrence is sufficiently low that, after a balanced discussion between patient and provider, one may opt to omit radiation (see "Omission" below). However, the majority of patients with invasive disease who have had a lumpectomy will require adjuvant radiation. No radiation is recommended for women with lobular carcinoma in situ (LCIS) except for those with pleomorphic subtype, which is treated as ductal carcinoma in situ (DCIS).

For patients with DCIS, while radiation has not been shown to impact survival, it has consistently demonstrated decreased rates of in-breast recurrence, including recurrence of

invasive disease.[3] In high-grade DCIS the risk of in-breast recurrence can reach 25%, thus adjuvant radiation is uniformly recommended.[4] For low- or intermediate-grade DCIS a spectrum of risk exists, and treatment decision-making necessitates a detailed discussion between patient and provider. Factors such as patient age, size of the tumor, and margin status may influence the decision. The Memorial Sloan Kettering Cancer Center offers a free web-based nomogram (http://nomograms.mskcc.org/breast/DuctalCarcinomaInSituRecurrencePage.aspx) which can be used to quantify risk based on DCIS features and receipt of radiation or endocrine therapy. Genomic tests are also of use in this setting, if available, including oncotypeDX® (Genomic Health, Inc., California, USA) and DCISionRT® (Prelude Corporation, California, USA). We recommend discussing these risks with the patient, with an explanation that in-breast recurrence would likely necessitate a mastectomy.

B. After mastectomy

Post-mastectomy radiation therapy (PMRT) is one of the more nuanced and controversial topics in breast cancer. While some patients may opt for mastectomy with the hopes of avoiding radiation, certain disease features may necessitate it. Post-mastectomy chest wall recurrence has high morbidity, and residual disease in the chest wall or nodal basins may seed distant metastases and impact survival, even in the setting of modern systemic therapies.

ii. Early-stage disease

For pure DCIS with negative margins, PMRT is not indicated. For the majority of cases, it is also not recommended for early-stage invasive disease. However, certain factors may place even T1-2N0 patients at high enough risk for locoregional recurrence to warrant PMRT.[5,6] High-risk features include large tumor size, high histologic grade, triple negative biomarker status, close or

positive margins (with no re-excision feasible), patient age (with younger patients at higher risk), omission of systemic therapy, and the presence of lymphovascular space invasion (LVSI). As before, there is a spectrum of risk, however PMRT should be considered with patients who present with three or more of these risk factors.

ii. Locally advanced disease

The Danish[7] and British Columbia[8] trials demonstrated not only a locoregional control benefit, but a significant overall survival benefit with the use of PMRT in high risk premenopausal patients. In the Danish trial, high risk was defined as size >5cm, axillary involvement, or invasion of skin or pectoral fascia. The British Columbia trial included patients with axillary involvement. While the mortality benefit of PMRT in node-positive patients has been consistent across many large, well-designed trials,[9] controversy remains within the subgroup of patients with 1-3 positive lymph nodes. This discussion is beyond the scope of this chapter, but several well-written review and guideline articles are available for further reading.[10-12] In general, PMRT should be offered to women with T3-4 disease and/or with 4 or more positive nodes. It should also be strongly considered for women with T1-2 disease and 1-3 positive nodes (See section 4, "Nodal irradiation").

iii. After neoadjuvant chemotherapy

This patient population also garners much controversy, and it is the subject of an ongoing large multicenter randomized trial (NSABP B-51/RTOG 1304). The decision to deliver PMRT after neoadjuvant chemotherapy (NAC) rests on several factors including clinical stage prior to NAC, pathologic response to NAC, as well as features generally considered to place patients at higher risk of recurrence such as a young age, triple negative biomarker status, high histologic grade,

LVSI, and margin status. Until randomized data from B-51 are available, we recommend following the MD Anderson Cancer Center approach,[13] in which PMRT is given to women with initial cT3-T4 or cN2-N3 disease, as well as ypN+ disease. Reviews are available for further reading.[14]

C. Omission

Two large randomized trials have attempted to identify subsets of women in whom omission of radiation after lumpectomy may be appropriate.[15,16] Briefly, these studies randomized older women (over age 65-70) with small, estrogen receptor (ER)-positive tumors with negative margins to receive lumpectomy with or without radiation therapy. Both studies identified a small but significant benefit in in-breast tumor recurrence, with no impact on disease-free or overall survival. As a result, some patients and providers may feel the risk is sufficiently low (4-5% without radiation, and 1-2% with radiation at 5 years post surgery) to omit radiation therapy in this population. When counseling patients, it is important to take life expectancy into account and to note that this risk will continue to increase over time (CALGB 9343 reported an in-breast recurrence risk of 10% at 10 years). Thus, we recommend a detailed discussion with patients, emphasizing the fact that radiation will indeed reduce their risk of recurrence, but that the overall risk is low. Patients who elect not to receive adjuvant endocrine therapy should be encouraged to have adjuvant radiation therapy.

D. Recurrent disease

Although resection followed by radiation provides excellent locoregional control in early and locally advanced breast cancer, long term follow up reveals in-breast recurrence in approximately 10% of early-stage patients at 10 years post-radiotherapy,[17] and locoregional recurrence in 14% of locally advanced breast cancer patients 18 years after

radiotherapy.[18] Presentation may thus include ipsilateral in-breast recurrence following breast conservation, chest wall recurrence following mastectomy, and/or regional nodal recurrence after either treatment strategy. Although these presentations vary, there are a few overriding principles to guide the approach to recurrence:

- Treatment with curative intent using aggressive systemic and local therapies should be favored over palliative treatment.
- Multimodality therapy including systemic therapy, surgery and radiation should be used to fully address gross disease.
- In radiation-naïve patients, comprehensive radiation to the breast or chest wall and regional lymph nodes should be offered during treatment for recurrence.
- In previously irradiated patients with a high risk of a further locoregional recurrence or in patients with unresectable recurrences, re-irradiation should be strongly considered.

i. Chest wall recurrence

Chest wall recurrences are best managed with a multidisciplinary approach. Whenever possible, surgery should be used as the upfront treatment. Following surgery, adjuvant radiation should be delivered. The need for radiotherapy is well supported by retrospective data demonstrating second recurrence rates ranging from 50% to 76% after surgery alone.[19,20] With the addition of adequate radiation doses and fields, local control rates can improve from 28% to 72%.[20] For unresectable recurrences, chemotherapy and radiotherapy should be utilized in the attempt to convert the patient to resectability, with the understanding that durable local control may be difficult to achieve without resection. In patients who have previously received radiation

therapy, chest wall recurrences may be reirradiated with caution, taking into account the time since the initial radiation course, the tolerance to the prior radiation, and weighing the morbidity of reirradiation toxicity against the potential morbidity of a locoregionally progressive chest wall recurrence. If available, the addition of hyperthermia to radiation may improve the response and locoregional control rates in this patient population.[21]

ii. In-breast recurrence

Patients who have had breast conservation surgery for breast cancer may experience recurrences at the original cavity or new primary tumors at other locations within the breast. Mastectomy is the standard approach to recurrences after breast conservation, yielding high rates of local control, although lower than those observed following upfront mastectomy.[22-25] Because most patients who undergo breast conservation received adjuvant radiation during the initial treatment course, re-irradiation is generally avoided when margin-negative mastectomy can be offered. However, in selected cases, with cautious consideration of the risks as above, reirradiation to the whole breast may be considered (see section 4, "Re-irradiation" regarding dosing in this setting). Additionally, a recent phase II prospective trial, RTOG 1014, investigated whether a breast conservation approach including external beam accelerated partial breast irradiation can be used for locally recurrent breast cancer after previous lumpectomy and radiation, with initial results demonstrating very rare grade 3 toxicity at 1 year.[26] These results indicate that breast conserving salvage with re-irradiation can be considered in appropriate patients with low volume in-breast recurrences, although effectiveness data have not yet been reported. Possible selection criteria for second breast-conserving approach after ipsilateral tumor recurrence are provided by German Society of Radiation Oncology (DEGRO) as follows:[27]

- Isolated ipsilateral breast tumor recurrence
- Limited size (<2-3 cm)
- Unifocal disease on ultrasound, mammography, and MRI
- Age ≥ 50 years
- Long interval between primary treatment and recurrence (≥ 48 months)
- Patient preference for second breast conservation followed by radiotherapy
- Second breast conservation is technically feasible and will result in acceptable cosmetic results

If no prior radiation was received, and a patient requests lumpectomy for surgical management, they may be managed as in the upfront setting with lumpectomy and adjuvant radiation.

iii. Regional recurrence

Nodal recurrences, in general, have a poorer prognosis than chest wall recurrences. However, a significant proportion of patients will be alive at 5 years, thus aggressive management is warranted.[28] Depending on the location and burden of recurrent disease, as well as the receipt of prior radiation, a multidisciplinary approach is recommended. If feasible, nodal dissection with adjuvant radiation and systemic therapy offers the best change of durable locoregional control. Unresectable isolated nodal recurrences may be treated definitively with chemotherapy and radiation, or they may be considered for management with stereotactic ablative radiation therapy (SABR or SBRT),[29] if available.

iv. Metastatic disease

Symptomatic metastatic disease should be treated with palliative radiation, as appropriate. Please see section 4, "Palliation" for a discussion on the management of specific palliative scenarios. For oligometastatic breast cancer (i.e., 1-5 metastatic sites), SABR to all sites of disease may offer a survival benefit.[29] If patients present with de-novo metastatic breast cancer, treatment of the locoregional disease has shown a mixed impact on survival.[30,31] Given the controversy, other factors may play in to decision making such as the response to systemic therapy, the locoregional burden of disease, and symptomatology.

When to Treat

A. Timing

Whole breast radiotherapy is conventionally administered in the adjuvant setting, following surgical resection with lumpectomy or mastectomy. There are instances in patients with locally advanced disease for whom a resection is not feasible or has a higher likelihood of resulting in a positive surgical margin, even after the use of neoadjuvant chemotherapy. Therefore, in these typically very locally advanced or inflammatory breast cancer settings, neoadjuvant radiotherapy along with radiosensitizing chemotherapy may be considered. [32-34]

Breast radiotherapy is typically initiated 3-6 weeks after surgical resection, although the exact timing is institution- and provider-dependent. If adjuvant chemotherapy is recommended, then radiotherapy follows the last cycle of chemotherapy, usually 3-4 weeks after the last chemotherapy cycle. This timing reduces the risk of additional acute toxicity from radiation therapy being administered concurrently with the chemotherapy regimen.

B. Sequencing with Systemic Therapy

Chemotherapy may be administered in the neoadjuvant or adjuvant setting. It conventionally precedes radiotherapy. However, in a randomized study comparing a chemotherapy-first arm to a radiotherapy-first arm in patients following lumpectomy, there was no advantage to performing one adjuvant therapy prior to the other treatment.[35] If patients are receiving Her2-directed systemic therapy, then this begins with neoadjuvant/adjuvant chemotherapy, continues concurrently with radiation therapy, and continues after the conclusion of radiation therapy.[36] If patients are candidates for endocrine therapy, then this treatment is typically initiated after the conclusion of adjuvant radiotherapy, although it may be administered concurrently without a clear worsening of acute or late toxicities from adjuvant radiation therapy.[37] In order to reduce the risk of poorly tolerating endocrine therapy or having side effects from it, endocrine therapy is initiated after patients have begun to recover from the acute toxicities of radiation therapy. Therefore, initiation of endocrine therapy usually occurs approximately one week to one month from the conclusion of radiotherapy.

C. Breast Reconstruction Issues

For patients who receive a mastectomy and breast implant reconstruction, there are potential cosmetic complications which can arise if post-mastectomy radiation therapy is delivered. These complications may include seroma or hematoma formation, infection, wound dehiscence, capsular contracture, and implant loss.[38] For patients who receive implant reconstruction, temporary tissue expanders are typically placed prior to adjuvant radiotherapy, with permanent implant exchange after the completion of radiation therapy. Fibrosis is a significant concern in this setting, and the development of this may eventually necessitate either surgical correction of the contralateral breast for symmetry or the treated breast in approximately 30% of individuals.[39] As an alternative to implant reconstruction, autologous reconstruction with a flap

may be performed. The major concerns with the addition of radiation therapy in this setting include flap fibrosis, necrosis, and contracture.[40] For patients who receive an autologous reconstruction, there is a risk of poor cosmetic outcome or reconstruction failure following adjuvant radiation therapy as well, although this risk is lower than in patients receiving implant reconstruction.[41,42] Flap reconstruction following the conclusion of radiation therapy may reduce some complications like fibrosis.[43]

What and how much to treat

A. Treatment volumes

The benefit of adjuvant radiation therapy after lumpectomy is clear, but appropriate treatment volumes are an area of active study. For early stage, clinically node-negative patients, radiation treatment volumes have historically included the entire breast, which is still an appropriate treatment option. For some women at sufficiently low risk, subtotal breast irradiation may be sufficient (see "Partial breast" below). However, the vast majority of post-lumpectomy patients with either DCIS or invasive disease should receive radiation to the whole breast (see section 5, "How to treat" for details regarding treatment fields).

i. Nodal irradiation

The draining lymphatics for the breast include the axillary nodes, the supraclavicular and infraclavicular nodes, and the internal mammary nodes (IMN). A number of factors are important when considering whether to include these volumes in the radiation field. One such factor is the surgical axillary evaluation. Two studies have demonstrated the equivalence of sentinel lymph node biopsy (SLNB) with adjuvant radiation to axillary lymph node dissection (ALND) in women clinically node negative disease but positive sentinel nodes.[44,45] In an

adequately dissected axilla, i.e. at least 10 lymph nodes removed, we recommend adjuvant radiation if four or more lymph nodes are positive or if any node has extracapsular extension (ECE). In women with fewer than four positive axillary nodes, the decision to radiate the axilla should be individualized to each patient. Factors such as age, hormone receptor status, LVSI, and receipt of systemic therapy should be considered. Two nomograms that can be used to help assess the risk of additional positive nodes may aid in decision making; one by Memorial Sloan Kettering Cancer Center (http://nomograms.mskcc.org/Breast/BreastAdditionalNonSLNMetastasesPage.aspx) and one by MD Anderson Cancer Center (http://www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln). In general, one should consider regional nodal irradiation if the risk of additional positive nodes is greater than 10%.

Many studies that demonstrated disease-free or overall survival benefits to regional nodal irradiation included the supraclavicular fossa, IMN, or both.[46-49] Larger treatment fields naturally increase the dose to normal organs, with modestly increased risks of side effects such as pneumonitis or possibly coronary artery disease. Additionally, radiation to the axilla increases the risk of lymphedema, especially following a complete ALND. In this context, we typically recommend comprehensive nodal irradiation to node positive or high-risk node negative patients, provided that normal tissue tolerances are respected.

Following mastectomy, the Danish and British Columbia trials mentioned previously included comprehensive regional nodal irradiation, which provides justification for including these areas. Additionally, the results of MA.20 and EORTC 22922 are frequently extrapolated to the post-mastectomy setting, as there is no reason to expect the risk of subclinical positive lymph

nodes in the supraclavicular or IMN regions is different based on the upfront surgical choice. Thus, we follow a similar treatment paradigm post-mastectomy, where we include comprehensive regional nodal irradiation in node positive or high-risk node negative patients if safely achievable. Radiation of the supraclavicular/IMN regions without inclusion of the axilla may be carefully considered in patients with an adequate axillary dissection with a small overall burden of nodal disease and an absence of ECE.

B. Dosing

i. Hypofractionation

Postoperative radiation for breast cancer has traditionally been given to a dose of 50 Gy in 2 Gy per fraction, or 50.4 Gy in 1.8 Gy fractions. These are still acceptable doses and are the current standard when including the regional nodal volumes. However when treating the breast only, other fractionation schemes are available. Large randomized trials have demonstrated noninferiority of hypofractionated regimens such as 42.5 Gy in 16 fractions or 40 Gy in 15 fractions when treating the breast, with or without the low axilla.[50,51] The updated American Society for Radiation Oncology (ASTRO) guidelines published in 2018 recommend hypofractionation for all patients, provided the intent is to cover the whole breast without an additional field to cover the regional lymph nodes.[52] A recent randomized trial demonstrated equivalent disease control and cosmesis using a hypofractionated regimen for PMRT,[53] however this study was performed only in patients who did not have breast reconstruction. For women with reconstructed breasts, we recommend standard fractionation.

ii. Boost

A boost is defined as the delivery of additional radiation dose to the lumpectomy cavity with a margin following whole breast radiation. Regardless of patient age, a boost improves local control, however there is data indicating that this effect is more pronounced in younger women.[54,55] Though no disease-specific or overall survival benefit has been shown, there is also minimal impact on toxicity, with only a modest increased risk for fibrosis. Thus, our practice is to recommend a boost for all post-lumpectomy patients. In patients older than 60, especially those with limited life expectancy, a boost can likely be avoided pending a balanced discussion with the patient. During standard fractionation, we recommend a boost of 10 Gy in 5 fractions. During hypofractionation, we recommend 10 Gy in 4 fractions. In the setting of close or positive margins, the boost may be increased to 16 Gy in 2 Gy fractions, however increasing the dose higher than 16 Gy increases the risk for fibrosis and negative cosmetic outcomes. Following mastectomy, many women may not require a boost to the chest wall. However certain characteristics such as triple negative disease, close/positive margins, or inflammatory disease place the patient at higher risk of local recurrence and a boost may be of benefit.[56]

iii. Special scenarios

In inflammatory breast cancer, dose escalation results in improved locoregional control rates. In general, radiation should be given to a dose of 50 Gy in 25 fractions or equivalent, with liberal use of tissue-equivalent bolus. A 10-16 Gy boost in 2 Gy fractions should be given to the chest wall, with higher doses used for women with a poor response to chemotherapy, close/positive margins, or patients <45 years of age.[57] Special attention should be paid to the brachial plexus dose in these situations. Radiation may also be considered for neoadjuvant treatment in patients

with a poor response to chemotherapy to facilitate surgery. In this setting, we recommend a dose to 45-51 Gy using 1.5 Gy fractions twice daily, with a 15 Gy boost.

C. Partial Breast Irradiation

Partial breast irradiation involves post-lumpectomy radiation delivered to a reduced volume that includes the tumor bed and a margin to account for the highest risk area. Advantages to this approach include decreasing both the volume of healthy tissue exposed to radiation and the duration of treatment without sacrificing tumor control. Multiple treatment techniques are included under this umbrella term, including intraoperative radiation therapy, accelerated partial breast irradiation using external beam or intracavitary brachytherapy techniques, or reduced field hypofractionated tangent irradiation. In each technique, treatment is planned to cover a uniform expansion of the cavity and surgical clips with the skin rind and chest wall excluded from the evaluation volume. Furthermore, the use of intraoperative, brachytherapy, or accelerated partial breast irradiation allows for shortening of the treatment course.

To this point, partial breast radiation yields similar ipsilateral tumor control across multiple studies.[58-61] Because the irradiated volume is significantly smaller than the whole breast for many patients, careful selection of low-risk patients is favored out of concern for increased ipsilateral in-breast recurrences. Indeed, both the ELIOT and TARGIT-A trials of intraoperative radiotherapy showed increased ipsilateral breast tumor recurrence, even in highly selected patients.[59,60] Intracavitary brachytherapy, intraoperative radiotherapy, and accelerated partial breast irradiation may be associated with increased adverse events—elevated rates of fat necrosis were reported following intraoperative radiotherapy,[60] and worse cosmetic outcome following both external beam and brachytherapy-based accelerated partial breast irradiation.[62,63] Of note, these trials included primarily patients with very low risk disease—low grade, small, hormone-

positive, node-negative tumors with widely negative resection margins in patients over 50 years old. Thus, whole breast irradiation should still be considered standard of care for patients with high-risk or node-positive tumors.

Patient Group	Risk Factor
Suitable	Invasive • Age ≥ 50 y • Margins ≥ 2 cm • Tis or T1 DCIS • Screen-detected • Low to intermediate nuclear grade • Size ≤ 2.5 cm • Margins ≥ 3 cm
Cautionary	Invasive • Age 40–49 y if all other "suitable" criteria met • Age ≥ 50 y if patient has at least one pathologic factor below and does not have any "unsuitable" factors *Pathologic factors* • Size 2.1-3.0 cm[a] or clinically unifocal with total size 2.1-3.0 cm[b] • T2 • Close margins (< 2 mm) • Limited/focal LVSI • ER (-) • Invasive lobular histology • Pure DCIS ≤ 3 cm if criteria for suitable not fully met • EIC ≤ 3 cm • Margins < 2 mm
Unsuitable	Invasive • Age < 40 y • Age 40–49 y and does not meet criteria for cautionary • Margins positive DCIS • > 3 cm

Table 1: American Society of Radiation Oncology guidelines

a The size of the invasive tumor component.

b Microscopic multifocality allowed, provided the lesion is clinically unifocal (single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

Partial breast treatment does offer an effective and more convenient option for selected low risk patients. To assist in the selection of patients appropriate for partial breast radiotherapy, the American Society of Radiation Oncology has provided the following consensus guidelines (Table 1).[64]

D. Recurrence, Reirradiation, Palliation

i. Recurrence

The chest wall is by far the most common site of locoregional recurrence after mastectomy, but nodal involvement is reported in at least a third of all recurrences.[65-72] Data from Washington University showed that the effective dose was dependent upon residual disease, with doses in excess of 50 Gy necessary for control of completely resected lesions, and that recurrences were far fewer in patients who underwent large field irradiation as compared to spot irradiation of the tumor. Therefore, complete irradiation of the chest wall and regional nodal volumes is recommended in radiation-naïve patients. Because the vascular supply may be diminished in previously treated patients and the cancer has biologically declared itself more treatment resistant, practice at M.D. Anderson Cancer Center is to increase the microscopic radiation dose ~10%, from 50 to 54 Gy, with boost volumes taken to 66 Gy.[73]

Those patients with positive surgical margins, regional spread at recurrence, or who are pursuing a second breast conservation surgery should be considered for re-irradiation, as discussed below.

ii. Re-irradiation

There are few level I data to guide the use of re-irradiation in the treatment of recurrent breast cancer, so the decision to re-irradiate should be guided by clinical judgement and shared decision making with the patient. Despite the paucity of prospective or randomized data, the relatively poor local control after surgical salvage alone supports the use of adjuvant re-irradiation in well-selected patients. In general, the decision of whether to offer re-irradiation will depend on the risk of second local recurrence after resection, initial treatment delivered, interval time to relapse, the extent of local recurrence, margin status, cosmetic considerations, and salvage options available for an additional recurrence. Patients who are at least one year out from initial treatment who do not show severe toxicity from their first course of radiotherapy should be considered for re-irradiation. Optimal dose, fractionation, target, technique, and modality are not yet defined, although a 2 Gy equivalent dose of at least 45-50 Gy is recommended, so long as cumulative doses do not exceed 110 Gy.[27] Several studies have investigated techniques focused on limiting late effects on normal tissue, including brachytherapy, accelerated partial breast irradiation, hyperfractionation, or hyperthermia.[74] In each case the goal is to maximize local tumor control while limiting radiation toxicity. Thus, unlike the radiation-naïve patient, re-irradiation fields are limited to the high risk area surrounding the tumor recurrence, with microscopic regional and distant disease control further addressed by systemic therapies. Local control and survival rates following re-irradiation vary, but in general replicate those seen in stage III breast cancer patients (reviewed in [74]).

iii. Palliation

Radiation therapy is very effective for palliation of breast cancer lesions that are either causing symptoms (e.g. pain, ulceration, or discharge) or threatening structural integrity or vital organ function (e.g. cortical bone destruction in a weight-bearing bone or neuraxial compromise). The

selection of dose, target, technique, and fractionation should be tailored for each patient to maximize palliation while minimizing inconvenience and financial toxicity. Dose and fractionation should take into account the long term prognosis for the patient. In general, larger total doses and smaller daily fractions are used in patients with a longer life expectancy, whereas larger doses over fewer fractions are used for patients with a more limited prognosis. For lesions in the breast, skin, or axilla, common radiation fractionation plans include 30 Gy in 10 fractions, 45 Gy in 15 fractions, or 50 Gy in 20 fractions. All of these regimens are well-tolerated, with the higher total doses providing more durable local control. For skin lesions, electrons and bolus are often used to ensure adequate dose to the skin surface.

Radiation therapy is very effective for the treatment of painful bone metastases. Treatment typically covers the gross tumor volume with clinical and setup margins. Single fraction regimens are equally effective as fractionated treatments at relieving pain. RTOG 9714 compared 8 Gy in a single fraction to 30 Gy delivered in 10 fractions and found that, although both arms were equivalent with regard to pain relief, retreatment in the single fraction arm was double that of the 30 Gy arm (18% v 9%).[75] Because patients with isolated bone metastases have long expected survival, many physicians offer fractionated regimens or dose-escalated hypofractionated regimens to reduce likelihood of retreatment. This concept has been challenged recently by a phase II trial out of MD Anderson evaluating dose-escalated stereotactic single fraction regimens against the 10-fraction standard. Initial report showed improved pain control and local control in patients receiving the stereotactic treatment, which may provide a more convenient and effective approach to bone metastases.[76] For patients with multifocal painful bone metastases, injectable radionuclide therapy with ^{153}Sm, ^{89}Sr, or ^{223}Ra can be an effective approach as well.[77,78]

Spinal cord compression is an oncologic emergency that requires immediate attention. Patients presenting with symptomatic compression should be started on high dose steroid therapy followed by neurosurgical decompression and post-operative radiotherapy – either fractionated or stereotactic. For unresectable symptomatic patients, palliative radiotherapy, usually 30 Gy in 10 fractions, is delivered to the affected spinal levels after 24 hours of steroid treatment. Typically, superior and inferior margins are delineated at a full vertebral level to assist in matching should the patient require additional courses above or below the treated lesion. Non-symptomatic cord compression or threat of compression can be addressed with standard palliative radiotherapy, as described above, or using spine stereotactic radiosurgery, in which an ablative dose is delivered to the tumor in 1-3 fractions. In either case, tumor control and preservation of function are superior if the patient's tumor can be resected prior to radiation. Stereotactic radiosurgery provides superior local control to fractionated treatment and may allow retreatment of previously treated lesions. However, this is a technically challenging treatment modality that should only be offered by centers with experience in its delivery.

Brain metastasis from breast cancer typically portends poor survival and has traditionally been treated with either resection and whole brain radiotherapy for isolated metastases, or whole brain radiotherapy for multiple metastasis. Whole brain radiotherapy is typically delivered to a dose of 30 Gy in 10 fractions, using an opposed lateral technique. The field must include the cribriform plate and usually extends inferior to C1/C2. For patients with leptomeningeal spread, an ominous sign, fields are extended anteriorly to cover the back half of the orbits, and inferiorly to C2/C3. More effective systemic agents and the advent of intracranial stereotactic radiosurgery are now commonplace for patients with brain metastases, some of whom now are living for years after intracranial seeding. Stereotactic radiosurgery allows the treatment of brain metastasis, or

the post-operative tumor bed, in 1-3 fractions of high dose radiation. Stereotactic radiosurgery offers equivalent local control with amelioration of cognitive decline, the major toxicity associated with whole brain radiation.[79-82] Patients with 10 or fewer metastases may be considered for radiosurgery,[83] although this number is institution and provider dependent.

How to treat

A. Simulation

The goals of simulation when deciding upon patient positioning, immobilization, and imaging modality are to create a robust and reproducible treatment position that allows the physician to identify and expose the target volumes while minimizing radiation exposure to healthy tissues. The primary organs at risk in treatment of breast cancer are the ipsilateral lung, heart, and contralateral breast. Because skin toxicity is often the most distressing acute side effect, care should be taken to minimize skin folds within the radiation field, which can lead to an auto-bolus effect and increased skin toxicity. Most commonly, patients are treated in the supine position with the ipsilateral arm abducted and externally rotated. The contralateral arm may also be positioned overhead for comfort and reproducibility. An angle of 5-15 degrees may be utilized to allow gravity to pull the breast tissue off of the clavicle and pull the heart down and away from the radiation field. The angle should be chosen to provide these benefits while minimizing skin-on-skin contact in the inframammary fold. An immobilization device, such as a Vac-Lok cushion or customized breast radiation board is used to limit intra- and interfraction motion.

Computed tomography (CT) simulation is the current standard for designing radiation fields, allowing the design of treatment fields based on each patient's three-dimensional

anatomy. Because there are no consistent anatomic boundaries to breast tissue visible on CT scan, the physical examination and clinical appearance must be considered during field design and daily treatment. This can be accomplished using radio-opaque wire to delineate the clinical borders of the breast tissue and surgical scars. The CT scan should include the full treatment target region as well as at least 5 cm margin superiorly and inferiorly to allow for accurate dose calculation. Isocenter placement and field design are then conducted virtually on the CT data set. Isocenter placement for each treatment technique is reviewed below. After position, simulation, and isocenter placement, marks should be placed on the patient to facilitate daily setup during treatment. In many centers, 2-3 small tattoos are placed on a stable area of skin (often in the low thorax, inferior to the breast), where there is less subcutaneous fat. Alternatively, lines can be drawn on the skin to allow isocenter alignment with in-room lasers. Patients are instructed to then protect these lines with clear adhesives or intermittently reapply faded lines.

B. Special techniques

i. Deep Inspiratory Breath Hold

For left-sided breast treatment, deep inspiratory breath hold can reduce the dose to the heart. During breath hold, the chest wall expands, and the diaphragm pulls the heart downward, thereby moving it out of the radiation field and substantially reducing the dose to the heart. Because cardiac complications are one of the most significant toxicities associated with breast cancer survivorship, minimizing dose to this region is critical.[17] The use of breath hold enables the mean heart dose to stay under 5 Gy, reducing the long-term risk of radiation-induced cardiac events.[84,85] This technique requires inspiration to a reproducible level, which is selected during simulation and employed during the CT simulation and each radiation fraction. Treatment

is gated to respiration, such that the beam is only on while the patient is maintaining the specified breath hold volume. To facilitate reproducibility, two breathing management strategies may be employed: the real-time position management system utilizes an infrared camera and a reflective marker box placed on the patient as a surrogate for inspiration depth.[86] The patient receives visual feedback indicating the level of their respiration and is coached to achieve a goal inspiratory level set by the physician or therapists. This level is then repeated each day during treatment. An alternative is the active breathing coordinator system, which uses a mouthpiece attached to a spirometer to limit the inspiration to a prespecified volume. Once that threshold is reached, a valve in the spirometer closes, preventing the patient from inhaling or exhaling. If neither of these systems is available, the image-guided voluntary deep inspiration breath hold technique can be used.[87] In this technique radiopaque surface markers are used to monitor breathing level, and patients are coached to breath to a reproducible depth. Onboard fluoroscopy is used during breath hold to ensure that the surface and underlying anatomy replicate the day of simulation, and the beam is manually controlled to deliver radiation only during breath hold.

ii. Prone simulation

Simulation and treatment in the prone position may offer better heart and skin sparing for patients with pendulous breasts, patients with left sided tumors who have difficulty with breath hold, or those whose anatomy precludes adequate target coverage without treating significant lung volumes. Prone treatment requires a special treatment board in which the breast hangs away from the thorax through a gap in the table. The ipsilateral arm is typically placed above the head. Medial and lateral borders of the target should be marked with radiopaque wire. The advantage is that it pulls the treatment target away from the chest wall, nearly eliminating any

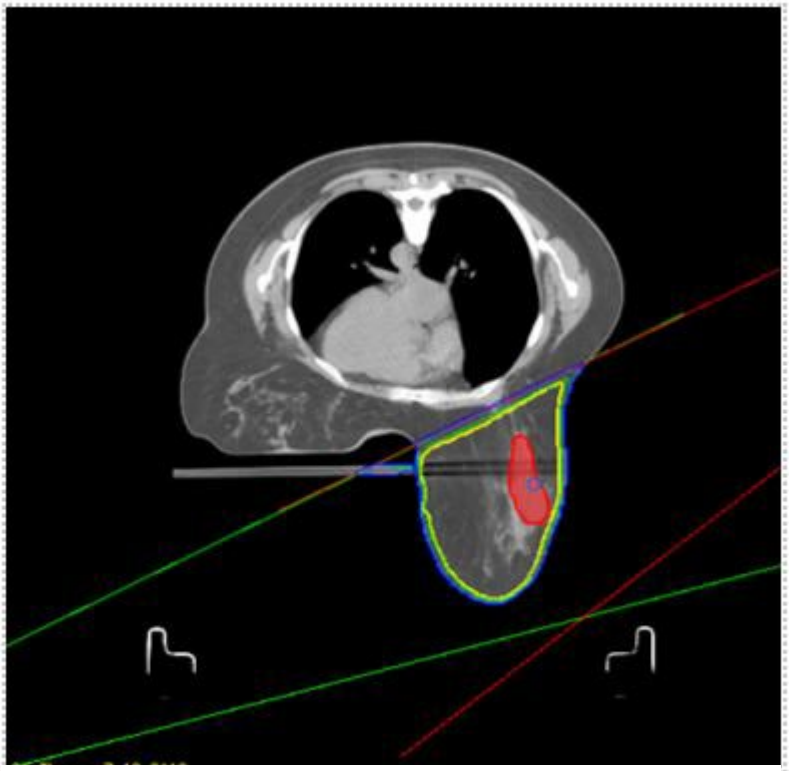

Figure 1: Prone positioning for intact breast irradiation. The tangential fields and isodose distribution are shown. Tumor bed is contoured in red.

heart or lung from the treatment field (Figure 1). This position can be less comfortable for patients, is more difficult to reproduce daily, and decreases coverage of axillary nodal volumes.[88] Furthermore, these setups require large bore CT simulators, which may not be available at all centers. Tattoos are often applied both to the patient's sides as well as on the back to ensure the same rotational set up each day.

C. Field Planning

i. Intact Breast

Opposed tangential fields are most commonly used for whole breast irradiation. The energy of these beams is typically 6 MV or higher, dependent on separation and anatomy. Higher photon energies are more penetrating, but caution should be used as they have more skin sparing than lower MV beams. Patients may be treated to the whole breast alone, or the tangential fields may be matched to additional beams covering the undissected nodal regions. The isocenter for the breast tangents typically bisects the field in the superior-inferior and medial-lateral dimensions and is placed at the depth of the pectoralis major muscle. The two matched beams are designed to fully cover the breast tissue while minimizing lung and heart exposure. To design these fields,

the medial tangent is first applied with adjustments to the gantry angle to achieve the coverage goal (Figure 2).

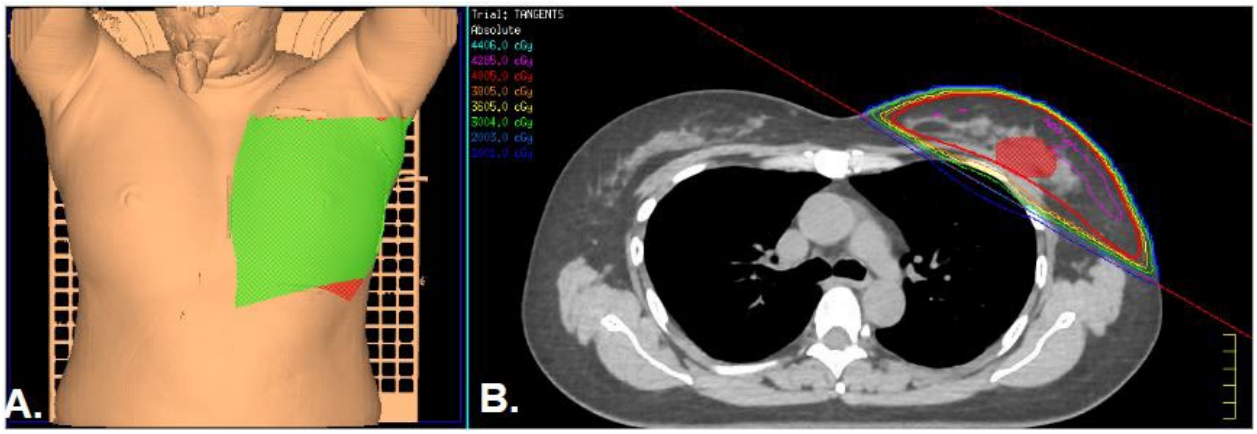

Figure 2: Tangential fields for intact breast treatment. A. Projection of fields on skin. B. Axial image showing the medial tangent beam and isodose distribution. The 100% isodose line is located at the pectoralis surface and the 95% isodose line encompasses the entire breast.

If a non-divergent superior border is desired (to match with a supraclavicular field), the treatment couch is rotated such that the feet are moved away from the gantry until the divergence matches the couch angle (typically ≤ 8°). To limit dose to the intrathoracic OARs, multileaf collimators or Cerrobend blocks are placed such that <2 cm of lung is exposed, and heart dose is completely ablated. Alternatively, the beam can be collimated such that the posterior block edge blocks the heart and lung (Figure 3.)

If desired, multileaf collimators or Cerrobend are then used to block the areas of the field superior to the target volume. For the opposed beam, the couch is rotated in the opposite direction and the gantry is then over-rotated to achieve a parallel posterior beam edge. Collimation or blocking are then adjusted such that the posterior beam edges remain non-divergent throughout the treatment field. To reduce hotspots these beams are wedged, or greater dose homogeneity can be achieved using a field-in-field technique to block hotspots.

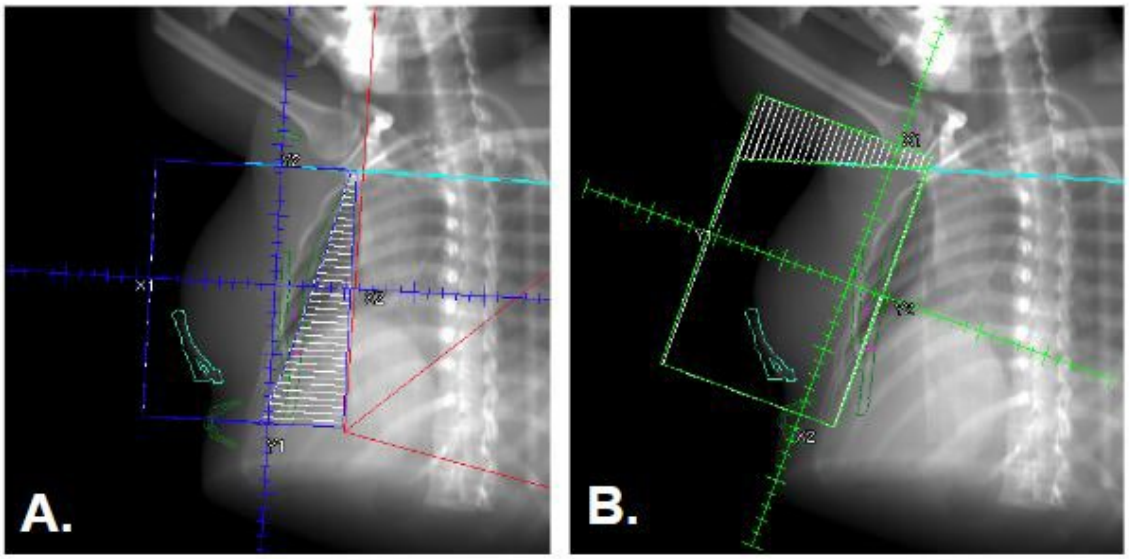

Figure 3. Heart and lung blocks for tangential breast fields. **A.** Digitally reconstructed radiograph (DRR) showing the multileaf collimator technique for blocking intrathoracic organs. **B.** DRR showing collimation technique to block the heart and lung. Surgical scar outline shown in cyan. Field borders shown in green.

ii. Supraclavicular fields

Selected patients with stage II disease, and all patients with stage III disease should be treated with radiation to the level 3 axilla, undissected level 2 axilla, and supraclavicular fossa (see section 4, "Nodal irradiation"). These nodal regions should first be contoured on axial slices to aid in adequate field design. For reference, consensus nodal volumes are depicted on the RTOG Breast Cancer Atlas (https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx). The esophagus can be contoured as an avoidance structure to minimize acute odynophagia and esophagitis during treatment. This can be facilitated by gently rotating the head toward the contralateral arm during simulation, which will also reduce skin-on-skin contact. This area is treated with a single anterior oblique beam with a 15-degree gantry rotation to avoid the spinal cord. Half beam block

technique with isocenter at the caudal border of the supraclavicular field, generally approximating the inferior clavicular head, is used to prevent divergence into the tangential fields. In patients whose entire breast or chest wall region is covered by a half beam in the superior-inferior dimension, this single isocenter can be used for the tangential fields and supraclavicular field—the "mono-isocentric technique." The supraclavicular half-beam is then matched to the tangential half-beams at the common isocenter preventing divergence between the fields without the need for couch rotation. This technique limits the cranio-caudal extent of the tangential fields to one half of the maximum beam width—typically 20 cm. For patients with long torsos, this may lead to a larger supraclavicular field and result in increased dose to the apical lung.

For patients without evidence of gross supraclavicular disease, the superior border should be above the acromioclavicular joint; medial border at approximately the pedicles of the vertebral bodies; and lateral border at the coracoid process of the scapula, if the low axilla is not part of the target, or lateral to the humeral head, if the low axilla is to be treated. A Cerrobend or multileaf collimator block is placed over the humeral head (Figure 4).

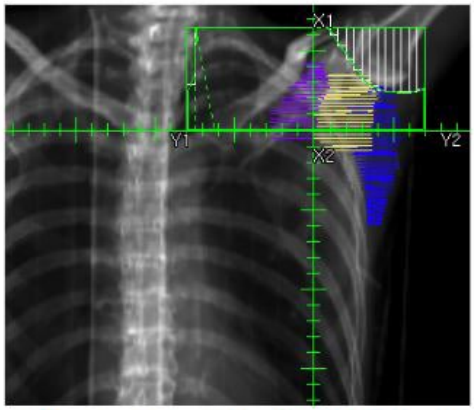

Figure 4. Supraclavicular fields for intact breast and regional nodal irradiation. Digitally reconstructed radiograph showing the undissected axilla (Blue, yellow, and purple) and the humeral head block.

For patients with gross supraclavicular disease, the superior border is typically raised to the level of the mandibular angle. Usually, adequate coverage of the nodal volumes can be achieved with only an anterior oblique beam, but rarely a posterior beam can be used to supplement dose to the deeper axillary apex and supraclavicular nodes.

iii. Chest Wall

In the post-mastectomy setting, adjuvant radiation includes treatment of the chest wall and the draining nodal basins. As with intact breast radiation, the chest wall is treated with tangential fields, with energy of 6 MV. A single isocenter can be placed at the border of the chest wall and supraclavicular fields. Each field is then treated using half-beam block technique, as described above. Most commonly, this isocenter is placed near the inferior clavicular head, although precise placement will depend upon patient anatomy and initial extent of disease. Commonly, bolus is used every other day to bring the dose to the surface of the skin. Bolus use can be titrated to balance treatment coverage with acute toxicity. When using a mono-isocentric technique, the common isocenter should be selected to ensure that no gross disease crosses the match line to ensure no cold spots within gross disease. Regardless of technique, post-mastectomy radiation must include the mastectomy flaps and scar in their entirety, from at least mid-sternum to the mid-axillary line or beyond, depending on initial disease extent, surgery, and patient anatomy. The inferior border should be at least 2 cm inferior to the initial inframammary fold. The medial border of the tangential fields depends upon whether the internal mammary nodal basins will be treated using matched electron fields or partially wide tangential fields (see below). The internal mammary nodal target includes the first three intercostal spaces and should be contoured to ensure coverage.

iv. Partially Wide Tangents

In this technique the medial border of the tangents is extended to allow for coverage of the internal mammary nodes within the tangential fields. As a result, a greater lung volume is exposed to the treatment field, and it can be difficult to achieve adequate nodal coverage without treating a significant heart volume. However, partially wide tangents do not require additional field matching and, especially when performed in concert with the mono-isocentric technique, allow for more rapid and simple daily treatments. After selecting a gantry angle that covers the full extent of the ipsilateral chest wall and internal mammary nodes, Cerrobend or multileaf collimators are used to block the heart and minimize lung dose without sacrificing dose to the target volumes. The resultant field often has an uneven medial border that extends into the contralateral breast/chest wall and extends more deeply into underlying lung (Figure 5).

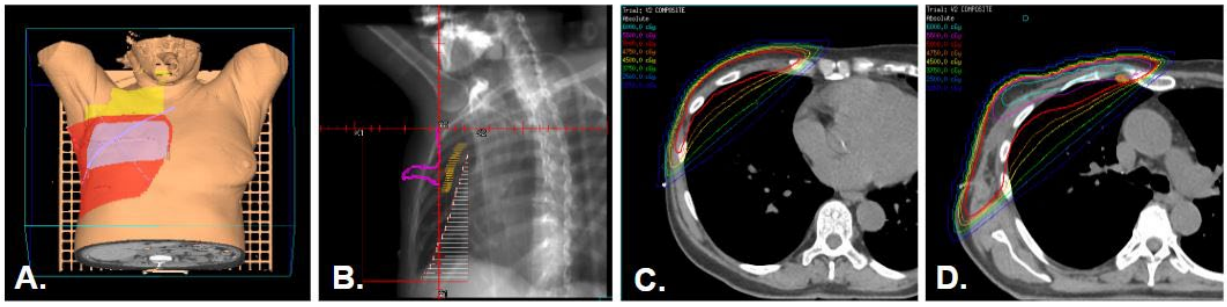

Figure 5. Partially wide tangent technique for treating internal mammary nodes. **A.** Projection of fields on skin. The red field represents the partially wide tangent, which extends slightly beyond midline. **B.** Digitally reconstructed radiograph showing tangent fields, which cover internal mammary nodes in first 3 intercostal spaces (shown in orange). Surgical scar shown in pink. Isodose distributions shown in upper **(C)** and lower **(D)** chest wall.

v. Medial Electron Match

Alternatively, an *en face* electron beam field can be used to treat the medial chest wall and internal mammary chain. This field should be matched on the skin to the supraclavicular and tangential fields. To allow for electron equilibration, the electron field must be at least 4 cm

wide. The field is shaped to cover the medial extent of the target to the tangent, including the full internal mammary nodal chain. The gantry angle is usually rotated such that the electron field is 10-15 degrees less rotated than the adjacent tangent field to minimize the "cold triangle" of tissue between the two fields. Match lines should be chosen to ensure the field match does not traverse gross disease, which could be underdosed as a result. Electron energy is selected to ensure complete coverage of the chest wall and nodal targets within the 90% isodose line. Because the target volume is often deeper in the cephalad chest wall than further caudad, the single electron field may be divided to allow for transition from higher-to-lower energy electrons as anatomy dictates. This technique may reduce radiation dose to the heart and lung, but requires more time during each treatment to ensure skin matching of the additional fields (Figure 6).

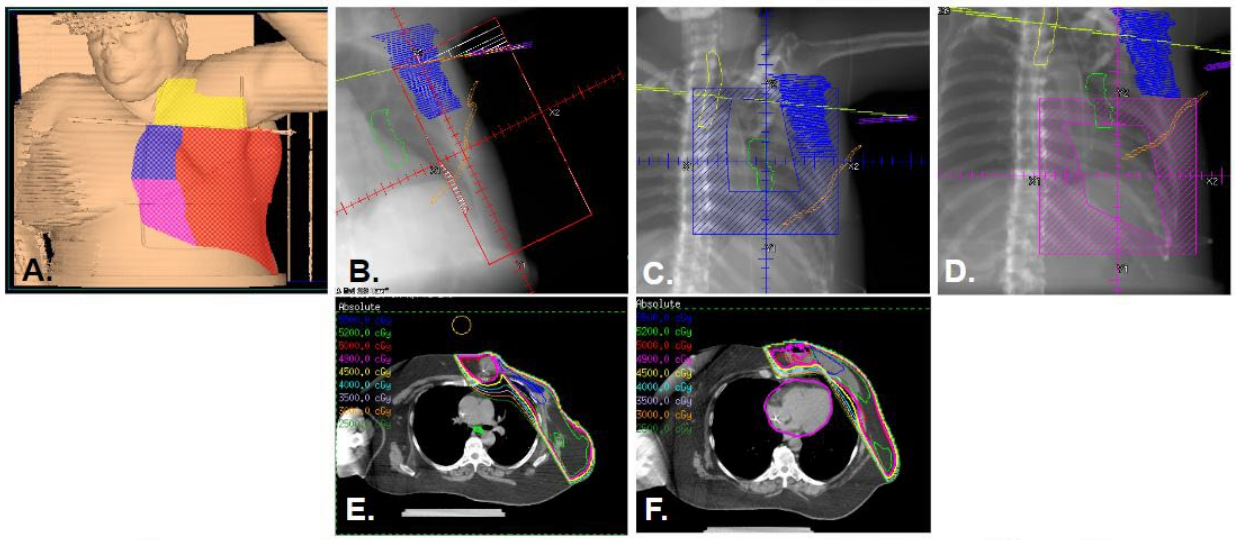

Figure 6. Medial electron match technique for treating internal mammary nodes. **A.** Projection of fields on skin. The red field represents the medial tangent field, matched on the skin to the superior and inferior medial electron fields. Digitally reconstructed radiographs showing tangent field (**B**), superior medial electron field (**C**), and inferior medial electron field (**D**). Internal mammary nodes shown in green contour; low axilla contour shown in blue. Surgical scar shown in orange. Isodose distributions shown in upper **(E)** and lower **(F)** chest wall.

vi. Non-monoisocentric technique

Alternatively, the breast or chest wall tangents may be matched to a supraclavicular field using unique isocenters for each field. This is appropriate for those patients with long torsos or whose anatomy favors the use of collimation to decrease dose to OARs, or to decrease ipsilateral lung dose. In this technique isocenter placement for the tangent is the same as with intact breast fields, although for PMRT, it is generally deep to the pectoralis major muscle, at the level of the chest wall. It is essential to rotate the couch toward the gantry in each field to create a non-divergent superior border. If collimation is used to block the heart, multileaf collimators are used to block the cephalad divergence in the breast radiation beam. During simulation, the match line can be chosen and marked with radiopaque wire. The supraclavicular field isocenter is then placed on the match line and half-beam block technique is used to prevent divergence into the tangential fields. During daily treatments, therapists should ensure that the fields match on the skin, and weekly port films are recommended to ensure proper positioning. If medial electron fields are used, they are matched on the skin as described above. Drawing the light field or laser alignments on the skin can assist with reproducible set up. This technique offers increased flexibility in field design, but is more time consuming and complex for daily setup purposes.

D. Plan Evaluation

During plan evaluation, attention should first be paid to ensure adequate coverage of all target tissues. Dose to normal tissue OARs are then reviewed to ensure tolerances are met. Finally, the plan should be reviewed for hot and cold spots, and care should be taken to minimize these regions.

Treatment goals:

Breast Only

Goals	Constraints
Breast *D100 > 98% of the Rx dose* **Breast** *V100% > 98% of the breast tissue*	• **Heart** *mean < 1 Gy (right-sided)* • **Heart** *mean < 2 Gy (left-sided)*
Tumor bed *D100 > 90% boost Rx dose*	• **Ipsilateral lung** *V20 Gy < 12%, V10 Gy < 20%, V5 Gy < 25%*
Hot spot *Dmax < 108%*	• **Spinal cord** *Dmax < 45 Gy (2 Gy/fraction)* • **Spinal cord** *Dmax < 36 Gy (hypofractionated)*

Comprehensive Nodal Radiation

Goals	Constraints
Breast *D100 > 98% of the Rx dose*	• **Heart** *mean < 4 Gy (if possible); otherwise < 15 Gy*
Breast *V100% > 98% of the breast tissue*	• **Heart** *V20 Gy < 4%, V10 Gy < 15%*
Tumor bed *D100 > 90% boost Rx dose*	• **Ipsilateral lung** *V20 Gy < 35%, mean < 20 Gy*
Nodal basins *D100 > 90% of the Rx dose* **Hot spot** *Dmax < 108%*	• **Spinal cord** *Dmax < 45 Gy*

Post-mastectomy Radiation

Goals	Constraints
Chest wall *D100 > 98% of the Rx dose*	• **Heart** *mean < 4 Gy (if possible); otherwise < 15 Gy*
Chest wall *V100% > 98% of the chest wall*	• **Heart** *V20 Gy < 4%, V10 Gy < 15%*
Boost volume *D100 > 90% boost Rx dose*	• **Ipsilateral lung** *V20 Gy < 35%, mean < 20 Gy*
Nodal basins *D100 > 90% of the Rx dose*	• **Spinal cord** *Dmax < 45 Gy*

Short-Term Side Effects and Management

There are several expected short-term side effects with adjuvant breast radiotherapy which may require management during the treatment course. The most common acute toxicities involve the skin; such as radiation dermatitis, hyperpigmentation, and desquamation.[89,90] The effects on the skin can be significant, with up to 30% of patients having moderate to severe radiation dermatitis.[90] Patients are typically counseled to use skin moisturizer throughout treatment, beginning on the first day of treatment, to minimize skin irritation, as well as barrier dressings in areas at higher risk for desquamation.[91] If pruritus occurs, then this can be managed with a corticosteroid cream.[92] If desquamation develops, then a thicker skin moisturizer and barrier dressings can be used to reduce skin-on-skin contact. Using softer clothing and bras may help with friction from seams on fragile skin. Wet desquamation is less common, but it can occur in patients as well. In such a situation, a treatment break may be considered to allow the skin to heal. An antibiotic agent such as silver sulfadiazine, sometimes in combination with barrier dressings, may be appropriate when wet desquamation occurs to help promote healing. Providing reassurance that these skin toxicities are expected and temporary is important throughout the treatment course, as the effects can be distressing. The effects are typically of more rapid onset and more pronounced when bolus is used due to the higher skin dose. Radiation dermatitis peaks in the final week of treatment or even the week after treatment.

In addition, fatigue from breast radiotherapy has been well-described.[93] While it is a common acute symptom, it is usually mild. Therefore, no active management aside from recommending extra rest and reassurance is usually recommended. Breast edema is a common occurrence during treatment, and while considered an acute side effect, it may persist for weeks to months

following radiotherapy.[94] Conventionally, this side effect is managed with observation or physical therapy if more significant.

Radiation pneumonitis is uncommon but may manifest 1-3 months after adjuvant radiotherapy.[95] It is characterized by a dry cough, shortness of breath, and and/or fever, with radiographic evidence of pneumonitis supporting the diagnosis. While most cases self-resolve without requiring active treatment, oral corticosteroids (prednisone) may be used when patients become symptomatic, often composed of a 2-4 week course which may be tapered over an additional 1-3 months.[96] In severe cases, patients may become oxygen-dependent and require intravenous corticosteroids, although this is rare following adjuvant breast radiotherapy and is usually attributable to superimposed pre-existing pulmonary disease or acute infection.

Of note, patients receiving hypofractionated breast radiotherapy have been shown to have reduced acute toxicity concerns (including less pain, fatigue, and skin reaction) as compared to patients receiving conventionally fractionated whole breast radiotherapy.[97,98] Therefore, in addition to patient convenience, the toxicity profile of hypofractionation may be favorable to conventional fractionation when feasible and appropriate.

Long-Term Side Effects and Management

With breast conserving therapy including lumpectomy and adjuvant radiotherapy, most patients have short-term side effects which resolve, and only approximately 10% of patients have grade 2 or greater long-term complications from treatment.[99] The potential long-term side effects from adjuvant breast radiation therapy include permanent cosmetic changes to the breast, lymphedema, range of motion limitations, neuropathy, rib fracture, cardiac disease, pulmonary fibrosis, and secondary malignancy.[99,100] While most patients rate their cosmetic outcome

following adjuvant radiotherapy as very good or excellent, potential permanent changes to the breast tissue and skin are possible. These changes may include fibrosis of the breast,[101] resulting in stiffening of the tissue and chest asymmetry. This risk is higher in patients who have a connective tissue autoimmune disorder, scleroderma or lupus with cutaneous manifestations.[102] Telangiectasias may develop and are associated with the severity of acute skin toxicity during treatment, increasing age of the patient, and smoking history.[101] Permanent skin pigmentation changes (i.e. hyper or hypopigmentation) are also possible, though they are usually subtle.

Lymphedema is a notable potential long-term side effect from treatment, but it is multifactorial in nature, with a higher risk in patients who have undergone mastectomy, axillary lymph node dissection, and radiotherapy including fields directed at the regional lymph nodes.[103] The management of lymphedema may involve observation, the use of arm sleeves to minimize swelling, and physical therapy. Neuropathy is a rare complication from breast radiotherapy (<1-2%), and it is often associated with the use of adjuvant chemotherapy or the treatment of the regional lymph nodes to a higher dose for clinical reasons.[104] Pain medication and physical therapy are the mainstays of treatment for this complication.

The added risk of cardiac-related death from adjuvant breast radiotherapy has been highlighted in recent years.[100,105] The most common strategy for managing this is prevention by using techniques including deep inspiratory breath hold or prone positioning to minimize radiation heart dose. Pulmonary fibrosis is similarly a concern from adjuvant breast radiotherapy.[95] It is associated with a higher volume of lung being treated to a higher radiation dose, usually in the context of treatment encompassing the regional lymph nodes. Pulmonary fibrosis may impair pulmonary function, though this is rarely clinically significant following adjuvant breast radiotherapy.

Secondary malignancy from adjuvant radiotherapy to the breast is very uncommon, with only approximately 3% of secondary malignancies which occur after breast cancer treatment being attributable to radiation therapy.[106] However, the risk for secondary malignancy increases with time and is thus more relevant for young patients. The majority of malignancies involve a second primary breast cancer or sarcoma in the treatment field, although lung cancer has also been described, especially if the patient has a tobacco smoking history.[100]

Clinical Scenario Conclusion

The patient is seen two weeks postoperatively and is noted to be healing well from surgery. Two weeks thereafter she undergoes a CT simulation for radiation planning. She is planned for adjuvant radiation to the whole right breast and comprehensive regional lymphatics to a dose of 50 Gy in 25 fractions using a 3-field conformal technique, followed by a boost of 10 Gy in 5 fractions to the lumpectomy cavity using electrons. She tolerates radiation well with grade 2 dermatitis which is managed with topical moisturizers and grade 1 fatigue. Following radiation, she is seen by medical oncology to initiate endocrine therapy.

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Chapter 18

Systemic Therapy for Breast Cancer

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Introduction

Breast cancer remains a major cause of cancer-related deaths among women worldwide. More than two million women are diagnosed each year, with approximately 800,000 deaths related to the disease worldwide. The existing epidemiological trend of low incidence and high mortality among low-middle income countries (LMICs) with respect to breast cancer is gradually but surely changing to worse with increasing incidence but no significant improvements in survival. The existing standardized guidelines are skewed towards the management of patients with resources in line with industrialized or developed communities. Due to constraints in terms of access and affordability, physicians in LMICs will have to use their discretion to make decisions backed by scientific evidence to deliver quality treatments using limited resources. In this review, we describe systemic therapies for early and advanced breast cancer with special emphasis on those that are relevant to LMICs.

Systemic therapy for early and locally advanced breast cancer (EBC & LABC)

The average age at diagnosis of breast cancer in LMICs is around 52 years, which is a decade earlier compared to High-Income countries (HIC). Population-based screening is not

routinely implemented in LMICs, and as a direct consequence, a significant majority are diagnosed at an advanced clinical stage.

In spite of potentially curative surgery for localized disease, a proportion of patients with breast cancer die due to systemic relapses attributable to micro-metastasis. In the past several decades, mechanistic models and clinical studies have indicated that breast cancer is a systemic disease and the risk of distant metastases depends not just on the anatomical stage but, more importantly, on tumor biology. Systemic therapy post-surgery has been firmly established as a modality to eradicate micrometastasis and has been conclusively shown to improve disease-free survival (DFS) and overall survival (OS). A better understanding of disease biology has led to the rational use of more effective systemic treatments, which have significantly contributed to improvements in survival.

The seminal work by Bonadonna et al. established Cyclophosphamide-Methotrexate-5Fluorouracil (CMF) as prototypic cyclic combination chemotherapy. This regimen was widely used in the 1980s and has been shown to be associated with sustained long-term improvements in OS. Based on the results of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) Oxford meta-analysis, Anthracycline (Doxorubicin, Epirubicin) based regimens have been shown to be superior to CMF. Several adjuvant studies and meta-analyses have shown an improved OS and relapse-free survival (RFS) with postsurgical Anthracycline–Taxane chemotherapy compared to Anthracycline alone, especially in high-risk breast cancer (high-grade node-negative and node-positive patients). Apart from chemotherapy, other systemic therapy options include hormonal therapy, for example (e.g.) Selective estrogen receptor modulators (SERM) and aromatase inhibitors (AI), and targeted therapy, e.g., anti-human epidermal growth factor receptor 2 (HER2 neu) monoclonal antibodies.

Depending on the clinical scenario, systemic therapy for localized breast cancer may be delivered before (neoadjuvant, preoperative) or after surgery (adjuvant, post-operative). Systemic therapy options for patients with early breast cancer (EBC) should take into consideration the age, comorbidities, menopausal status, tumor burden, nodal status, the biology of the tumor, and most importantly, the patient's wishes. Other important issues that determine the choice of systemic therapy include the individual's predicted risk of relapse and sensitivity to systemic treatment. Fertility preservation strategies should be discussed before initiation of any systemic therapy, especially in younger premenopausal patients.

Neoadjuvant systemic therapy (NST) has been shown to be equivalent to adjuvant (post-operative) chemotherapy in terms of DFS and OS. NST provides an appropriate strategy to improve clinical outcomes for breast cancer, irrespective of the Estrogen receptor (ER), Progesterone receptor (PR), and HER2 neu status. The primary goal of NST is to achieve tumor down-staging and increase the feasibility of breast conservative surgery (BCS) among women who would otherwise require a mastectomy due to unfavorable breast-to-tumor ratio. Other reasons include converting inoperable LABC (large T3 and T4) to operable disease, early administration of systemic therapy to target micro-metastatic disease in individuals at highest risk of occult systemic disease, and de-escalating axillary surgery to sentinel lymph node biopsy (SLNB) for those who have a clinical complete response in the axillary lymph nodes. For patients with Triple Negative Breast cancer (TNBC - ER, PR, and HER2 neu negative) or HER2 neu positive subtypes, failure to achieve a pathological complete response (pCR) post-NST portends a worse outcome. NST allows for a tailored approach to systemic therapy after breast surgery, wherein therapy escalation can be offered to those with residual disease to improve clinical outcomes.

Though there are many advantages to NST, performing surgery upfront is an acceptable approach in places where a multidisciplinary comprehensive setup is unavailable.

Case scenario

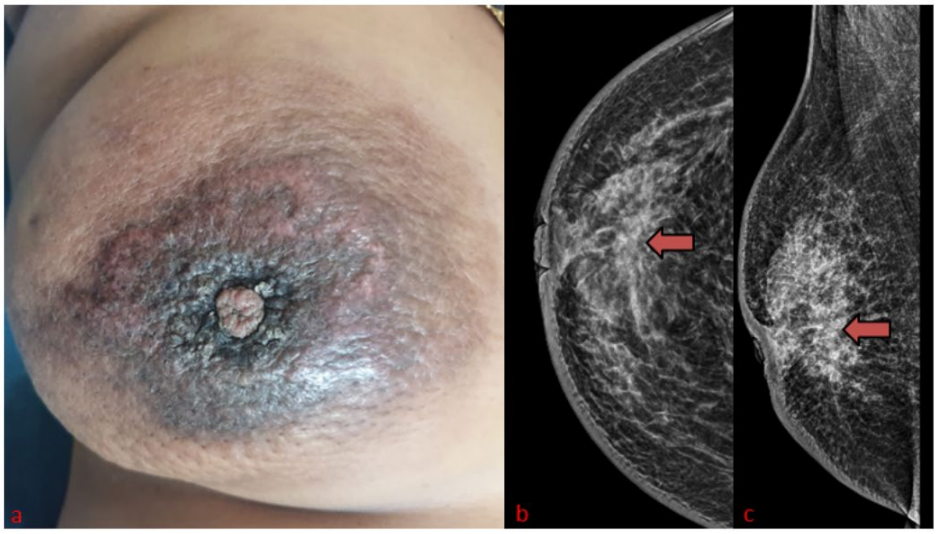


Figure 1: a) Right breast mass lesion in central retro-areolar location; peau d'orange, skin thickening and retracted nipple areola complex.
b) & c) - Mammogram - Cranio-caudal and mediolateral oblique views showing Ill-defined isodense lesion with spiculated margins & architectural distortion with faint foci of micro-calcification, nipple retraction & diffuse skin thickening in the inner central quadrant (4'o clock position – arrows) of the right breast.

Ms KB, is a 50-year-old post-menopausal lady evaluated for complaints of right (R) breast lump of 4 months duration. On physical examination, there was (R) breast mass palpable in retroareolar region, 7cm x 5cm in size, with peau d'orange, nipple, and areolar retraction and palpable 2 cm (R) axillary lymph nodes (Figure 1a). Bilateral mammography showed a BIRADS V lesion (R) breast (Figures 1b and 1c). Core needle biopsy of (R) breast lump revealed Grade 3 Invasive ductal carcinoma IDC. Immunohistochemistry (IHC) was negative for ER, PR, and HER2neu receptors. Her staging workup revealed no evidence of systemic metastasis. She was clinically staged as Carcinoma (R) breast, T4bN1M0, TNBC. In view of her inoperable LABC, she was advised NST to downstage the disease prior to surgery.

NST in TNBC: The optimal chemotherapy regimen for NST for TNBC is not clearly defined. Several randomized clinical trials (RCT) have focused on surrogate endpoints, especially pCR, to compare different protocols. The EBCTCG meta-analysis showed that, in comparison to adjuvant chemotherapy, NST resulted in higher BCS rates (65 vs. 49%); higher rates of local recurrence (21 vs 16% at 15 years; hazard ratio [HR] 1.37, 95% CI 1.17-1.61) but similar rates of distant metastasis, overall and breast cancer-specific survival. Further, in the neoadjuvant setting, several studies demonstrated higher pCR rates with the addition of a Taxane (Paclitaxel and Docetaxel) to Anthracycline. Standard NST usually includes a combination of Anthracyclines and Taxane chemotherapy.

Dose-dense chemotherapy schedules: In the EBCTCG individual patient-level meta-analysis of trials comparing 2-weekly (dose-dense) versus standard 3-weekly schedules and of trials comparing sequential versus concurrent administration of Anthracycline and Taxane chemotherapy, dose-dense protocol resulted in fewer breast cancer recurrences (10-year recurrence risk 28·0% vs. 31·4%; Risk Ratio (RR) 0·86, 95% CI 0·82-0·89; p<0·0001) and improved 10-year breast cancer-related mortality (18·9% vs. 21·3%; RR 0·87, 95% CI 0·83-0·92; p<0·0001) compared to standard dose regimens. The improved effectiveness of dose-dense chemotherapy was more pronounced in TNBC. There was no difference in either DFS or OS between the concurrent and sequential schedules. As part of dose-dense regimens, anthracyclines are delivered twice weekly. Taxanes, especially Paclitaxel, can be delivered twice weekly for four cycles or weekly for 12 weeks. Docetaxel is conventionally not used as part of dose-dense regimens. Though dose-dense chemotherapy may be the most optimal approach in TNBC, non-dose-dense regimens are also acceptable in situations where the former may not be feasible.

Addition of Platinum analogues in TNBC: Nearly 80% of the germline BRCA mutation-related breast cancers are triple-negative. A subset of TNBC exhibits defects in Homologous recombination (HR) based DNA repair, even in the absence of a germline BRCA mutation referred to as BRCA-ness. BRCA mutations or BRCAness results in tumors that are particularly sensitive to interstrand cross-linking agents like platinum analogues and alkylators. Despite strong pathobiology and the rationale for utility, there is no consensus on the addition of platinum compounds (Cisplatin or Carboplatin) in the neoadjuvant setting, even in BRCA mutant patients. The decision to use platinum compounds should be individualized. It can be considered in younger patients and those with larger tumors who have suboptimal response to anthracyclines. Weekly regimens are better tolerated, and Carboplatin seems to be the preferred choice. One should keep in mind the increased toxicities with the addition of platinum, which may compromise the delivery of the more time-tested taxane chemotherapy.

Targeted agents and Immunotherapy: Despite the higher probability of germ-line mutations (e.g., BRCA genes) in young patients with TNBC, clinical trial data does not support the use of targeted agents blocking the poly (ADP-ribose) polymerase (PARP inhibitors) in the neoadjuvant setting. The KEYNOTE 522 study has shown that the addition of Pembrolizumab to Anthracycline-Taxane/carboplatin containing NST results in higher pCR rates and event-free survival (EFS) in patients with TNBC.

Tailoring adjuvant treatment based on response to NST: The presence of residual disease post-NACT portends a worse outcome, and several trials have explored adjuvant therapy escalation to improve clinical outcomes. The CREATE-X trial randomized patients with TNBC and Hormone receptor (HR) positive breast cancer who did not achieve pCR after NST to 4-6 months of oral Capecitabine versus no additional therapy. The final analysis showed an absolute

gain in DFS and OS for the Capecitabine arm. In the subset analysis, TNBC patients appeared to get the greatest benefit from Capecitabine with an absolute gain in DFS of 13.7% (HR 0.58 95% CI 0.39 – 0.87) and OS of 8.5% (HR 0.52 95% CI 0.30 – 0.90).

A simplified stage-based algorithm for systemic therapy in TNBC is described in Figure 2a (NACT) and Figure 2b (adjuvant chemotherapy).

Figure: 2a

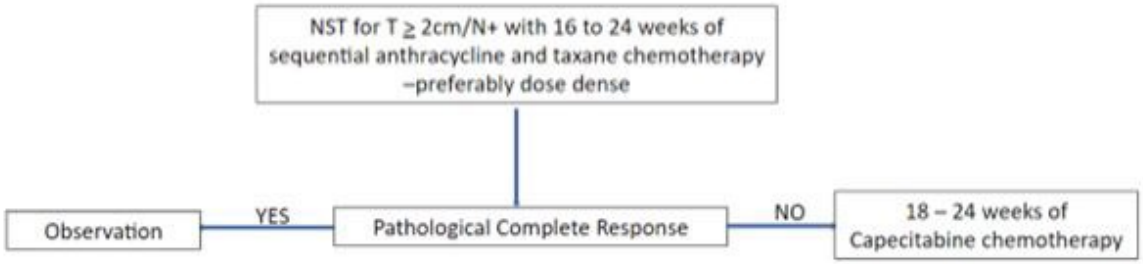


Figure:2b

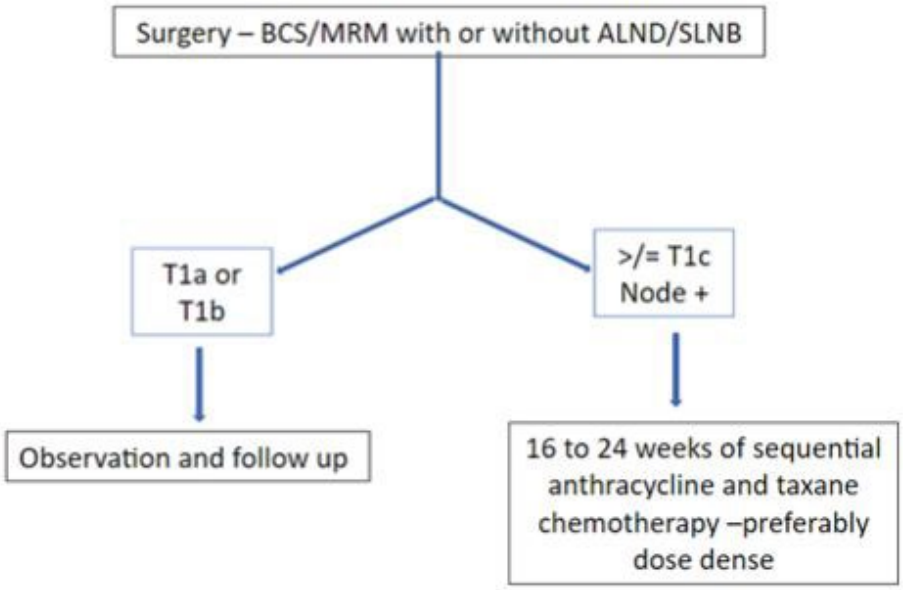


Figure 2: Systemic therapy algorithm for Triple Negative Breast Cancer

a) Neoadjuvant systemic therapy (NST)
b) Adjuvant therapy

Patients who are T1 and clinically node-negative should undergo upfront surgery. The benefit of adjuvant chemotherapy is unclear in node-negative T1a, and T1b tumors and has to be individualised. T1c tumors seem to benefit from adjuvant chemotherapy. Ideally, all patients with a tumor size of 2 cm or more, irrespective of nodal status, should undergo Anthracycline-taxane-containing NST followed by surgery and radiotherapy as appropriate. Capecitabine should be offered for those who fail to achieve a pCR after NST. However, due to some reason, if NST cannot be delivered, it is acceptable to offer surgery followed by adjuvant systemic therapy and radiotherapy.

HER2 neu positive breast cancer

Up to 15% of all invasive breast cancers show increased amplification of HER2 oncogene. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) consensus panel defines HER2-neu-positive breast cancers as those showing uniform intense membrane staining for HER2 in 10 percent or more of tumor cells on IHC or those tested with fluorescent in situ hybridization (FISH) showing HER2/chromosome enumeration probe 17 (CEP17) amplification ratio of 2.0 or more and HER2 copy number signals per cell of four or more. All newly diagnosed breast cancer patients should be offered HER2 testing using standard methodologies recommended by ASCO/CAP HER2-neu testing guidelines.

Trastuzumab, a monoclonal antibody against the HER2 neu protein is used to treat both early-stage and advanced HER2 neu positive breast cancer. The benefits of adding Trastuzumab to chemotherapy in an adjuvant setting are well-proven in multiple RCT and Meta-analyses. Updated data show that trastuzumab added to polychemotherapy results in nearly 10% absolute OS advantage. Despite approvals for Pertuzumab and Trastuzumab Emtansine (TDM1) in

neoadjuvant and adjuvant settings, respectively, lack of access and affordability limit their use in LMICs.

A risk-based algorithm suitable for broader application in LMICs is described in Figure 3. Barring node-negative tumors that are less than 5 mm (T1a), Trastuzumab is indicated in all other stages. For those with lower-risk tumors (Stage 1 – T1b & c), weekly Paclitaxel for 12 weeks with Trastuzumab for a year is the standard of care. For patients with Stage II and Stage III HER2-neu-positive breast cancer, a sequential regimen of Anthracycline followed by Taxane in combination with Trastuzumab or a non-anthracycline combination of Docetaxel, Carboplatin, and Trastuzumab are commonly prescribed (Table 1 enumerates prescribing information and standard protocols). Concurrent Trastuzumab with Taxane chemotherapy is superior to sequential administration post-chemotherapy. Concurrent administration with anthracyclines should be avoided. The duration of trastuzumab therapy is generally 52 weeks if not limited by cardiac morbidity.

Figure 3: Systemic therapy for HER2 neu positive breast cancer

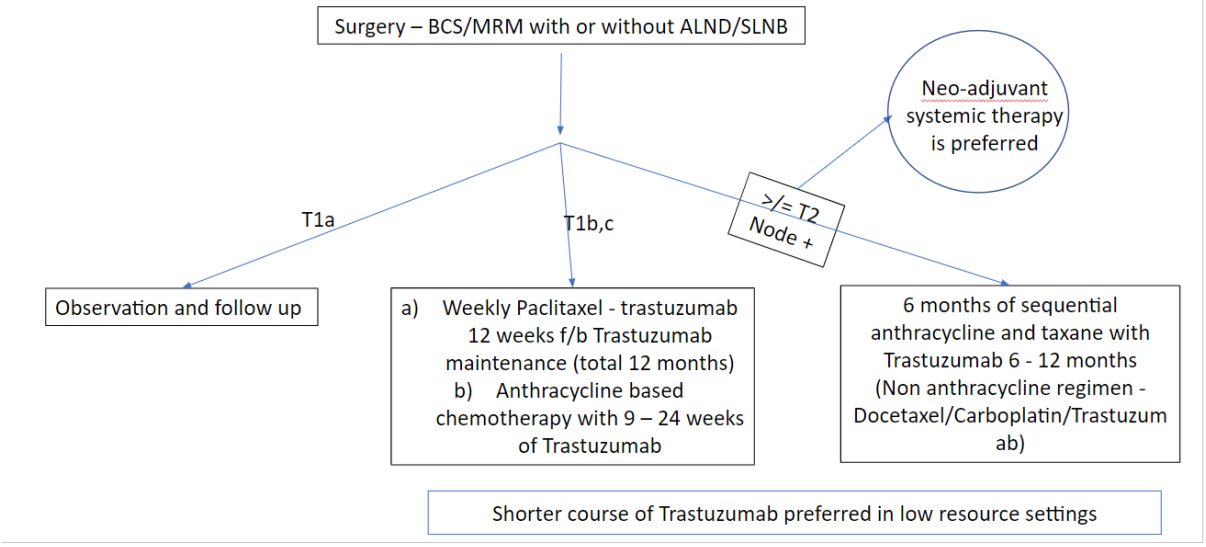


Table 1: Commonly prescribed protocols: Preoperative and adjuvant regimens

HER2 negative protocols	HER2 positive protocols
Dose-dense AC followed by paclitaxel **Doxorubicin 60 mg/m2 IV, day 1 Cyclophosphamide 600 mg/m2 IV day 1** **Cycled every 14 days for 4 cycles. Followed by: Paclitaxel 175 mg/m2 by 3 h IV infusion day 1 Cycled every 14 days for 4 cycles.**	Dose-dense AC followed by T + trastuzumab Doxorubicin 60 mg/m2 IV-day 1 Cyclophosphamide 600 mg/m2 IV day 1 Cycled every 14 days for 4 cycles. Followed by: Paclitaxel 80 mg/m2 by 1 h IV weekly for 12 weeks + Trastuzumab 4 mg/kg IV with first dose of paclitaxel followed by Trastuzumab 2 mg/kg IV weekly up to completion of Paclitaxel and then 6 mg/kg every 3 weekly to complete 1 y of treatment.
Dose-dense AC followed by weekly paclitaxel Doxorubicin 60 mg/m2 IV-day 1 Cyclophosphamide 600 mg/m2 IV day 1 **Cycled every 14 days for 4 cycles. Followed by: Paclitaxel 80 mg/m2 by 1 h IV infusion weekly for 12 weeks.**	
TC : Docetaxel 75 mg/m2 IV day1 Cyclophosphamide 600 mg/m2 IV day 1 **Cycled every 21 days for 4 cycles**	**TCH:** Docetaxel 75 mg/m2 IV day 1 ; Carboplatin AUC 6 IV day 1 Cycled every 21 days for 6 cycles with: Trastuzumab 4 mg/kg IV week 1 followed by: Trastuzumab 2 mg/kg IV for 17 weeks followed by: Trastuzumab 6 mg/kg IV cycled every 21 days to complete 1 y of therapy.
AC followed by docetaxel every 3 weeks Doxorubicin 60 mg/m² IV on day 1 **Cyclophosphamide 600 mg/m² IV day 1** **Cycled every 21 days for 4 cycles.** **Followed by: Docetaxel 100 mg/m² IV on day 1 Cycled every 21 days for 4 cycles.**	APT regimen:Paclitaxel 80 mg/m2 by 1 h IV weekly for 12 weeks + Trastuzumab 4 mg/kg IV with first dose of paclitaxel followed by Trastuzumab 2 mg/kg IV weekly up to completion of Paclitaxel and then 6 mg/kg every 3 weekly to complete 1 y of treatment
EC chemotherapy **Epirubicin 90 mg/m² IV-day 1 Cyclophosphamide 600 mg/m² IV day 1** **Cycled every 21 days for 8 cycles.**	
TAC chemotherapy **Docetaxel 75 mg/m² IV day 1** **Doxorubicin 50 mg/m² IV-day 1 Cyclophosphamide 500 mg/m² IV day 1** **Cycled every 21 days for 6 cycles.**	
CMF chemotherapy4 **Cyclophosphamide 100 mg/m² PO days 1–14 Methotrexate 40 mg/m² IV days 1 & 8** **5-fluorouracil 600 mg/m² IV days 1 & 8** **Cycled every 28 days for 6 cycles**	AC followed by T + trastuzumab + pertuzumab Doxorubicin 60 mg/m2 IV-day 1 Cyclophosphamide 600 mg/m2 IV day 1 cycled every 21 days for 4 cycles followed by: Pertuzumab 840 mg IV day 1 followed by 420 mg IV + Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV; Paclitaxel 80 mg/m2 IV days 1, 8, and 15 cycled every 21 days for 4 cycles Followed by: Trastuzumab 6 mg/kg IV day 1 Pertuzumab 420 mg IV day 1 Cycled every 21 days to complete 1 y of therapy

The rate of grade III or more cardiac failure or cardiac-related deaths in patients receiving Trastuzumab combination therapies ranges from 0% to 4.1%. Careful cardiac monitoring during and after the therapy is an essential prerequisite for considering HER2-targeted therapy. Potential risk factors associated with the development of trastuzumab-related cardiotoxicity include previous or concurrent anthracycline use, age greater than 50, and pre-existing cardiac dysfunction or systemic hypertension. Those who are ER-positive in addition to HER2 positivity (Triple positive) should be offered 5-10 years of hormonal therapy (see below).

The role of shorter duration of Trastuzumab has been tested in various trials with the hypothesis that the shorter course (9 weeks or six months) would result in non-inferior efficacy with lower cardiac and financial toxicity compared with the standard duration therapy. The best evidence for a shorter course of anti-HER2 therapy comes from the PERSEPHONE trial, which has shown the non-inferiority and lower cardiotoxicity of 6 months versus standard 12 months exposure to trastuzumab. However, a recent meta-analysis showed that except in tumors with a low risk of

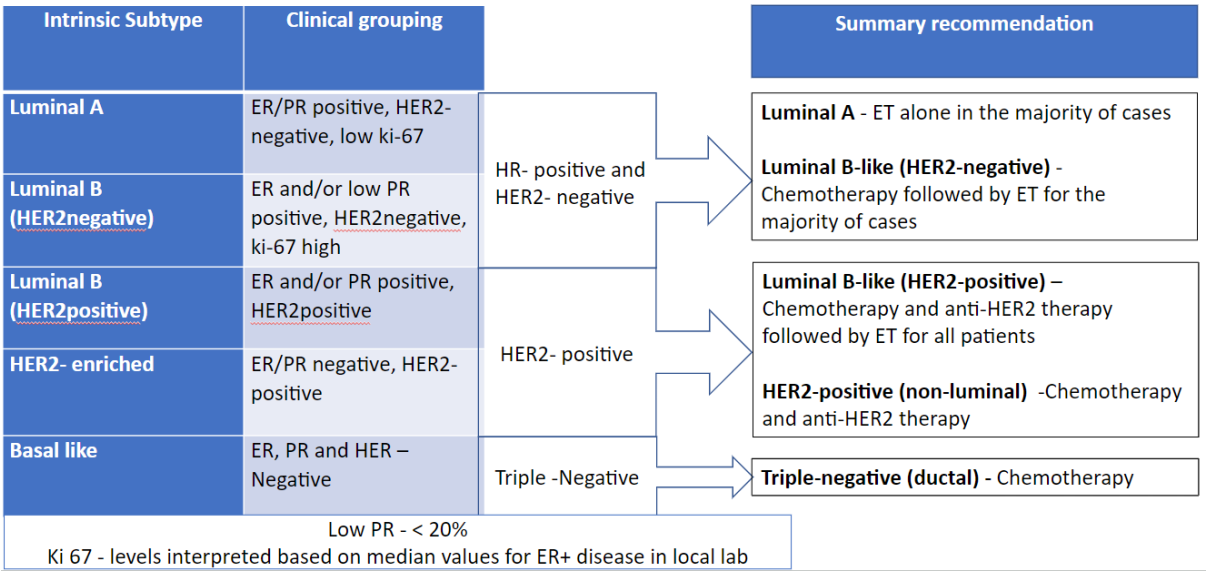
recurrence, the shorter duration was not inferior to the long course. The limited clinical experience presented by LMICs makes a clear case for shorter courses of Trastuzumab with retained clinical benefit, significantly reduced costs, and improved access to eligible patients. Though the large body of available scientific evidence suggests that Trastuzumab for a year is standard, the incremental clinical benefit of the longer course over the short is likely to be small and associated with additional cardiac toxicity. It is also important to note that most patients in these trials received an Anthracycline-containing chemotherapy regimen. Hence, in a low-resource setting where it is not feasible to provide for standard duration Trastuzumab, a shorter course with anthracycline-containing chemotherapy is an acceptable option.

In the past few years, dual anti-HER2 blockade with Pertuzumab and TDM1 (a novel drug antibody conjugate) have been incorporated in the management of HER-2-positive tumors. The addition of Pertuzumab to Trastuzumab in the neoadjuvant setting has been shown to improve the pCR rates. However, the APHINITY trial in the adjuvant setting has shown modest improvements in DFS with the addition of Pertuzumab to Trastuzumab. The recent update continues to show DFS benefits with no improvement in overall survival. The KATHERINE study randomized patients who did not achieve pCR after 12 weeks of neoadjuvant anti-HER2 therapy to continue Trastuzumab or change to TDM1. The invasive DFS was superior for the TDM1 arm compared to continuing Trastuzumab. As with TNBC, neoadjuvant therapy is preferred for those with tumors more than 2 cm, irrespective of nodal status. This helps tailor adjuvant therapy based on the achievement of pCR. However, both TDM1 and Pertuzumab are associated with additional adverse events and are extremely expensive, precluding their use in LMICs.

Hormone receptor-positive breast cancer (Luminal subtypes)

ER-positive cancers are classified as Luminal subtypes A and B and are associated with better prognosis. The criteria used for this classification are shown in Table 2. The individual's prognosis is estimated based on the tumor burden (Tumor size and nodal status) as well as the disease biology (grade, proliferation markers, e.g., Ki-67 index, vascular invasion, genomic profiling, etc) and presumed response to ET (Luminal A greater than Luminal B).

Table 2: Immunohistochemically defined subtypes of breast cancer



Systemic chemotherapy in Luminal subtypes: Endocrine manipulation with selective estrogen receptor modulator (Tamoxifen) or Aromatase inhibitors (Anastrozole, Letrozole, and Exemestane) remains the mainstay of therapy for patients with Luminal subtypes. Luminal A subtype has a better prognosis compared to Luminal B and is likely to benefit less from adjuvant chemotherapy. Hence, the potential survival gains with adjuvant chemotherapy in Luminal

subtypes must be weighed against the potential impact of cytotoxic chemotherapy on overall health and quality of life.

Among HR-positive breast cancer, polychemotherapy regimens with or without an Anthracycline (4-6 cycles of Docetaxel and cyclophosphamide) are associated with improvements in DFS and OS. The benefit is largely independent of endocrine therapy, nodal status, or other tumor characteristics. Though the relative benefits of chemotherapy are similar across subgroups, the absolute benefits may vary depending on the individual's risk status. For instance, the degree of absolute benefit in a patient with Luminal A cancer with low tumor burden is likely to be extremely small. In such a situation, the short- and long-term adverse events associated with chemotherapy might vastly exceed the benefits. Such patients should receive endocrine therapy alone. Patients with Luminal B cancers and those with Luminal A with higher tumor burden are likely to benefit from chemotherapy in addition to endocrine therapy.

Multiple genomic profiling tools to assess the risk of recurrence and predict benefits from systemic chemotherapy are available. The best prospectively studied tools are the Oncotype Dx and MammaPrint. Other genomic profiling tools include Prosigna, Endopredict, Breast Cancer Index, etc. These tools are commercially available but extremely expensive and hence, beyond the reach of most patients treated in a resource-constrained setting. Alternatives to these genomic profiling tools are several online tools like NHS Predict Plus, NPI, and Adjuvant Online (temporarily unavailable), which can be used in low-resource settings to help predict the risk of recurrence and potential benefit from adjuvant chemotherapy and hormonal therapy. NST in Luminal subtypes is used in situations where downstaging is required to facilitate BCS or in LABC to achieve a margin-negative resection. Anti-HER2 agents are used in Luminal B subtypes that are HER2 positive.

Adjuvant endocrine therapy in Premenopausal women: The standard adjuvant endocrine therapy for premenopausal patients is Tamoxifen for 5 – 10 years. Five years of adjuvant Tamoxifen reduces the annual breast cancer death rate by 31%, which is independent of chemotherapy use, PR status, or other tumor characteristics. Ten years of Tamoxifen is associated with better overall survival compared to five years. However, this additional benefit also comes with more toxicity in the form of a higher incidence of endometrial cancers and thromboembolic complications. Hence, the benefits of longer duration must be weighed against the potential risks, especially in women with additional comorbidities. In patients who become postmenopausal during the first five years of Tamoxifen, a switch to an Aromatase inhibitor should be considered.

A correlation between survival and chemotherapy-induced amenorrhea has been consistently demonstrated in several prospective and retrospective studies. Ovarian function suppression (OFS) for five years should be strongly considered in patients who remain premenopausal at the end of adjuvant systemic chemotherapy and have a higher estimated risk of recurrence based on age, tumor burden, and disease biology as determined by clinicopathologic characteristics. Oophorectomy or GnRH analogues can be used for OFS. For high-risk HR-positive premenopausal women, 5-10 years of an aromatase inhibitor (preferred) or tamoxifen with OFS is a standard of care. The additional short- and long-term adverse events associated with OFS, especially in younger women, should be discussed in detail before going ahead with the same.

Adjuvant endocrine therapy for post-menopausal women

Post-menopausal women should receive a minimum of five years and may additionally benefit from up to 10 years of adjuvant aromatase inhibitors. The benefits of aromatase inhibitors over Tamoxifen are likely to be more pronounced in the higher-risk groups based on the clinical and genomic profiles. Tamoxifen and AI have different toxicity profiles. The benefits of longer duration of AIs in post-menopausal women should be balanced against the increased incidence of osteoporosis and bone fractures. Most of the incremental benefits of longer duration of AIs are in the reduction of contralateral second primary breast cancers.

In addition to aromatase inhibitors, one should also consider the administration of bisphosphonates, Zoledronic acid, given once every six months for three years. The use of Bisphosphonates not only results in a lower incidence of osteoporosis and fractures but also brings down the risk of distant metastasis and prolongs overall survival. The recommendations and algorithm for adjuvant chemotherapy and endocrine therapy in HR-positive EBC are enumerated in Figures 4a & 4b.

Figure 4a

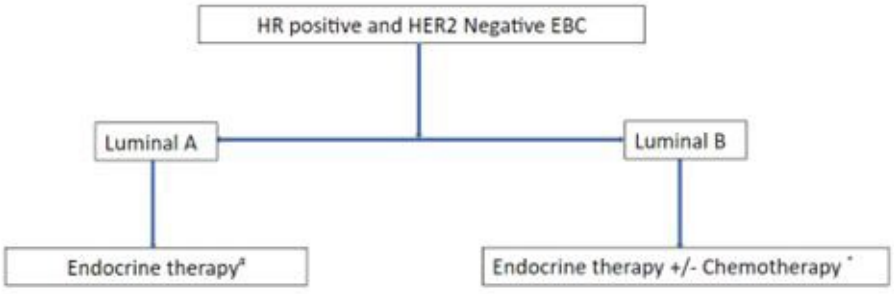


*Figure 4a: Systemic therapy for ER+Her2- breast cancer: #Consider chemotherapy if high tumor burden (4 or more LNs, T3 or higher, * Depending on Tumor burden, level of ER and PR expression, proliferation index, genomically assessed risk, and patient preference)*

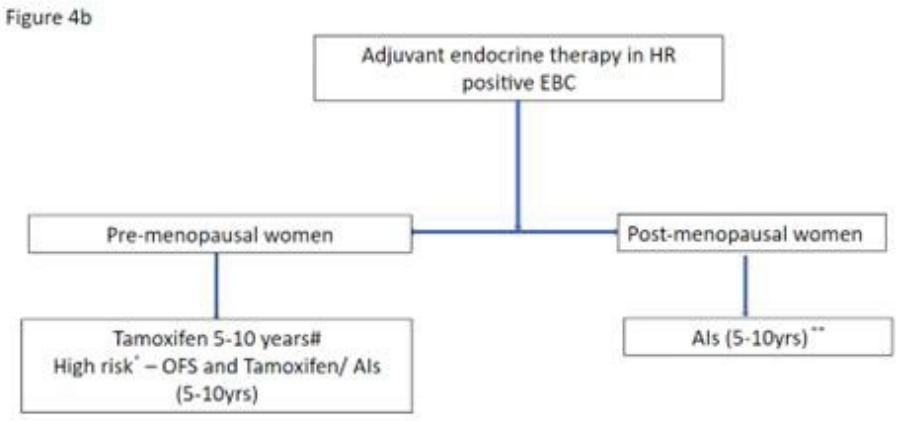


Figure 4b: Endocrine therapy according to menopausal status

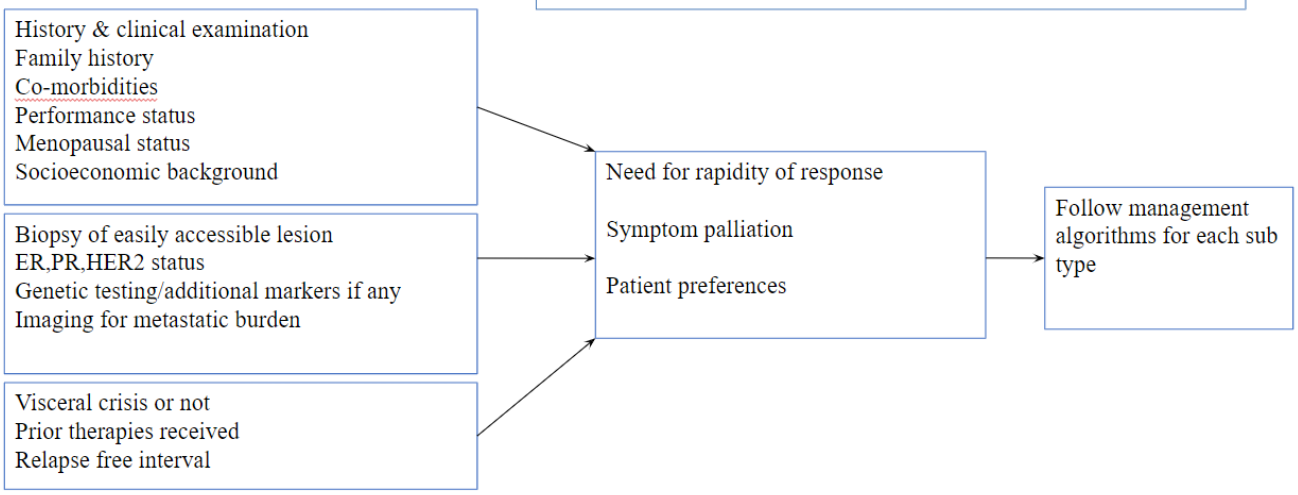
Neoadjuvant endocrine therapy may be used in selective post-menopausal women with Luminal A subtype who are unlikely to tolerate or do not wish to undergo chemotherapy but require downstaging before surgery. Aromatase inhibitors are preferred in this setting. Neoadjuvant hormone therapy is used for up to 6 months or until maximal response.

Systemic therapy for Advanced Breast Cancer (ABC)

ABC remains an incurable disease. The therapeutic goals in ABC are to prolong survival and maintain good quality of life (QOL). The median OS can widely vary from just over a year for TNBC to around five years for HR-positive or HER2-neu-positive subtypes. The prognosis might vary depending on many factors, including age at diagnosis, performance status, de novo versus relapsed disease, HR or HER2 neu status, extent and sites of metastases, and disease-free interval (DFI) from the last therapy.

In all patients who have relapsed, a repeat biopsy from a metastatic lesion should be carried out wherever feasible. This is to confirm the diagnosis of breast cancer as the primary and recheck the receptor status. At relapse, around 15% can have a change in the receptor status, which will impact therapy. Overall, the treatment decisions depend on HR and HER2 neu status, previous therapies and their toxicities, DFI, tumor burden, biological age, Performance status (PS), comorbidities, menopausal status (for HR-positive), need for a rapid disease/symptom control, socio-economic and psychological factors, available therapies in the patient's country and most importantly, patient's preferences. Considering that ABC is incurable, no active treatment for the cancer and continuation of symptomatic care only should be actively discussed as an option wherever appropriate. This is especially relevant in low-resource settings. Algorithms for upfront evaluation and disease management are enumerated in Figure 5.

Figure 5: Approach to management of advanced breast cancer



Case scenario

Mrs. VL, a 41-year-old premenopausal lady with no comorbidities, Eastern Cooperative Oncology Group (ECOG) PS-1, presented with a lump in her left breast of 6 months duration. Examination revealed a cT4bN1 left breast lump with palpable axillary lymph nodes. She had a minimal cough but no breathlessness. Biopsy of breast lump showed Grade 2 IDC, ER 90%, PR 70%, and HER2 neu negative. A whole-body Fluoro-deoxy-glucose FDG, Positron-emission tomography (PET) CT scan showed FDG avid left breast lump with axillary lymph nodes and bilateral lung metastasis, largest 3 cm in the right lung (Figures 6a & 6b describe the baseline and post-therapy PET/CT images, with arrows highlighting the response to 1st line therapy at primary and metastatic sites of disease).

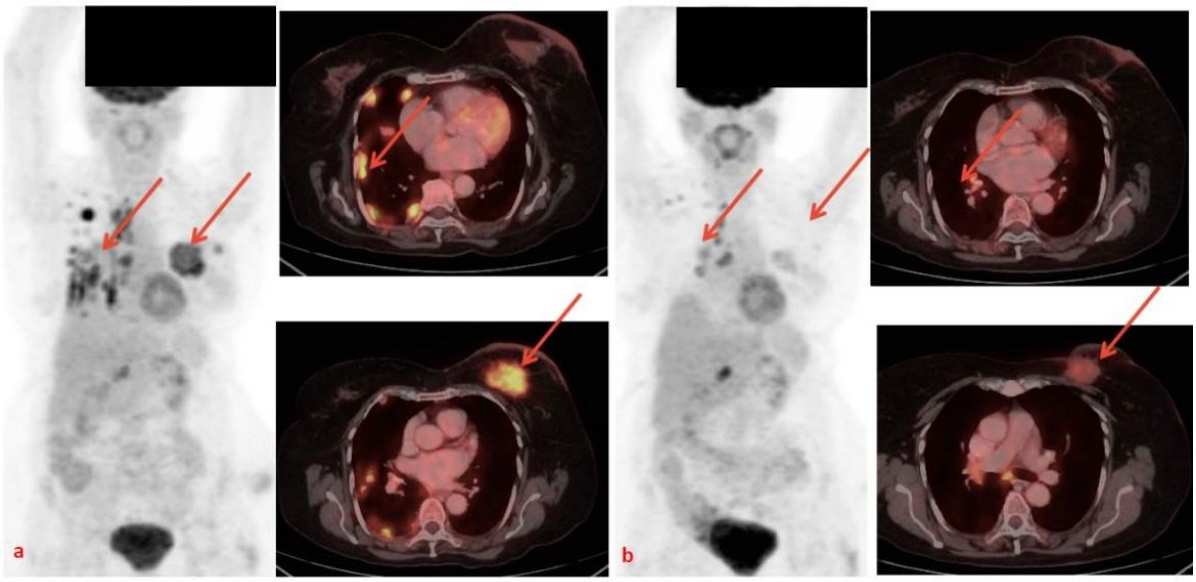


Figure 6: 41 year old lady with left breast cancer (Gr 2 IDC, ER 90% PR 70% and HER2 neu negative) and lung metastasis. She had visceral metastasis but was not in visceral crisis. Figure 6a & 6b describe the baseline and post therapy PET/CT images respectively, with arrows highlighting the response to 1st line therapy at primary and metastatic sites of disease

HR-positive HER 2 neu negative ABC

Endocrine therapy (ET) remains the mainstay of therapy for HR-positive disease, except for those who fit into the definition of primary endocrine resistance or visceral crisis. Primary Endocrine resistance refers to an absolute lack of response to a previous ET or a very short time to relapse. Visceral crisis is defined as impending organ dysfunction as assessed by signs, symptoms, laboratory studies, and rapid progression of disease. It implies important visceral compromise clinically, indicating the need for a more rapidly efficacious therapy. ET is generally not the preferred therapy for those who need rapid response. However, the mere presence of visceral metastasis is not a visceral crisis and, hence, not a contraindication for ET. Both combination and sequential single-agent chemotherapy are reasonable options for patients who need rapid responses.

Endocrine modulation can be achieved by a) OFS using GnRH/LHRH analogues (Triptorelin/leuprolide/goserelin) or oophorectomy/radioablation, b) SERMs (Tamoxifen) c) Aromatase inhibitors (anastrozole/letrozole/exemestane) and d) Selective estrogen receptor down regulators (SERD, Fulvestrant) or e) a combination of the above. Endocrine agents can also be combined with targeted therapies, e.g., Cyclin-dependent kinase 4-6 inhibitors (CDK 4-6i), mTOR inhibitors, or PIK3C inhibitors. The preferred first-line ET for those who have relapsed depends on the type and duration of adjuvant ET, the time from the end of adjuvant ET, and patient preferences.

All premenopausal women with ER-positive ABC should be rendered postmenopausal by either oophorectomy, radiation to the ovaries, or GnRH analogue. After OFS, premenopausal women are treated similarly to post-menopausal women. OFS by bilateral oophorectomy is

economical, achieves quick and definitive estrogen suppression to the post-menopausal range, and is preferred. GnRH agonists are expensive, associated with initial estrogen surge, and take longer to achieve castrate estrogen levels. The effectiveness of radioablation is in the range of 70-80% and hence the least preferred method. Single-agent tamoxifen is a reasonable option for pre-menopausal women who decline OFS.

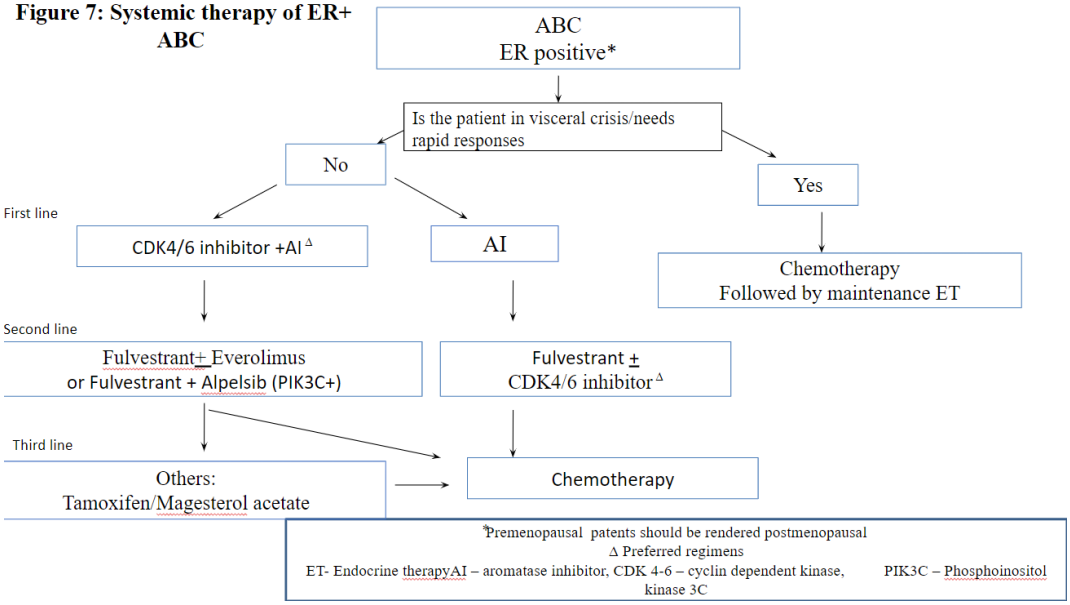
Following OFS, AIs (Letrozole, Anastrozole, Exemestane) remain the most widely used first-line ET. AIs are superior to Tamoxifen in terms of response rates and PFS but not OS. Fulvestrant, a SERD is superior to AIs in terms of PFS. This benefit is limited to patients with non-visceral disease only. The disadvantages of Fulvestrant over an AI are that it is expensive and is to be given as an intramuscular injection, one in each buttock until progression.

In the past few years, the combination of AI with CDK 4-6 inhibitors (CDK 4-6i - Palbociclib, Ribociclib, Abemaciclib) has been shown to be vastly superior to AI alone in terms of PFS. In the first-line treatment of patients with HR-positive, HER2-negative ABC, the combination of an AI with a CDK 4-6 inhibitor resulted in a median PFS improvement of around 10 – 12 months compared to AI alone. Similarly, in patients who progress on an AI, the addition of CDK 4-6i to Fulvestrant resulted in significant improvement in median PFS (6–7 months) and OS. The addition of CDK 4-6i also increases toxicity, the most important being neutropenia and thrombocytopenia. Grade 3-4 neutropenia is common, but transient and febrile neutropenia is rare. Though AI or Fulvestrant with a CDK 4-6i is the preferred choice in patients with endocrine-sensitive and resistant patients, respectively, these agents are expensive and are beyond the reach of most patients in LMIC. Unfortunately, no proven biomarkers predict the clinical benefit of CDK 4-6i.

Everolimus (mTOR inhibitor) plus an AI is another option in the second-line setting for patients with endocrine-resistant disease. Despite significant prolongation in PFS, its poor adverse event profile makes it a less popular treatment choice. Tamoxifen or Fulvestrant can also be combined with Everolimus. Based on the SOLAR 1 study, Alpelsib (PIK3C inhibitor), in combination with Fulvestrant, was approved for patients with endocrine-resistant disease who test positive for PIK3C mutations in plasma or tissue DNA.

Megestrol acetate and estradiol may be used if all other options have been exhausted. It is acceptable to repeat a previously used agent if it resulted in a reasonably good PFS in the past. Concurrent chemotherapy and ET have not shown a survival benefit and are associated with a worse adverse event profile. Maintenance of ET after Chemotherapy to maintain benefits is routinely practiced despite no randomized study to prove its benefit. The optimal sequencing of endocrine therapies also remains to be studied. Factors to guide therapy options include previously used agents (in the curative or advanced setting), disease burden, patients' preferences, costs, and availability. Figure 7 describes the criteria for the selection of different endocrine therapies for 1st line and for subsequent disease progression in ER-positive ABC.

Figure 7: Systemic therapy of ER+ ABC



Though our patient had visceral disease, she was not in a visceral crisis and, hence, was a candidate for hormonal therapy. She underwent surgical oophorectomy followed by Letrozole 2.5 mg once daily. Reassessment after three months showed a good partial response in primary and lung metastasis. She progressed after ten months.

HER2 neu positive ABC

HER2-neu-positive ABC has an aggressive clinical phenotype. However, since the discovery of anti-HER2 therapies, the outlook for these patients has steadily improved. Following the introduction of Trastuzumab in 1998, there have been a multitude of drugs that have been approved by the FDA. The various strategies for inhibiting this pathway are: a) Anti-HER2 monoclonal antibodies (Trastuzumab and Pertuzumab), b) Antibody–drug conjugates (TDM1, trastuzumab deruxtecan), c) Novel tyrosine kinase inhibitors (Lapatinib, Neratinib - irreversible pan HER2 inhibitor, Tucatinib - selective HER2 inhibitor). Of these, drugs that are approved for clinical use include Trastuzumab, Pertuzumab, TDM1, Neratinib, Lapatinib, and Trastuzumab deruxtecan**.** However, barring Trastuzumab, which has a biosimilar, and Lapatinib, the generic version of which is available, the other drugs are not widely used in resource-limited settings.

Anti-HER2-based therapy should be considered as the first line strategy in the management of patients with HER2 neu positive ABC unless contraindicated. The choice of any anti-HER2 agent/combination depends on the previous anti-HER2 agent used, relapse-free interval, cost, and access. Patients with HER2 positive ABC may be either those who relapsed after adjuvant Trastuzumab or present with de novo metastatic disease. For those who present de novo metastatic disease or after a year of completion of adjuvant Trastuzumab, dual anti-HER2 therapy with Trastuzumab and Pertuzumab in combination with chemotherapy is the treatment of

choice. Pertuzumab is a humanized monoclonal antibody that binds to HER2 on the extracellular domain II, a different domain than that of trastuzumab, preventing homo and heterodimer formation. The addition of Pertuzumab to Docetaxel and Trastuzumab as first-line therapy improved OS by an unprecedented 16 months compared to Docetaxel and Trastuzumab alone. With a median OS of nearly five years and 37% surviving at eight years, dual anti-HER2 therapy with chemotherapy is clearly the preferred regimen in this clinical setting. If there is a lack of access to Pertuzumab, monotherapy with Trastuzumab and chemotherapy (Vinorelbine or a Taxane) is an acceptable option.

After a fixed duration of chemotherapy (6-8 cycles), the anti-HER2 drug (dual or monotherapy) should be continued as maintenance therapy until progression or unacceptable toxicity. Stopping anti-HER2 therapy after several years of durable complete remission may be feasible in some patients.

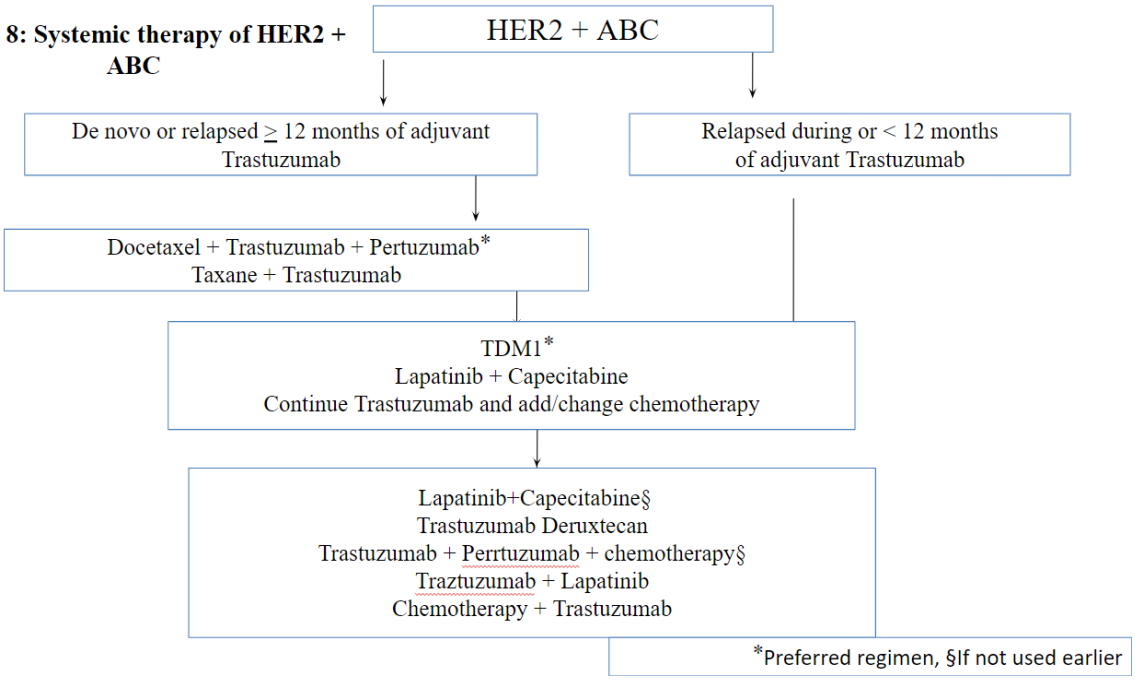
For those who relapse during or within 12 months of adjuvant Trastuzumab and those who progress during Trastuzumab with or without chemotherapy for metastatic disease, TDM1 is the optimal choice. T-DM1 is an antibody–drug conjugate of DM1, a cytotoxic derivative of maytansine, which has a potent antimitotic activity that binds to microtubules. TDM 1 is associated with a better OS compared to Capecitabine and Lapatinib. There is a lack of extensive prospective data on the use of T-DM1 after dual blockade with Trastuzumab and Pertuzumab. For patients who do not have access to TDM1, options include continuing Trastuzumab and adding a chemotherapy drug or a combination of Capecitabine and Lapatinib.

Trastuzumab and Pertuzumab can still be used in the third or subsequent lines in HER2 neu positive ABC for those patients who did not receive them in the first line. For later lines of

therapy, trastuzumab can be administered with several agents like capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine, or metronomic chemotherapy. Ideally, patients should be exposed to as many available anti-HER2 agents as possible to achieve the best survival. Newer anti-HER2 therapies include Trastuzumab Deruxtecan and Tucatinib, which have shown efficacy even in heavily pre-treated patients.

For patients with ER-positive/HER2-positive ABC with low-burden disease, who are unlikely to tolerate chemotherapy or have a strong preference against chemotherapy, ET plus an anti-HER2 therapy is acceptable as first-line therapy. In such situations, ET with dual anti-HER2 therapy is preferred. However, this approach of ET with anti-HER2 agents should be reserved for highly selective patients. Alternatively, patients with ER and HER2-positive ABC can continue ET plus anti-HER2 therapy as maintenance therapy until progression or unacceptable toxicity after the initial phase of chemotherapy with anti-HER2 therapy. Trials directly comparing Chemotherapy plus anti-HER2 therapy versus ET plus anti-HER2 therapy are currently ongoing. Figure 8 describes the treatment strategies for HER2-positive disease.

Figure 8: Systemic therapy of HER2 + ABC



Patients with HER2-neu-positive breast cancer have a higher incidence of brain metastasis. Though a baseline Magnetic resonance Imaging MRI of the brain is not recommended, the threshold to do so should be low. Any symptom, which may even remotely be secondary to suspected Central nervous system (CNS) metastasis, should be investigated aggressively. Those with isolated failures in the brain may be treated with CNS-directed therapy (Radiotherapy or surgery) and continued on the same systemic therapy. Those who have multiple sites of progression in addition to CNS need a change of systemic therapy along with CNS-directed therapy.

Cardiac safety is an important consideration for patients treated with HER2 inhibitors who are at increased risk of developing left ventricular dysfunction. Regular monitoring of cardiac function with a 2D echocardiogram or MUGA scan is recommended.

Triple Negative Breast Cancer

Triple-negative breast cancer is associated with a high risk of early recurrence and generally portends a poor prognosis. The median survival for advanced TNBC is around a year. More than one-third of all TNBC present with distant metastases, either recurrent or de novo. About 15-20% of all patients with TNBC, irrespective of age at diagnosis, harbor a germline mutation in one of the BRCA genes. For many years, chemotherapy has been the cornerstone for the treatment of patients with metastatic TNBC. However, potentially less toxic and more efficient strategies such as PARPi (polyadenosine diphosphate ribose polymerase inhibitors) in germline BRCA mutation carriers (gBRCAmut) and immunotherapy in patients with PD-L1-positive tumors are changing this paradigm.

Performance status, disease burden, prior chemotherapy regimens, RFI, risk of adverse events, and patient preferences should be taken into consideration to decide on the most appropriate strategy for the individual patient. For patients with de novo metastatic disease and those who relapse after a year of adjuvant chemotherapy, single-agent chemotherapy with taxanes (Docetaxel/paclitaxel) as first-line chemotherapy remains the treatment of choice. While combination chemotherapy increases the response rates, they are associated with more toxicities and poorer quality of life without any survival advantage. Combination chemotherapy is preferred in selective patients with a visceral crisis or who are highly symptomatic (e.g., lymphangitis carcinomatosa) and need rapid responses for faster symptom relief.

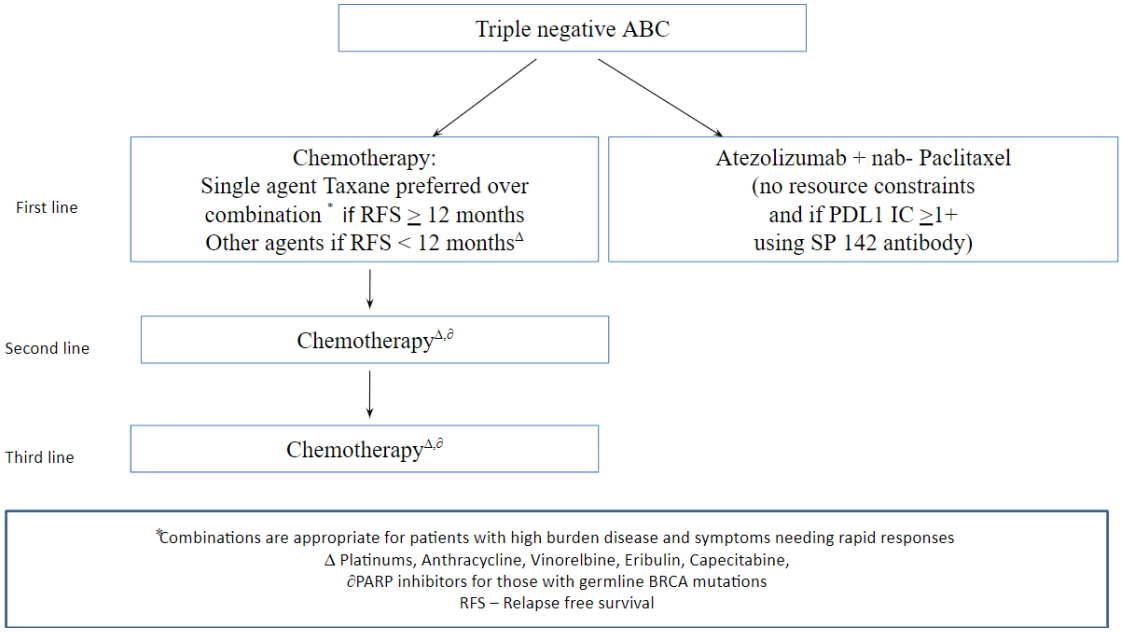
The phase 3 randomized Impassion130 study evaluated Atezolizumab (PD L1 inhibitor) plus nab-paclitaxel versus nab-paclitaxel alone in patients with metastatic TNBC. In the intent to treat the population, the addition of Atezolizumab demonstrated superior PFS (7.2 months versus 5.5 months; HR 0.80) with non-significant OS benefit. However, in a predefined subgroup analysis, patients having PD-L1 positive (PD-L1 expression on tumor-infiltrating immune cells (IC) $\geq$ 1 using SP 142 antibody) had better PFS and OS (25 vs 18 months, HR 0.71, 95% CI 0.54 – 0.94). For the first time, the 2-year mark for overall survival was breached in a subgroup of patients with TNBC. The combination of Atezolizumab plus nab-paclitaxel has been approved by the FDA as first-line therapy in patients with PD-L1 positive (IC $\geq$ 1) TNBC. However, in view of difficulties in getting PDL 1 testing and the prohibitive cost of immune checkpoint inhibitors, most patients in LMICs continue to receive single-agent chemotherapy as the first-line treatment in metastatic TNBC.

For patients who progressed on taxanes and anthracyclines or have a relapse in less than 12 months after adjuvant therapy, other chemotherapeutic options include capecitabine, eribulin, gemcitabine, cisplatin/carboplatin, vinorelbine, and ixabepilone.

The TNT trial compared the efficacy of Carboplatin to Docetaxel in metastatic TNBC with planned crossover at progression. In the intent to treat the population, the efficacy of carboplatin was similar to Docetaxel. In those with gBRCAmut, carboplatin resulted in a doubling of response rates and longer PFS. A Cochrane meta-analysis on the role of platinum agents in metastatic breast cancer concluded that there is preliminary low-quality evidence of a moderate survival benefit from platinum-based regimens with metastatic TNBC. Hence, it may be prudent to expose all patients with metastatic TNBC to a platinum agent.

In metastatic gBRCAmut patients, PARP inhibitors Olaparib and Talazoparib have shown improvement in response rates and PFS compared to standard-of-care chemotherapy. Platinums and PARP inhibitors are important treatment options for patients with advanced gBRCAmut TNBC. Platinums are cheap, require intravenous administration, and have potential adverse events. While PARPi have the advantage of oral administration and a favorable toxicity profile, high-cost limits access to these agents in many parts of the world. For patients with gBRCAmut TNBC with good performance status and no major comorbidities, early treatment with platinum compounds (carboplatin or cisplatin single agent) is encouraged. At this time, most patients in LMICs lack access to PARPi. The Summary recommendations and algorithm for decision-making regarding 1st line and subsequent therapies is enumerated in Figure 9 for TNBC.

Figure 9:Systemic therapy of Triple negative ABC



Newer agents being explored include a) Androgen receptor blockers for those with Androgen receptor-positive disease, Bicalutamide and enzalutamide demonstrating clinical activity and benefit in small phase 2 studies, b) Antibody-drug conjugates like Sacituzumab govitecan (antibody–drug conjugate in which SN-38 is coupled to antibody targeting anti-trophoblast cell-surface antigen 2) c) Ipatasertib (oral ATP-competitive, selective AKT inhibitor).

Early incorporation of palliative care is of paramount importance in patients with ABC. Apart from palliative systemic therapy for the cancer, bisphosphonates for those with bone metastasis, aggressively treating symptoms, especially pain, addressing social and emotional needs, and other spiritual and social concerns help improve quality of life. Patients and caregivers should be encouraged to actively participate in decision-making. It is important to stop active treatment of the disease at the right time and continue only symptom management.

Improving access to improve outcomes

Though, in an ideal world, everyone should be treated alike, inequalities in care are a reality and here to stay. Wherever possible, physicians should follow well-established guidelines and treatment algorithms published by reputed societies. However, as more expensive newer therapies continue to be approved, the gap between the LMICs and higher-income countries in terms of access to the standard of care treatments continues to widen. A significant proportion of these newer therapies result in modest improvements in DFS without demonstrable OS benefit. Hence, it is important to consider value-based approaches rather than indiscriminately use therapies that may not be appropriate for LMICs. Though not perfect, available tools like the ASCO's value framework of net health benefit, ESMO's magnitude of clinical benefit scale, or the Drug abacus should be used to assess the value and price of a particular therapy.

There is an urgent need in LMICs to reduce the cost of therapies, which results in clinically significant improvements in outcomes like Trastuzumab in EBC or hematopoietic growth factors, which help in delivering dose-dense chemotherapy, etc. It is essential to be reminded that in LMICs, a significant majority of patients need to pay from their pockets for these life-saving interventions. Hence, safe and effective alternatives have to be employed to improve affordability and access. Biosimilars, which have undergone robust clinical development and good-quality generic chemotherapy drugs, should be used wherever possible to reduce treatment costs. There is ample evidence that the use of biosimilars can reduce costs by 50%, leading to broader usage of drugs and more lives saved. In the future, it is expected that active public-private partnerships, encouraging biosimilars and generics, incorporation of treatments with greater value, and innovations in drug development will allow more patients to access effective life-saving cancer treatments.

Salient points

Early and locally advanced breast cancer

- Systemic adjuvant therapy (post-surgery) should be tailored to the risk of relapse, which depends on disease biology and anatomic stage
- Neoadjuvant systemic therapy (NST) is preferred in HER2 positive and Triple negative (TNBC) tumors $\geq$ 2 cm
- NST improves breast conservation rates, targets micrometastasis early, downstages locally advanced breast cancer helps tailor adjuvant therapy based on achievement of pCR
- Chemotherapy consisting of Anthracycline and Taxanes improves relapse-free and overall survival in all subtypes of breast cancer. Non anthracycline combinations may also be used selectively
- Platinum compounds should be used selectively in TNBC, and capecitabine for 4-6 months should be offered to those who do not achieve pCR
- One year of (Neo)Adjuvant Trastuzumab should be administered for HER2-positive breast cancer
- Shorter periods (9 or 24 weeks) of Trastuzumab may be offered to selective patients in specific situations
- Luminal A with high tumor burden and Luminal B subtypes are more likely to benefit from adjuvant chemotherapy
- Adjuvant endocrine therapy (ET) with Tamoxifen in premenopausal women and Aromatase inhibitors (AI) in post-menopausal women should be administered for 5-10 years
- Premenopausal women with a higher risk of relapse stand to benefit from ovarian function suppression in addition to other systemic treatments

- Adjuvant Bisphosphonates improve bone health and overall survival in postmenopausal women with ER-positive breast cancer on AI

Advanced breast cancer

- Advanced breast cancer (ABC) is an incurable disease. The goals of therapy are improving survival and maintaining good quality of life
- Re-biopsy from a relapsing site should be performed wherever possible
- Multiple factors, including age, comorbidities, performance status, Endocrine and HER2 neu status, disease-free interval, need for rapid disease control, and most importantly, the patient's wishes, should be taken into consideration before any decision on therapy
- Patients in visceral crisis needing rapid responses should be offered chemotherapy. Except in select situations, single-agent sequential chemotherapy should be offered in preference to combinations
- All premenopausal women with ABC should be rendered postmenopausal. AI with or without cyclin-dependent kinase inhibitors should be the first line of therapy
- Anti-HER2 therapy with chemotherapy should be considered as first-line treatment for those with HER2-positive ABC
- Patients with HER2-positive disease have a higher incidence of brain metastasis. The threshold for performing brain imaging should be low
- Chemotherapy forms the mainstay of treatment for advanced TNBC. Early use of Platinum compounds should be encouraged in TNBC, especially in the BRCA-mutant subgroup
- Early incorporation of palliative care is essential and ensures better outcomes in ABC, especially in terms of quality of life
- Wherever feasible, the use of good-quality biosimilars and generics should be encouraged

Recommended reading

1. Indian Council of Medical Research ICMR - https://www.icmr.nic.in/sites/default/files/guidelines/Breast_Cancer.pdf
2. European Society of Medical Oncology ESMO - https://www.esmo.org/guidelines/breast-cancer
3. American Cancer Society guidelines
4. Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer - https://ascopubs.org/doi/pdf/10.1200/JCO.2018.79.2697
5. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer - https://ascopubs.org/doi/pdf/10.1200/JCO.2018.78.8604
6. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer - Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer https://ascopubs.org/doi/pdf/10.1200/JCO.2018.79.2697

Chapter 19

Management of Early Operable Breast Cancer

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Case Scenario

A 60-year-old postmenopausal woman (G4P3) presents with a 6-week history of a palpable mass in the upper outer quadrant of her right breast. The mass is non-tender. She believes it has increased slightly in size since first noticing it. She denies any skin changes or nipple discharge. Upon physical exam, there is a 1.5 cm mass in the upper outer quadrant of her right breast, 10:00 position, 7 cm from the nipple. The mass is mobile and does not involve skin. No visible skin changes or peau d'orange are present. Nipples are not inverted. There are no additional masses in either breast and no clinical lymphadenopathy in the cervical, supraclavicular, infraclavicular, or axillary nodal basins bilaterally.

Overview of Early Operable Breast Cancer Management

Local Management

Early breast cancer (Stage I, IIA, or IIB) is generally treated with upfront surgical management. This consists of tumor excision to clear margins and nodal staging. Depending on tumor, patient, and resource factors, surgical management may involve breast conservation or mastectomy. Nodal staging may be done via sentinel node biopsy or levels I and II axillary node dissection.

While modified radical mastectomy is often the chosen method of surgical treatment in resource-limited settings, breast-conserving therapy is an oncologically sound alternative if resources exist. Similarly, sentinel node biopsy offers a less invasive mechanism to stage the axilla. However, this approach is more resource-intensive and may not be feasible in some environments.

Radiation therapy is generally recommended in the management of early breast cancer treated with breast-conserving surgery. It may be avoided if mastectomy is performed, but this decision is based on final surgical pathology and must consider tumor size and nodal involvement. If resources exist, each patient should be referred to a radiation oncologist to discuss the type of radiation therapy most appropriate for their specific situation.

Systemic Management

The use of systemic therapy in the treatment of early breast cancer is typically adjuvant in nature. Ideally, the discussion of systemic therapy should be multidisciplinary in nature, with medical oncologist involvement. The choice of systemic treatment employed for a particular patient will be based on their staging and pathology. For early breast cancer, chemotherapy, endocrine therapy, and anti-HER2 therapy may be utilized. Chemotherapy is typically anthracycline-based, with or without the use of taxanes. [1] The type of endocrine therapy a patient receives is dictated by the hormonal receptor status of the tumor, as well as the patient's menopausal status. Selective Estrogen Receptor Modulators (SERM) and Aromatase Inhibitors (AI) are the two types of endocrine therapies. For women with HER2 (+) tumors, the addition of anti-HER2 therapy like trastuzumab is indicated.

Presentation, Resources, and Geographic Factors in LMIC

A significant issue to consider when discussing the treatment of early breast cancer in low- and middle-income countries (LMICs) is that the majority of patients in these settings present with later-stage disease. This disparity holds true for all resource-limited settings. Though many breast cancer patients in this environment are more likely to present with locally advanced or late-stage breast cancer, it is essential to provide appropriate guidelines for the treatment of early breast cancer.

Additionally, the authors recognize that wide disparities in access to medical resources exist across LMICs. It is unreasonable to compare a wealthier middle-income country with a stable, more industrialized economy to that of a resource-poor, predominantly rural country. This is also true within countries when comparing urban centers to rural villages. It is impossible to provide a "one-size-fits-all" prescription for early breast cancer management in resource-constrained settings. The lived realities of patients and providers in each country or region may be vastly different. The prescriptive models for the treatment of early breast cancer provided will allow each physician to make individual analyses of local resources in order to craft a treatment plan.

Assessment of Local Resources

Breast Health Global Initiative Model

In 2005, the Breast Health Global Initiative convened its second panel of experts to discuss breast health in countries with limited resources. Multiple papers were released discussing access to care, detection, diagnosis, pathology, and treatment. In these papers, a framework emerged designating countries/regions based on their level of resources: basic, limited, enhanced, and maximal. [2] A provider's ability to diagnose a patient with early breast cancer, let alone treat

them, will look very different in a basic resource country as compared to a maximal resource country. Some LMICs do not have the finances or healthcare infrastructure to carry out population-based mammographic screening or offer specific treatment modalities. However, a tiered system of breast health awareness and education targeted outreach towards at-risk groups can be used in order to increase the likelihood of detecting early-stage breast cancer in all settings.

Public Education

The importance of public education for breath health awareness cannot be stressed enough. This is particularly true in resource-poor countries. If population-based screening and/or regular primary care interaction is not available, patients must understand when to seek medical care. Globally, it is necessary to emphasize the importance of women's overall health and breast health specifically to validate the need for early detection and treatment. A proper public education campaign must tackle the stigma associated with a breast cancer diagnosis. If a woman fears her family or community will treat her poorly if she admits to a breast cancer diagnosis, this will delay diagnosis, or she may not seek care at all. This will inevitably increase the likelihood of late-stage diagnoses. With this in mind, men must also be targeted for education, especially within more patriarchal societies in which women must seek permission for certain activities. While overcoming potential structural, political, and economic barriers is essential, proper public education about breast health is necessary for the early detection and treatment of breast cancer.

Breast health awareness is particularly important in resource-poor areas where population-based screening is not readily available. Patients need to understand when to seek care to allow for earlier detection. This could allow for diagnosis at earlier stages and, thus, more favorable treatment options. Educators should emphasize that breast cancer is not immediately fatal,

especially early on, and that delay in diagnosis could prove detrimental. However, a proper public awareness campaign cannot only focus on the downsides of delaying care but must strongly emphasize the benefits of early treatment. If the public understands early treatment means a greater chance of long-term survival, then they will be more likely to seek care earlier in their disease process.

The designers of the public education campaign must reflect on social and cultural considerations. Not doing so could result in maintaining barriers to treatment. Such barriers could include fatalism, an inability to act autonomously, fear of stigma from diagnosis, fear of exclusion due to diagnosis, language or educational barriers, or preference towards traditional healers. [3].

Detection

The ability to detect early breast cancer will be based on one's access to resources. Resource-poor countries and regions may only have access to a provider who can perform a clinical breast exam. Even accessing a healthcare provider may be impossible in some parts of the world. Methods of detection include mammogram, ultrasound, clinical breast exam, and breast self-exam.

Mammography/Ultrasound

Detection of early breast cancer using population-based mammographic screening is the ideal scenario. [4]LMICs may not be able to develop and implement this kind of screening due to resource or geographic constraints. If screening is not possible, then the next best thing would be the utilization of diagnostic imaging with mammography or ultrasound on a case-by-case basis

when a patient has signs or symptoms. In resource-limited areas, all imaging options may be unavailable to the majority of patients.

Clinical Breast Exam

A thorough clinical breast exam (CBE) is crucial to the diagnostic process at any level of resources. CBE becomes especially important in areas where access to imaging is unavailable or not readily available. This is true for both symptomatic and asymptomatic patients. Though data has suggested that CBE and mammography are equal in terms of breast cancer mortality, it should be noted the American College of Physicians released guidance for screening of average-risk women which stated that clinical breast exam should not be used as a method of screening. [5] However, ACP said that clinical breast exams performed by an experienced provider may be the best option in low-resource countries.

Breast Self-Exam

Breast self-exam (BSE) is of questionable benefit in the setting of maximal or enhanced resource capabilities. However, in situations without access to a provider who is capable of performing a clinical breast exam, a breast self-exam is the best option. Patients should be educated on how to perform a breast self-exam. Part of a holistic public education campaign must be directed toward patients who are particularly unable to access health care regularly. For patients in rural areas, it could provide enhanced detection for patients with borderline advanced disease. However, it may be difficult for patients to detect breast cancer while still in the early stages.

Diagnosis

Proper breast health awareness and education will facilitate early diagnosis. Obtaining a diagnosis is a multifaceted process involving multiple actors. Assuming detection has occurred,

either via screening or imaging/exam based on symptoms, a formal diagnosis requires tissue sampling. Three main options are available: fine needle aspiration (FNA), core needle biopsy (CNB), and surgical biopsy. The presence of a credentialed provider, if available, is preferable for each type of procedure.

Fine Needle Aspiration

Fine needle aspiration involves the aspiration of cells with a small gauge needle. This can be performed by palpation or under image guidance. The advantage of an FNA for LMIC providers is that it is the least invasive and least expensive method. It is a rapid procedure and generally does not require anesthetic or anesthesia. It can be performed easily in any location and has a lower risk of complications such as bleeding. Fine needle aspiration involves training, the requisite medical equipment, and cytopathology services to analyze the obtained tissue. FNA has limitations, however. FNA is unable to provide the architecture of the tumor and thus cannot differentiate between invasive and *in situ* disease. Additionally, FNA does not allow for analysis of grade or receptor status. This is best for Basic and Limited resource level countries as long as the facilities for adequate cytopathology expertise are available.

Core Needle Biopsy

Core needle biopsy is performed with a larger bore needle and obtains more tissue than an FNA. It is likewise performed by palpation or with imaging guidance, performed by a qualified proceduralist. It is costlier than FNA but provides more information and thus has higher sensitivity, specificity, and diagnostic accuracy. It provides the architecture of the tumor, is more able to differentiate invasive versus in situ disease, and can be used to determine receptor status if facilities are available. This approach has a higher risk of hematoma and generally requires the use of an anesthetic. Training is needed to be able to safely and accurately perform a core

needle biopsy and analyze the specimen accurately. Limited resource-level countries and higher are likely to be able to employ this method of biopsy.

Surgical Biopsy

The final method of obtaining tissue for diagnosis is a surgical biopsy. This may be done as an excisional biopsy, wherein the entire lesion is excised, or an incisional biopsy, where a small portion of a more significant lesion is removed. For small lesions, excisional biopsy is preferred. It provides enough tissue for accurate diagnosis and may altogether remove the tumor. Incisional biopsy is generally reserved for larger masses. Surgical biopsy is the most invasive method by far, but it is the most accurate as it provides the most tissue for analysis and has the lowest false negative rate. It requires prior imaging and localization of the lesion unless palpable. It also involves some form of anesthetic and has the highest postprocedural complication rate. It can be performed in all countries with surgical, anesthesia, and pathology services.

Operative Management

Optimal surgical management of early-stage breast cancer involves both destruction of the tumor and nodal staging. If local resources exist, this may be performed via a breast conservation and sentinel node approach. A more extensive surgical approach must be considered if this is not feasible. In many resource-constrained areas, the surgical management of choice for all breast cancer (regardless of stage) is modified radical mastectomy, the combination of mastectomy and level I and II axillary node dissection. This approach allows for safe and accurate tumor excision and nodal staging with limited required resources.

Breast-Conserving Surgery (BCS)

BCS involves lumpectomy or partial mastectomy. Essential requirements of this BCS include the ability to localize the tumor via palpation or image-guided techniques such as wire or seed localization. This approach requires adequate pathologic resources to assess margin status. All BCS aims to excise the invasive disease with clear margins or "no ink on tumor."

Benefits of BCS include decreased morbidity, preservation of the breast, increased aesthetic satisfaction, and improved quality of life. When combined with adjuvant radiation, BCS is comparable to mastectomy in terms of overall survival.

Palpable lesions are more straightforward to excise. These masses should be excised to clear margins based on surgeon palpation.

Non-palpable lesions detected on screening imaging will require image-guided localization in the preoperative setting to guide the excision. This can be accomplished in many ways. Most commonly, a wire is placed into the breast at the site of the lesion under mammographic or ultrasound guidance. Preferably, a mammogram is then obtained to document the position of the wire in relation to the lesion.

The surgeon then excises the tissue surrounding the wire. The volume of tissue excised is based on the presumed size of the lesion on preoperative imaging. Ideally, if a biopsy clip was placed at diagnosis, the surgical specimen is imaged intraoperatively to ensure it contains the clip. This documents that the biopsied cancer has been excised. However, this approach requires specimen imaging and may not be feasible based on local resources.

Other localization techniques for non-palpable lesions include i125 seed placement and magnetic seed placement. The seeds themselves are costlier than wires. These approaches require additional equipment, such as a sentinel node probe with appropriate settings to detect the position of the seed. Handling the radioactive seeds requires special training and disposal. Wire localization remains the most cost-effective approach to tumor localization.

Another essential component of breast conservation is its reliance on adjuvant radiation to decrease the risk of local recurrence. Data has consistently demonstrated increased rates of ipsilateral breast tumor recurrence (IBTR) in women undergoing BCS without radiation. The addition of adjuvant radiation can reduce IBTR by 50%. [2] In addition to the decrease in loco-regional recurrence (LRR), data also suggests that post-lumpectomy radiation also reduces the risk of breast cancer death. [6]

As such, breast conservation generally should not be performed in the absence of access to adjuvant radiation therapy.

Radiation may be safely omitted in women >70 years old with ER+, stage 1 breast cancer who receive adjuvant endocrine therapy. [A trial demonstrated a 3% absolute reduction in local failure with adjuvant radiation. No difference in rates of distant metastases or overall survival was demonstrated. [7]

Mastectomy

Mastectomy allows the removal of all the breast tissue, including the lesion, without the need for localization techniques. This is an effective local treatment for breast cancer and may negate the need for adjuvant radiation in some cases. Overall complication rates are low.

Mastectomy may be performed in conjunction with breast reconstruction. Multiple options and timing for breast reconstruction exist. It is important to note that reconstruction does not impact LRR or overall survival. While clear benefits live in terms of patient satisfaction, aesthetic outcomes, quality of life, and psychosocial function, the cost and complexity of breast reconstruction may be prohibitive in limited resource settings.

Nodal Staging

Nodal staging is an essential part of the surgical management of operable breast cancer. The presence of nodal metastases increases the disease stage and confers a worse prognosis than node-negative disease. It also alters adjuvant treatment decision-making. Surgical nodal staging should be completed at the same time as tumor extirpation by BCS or mastectomy.

In patients with clinically N0 disease, a sentinel node biopsy has become the gold standard for nodal staging. This technique utilizes blue dye and/or technetium-labeled sulfur colloid (tech99) to identify the first draining nodes in the axillary basin. The sensitivity and specificity of this technique have been widely validated.

A significant benefit of this approach is decreased morbidity. Specifically, the risk of postoperative ipsilateral arm lymphedema is significantly reduced with sentinel node biopsy. Patients reported that their quality of life and arm function are also improved with this approach.

From a resource standpoint, sentinel node biopsy requires the injection of at least one dye for mapping. The use of the tech99 radioisotope requires equipment (sentinel node probe) to localize the nodes. Blue dye alone does not need this probe. However, the identification of blue nodes by tracing lymphatic channels may be technically challenging. Use of a single dye, while less resource-intensive, results in a higher false negative rate.

The alternative to sentinel node biopsy is the complete level I and II axillary node dissection (ALND). This allows for accurate nodal staging. The clear benefit of ALND is the relative lack of resources required to perform the procedure. No localization techniques or injections are necessary. No additional equipment outside standard surgical instruments is needed. Drawbacks to ALND include increased morbidity; specifically, the risk of postoperative lymphedema is significantly higher.

Pathologic Evaluation

Accurate pathologic evaluation is essential for treatment planning and prognosis. Universal parameters should be provided in the pathologic evaluation of surgical specimens, including tumor size, grade, histopathologic type, and lymph node status. This allows for accurate TNM staging. A globally recognized system facilitates consistent, reproducible staging and better treatment decisions and prognostic evaluation. Pathologic TNM staging does not require significant resource utilization.

Accurate assessment of margin status is essential in the setting of breast-conserving surgery. This determines if re-excision is required. Positive margins confer an increased risk of LRR. If resources allow for BCS, assessing margin status must also be considered a needed resource. The same applies to the assessment of sentinel node status. This is required to determine if additional nodal surgery is recommended and is a required resource in a location performing sentinel node biopsies. Measurement of hormone receptor status (estrogen receptor and progesterone receptor) is used to predict response to specific types of therapy. However, if endocrine therapy such as Tamoxifen and aromatase inhibitors or ovarian ablation approaches are not widely available, the utility of ER/PR assessment is limited.

In some cases, HER2/neu measurement is costly and requires immunohistochemical (IHC) and fluorescence in situ hybridization (FISH) analyses. If anti-HER2 therapy is not widely available, the utility of this assessment is also limited.

Medical Management

In women with early-stage breast cancer, adjuvant systemic therapy is considered to decrease the risk of recurrence. This decision is based on the sensitivity of the tumor to available agents, the ability of the patient to undergo systemic treatment, and the predicted benefit of such treatment. Prognostic factors that suggest benefit from adjuvant systemic therapy include age, tumor grade, tumor size, nodal burden, and patient comorbidities.

Endocrine therapy

Adjuvant endocrine therapy in the form of a SERM, such as Tamoxifen or an aromatase inhibitor (AI), significantly decreases the risk of local and distant disease recurrence and improves overall survival in hormone receptor-positive (HR+) disease. [8]

National Comprehensive Cancer Network (NCCN) Guidelines recommend using Tamoxifen for at least five years in pre-menopausal women at diagnosis [1]. Consideration of the addition of ovarian suppression in women at higher risk of recurrence due to young age, high-grade disease, or lymph node involvement is also recommended based on SOFT and TEXT trials. [9]

For women who are post-menopausal at diagnosis, the use of an AI for at least five years is recommended. Commonly used AIs such as Letrozole, Anastrozole, and Exemestane confer similar risks and side effect profiles.

In resource-limited settings, it is imperative to consider medication costs. Tamoxifen is considerably more cost-efficient and more readily available than AI in many LMICs. As such, the use of Tamoxifen in HR+ post-menopausal patients should be considered if AI is unavailable or the cost is prohibitive. The use of Tamoxifen in HR+ post-menopausal women is well documented. [8]

The duration of adjuvant endocrine therapy should be at least five years; consideration for an additional five years is recommended. Reassessment of menopausal status is recommended for pre-menopausal women on Tamoxifen if AI is available.

Ovarian Function Suppression (OFS)

OFS can be achieved permanently via oophorectomy or ablative radiation or temporarily with the use of luteinizing hormone-releasing hormone (LHRH) agonists. In low-risk patients with HR+ disease, ovarian ablation is not recommended. However, in high-risk pre-menopausal patients, OFS plus endocrine therapy may reduce the risk of LRR and provide a limited overall survival benefit. [9] In resource-limited settings, the cost of medical OFS may be prohibitive. The side effects of permanent ovarian function interruption, such as increased risk of cardiovascular disease, must be considered when debating the use of OFS in early breast cancer treatment.

Systemic Chemotherapy

As per current NCCN guidelines, the benefit of chemotherapy in the setting of early-stage breast cancer may be assessed using genomic assays to determine recurrence risk. [1] Such tests may not be available or affordable in resource-limited areas. Alternately, prognostic factors predictive of recurrence, such as patient age, tumor size, grade, nodal burden, presence of lymphovascular

invasion, and receptor status, can be used to determine which patients may benefit from chemotherapy. This makes careful pathologic assessment an essential tool in treatment planning.

For example, patients with triple-negative or HER2-positive tumors often benefit from systemic chemotherapy, even in the setting of early-stage disease. The drug regimen of choice will be based on availability, cost, and the benefit of systemic treatment. Combination regimens are more effective than single-agent approaches.

Taxane-containing regimens (i.e., doxorubicin plus cyclophosphamide followed by paclitaxel AC-T) have been demonstrated to improve DFS and OS in early operable breast cancer. [10] The use of CMF chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil) has been shown to improve DFS and OS compared to no chemotherapy. [1] This drug regimen may be more readily available in some resource-limited areas.

Overall, the delivery of chemotherapy is intravenous and must follow a specific schedule. Dose reduction or early termination of treatment decreases benefits. Facilities must be available for administration and assessment of possible chemotherapy-related toxicities. These include laboratories for hematologic monitoring, transfusion services, the ability to monitor cardiac function, and facilities that allow for the admission, treatment, and monitoring of patients as needed.

Anti-HER2 Therapy

NCCN guidelines recommend the use of HER2-targeted therapy with chemotherapy in patients with HER2-positive disease >1cm in size. For tumors measuring 0.6- 1cm or those with nodal micrometastases, consideration of the above regimen is also recommended. Trastuzumab is a well-studied and routinely used anti-HER2 agent. [1]

As with systemic chemotherapy, the use of anti-HER2 therapy is dependent on the ability to assess the HER2 status of the tumor, as well as the availability and cost of the drug in resource-limited settings. The above-mentioned facility and personnel requirements are also necessary.

Adjuvant Radiation

The use of adjuvant radiation must be carefully considered in each patient. The availability of facilities and personnel and the ability of the patient to undergo timely and daily treatments must be weighed prior to making surgical decisions. If adjuvant chemotherapy is planned, radiation should be planned after completion of chemotherapy.

Breast-Conserving Therapy (BCT)

Adjuvant whole breast radiation (WBRT), together with breast-conserving surgery, forms the basis of BCT. The vast majority of patients who undergo lumpectomy are recommended to undergo adjuvant radiation. The addition of adjuvant radiation can reduce IBTR by 50%. [6] In addition to the decrease in locoregional recurrence (LRR), data also suggests that post-lumpectomy radiation also reduces the risk of breast cancer death. [6] If radiation is not available, or the patient is unable to commit to treatment for financial or geographic reasons, breast conservation should not be recommended.

As previously mentioned, a small subset of early-stage patients (>70 years old, ER+, receiving adjuvant endocrine therapy, node-negative T1 tumors) may safely avoid radiation in the setting of BCS [7] CT-based treatment planning is recommended where available to delineate targets and decrease dosage to adjacent organs such heart and lungs.

Whole breast radiation (WBRT) is considered standard therapy post lumpectomy and targets all breast tissue. An additional boost may be given to the tumor bed in patients considered at high risk for recurrence. The standard WBRT regimen is a 45-50.4 Gy dose in 25-28 fractions. [1]

The tumor boost dose is an additional 10-16 Gy in 4-8 fractions and is recommended for higher risk characteristics such as high-grade disease, age <50, or focally positive margins. [1] It is important to note that surgical re-excision to negative margins is preferred whenever possible. Treatment is recommended on a 5-day per week schedule.

Hypofractionation may be considered to decrease the number of doses required. This approach is endorsed by recent NCCN guidelines and involves 40-42.5 Gy given in 15-16 fractions. [1] Advantages to this approach in LMIC are the decreased number of treatments required, therefore reducing patient visits and resource utilization. Local tumor control and cosmetic outcomes are similar to hypofractionation as compared to standard WBRT. [1]

Post Mastectomy Radiation (PMRT)

As mentioned, BCS should not be performed without radiation availability. In that circumstance, mastectomy is recommended. However, radiation may still be recommended in the post-mastectomy setting.

PMRT is recommended in patients with large tumors (>5cm) or with positive margins. Dosing is 45-50.4 Gy in 25-28 fractions plus a scar boost of 18.-2 Gy to a total of 60 Gy dose. Again, the recommended schedule is five days per week. [1]

Regional Nodal Radiation: Regional nodal radiation is recommended in addition to WBRT or PMRT in patients with nodal disease. Dosing is identical at 45 – 50.4 Gy in 28 fractions to the

nodal fields, administered on a 5-day/week schedule. Infraclavicular, supraclavicular, internal mammary, and axillary nodal basins should be targeted. [1]

Conclusion

Breast cancer is a heterogeneous disease, making treatment, even in the early operable setting, necessarily heterogeneous as well. Multiple considerations, such as patient factors, disease factors, and local resource availability, must be considered when making treatment decisions.

In many parts of the world where healthcare resources and infrastructure are limited, surgery is the mainstay of management for early operable breast cancer. Adjuvant treatment options such as endocrine therapy, chemotherapy, and radiation are recommended when resources exist.

It is essential to address both the medical and non-medical barriers to breast cancer treatment in low- and middle-income countries. The vast majority of patients present with late-stage disease or do not have access to screening systems to detect early disease. Geographic factors can prohibit access to care. Specific cultural barriers or beliefs may prevent women from seeking treatment. Education of not only patients, but healthcare providers, government agencies, and the general public is essential to diagnose and treat early-stage breast cancer.

Much of the research used to make treatment recommendations assumes adequate resources to provide such treatment. Additionally, patients from low- and middle-income countries are grossly underrepresented in studies on breast cancer management.

The management of early breast cancer in resource-limited settings must address both the disease and the disparities present in order to provide high-quality breast cancer care. (Figure 1).

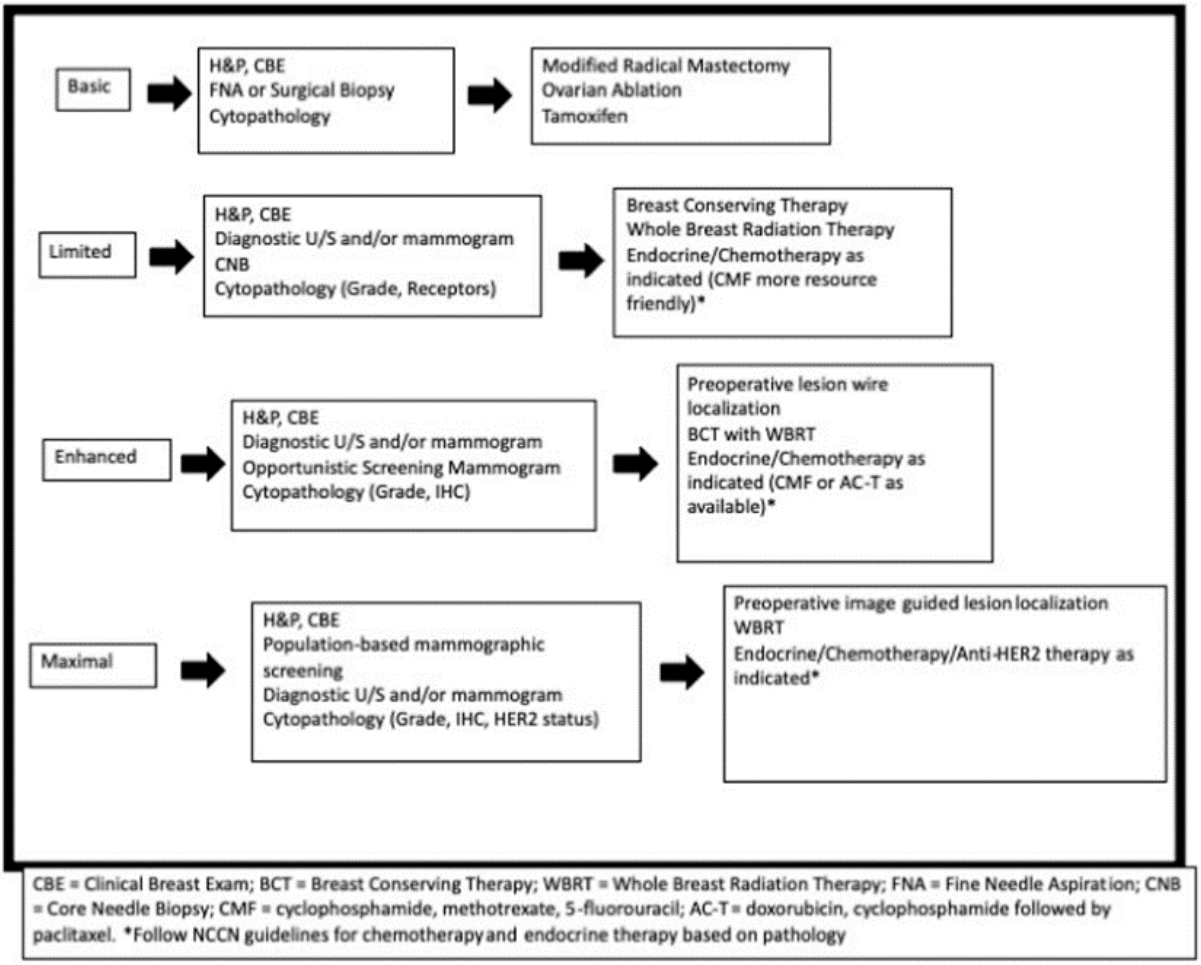

Figure 1: Treatment based on resources available

Resources

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Chapter 20

Breast Preoperative and Postoperative Care Checklist

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Case Scenario

A 67-year-old woman presents to your clinic after screening mammography identified a 2.5 cm spiculated mass in the upper outer quadrant of the right breast classified as BI-RADS 5, prompting percutaneous biopsy of the lesion. The pathology results identified infiltrating ductal carcinoma, ER+, PR+, and HER2-. She is asymptomatic and cannot feel the lesion. Her medical history includes hyperlipidemia, hypertension, diabetes mellitus, and a myocardial infarction five years ago. Her surgical history consists of an open appendectomy under general anesthesia 30 years ago, and she reports no complications. Her prescribed medications include aspirin, atorvastatin, clopidogrel, metformin, and metoprolol. She also takes an herbal supplement, kava, for its anxiolytic effects. She has no known allergies. She has smoked a pack of cigarettes daily for 45 years and drinks alcohol socially but denies any other substance use. Her family history includes ovarian cancer in her mother, diagnosed at age 62, and prostate cancer in her brother, diagnosed at age 58. She is retired and lives with her husband locally. Her exam is unremarkable for palpable mass or regional lymph nodes. After discussing the options, she would like to consider breast conservation.

1. Which of her medications should be held preoperatively and with what interval?

2. Is there any benefit to preoperative smoking cessation in this patient?
3. What is her ASA classification? What does this suggest about her perioperative risk?
4. What additional assessment should be utilized in patients over age 65?
5. What preoperative testing is indicated in this patient?

Background

Perioperative management begins in the pre-hospital setting when planning for surgery. Education should be a top priority. A well-informed patient should be able to express an understanding of the scheduled procedure(s), including risks, benefits, and alternatives. Providing a copy of the most up-to-date guidelines for the management of their diagnosis can aid in education. Printed summaries demonstrating alternatives and rationale for the management plan will foster confidence in both the surgeon and the upcoming procedure.

Surgically treatable conditions account for an estimated 11% of the international disease burden, equating to hundreds of millions of operations performed annually. There is an accepted risk of complications related to surgery and anesthesia, and the risk is believed to be much higher in developing countries. However, data suggest at least half of all surgical complications are avoidable [13]. The World Health Organization (WHO) developed the WHO Surgical Safety Checklist in 2007 to decrease medical errors and adverse events and improve communication in surgery [22]. Utilization of this checklist has since been associated with significant reductions in morbidity and mortality in varying geographic locations, patient populations, and procedures [1, 13]. In the following years, this checklist was modified for specific uses, and additional checklists were developed. The following information has been compiled as a detailed

preoperative and postoperative care checklist to facilitate improved care for breast cancer patients and reduce perioperative complications.

Preoperative Outpatient Visit

- Patients should be thoroughly interviewed, and pertinent answers should be documented regarding the following:
    - A complete *History of Present Illness* (HPI), including any previous workup
    - Any new symptoms that have not been previously addressed by a clinician
        - These should be evaluated at the discretion of the clinician
    - An entire *Medical History,* including active medical problems
    - A complete list of prescription medications, over-the-counter medications, supplements, and herbs
    - Any *Surgical History,* including any implants or prosthetics (i.e., pacemaker/defibrillator, ventricular assist devices, medication pumps, stents, etc.), level of anesthesia (regional, monitored anesthesia care [MAC], or general) utilized, and any adverse reactions (i.e., to skin preparation, anesthetic, medications, etc.)
    - History of *Allergic Reactions,* including inciting agents and symptoms developed
    - A targeted *Family History*, making sure to ask about any relatives with a known hereditary cancer syndrome, history of cancer in family members (including age of onset), and outcome of treatment in a relevant family member(s). If the patient has a family history of any problems associated with anesthesia, the nature of these problems and any details known about the causative agent(s) should be documented. The patient should be advised to discuss this family history with the anesthesiologist prior to surgery.
    - A *Social History* including (but not limited to)

        - Living situation (i.e., details of living arrangements- permanent vs temporary residence, alone or with others, presence of dependents, or other factors that may impact recovery and follow-up)
        - Substance use/dependence, including present or past tobacco use (frequency of use, duration of use, and date of cessation if applicable), alcohol consumption, and use of illicit substances (including prescription medications not prescribed to the patient)
        - Employment status
        - Financial status (including whether insured, affordability of medications, etc.)
        - Religion or spirituality that may impact medical decision-making
- Every patient should have a complete *Review of Systems* (ROS)
- Every patient should have a thorough but focused *Physical Exam*, especially bilateral breast and regional lymph nodes, including axillary, cervical, supraclavicular, and infraclavicular nodes
- This should be obtained if the patient requires further imaging or biopsy, and a definitive plan should be deferred. When results are available, or if imaging and/or biopsy results have already been acquired:
    - Determine the BIRADS category and its implications on the treatment plan [4].
    - Discuss implications of pathology on recommended treatment plan, prognosis, and long-term significance
- Based on the known or suspected diagnosis:
    - Determine recommended treatment plan per local guidelines (such as the National Comprehensive Cancer Network [NCCN]) and review with patient

- Educate the patient on the risks, benefits, and alternatives of the recommended therapy

- Perform preoperative risk stratification utilizing a validated tool to inform both the clinician and the patient of their specific complication risk, assist the patient in making informed decisions, and convey realistic expectations

    - American Society of Anesthesiologists (ASA) Class (Table 1) [2].

ASA PS Classification	Definition	Adult Examples (Including, but not limited to):
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases without substantive functional limitations. Examples: current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; one or more moderate to severe diseases. Examples: poorly controlled DM or HTN, COPD, morbid obesity (BMI 40+), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction in EF, ESRD undergoing dialysis regularly, history (>3 months) of MI, CVA, TIA, or CAD/stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples: recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of EF, sepsis, DIC, ARF or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples: ruptured abdominal or thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the setting of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	N/A

Table 1: American Society of Anesthesiologists (ASA) Physical Status Classification System: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESRD, end-stage renal disease; MI, myocardial infarction; CVA, cerebral vascular accident, TIA, transient ischemic attack; CAD, coronary artery disease; DIC, disseminated intravascular coagulation; ARF, acute renal failure.

    - American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for surgical risk [11].

    - The ACS National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator [3].

- Inform the patient that unanticipated intraoperative findings may require alteration of the procedure and overall treatment plan

- Determine what (if any) preoperative testing should be performed (Table 2) [21].

Test	Minor Surgery in a Healthy Patient				Clinically Significant and Changing Disorders and/or Medications																		
	<45y/o	45-54y/o	55-69y/o	>70y/o	Hypertension	Smoking	Morbid Obesity	History of Stroke	Cancer (?Metastatic)	Seizure Medications	Cardiovascular Disease	Respiratory Disease	Diabetes Mellitus	Hepatic Disease	Renal Disease	Fluid or Electrolyte Loss	Autoimmune disorders/Lupus	Alcohol/Drug Abuse	Steroids/Cushing's Syndrome	HIV	Parathyroid Disease	Unstable Thyroid Function	Anticoagulant/Bleeding Disorder
ECG		M	Y	Y	Y	Y	Y	Y	Y		Y*	Y	Y*	Y	Y	±*	Y	Y*	Y	Y	Y*	Y*	
CBC + platelets		Y	Y	Y			Y	Y	Y	Y	Y	Y	Y*	Y*	Y*	Y*	Y*	Y*	Y*	Y*	Y	Y*	Y*
Electrolytes				Y	Y		Y	Y	Y		Y	Y	Y*	Y*	Y*	Y*	Y*	Y*	Y*	Y	Y*	Y*	
BUN/Creatinine				Y	Y			Y	Y		Y	Y	Y*	Y*	Y*		Y*	Y*	Y*	Y	Y	Y*	
Glucose				Y			Y	Y	Y		Y		Y	Y*	Y*			Y*	Y*	Y	Y	Y*	
LFTs									Y	Y				Y*				Y*		Y			
Calcium																					Y		
PT/PTT														Y*	Y*		Y*	Y*					Y*
CXR									S			Y								S			
Hormone Levels																					Y		
Bleeding Time																							±
Drug levels										S								±					
Tumor markers									S														

Modified version of Table 10-1: Suggestions for Adult Preoperative Testing, Sabiston Textbook of Surgery (20th Edition), which was adapted from Halaszynski TM, Juda R, Silverman DG: Optimizing postoperative outcomes with efficient preoperative assessment and management, Crit Care Med 32:S76-S86, 2004. NOTE: times and tests listed are suggestions to be utilized in adjunct with the recommendations of the surgeon and anesthesiologist. Additional tests should be performed, or a suggested test omitted as deemed appropriate, with the purpose of preoperative testing being to generate potentially clinically significant information in the context of the patient and planned intervention. Boxes marked with an asterisk (*) are ideally performed <30 days before surgery, and the remaining testing is generally acceptable within 90 days of surgery.

Table 2: S based on surgeon judgment; Y, usually indicated;, if the situation is acute or severe.*

- Routine preoperative testing is less predictive of perioperative morbidity (vs ASA status or AHA/ACC guidelines for surgical risk) and is not cost-effective [21]. ASA physical status classification has been shown to be independently predictive of increasing morbidity and mortality across procedure types [12].

- The goal of preoperative testing should be to uncover issues that require additional workup or that may be amenable to preoperative optimization, to minimize perioperative risk

        - New guidelines for genetic testing by the American Society of Breast Surgeons recommend offering genetic testing for any patient with personal history of breast cancer [16]. The significance of this recommendation has been debated and should be subject to availability as well as the clinician's assessment of the potential impact on surgical decision-making.

- A checklist for optimal preoperative assessment of geriatric patients (age >65), developed by the ACS and the American Geriatrics Society (AGS), improves perioperative care [6]:
    - In patients without known history of cognitive impairment or dementia, assess cognitive ability & capacity to understand the anticipated surgery
    - Screen for depression
    - Identify risk factors for postoperative delirium
    - Screen for alcohol and other substance abuse/dependence
    - Perform a preoperative cardiac evaluation according to the ACC/AHA algorithm for patients undergoing noncardiac surgery [11]
    - Identify the patient's risk factors for postoperative pulmonary complications and implement appropriate prevention strategies
    - Document functional status and history of falls
    - Determine baseline frailty score
    - Assess nutritional status and consider preoperative interventions if at severe nutritional risk
    - Take an accurate and detailed medication history and consider appropriate perioperative adjustments. Monitor for polypharmacy
    - Determine the patient's treatment goals and expectations in the context of possible treatment outcomes

- Determine the patient's family and social support system
- Order appropriate preoperative diagnostic tests focused on elderly patients

- Preoperative planning
  - Obtain contact information for emergency contacts, as well as the power of attorney and/or surrogate decision-maker as applicable
  - Determine code status
  - Discuss therapy that may be indicated postop, including radiation, chemotherapy, and/or hormone blocking therapy (may depend on pathology or intraoperative findings; inform patient of these possibilities)
  - If appropriate, patient may be offered immediate vs delayed reconstruction. If the patient is interested, referral to a plastic surgeon will need to take place preoperatively
  - Indications for consideration of contralateral prophylactic mastectomy can be introduced. In patients with germline mutations or a strong family history of breast cancer, the pros and cons of a contralateral prophylactic mastectomy can be discussed [21].

- Instructions
  - The patient should be clearly instructed which medications need to be stopped prior to surgery, as well as the recommended date of cessation. The risks and benefits of holding each medication need to be considered, and consultation with the prescribing physician is recommended. In patients with impaired renal or hepatic function, the recommended interval to discontinue certain medications may need adjustment. The nature of the surgical procedure and potential postoperative risks must be considered when determining when to restart held medications.
    - Antiplatelet agents:
      - If the risk of bleeding outweighs the risk of withholding therapy:

        - Acetylsalicylic acid should be discontinued 7-10 days before surgery [8].
        - P2Y12 inhibitors should be stopped 7-10 days before surgery [8].

- Anticoagulants:
    - Vitamin K antagonists (e.g., warfarin) should be discontinued 5 days before surgery & restarted within 24 hours postop [8].
    - Low molecular weight heparin (LMWH) should be held 24 hours before surgery and restarted about 48-72 hours postop [8].
    - Unfractionated heparin should be held within 6h of surgery and restarted within 12-24h postoperatively [8].
    - Novel oral anticoagulants, including direct thrombin inhibitors (i.e. dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban) should be discontinued 24-48h preop depending on anticipated bleeding risk and restarted within 24h postop [15].
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - These should be discontinued starting 1-3 days before surgery, depending on the half-life of the drug used by the patient [21].
- Diabetic medications [14].
    - Oral hypoglycemic agents:
        - Long-acting agents (i.e., chlorpropamide or glyburide) should be discontinued 2-3 days before surgery
        - All others should be discontinued the evening before surgery

- Insulin
    - Subcutaneous insulin pumps should be inactivated the morning of surgery
    - Short-acting insulin should be held the morning of surgery
    - In patients taking intermediate-acting insulin, insulin, and glucose should be given preoperatively (1/2 their morning dose of intermediate-acting insulin and 5% IV dextrose at 100-125 mL/hr). Subsequent insulin doses should be guided by intermittent blood glucose measurements (every 4-6 hours)
- Diuretics
    - These should be held in most patients on the morning of surgery (except patients with congestive heart failure [CHF]) [21].

- The patient should be aware of the implications of relevant substances to anesthesia, surgery, and recovery and advised to abstain from these substances (particularly tobacco, opiates, and alcohol).
- It is recommended to abstain from smoking for 4 weeks prior to surgery to minimize the risk of postoperative complications and/or poor wound healing [21].
    - In the case of malignancies, surgical intervention should not be delayed due to active tobacco use if the risk of postponing surgery includes a significant risk of disease progression which outweighs the potential benefits of delaying the procedure. As smoking has a significant impact on wound healing, the compounded risk associated with the addition of other concomitant procedures (i.e., immediate reconstruction) should be considered [10, 17].

- The patient should be given concise but thorough preoperative instructions:

- Shower with chlorhexidine gluconate (CHG) or other available antibacterial soap the evening before surgery
- No oral intake after midnight vs Enhanced Recovery After Surgery (ERAS) protocol (see Table 3) [18].

Table 3: Enhanced Recovery After Breast Surgery (ERAS) Protocol

Preoperative protocol	• Preop counseling of perioperative expectations and multimodal non-narcotic pain control • Clear liquids (electrolyte drinks recommended) up to two hours preoperatively • Preoperative area oral medications: 975 mg acetaminophen and 300 mg gabapentin
Intraoperative protocol	• Intraoperative maintenance of euvolemia and normothermia • Antiemetic protocol upon anesthesia administration • Long-acting local analgesia infiltration prior to incision (1:1 mixture of 1.3% bupivacaine liposome suspension with 0.5% bupivacaine hydrochloride injection) • At least 20 cc of liposomal bupivacaine mixture infiltrated into skin, subcutaneous tissue, chest wall (including axilla[e] and/or drain site[s] if applicable) prior to closure • Administration of 15 mg IV ketorolac during closure
Postoperative protocol	• Early cessation of intravenous fluids, early ambulation, and unrestricted diet • Ibuprofen 600 mg every eight hours alternating with 650 mg acetaminophen every 8 hours for 4-5 days

Table 3 legend: patients with contraindications to any of the above medications should be given an alternative
[18]

  - Per ASA guidelines, patients should stop intake of solids at least 6 hours before surgery and clear fluids at least 2 hours before surgery [21].
- Bring necessary medical devices if an overnight stay is anticipated (i.e., CPAP machine)
- Bring information on medical devices or implants (i.e., pacemaker)
- Removable dentures, artificial nails, and jewelry should be removed prior to surgery
- If anticipated discharge is within 24h of receiving anesthesia, arrange for transportation home (no driving) and someone to be available for assistance if needed during that time
  - It is recommended to have someone with the patient for 24h if given general anesthesia or a minimum of several hours postop if MAC (also known as conscious sedation).

        - If the procedure only requires local or regional anesthesia and no opioids are administered, the patient can drive home as soon as discharged

    - If preop labs are needed (including type and screen), give instructions on when/where this will be done. If necessary, give instructions on how to donate autologous blood ahead of time to be available during surgery

- If drains may be used, educate the patient on their purpose and care. If possible, give this in writing so they have it available at home after discharge. Supply a log for recording drain output.

- If medications will be given at discharge, consider giving scripts to the patient to fill prior to surgery so they will already have them upon discharge

- Schedule postop visit

- Give the patient contact information if questions or concerns arise

    - Instruct them to call with any changes to health or medications, new symptoms, or other concerns

- The patient should be given a printed copy of postoperative expectations, anticipated restrictions, and any permitted/recommended postoperative exercise/stretching regimens for implementation in the immediate postoperative period.

Preoperative on the Day of Surgery

- Verify the following for all patients

    - Any changes to health or medications since clinic visit

    - Any new symptoms

    - Confirm allergies, especially to medications, latex, or iodine

    - Confirm emergency contact(s)

    - Dentures, artificial nails, jewelry, undergarments, etc. removed
    - Belongings logged and stored
    - Confirm patient identity, planned intervention, and surgical site
    - Confirm nothing by mouth since midnight vs ERAS protocol adherence
- Check patient's vitals for any new abnormalities
- Complete any indicated day-of-surgery workup
    - All women of childbearing age should receive a urine pregnancy test the morning of surgery unless the uterus and/or ovaries are surgically absent
- The anesthesiologist should meet the patient, perform airway examination, and obtain informed consent for the type of anesthesia planned.
- The surgeon should have the patient confirm the surgical site and write initials
- The surgeon should obtain informed consent for the planned intervention(s)
- The patient should receive prophylactic antibiotics within 1 hour of incision if indicated
    - First-line therapy: first-generation cephalosporins [7].
    - Alternative prophylactic antibiotics should be given if the patient is allergic to beta-lactam antibiotics (clindamycin), or if the patient has a history of MRSA (vancomycin; must be dosed between 1-2 hours before incision) [7].

In the Operating Room (OR)

- The World Health Organization (WHO) has compiled and published a Surgical Safety Checklist, which has been shown to significantly reduce perioperative morbidity and mortality when utilized (see Table 4). [1, 13, 22]

Table 4: Surgical Safety Checklist (WHO)

When:	Team members (at minimum)	Checklist	Possible responses
Before induction of anesthesia	Nurse and anesthetist	Has the patient confirmed his/her identity, site, procedure, and consent?	y
		Is the site marked?	y/N/A
		Is the anesthesia machine & medication check complete?	y
		Is the pulse oximeter on the patient and functioning?	y
		Does the patient have a: • Known allergy? • Difficult airway or aspiration risk? • Risk of >500 ml blood loss (7 ml/kg in children)?	 n/y n/y & equipment/help available n/y & CVC/2 IV & fluids planned
Before skin incision	Nurse, anesthetist, and surgeon	Confirm all team members have introduced themselves by name and role	
		Confirm patient's name, procedure, and where the incision will be made	
		Has antibiotic prophylaxis been given within the last 60 minutes?	y/N/A
		Anticipated critical events: To surgeon: • What are the critical or non-routine steps? • How long will the case take? • What is the anticipated blood loss? To anesthetist: • Are there any patient-specific concerns? To nursing team: • Has sterility (including indicator results) been confirmed? • Are there equipment issues or any concerns?	
		Is essential imaging displayed?	y/N/A
Before patient leaves the operating room	Nurse, anesthetist, and surgeon	Nurse verbally confirms: • The name of the procedure • Completion of instrument, sponge, and needle counts • Specimen labelling (read labels aloud, including patient name)	
		• Whether there are any equipment problems to be addressed	
		To surgeon, anesthetist, and nurse: • What are the key concerns for recovery and management of this patient?	

Table 4: in the "possible responses" column, if listed, these are the only allotted options. If blank, this is individualized to the patient and case. CVC, central venous catheter; The WHO also notes the disclaimer, "This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged" [13].

- Prior to induction of anesthesia, all necessary equipment should be present and accessible
    - Includes all necessities for general anesthesia regardless of type of anesthesia planned
    - Monitors to display blood oxygen level, measures of ventilation such as end-tidal CO2, and/or expiration volume, blood pressure and heart rate (at least every 5 min), continuous electrocardiogram, and temperature should all be present and

functioning. Equipment should also display delivered oxygen concentration and ventilator pressure [21].

  - Supplemental oxygen, endotracheal tube (or other airway), advanced cardiac life support (ACLS) drugs, vasopressors, IV fluids, and all medications required for general anesthesia (regardless of planned anesthetic method) should be in the room [19].

- Careful positioning/padding, offloading of pressure areas where possible, and secure to table

- Perform wide sterile preparation of the surgical site and allow to dry for recommended amount of time-based on the agent used

- Drape patient with sterile, water/body fluid resistant/impermeable drapes

- Full surgical scrub followed by sterile donning of gown/gloves that are water/body fluid resistant/impermeable

- Perform a "time out," confirming patient identity, planned procedure, and site marked by surgeon. Allergies and use of preoperative antibiotics should also be confirmed.

- Prior to skin incision, all surgical equipment anticipated for use should be present and accessible

  - Ensure availability of equipment for all possible procedures (i.e., sentinel lymph node biopsy, axillary lymph node dissection)

- After the procedure ends

  - Confirm procedure(s) performed, postoperative diagnosis, any unanticipated events or findings, description of any specimens, estimated blood loss (EBL), and disposition (discharge from PACU vs. overnight floor admission vs. ICU admission etc.)

- Complete operative note with documentation of the above and detailed description of procedure performed

In the Post-Anesthesia Care Unit (PACU)

- After general anesthesia or MAC, all patients should be monitored continually for at least 30-60 minutes with attention to ventilation, oxygenation, circulation, level of consciousness, and temperature.
    - Pulse oximetry or other quantitative assessment of oxygenation should ideally be utilized
    - A physician capable of managing cardiopulmonary resuscitation should be available for all PACU patients [20].
- Document descriptions of incisions, drains, and other wounds
- Manage postoperative pain and/or nausea. If opiates are administered, naloxone should be readily available.
    - ERAS protocol can reduce or eliminate post-operative narcotic use [18].
    - Towel padded ice packs can be utilized in 15-minute increments
- Monitor for complications such as bleeding
- If a urinary catheter is placed for surgery, plan to remove it immediately after surgery if possible. If discharge is planned from PACU patient should urinate independently before being cleared for discharge
- Clearance by a physician or via predetermined discharge criteria should be obtained before the patient moves to a phase II recovery area, short-stay unit, or inpatient bed. Criteria that must be met include (but are not limited to) [21]:
    - Patient is awake and oriented (or at baseline mental status)
    - Vital signs are stable

- Patient is breathing without difficulty (protecting airway and maintaining oxygenation)
- Pain, nausea, vomiting, and/or shivering adequately controlled
- No evidence of surgical complications (i.e. bleeding)

During Admission (If Applicable)

- Determine postop risk for venous thromboembolism (VTE) and provide appropriate prophylaxis.
  - The Caprini Risk Assessment Model (Table 5) is one guide for decision-making that determines a score that estimates VTE risk by adding points for various risk factors. The patient's risk level determines recommendations for prophylaxis [5].

Table 5: Caprini Risk Assessment Model for Venous Thromboembolism in General Surgical Patients

1 Point	2 Points	3 Points	4 Points
• Age 41-60 yr • BMI >25 kg/m2 • Minor surgery • Lower extremity edema • Varicose veins • Pregnancy or postpartum • Oral contraceptive • Hormonal therapy • Unexplained or recurrent abortion • Sepsis (<1 month) • Serious lung disease such as pneumonia (<1 month) • Abnormal pulmonary function test (ie COPD) • Acute myocardial infarction • Congestive heart failure (<1 month) • Bed rest • Inflammatory bowel disease	• Age 61-74y • Arthroscopic surgery • Laparoscopy >45 min • Major open surgery >45 min • Cancer • Plaster cast • Bed bound for >72 hours • Central venous access	• Age 75+ years • Prior episodes of VTE • Family history of VTE • Prothrombin 20210 A • Factor V Leiden • Lupus anticoagulants • Anticardiolipin antibodies • High homocysteine levels • Heparin induced thrombocytopenia • Other congenital or acquired thrombophilia	• Stroke <1 month • Fracture of hip, pelvis, or leg • Elective arthroplasty • Acute spinal cord injury <1 month

Table 5: the sum of all points determines Caprini score

- Low risk (0-1 point): early ambulation
- Moderate risk (2 points): mechanical prophylaxis with intermittent pneumatic compression (IPC)(preferred) or elastic stockings (ES) or low dose unfractionated heparin (LDUH) or low molecular weight heparin (LMWH)

        - High risk (3-4 points): mechanical prophylaxis with IPC or ES and/or LDUH or LMWH
        - Highest risk (5+ points): LMWH or LDUH (unless contraindicated) alone or in combination with mechanical prophylaxis
    - If the patient has severe peripheral arterial disease, congestive heart failure, and/or an acute superficial/deep vein thrombosis, mechanical prophylaxis may be contraindicated, and alternative measures should be considered.
    - If high risk for major bleeding and 3+ points, utilize IPC (or ES) until the risk of bleeding diminishes and pharmacologic thromboprophylaxis can be initiated [5].

Before Discharge

- Confirm patient has prescriptions for analgesics, antiemetics, stool softeners, or antibiotics as indicated
- Give instructions on when to restart medications held preoperatively
- Advise the patient to avoid heavy lifting, reaching, and climbing for 1-2 weeks postoperatively, 3-4 weeks if axillary surgery or mastectomy were performed. Patients should be redirected to the postoperative care instructions and restrictions given preoperatively in the office.
- Educate patient on expected recovery
    - If surgical bra is given, instruct patient to leave in place for 24h postop. After this, they can remove to shower. Supportive surgical bras should continue to be worn 24 hours/ day for one week or longer at the discretion of the surgeon.
    - If the patient was a smoker preoperatively, educate on the benefit of cessation (or continued abstention) for optimal healing and recovery.

- Advise the patient to sleep with slight head elevation and to avoid lying prone, on any drains, or on the side of the surgical site to improve healing.

- Ensure patient has contact information for questions or concerns that arise
  - Educate the patient on possibility of seroma or hematoma formation postoperatively
  - Educate the patient on concerning signs/symptoms (fever, erythema and warmth of incision, etc.)
- Confirm postoperative follow-up appointment in place

Postoperative Visit Checklist

- Postop wound check
  - Drain removal if applicable
- Consider a gentle exercise regimen to facilitate conservation of shoulder range of motion and avoid stiffness. Referral to a physical or occupational therapist can be considered for assistance in creating a regimen for each patient. The American Cancer Society developed an informative webpage with assistance from the Oncology Section of the American Physical Therapy Association that can be referenced for use in self-directed therapy [9].
- Review pathology/cytology and implications (give patient a copy for records)
  - If margins or nodes are positive for disease, follow pertinent management guidelines as outlined in a separate chapter.
- Discuss recommended additional treatment (if applicable), any alternatives, and the risks/benefits of both undergoing the treatment and abstaining
- Refer to medical oncology, radiation oncology, plastic surgery, genetic counselor, palliative care, etc., as applicable.
- Educate patient on their future screening guidelines and recommended long term follow-up

- Schedule next appointment

Case Scenario (Continued)

1. Preoperative medication cessation should be determined by the risks and benefits of holding each therapy, and consultation with the prescribing physician is recommended. This patient is taking dual antiplatelet therapy, which significantly increases her risk of perioperative bleeding. It is appropriate to consult with her cardiologist to determine whether she can safely withhold one or both of these medications for the recommended seven days before surgery. She is taking a beta-blocker and a statin, which should both generally be continued perioperatively [21]. She is also taking metformin, which she should not take starting the evening before surgery. Kava, an herb this patient takes for proposed anxiolytic effects, has been shown to increase the sedative effect of anesthetics. She should discontinue this at least 24 hours before surgery [21].

2. A 45-pack-year smoking history puts this patient at risk for postoperative pulmonary and wound-healing complications. Smoking cessation can improve pulmonary function and wound healing even if limited to the weeks before and after surgery. This is also a good opportunity to suggest long-term smoking cessation.

3. This patient is classified as ASA PS 3, which indicates an increased risk of perioperative morbidity and mortality with any surgical procedure when compared with ASA PS 1 or 2 [12]. She should be educated on her elevated risk, and the addition of a surgical risk calculator (i.e., ACS NSQIP [3]) should be considered to characterize further risks related to her procedure and specific complications.

4. A checklist for optimal preoperative assessment of patients over age 65, developed by the ACS and the American Geriatrics Society (AGS), has been shown to improve perioperative care when utilized (see “Preoperative Outpatient Visit” for full checklist) [6].

5. Preoperative testing for this patient should include an EKG, CBC with platelets, electrolytes, BUN/creatinine, LFTs, glucose, and PT/PTT (see table 1). Her breast cancer

diagnosis is sufficient to offer genetic testing (and associated counseling), especially in the setting of two immediate family members with cancers that could be attributed to hereditary cancer syndromes [16].

Salient points

- Education should be a top priority. A well-informed patient should be able to express an understanding of the planned procedure(s), including risks, benefits, and alternatives.
- The goal of preoperative testing should be to uncover issues that require additional workup or that may be amenable to preoperative optimization, to minimize perioperative risk
- Routine preoperative testing is less predictive of perioperative morbidity (vs ASA status or AHA/ACC guidelines for surgical risk) and is not cost-effective [21]. ASA physical status classification has been shown to be independently predictive of increasing morbidity and mortality across procedure types [12].
- Utilization of the ACS/AGS checklist for optimal preoperative assessment of geriatric patients has been shown to improve perioperative care in this population [6] significantly.
- Utilization of the WHO Surgical Safety Checklist has been associated with significant reductions in morbidity and mortality in varying geographic locations, patient populations, and procedures [1, 13]. If possible, this checklist, or a modified version more applicable to your institution, should be implemented at an institutional level. If this has not yet been formally implemented, each surgeon should take the initiative to utilize this checklist for each case.
- At each patient's postoperative visit, long-term management and/or surveillance plan(s) should be discussed. This information should also be forwarded to the patient's primary care physician.

Suggested reading

- WHO Surgical Safety Checklist [22].
- A Surgical Safety Checklist to Reduce Morbidity and Mortality in a Global Population, New England Journal of Medicine [13].
- ASA class is a reliable, independent predictor of medical complications and mortality following surgery, International Journal of Surgery [12].
- Testing for Hereditary Breast Cancer from the American Society of Breasts Surgeons, Annals of Surgical Oncology [16].
- 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery, Journal of the American College of Cardiology [11].
- A pilot study of a breast surgery Enhanced Recovery After Surgery (ERAS) protocol to eliminate narcotic prescription at discharge, Breast Cancer Research and Treatment [18].

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Chapter 21

Mastectomy

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Case Presentation

BD is a 62-year-old female with a maternal aunt with breast cancer in her 50s and a maternal grandmother with ovarian cancer in her 50s. She has been feeling a lump in her right breast for the last six months that grew and eventually broke out of her skin. She has no systemic symptoms.

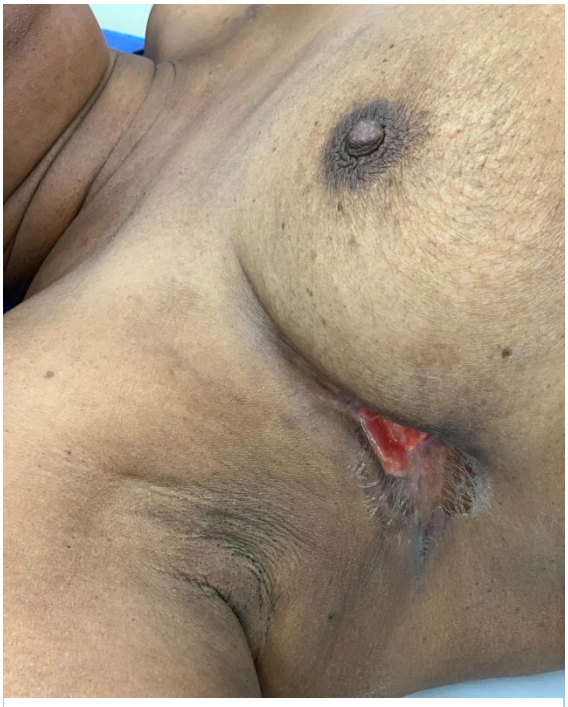


Figure 1: Right T4c breast tumor

Upon physical examination, she exhibits no signs of metastatic disease. Figure 1 shows her right breast, with a 4x5 cm mass in the lateral aspect of the breast, on the border of the pectoralis major muscle, that is ulcerating through the skin and is fixed to the chest wall. Her left breast exhibits no abnormality, and no pathological axillary or supraclavicular nodes are palpated bilaterally.

A punch biopsy from the lesion proves an invasive ductal carcinoma, grade 3, with ER 90%, PR 5%, HER2-negative, and Ki67 80%. There is no evidence of metastatic disease upon workup. The patient received neoadjuvant chemotherapy (ddAC+T) with only minimal clinical response. Due to the involvement of the pectoralis muscles and possibly the chest wall, she is planning for a right radical mastectomy.

Introduction – Historical Perspective

The worldwide incidence of breast cancer reaches 2 million cases, resulting in over 600,000 deaths, making it the leading global cause of death for women. The odds of developing breast cancer in a lifetime seem to be lower in lower socio-demographic index (SDI) countries, 1 in 38 women, compared to 1 in 11 women in high SDI countries[1]. But while most cases of breast cancer in the industrialized world are diagnosed at an early stage, with a majority of patients being cured of their disease, over half of women in low SDI countries, with limited or no access to healthcare resources and education, will be diagnosed in late stages (American Joint Committee on Cancer [AJCC] 8th edition stage III or IV[2]), and the majority of those women will die of metastatic disease[3,4]. More advanced disease upon diagnosis, in conjunction with lower availability of costly adjuvant modalities, namely radiation therapy and chemotherapy, leaves surgery at the forefront of breast cancer treatment in developing countries, and the mastectomy, with its different variations, as its primary weapon.

The earliest potentially curative mastectomy, Halsted's radical mastectomy, stems from the anatomical and surgical principles of loco-regional control by using wide local excision, including the lymphatic basin in the specimen, and not violating the tumor's integrity[5–7]. It involves a teardrop incision encompassing the skin of the breast and extending along the

deltopectoral groove towards the axilla, through which the entire breast tissue en-bloc with the pectoralis major and minor muscles is extirpated and the axillary content, including levels I, II and III, is dissected[8]. With this procedure, local and regional recurrence decreased to 6% and 22%, respectively, and 5-year disease-free survival (DFS) rates were reported to exceed 50% by the middle of the 20th century[9].

The modified radical mastectomy (MRM), in which the pectoralis muscles are preserved, was shown to have equivalent results to the radical mastectomy as early as 1940[10,11]. But it wasn't until the 1970s, with the publication of randomized prospective trials showing its equivalence, as far as overall and disease-free survival and local and distant recurrence, that the MRM started to gain favor, becoming the "gold standard" surgery for locally advanced breast cancer[12–15].

Simple mastectomy or total mastectomy, which are equivalent terms, entails the excision of the breast, including the nipple-areolar complex, but without a dissection of level I and II axillary nodes. The results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, as well as other trials conducted in the pre-chemotherapy era, demonstrated the equivalence of simple mastectomy with adjuvant radiation to the radical mastectomy, in terms of overall survival and disease-free survival, with higher rates of local and regional recurrence in clinically node-positive patients, or when radiation was omitted[16–18]. These trials were followed by trials introducing breast-conserving surgery in conjunction with adjuvant radiation for early (stage I and II) breast cancer, showing its equivalence to MRM[19–22]. And with these trials, the prevalence of mastectomy declined as breast conservation became a consensus in the 1990's[23].

General indications and contraindications for mastectomy

Indications for mastectomy are shown in Table 1:

- Invasive carcinoma of the breast or DCIS, not amenable to breast conserving surgery:
    - Unavailability of post-operative radiation or if radiation is contraindicated
    - Large tumor to breast ratio, due to tumor size or multicentricity
    - Tumors involving the skin or chest wall and inflammatory breast cancer, preferably after neoadjuvant chemotherapy
    - Locally recurring breast cancer after breast conserving surgery
- Breast sarcomas
- Malignant phylloides tumors
- Breast trauma
- Prophylactic mastectomy – for high risk patients (mutation carriers, s/p mantle radiation)

Indications for the addition of ALND in invasive carcinoma of the breast:

- Metastatic axillary node(s)
- In the clinically negative axilla (relative), consider in T3 and T4 tumors and when lacking of availability of sentinel lymph node biopsy (SLNB) or adjuvant radiation

Contraindications and considerations against mastectomy:

- Metastatic disease
- Palliative (“toilet”) mastectomy would be considered relatively contraindicated, when the patient is a high surgical risk and has a short expected survival

- Upfront surgery in inflammatory breast cancer or locally advanced tumors with chest wall or skin involvement, when neoadjuvant chemotherapy is available
- In elderly women with large breasts, a unilateral mastectomy might cause imbalance and partial mastectomy should be considered

Name	Includes	Specific indications
Radical mastectomy	MRM + pectoralis major + pectoralis minor (today, a partial resection of the involved elements of the muscles would be advocated)	Indications of MRM plus: • Locally advanced disease, with involvement of the pectoralis muscle(s), unresponsive to neoadjuvant therapy. • Involvement of pectoralis muscle(s) upon loco-regional recurrence. • Need for re-operation due to positive posterior involvement of muscle after less radical surgery
Modified radical mastectomy	Enbloc Simple mastectomy + ALND	Indications of simple mastectomy plus: • Axillary involvement or other indication for ALND
Simple mastectomy	All breast tissue including nipple areolar complex with a wide incision including a large part of the skin overlying the breast	• Inability to perform breast-conserving surgery for invasive disease or DCIS • Other indications for mastectomy
Skin sparing mastectomy	All breast tissue including nipple areolar complex with an incision preserving most of the breast's overlying skin	Indications of simple mastectomy plus: • No skin involvement by tumor • Ability to reconstruct the breast with volume replacement

Table 1: Different indications for different procedures

Technique

(1) Preoperative planning – Preparing for surgery

Planning the appropriate surgery will take into consideration the extent of surgery necessary. This would entail first defining the purpose of surgery – curative intent for a local or locally advanced disease or a palliative surgery for a metastatic disease with a very symptomatic local, draining or bleeding breast cancer. The extent of surgery with a curative intent would take into consideration, on the one hand, the extent of disease: the size of the tumor, its location in the

breast, and the level of involvement of regional structures (i.e., skin, chest wall musculature or other structures), and on the other hand, the availability of multidisciplinary treatment modalities. When lacking the possibility of postoperative radiation or for sentinel lymph node evaluation, breast or axillary conserving surgery is no longer an option, and a more extensive operation might be considered both for the breast and for the lymphatic basin. If breast reconstruction is available and considered, this might affect the choice of incision and extent of skin resection.

After induction of general endotracheal anesthesia, antibiotics, usually cephalosporin, are introduced about 30 minutes before incision in order to reduce wound infection by up to 40%. DVT prophylaxis, either with perioperative compression boots or subcutaneous heparin, is also recommended. The patient is positioned supine close to the operating table's margin, with some surgeons using a roll to elevate the ipsilateral shoulder, while others point to the risk of brachial plexopathy with this technique. The ipsilateral upper extremity is extended laterally on a padded arm-board, either prepped into the surgical field with a stockinet (allowing for arm adduction during surgery) or not, depending on surgeon preference. The surgeon and assistant are positioned on either side of the arm-board, and the bed can be angled to allow more room between the surgeon and the anesthesia team. Then the operative field is prepped and draped, including the ipsilateral breast, thorax over the midline, lower neck, and anterior arm (or the entire arm if in the field). When an oncoplastic or contralateral symmetry procedure is planned, the contralateral breast is also prepped into the field.

(2) Considerations of incision and consequent wound closure possibilities

Many classical incisions have been advocated over the years by different masters (Figure 2). Each of these incisions serves its purpose and would be advantageous in different situations. The

more common incisions today are the Stewart and the Orr incisions.

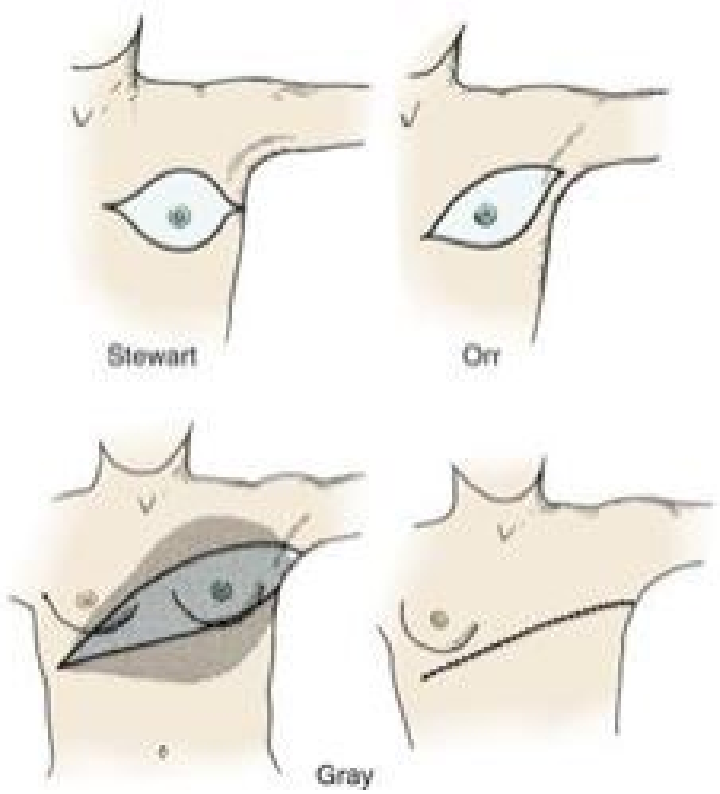


Figure 2: The different incisions for a mastectomy adapted from Bland and Copelan's The Breast, ed Klimberg et al, Elsevier, 6th ed, 2024, Philadelphia.

When planning the skin incision, the first consideration is whether or not a reconstruction is planned (either in the same surgery or in subsequent surgery), in which case skin flaps would need to be preserved, as well as the inframammary fold, if possible. For the purpose of this chapter, we will discuss the conventional technique when no immediate or delayed reconstruction is planned. In these cases, the eventual desired result after mastectomy would be flat skin flaps comfortably draping the chest wall. The choice of incision should consider tumor location and whether the skin overlying the tumor is to be included in the specimen. A gross skin margin of 1-2 cm is usually adequate to achieve final pathological tumor-free margins.

Though each incision is different, there are anatomical landmarks that are universally relevant in planning and carrying out a mastectomy, and it is helpful to mark them, regardless of the incision chosen. These include the borders of the standard mastectomy dissection and include (1) the lateral border – anterior margin of latissimus dorsi muscle, (2) the medial border – lateral margin of the sternum, (3) the superior border – the clavicle (or subclavius muscle) and (4) the inferior border – the inframammary fold (or 2-3 cm below it). In addition, the surgeon could mark the landmarks that might help in planning the incision: the anterior axillary line and the pectoralis major's lateral border.

When drawing the incision itself, the surgeon would first mark the two corners of the incision. In a Stewart incision, for example, the medial corner would be marked at the lateral border of the sternum, and the lateral corner at the anterior surface of the latissimus dorsi muscle, both approximately at the level of the nipple. Whatever the two corners are chosen, the breast is retracted to one side (usually caudally), and a line is drawn connecting the two corners. Then it is retracted to the other side (usually cranially), and another line is drawn connecting the two corners. This will create the shape of the incision, allowing the approximation of the two skin flaps against the chest wall without skin redundancy. The Stewart incision is appropriate for centrally located tumors, or depending on breast size and shape, within this incision's markings. Variations on this incision or on the other classic incision, including the Orr incision or any other incision demonstrated in Figure 2, can be done using these principles, taking into consideration the exact positioning of the tumor and the size of the breast. Figure 3 demonstrates the incision marking for BD. Notice that it includes the T4c tumor with a 2 cm skin margin around it, as well

as the nipple-areolar complex, while its two corners are located at the lateral border of the sternum and at the anterior aspect of the latissimus dorsi muscle.

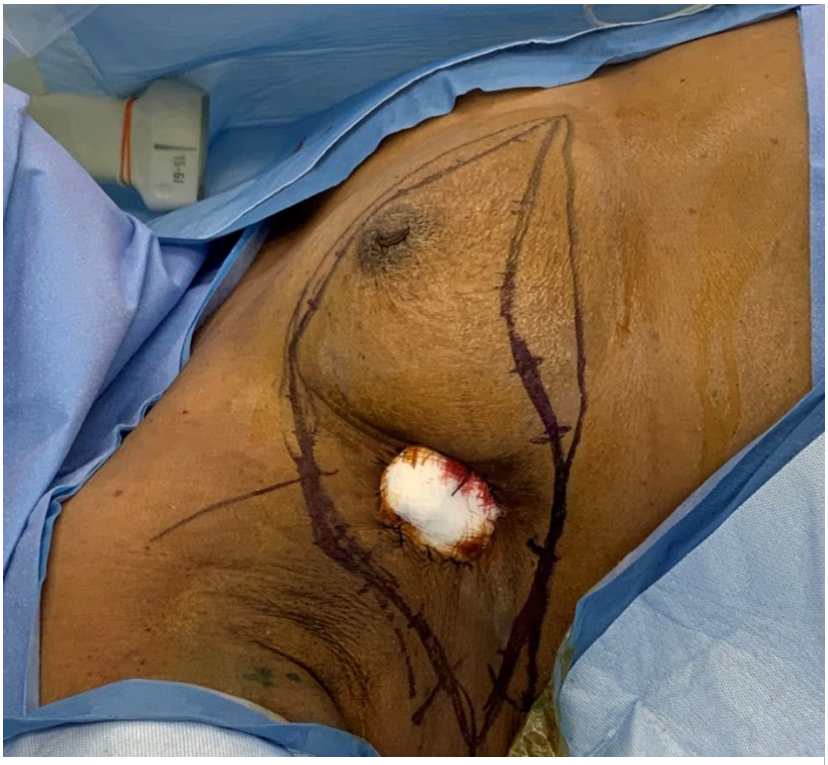


Figure 3: Drawing of an incision for a right breast T4c tumor, which includes the tumor with a 2 cm skin margin as well as the nipple-areolar complex.

(3) Surgery in detail

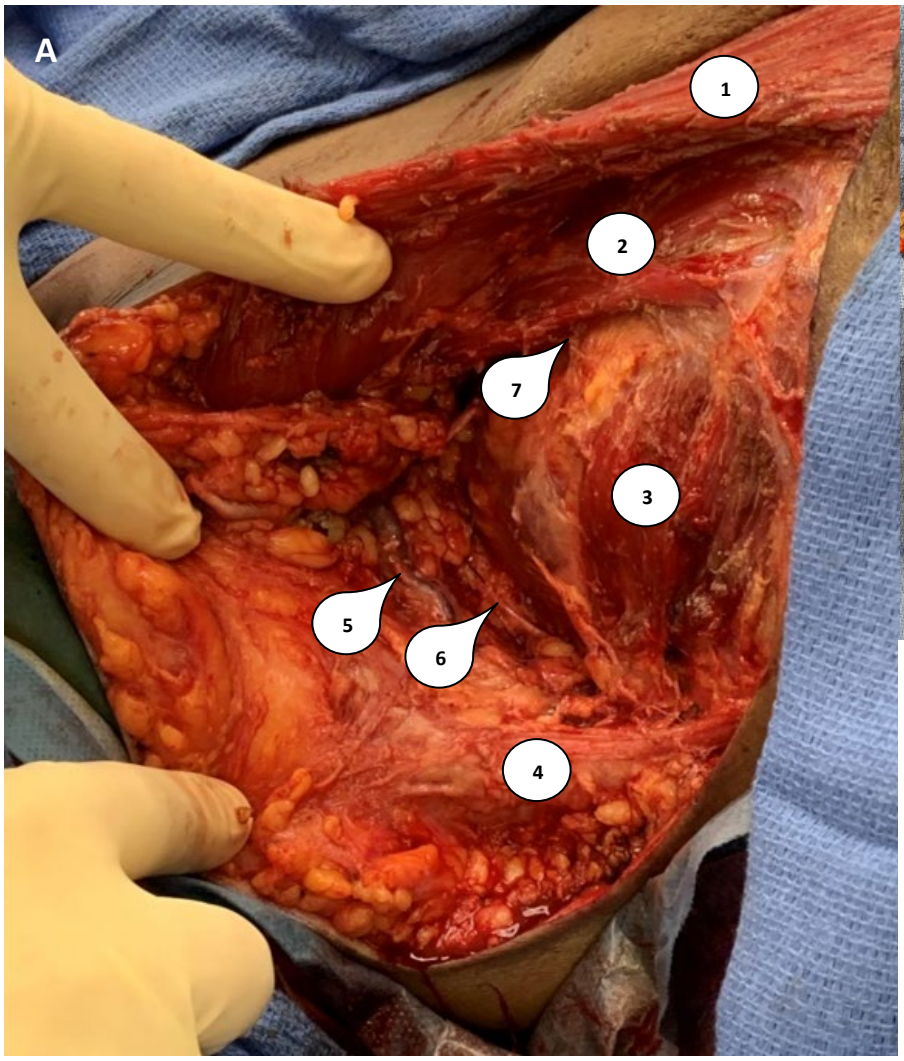
After incision, skin hooks or towel clips are placed at the edge of the skin flap, and traction, perpendicular to the plane of dissection, is applied – the skin should be raised "straight up" in 90 degrees to the chest wall. On his part, the operating surgeon creates counter-traction on the breast parenchyma to provide good visualization of the a-vascular plane, just between the subcutaneous fat and the breast parenchyma and fat. This anatomical plan should be followed while maintaining an even thickness to the skin flap. The aim is to maintain the skin flap's blood supply and to avoid "button-holing" the flap; the "upward" tension on the skin flap is central to avoiding this back walling. Skin flap thickness varies between patients and depends on their age and body habitus, and it would ideally be 6-8 mm. A technique that is very helpful in facilitating the identification of this avascular plane is using Hagar dilators to identify and create this space. Hagar dilators are introduced in increasing diameters (19 to 44 French) into this potential space with one hand, while the second hand is used to produce counter-traction on the skin. Then the skin flap is raised

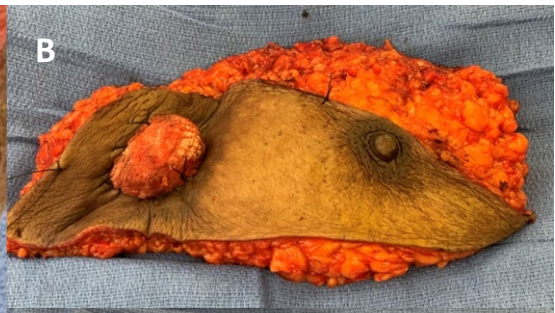
using retractors (such as S-retractors) introduced into the holes created by the dilators, revealing the subcutaneous bridges, including Cooper's ligaments, to be dissected.

After separation of the breast tissue from the skin flaps, cranially up to 2 cm inferior to the clavicle, medially up to the lateral border of the sternum and inferiorly down to the inframammary fold, and laterally to the latissimus dorsi, separation of the breast from the chest wall commences. Dissection is carried, at the superior aspect of the breast, down to the pectoralis major muscle to identify its fibers. Then the breast is dissected off the pectoralis major, with caudal traction on the breast tissue, dissecting parallel to the pectoralis fibers. Some would argue that dissection should include the pectoralis major fascia, a practice that would minimize the possibility of leaving breast tissue behind, while others would argue that this practice is oncologically unwarranted and would produce more persistent seromas. During dissection, the surgeon should avoid injury to the perforating intercostal branches of the internal mammary artery along the medial border of dissection. Once the breast has been dissected off the pectoralis major muscle, attention is turned toward the lateral border and the axilla. To note, when there is involvement of the pectoralis major (or minor) muscle by tumor, it is no longer advocated to perform a classic Radical Mastectomy, in which these muscles are excised in their entirety. Rather, a resection of only the involved portion of the muscle, *en bloc* with the breast and tumor specimen, ensuring negative gross margins, is performed.

When performing a simple mastectomy with no dissection of the axillary content, at this point, the specimen is dissected away from the lateral aspect of the chest wall without entering the axillary space. Still, up to 35% of simple mastectomy specimens have been shown to include axillary lymph nodes[16]. When performing a standard Modified Radical Mastectomy, level I and II axillary nodes are dissected *en bloc* with the specimen (Figure 4). The axillary dissection starts

by separating the specimen from the lateral aspect of the pectoralis major and minor muscles and defining the most cranial aspect of dissection as the axillary vein. During this dissection, attention should be given to the medial pectoral bundle enervating the pectoralis major and minor muscles. Sacrificing this innervation would cause eventual atrophy of the pectoralis muscles. The axillary content is swept off the chest wall from medial to lateral. This is done, while preserving the fascia of the serratus muscle, with motions that are cranial to caudal. This will lower the chance of injury to the axillary vein and will allow a safer identification and preservation of the long thoracic nerve (innervating the serratus muscle, the injury of which will cause a “winged scapula”) and, more posteriorly, the thoracodorsal bundle (lying over and supplying the central level of the latissimus dorsi muscle). After separating from the chest wall and these nerves, ensuring the nerves are well visualized, the specimen is separated from the remainder of the latissimus dorsi muscle. During this dissection, identification and preservation of the intercostobrachial nerve(s), coursing from medial to lateral, should be attempted whenever they are not grossly involved. This will preserve sensation in the medial aspect of the arm and axilla. The specimen should be oriented before removal from the field.





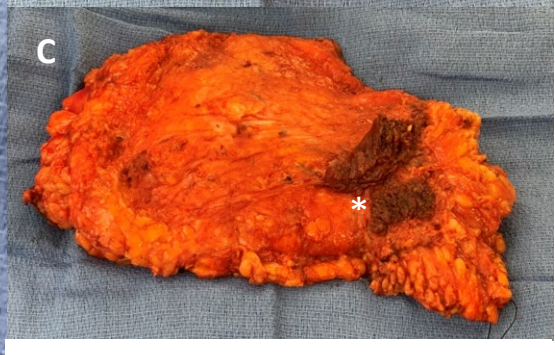


Figure 4: Post mastectomy cavity and specimen. (A) Cavity:
1. Pectoralis major muscle
2. Pectoralis minor muscle
3. Serratus muscle
4. Latissimus dorsi muscle
5. Thoracodorsal nerve and vessels
6. Long thoracic nerve
7. Medial pectoral bundle
(B) Anterior aspect of specimen
(C) Posterior aspect of specimen with pectoralis and serratus muscles enbloc (*)

Special considerations

(1) In the rare occasions when a classic radical mastectomy is warranted, after the creation of the skin flaps, attention is given to exposing the humeral insertion of the pectoralis major muscle at the superior-lateral aspect of the wound. After its exposure and transection, which can be facilitated by encircling the muscle with an index finger, the pectoralis major is rotated medially, and dissection continues along the cranial border of the muscle and its attachment to the clavicle. Then the tendinous insertion of the pectoralis minor muscle to the coracoid process is dissected

in the same manner, avoiding injury to the axillary vein. Both muscles are rotated medially and are dissected off the chest wall. On the lateral border, the medial pectoral nerve, innervating both muscles, is identified and ligated, and as dissection continues, the lateral pectoral nerve (which is located more medial and superior) is likewise identified and ligated. The dissection is continued on the medial aspect, freeing the pectoralis major from its medial insertions into ribs 1-6 and the pectoralis minor from its medial insertions into ribs 2-5. Placement of the surgeon's hand posteriorly to the specimen, retracting inferior-laterally facilitates the dissection. As s/he advances, the surgeon will encounter multiple perforator vessels, such as the intercostal arteries and the branches of the lateral thoracic artery. These vessels should be identified and ligated. This dissection will naturally include Rotter's nodes and will expose the axillary content with full visualization of the axillary vein up to the level of Halsted's (costoclavicular) ligament.

(2) When gross involvement of level III nodes is suspected, an extended dissection of level III nodes should be considered. This could be done by using the Patey technique[24]. It includes the removal of the pectoralis minor muscle for better access to clearing level III axillary nodes. This makes pectoral nerve preservation more challenging. In such cases, the ipsilateral shoulder is positioned in abduction into the field, held by the assistant, and giving relief to the brachial plexus. The borders of the pectoralis minor are digitally delineated, and its insertion into the coracoid process is defined and divided. An index finger can be placed between the muscle and the brachial plexus for its protection during this division. The muscle is dissected off the chest wall until its separation from its insertions to the ribs 2-5. Great attention should be given to the medial and lateral pectoral nerves penetrating the pectoralis minor, in attempting to preserve them during this dissection. After separating the pectoralis minor, dissection of the axillary lymphatic content commences cranial to caudal from the anterior and inferior aspect of the

axillary vein. Dissection superior to this vein may cause harm to the brachial plexus. The most super-medial aspect of dissection is the Halsted's (costoclavicular) ligament, which should be marked with a clip. All loose areolar and lymphatic tissue inferior to these structures is swept off the chest wall while preserving the fascia of the serratus muscle and down to the latissimus dorsi while preserving the long thoracic and the thoracodorsal bundles, as described above for a standard modified radical mastectomy or an axillary dissection alone.

Wound closure

After thorough irrigation and hemostasis are achieved, the wound is ready to be closed. Most recommend the placement of either one or two closed-suction drains through an incision in the lateral aspect of the inferior flap. The drain should be left in the dependent part of the wound towards the axilla, reaching up to 2 cm from the axillary vein. If a second drain is used, it is placed in the inferior portion of the pectoralis muscle towards the medial aspect of the wound.

The wound is then closed with one or two layers. We recommend closing with a single layer of continuous subcuticular 3-0 PDS, but any absorbable or non-absorbable suture should work (Figure 5). Tension on the suture line should be avoided. There are several solutions for large wound gaps. The most simple and surprisingly effective solution would be to extend the skin flaps both

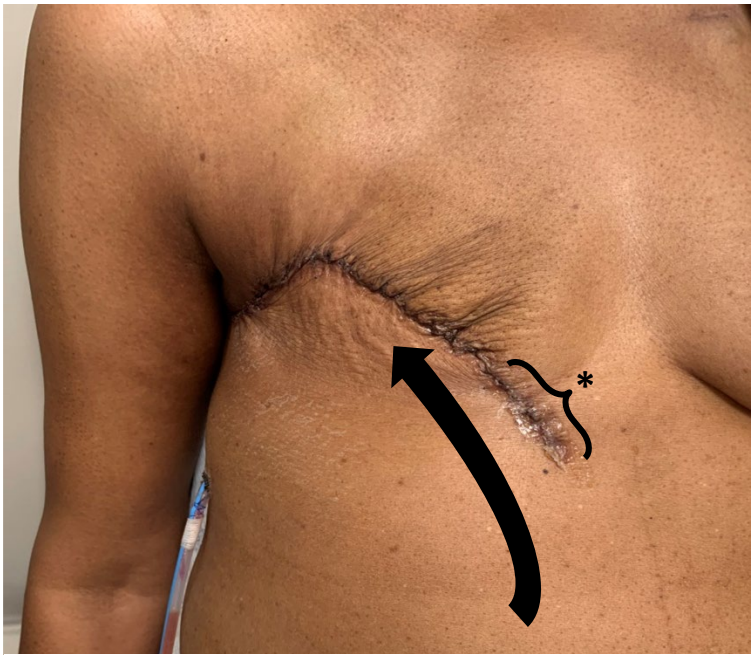


*Figure 5: Wound closure, demonstrating an inferio-medial elongation of the medial incision (indicated by *), to allow flap rotation (indicated by an arrow) and skin closure*

cranially above the clavicle and caudally much below the inframammary fold to alleviate the tension on the flaps. The medial aspect of the incision can also be extended inferiorly and slightly medially to facilitate rotation of the inferior flap. These maneuvers are usually sufficient to close most mastectomy wounds. In extreme situations with extensive resections due to very advanced disease, more extensive skin or myocutaneous flaps could be mobilized, or skin grafts could be used.

Post-Operative Care and Complications

In the postoperative period, dressings should remain for 24-48 hours and then be removed. The drains should stay in place for 5-7 days and until each one accumulates less than 30 ml over 24 hours. Vigorous movement of the arm and its extension should be avoided until the drains are removed. Nevertheless, it has been proven that early physical therapy in the postoperative period significantly contributes to patients' return to normal arm function as well as to the reduction of pain and improvement in their quality of life without an increase in post-operative complications[25,26]. Therefore, we recommend that active rehabilitation with range of motion exercises should be strongly encouraged after drain removal.

Immediate complications

- Bleeding, which might necessitate a return to the OR for hemostasis. The chance for bleeding can be minimized by through hemostasis in the OR, including ligation of non-bleeding vessels, before wound closure.
- Wound dehiscence and/or flap ischemia and necrosis. When there is no full-thickness necrosis of the flaps, this complication can usually be managed conservatively, with wound care and office debridement when necessary. More extensive cases might need to return to the OR for debridement and irrigation if the local conditions do not allow for closure with a local flap; the wound might be left open for secondary healing or a delayed closure, either primary or with a skin graft. The chance for this complication can be

minimized, first, through meticulous dissection, preserving the blood supply of the skin flaps by preserving an adequate flap thickness and by preserving the perforators, and second, by making sure the wound is closed with no tension.

- Seroma accumulation and possible infection, necessitating drainage and possibly antibiotic treatment.

Late complications

- Lymphedema
- Frozen shoulder or loss of range of motion or function of the ipsilateral arm. This complication can be minimized through dedicated and persistent range of motion exercises, starting gradually in the early postoperative period. In addition, minimizing post-operative pain through the use of local analgesics during surgery, Enhanced Recovery After Surgery analgesia protocols, and trigger-point injections of local anesthetics when needed[27].
- Nerve injury resulting in functional disability, most noted is the "winged scapula" deformity due to injury to the long thoracic nerve.
- Chronic pain, which can be minimized by the above-mentioned recommendations.

Summary

- Choice of surgery is dependent on the extent of the disease, but also on the availability of adjunct treatment modalities, namely radiation and sentinel lymph node biopsy.
- When adjunct modalities are lacking or in the presence of locally advanced disease with positive axillary nodes, the modified radical mastectomy is the "golden standard."
- Modified radical mastectomy encompasses the excision of the breast, including the nipple-areolar complex, as well as the axillary level I and II content, and is equivalent in terms of oncological outcome to the radical mastectomy, in which the pectorals major and minor muscles are excised.

- The borders of dissection include the lateral border of the sternum medially, the clavicle superiorly, the inframammary fold inferiorly, and the anterior border of the latissimus dorsi muscle laterally.
- Variations on mastectomy can include removal of level III lymph nodes (when involved), utilizing the Patey technique, and inclusion of involved muscle structures, without a formal radical mastectomy.
- When choosing an incision one must consider the location of the tumor and level of skin involvement, its location in relation to the nipple-areolar complex, and the ability to approximate the skin flaps and smoothly close the wound.
- When wound closure proves difficult, extending the dissection of superior and inferior skin flaps and extending the incision to create a rotational flap would be sufficient in most cases.

Video reference (Youtube)

Modified radical mastectomy: www.youtube.com/watch?v=dD2emF1E5S8

Modified radical mastectomy: www.youtube.com/watch?v=ObkeBBQCH1U

Explanation for patients: www.youtube.com/watch?v=wQcAnmx_wU8

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Chapter 22

Breast Conservation Surgery and Oncoplastic Techniques in Low- and Middle-Income Countries

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Case Presentation

A 50-year-old female presented after an abnormal screening mammogram of the left breast. Diagnostic imaging showed a suspicious cluster of calcifications at 2 o'clock, 11 cm from the nipple. A stereotactic biopsy confirmed the presence of ductal carcinoma *in situ* (DCIS), grade 1, with positive hormone receptors. She had no suspicious findings in the right breast, confirmed by clinical exam, mammogram, and MRI. The patient elected to proceed with a left breast ultrasound-guided partial mastectomy with tissue rearrangement, left sentinel lymph node biopsy, and right reduction mammoplasty for symmetry. At the time of the initial clinic visit, a round clip was placed in the biopsy site hematoma for operative visualization.

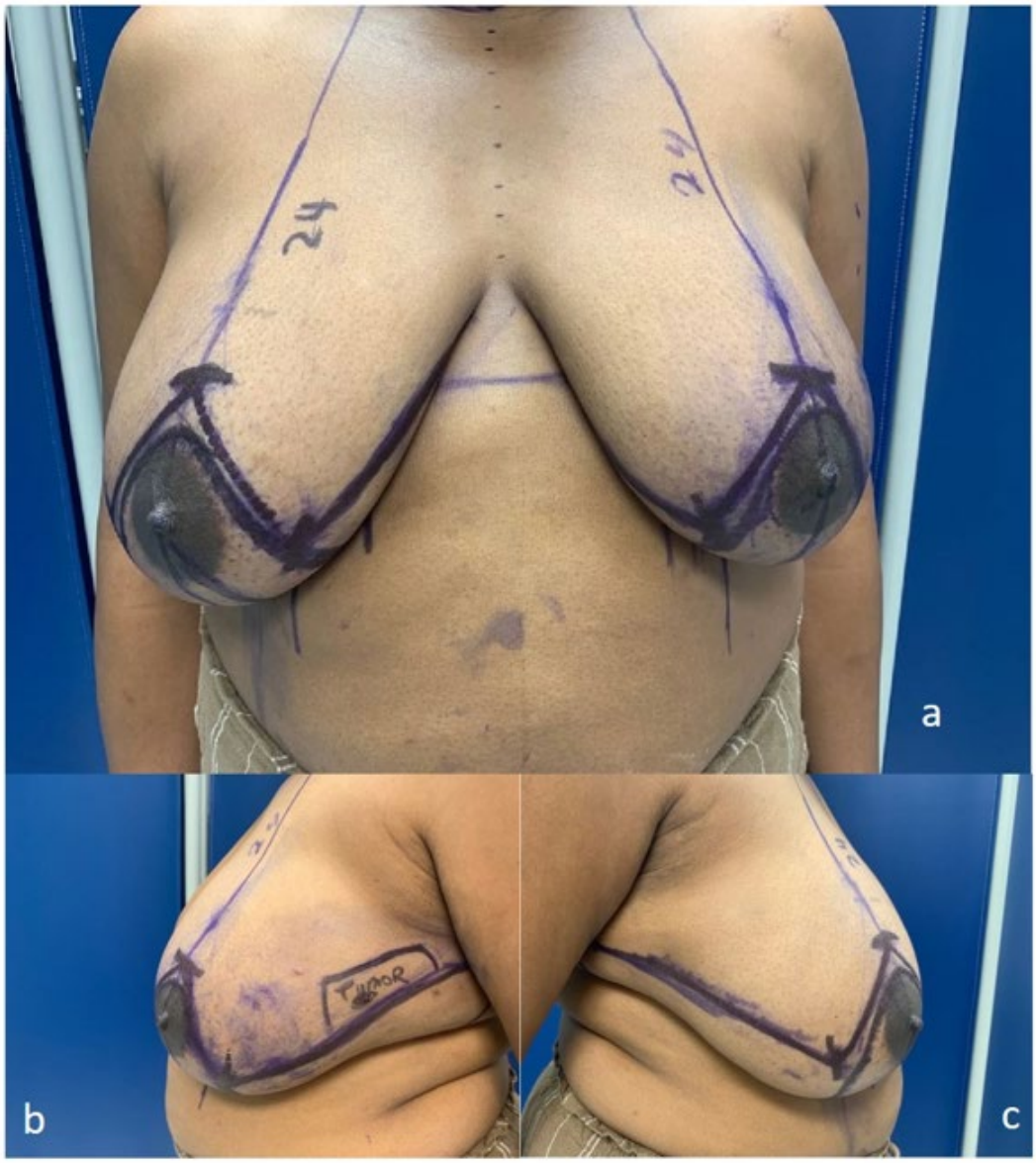

Figure 1. Surgical markings are done in the upright position and photographically documented. a) Completed markings. b) Lateral view ensuring with ultrasound or other technique that the tumor is encompassed within excision triangles. c) Contralateral lateral view.

The patient was marked in the clinic in the upright position on the day prior to surgery (Figure 1). The ultrasound was used preoperatively to verify that the cancerous lesion was encompassed within the markings.

The patient's surgery was completed, and she was discharged home postoperatively (Figure 2).

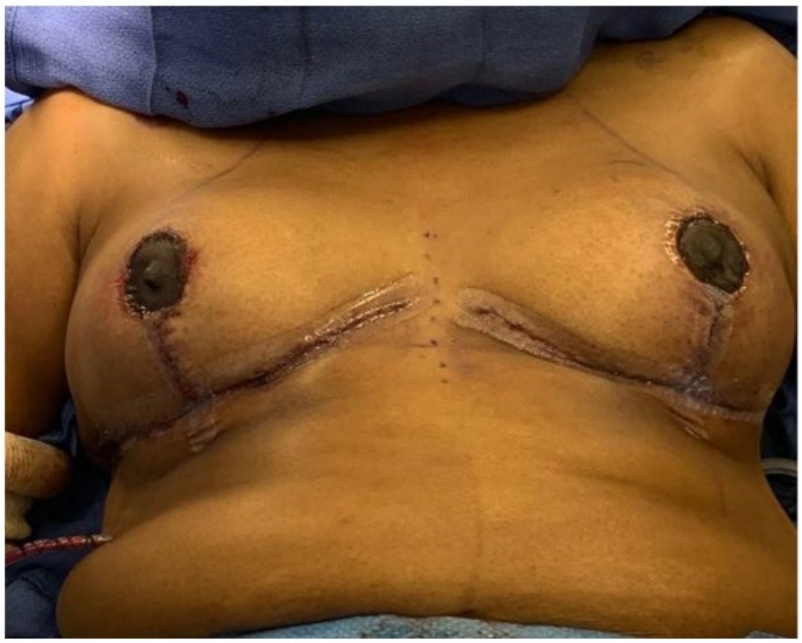

Figure 2. Immediate postoperative results.

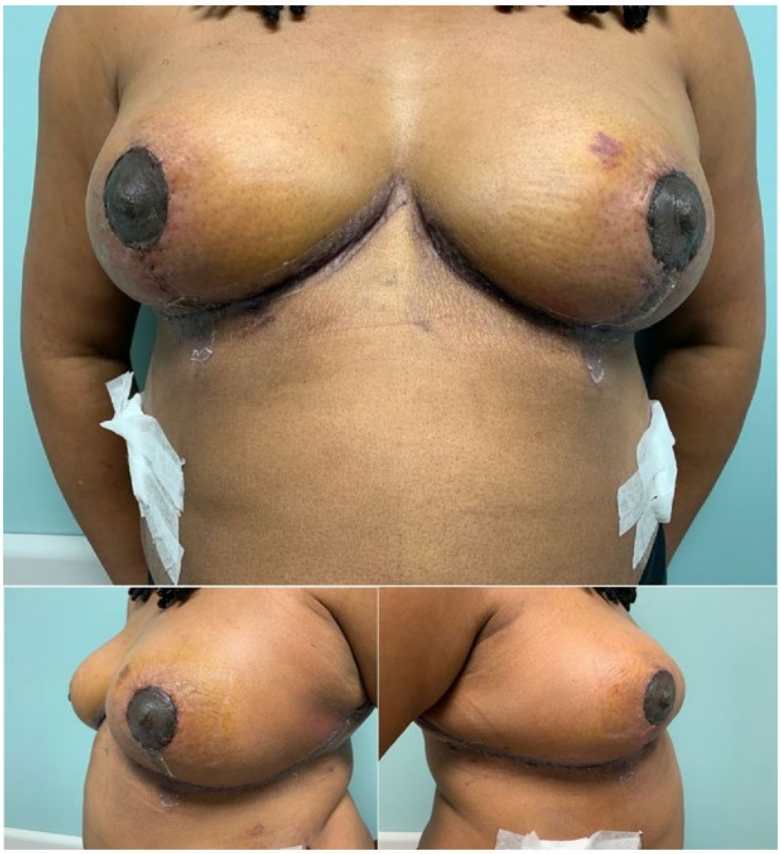

Figure 3. Results at 2 weeks postoperatively, after drain removal.

The first follow-up visit was on postoperative day #7 (Figure 3), at which time her bilateral drains were removed. Final pathology confirmed the presence of 12 mm of DCIS, grade 2, and that the specimen margins were widely negative. Post-surgical treatment multidisciplinary recommendations included endocrine therapy with tamoxifen and adjuvant radiation therapy (XRT). Her surveillance plan included a left-sided diagnostic mammogram six months after her surgery, along with a physical exam of bilateral breasts and a bilateral mammogram due one year from her prior bilateral mammogram.

Introduction

While this technique has been utilized to some extent since the 1920s, breast conservation surgery (BCS) rose in popularity in the late 1980s and early 1990s when multiple studies were published demonstrating the equivalency of local recurrence following both total mastectomy and partial mastectomy plus XRT[1-4]. The data additionally showed a benefit in quality of life for the patients. However, over the last three decades, barriers to this therapy have also come to light. In this chapter, we will discuss how the principles of BCS, global obstacles to BCS, and the rise of oncoplastic techniques have allowed patients to have better acceptable cosmetic outcomes and the ability to achieve breast symmetry. These options have made the choice to save the breast tissue more appealing to patients.

Breast conservation surgery is defined as surgical management of breast cancer without removal of the entire breast while including evaluation of the axilla if indicated and the addition of XRT for locoregional control. The addition of XRT is contingent on tumor characteristics, patient age, tumor size, and the presence or absence of negative margins. The principles of this treatment include methods for tumor localization, standards for negative margins, and guidelines for XRT.

Dr. Bernard Fisher first published his breast-conserving approach to tumors up to 4 cm in size in a 1985 paper reporting data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 study.1 Results showed that at five years, segmental mastectomy to tumor-free margins followed by breast irradiation is appropriate therapy when compared to total mastectomy. This publication was followed up by 8-year, 12-year, 15-year, and subsequently 20-year results[5-8], which confirmed the initial data. These promising trials began the surge in the popularity of BCS. The findings were corroborated by multiple international trials[9,10]. With the

success of follow up studies, an international conference was held in 2005 in Milan, Italy, to further define an appropriate role for BCS[11]. A summary of the results of the randomized controlled trials comparing BCS to mastectomy is seen in Table 1.

Author	Follow-up (years)	Number of patients	Tumor characteristics	Local recurrence		Overall survival	
				BCS	Mastectomy	BCS	Mastectomy
Fisher, et al.[8]	20	1865	≤ 4 cm, any N	14.3%	10%	46 ± 2%	47 ± 2%
Litière, et al.[2]	20	868	Stage I-II (T1-T2, N0-N1)	9%	2%	39.1%	44.5%
Veronesi, et al.[3]	20	701	T1N0	8.5%	2.3%	41.7%	41.2%
Blichert-Toft,et al.[69]	20	793	Unifocal, any size, any N	5.9%	6.7%	42.5%	47.1%
Arriagada, et al[10]	15	179	T1, any N	13%	18%	73%	65%

Table 1. Randomized controlled trials comparing BCS with mastectomy.

Intuitively, early detection of breast cancer is an important component of BCS: the smaller the tumor, the greater the chance of being a candidate for BCS. The combination of removal of the tumor with the addition of XRT, in most cases, supports the concept that less locoregional advancement increases BCS candidacy. Per the World Health Organization (WHO), "The objective is to identify the disease at the earliest possible opportunity and link the patient to diagnosis and treatment without delay."[12] This process includes education on symptoms and access to care, early detection with screening or evaluation if a mass is noted, followed by expedited physician evaluation, diagnosis, and access to treatment. This may shift the focus in low-middle income countries (LMICs) from screening to early detection to keep BCS as an oncologically safe practice. Unfortunately, most LMICs suffer from a lack of specialists. The promotion of early education and the knowledge of when to seek evaluation for breast changes is

often overlooked. The option for BCS is rarely available secondary to disease presentation, availability of XRT, or the surgeon's preference or experience.

With the focus on improving surgical outcomes came a better understanding of the mobility of the breast via displacement of breast tissue after the removal of the index tumor with negative margins. BCS outcomes have become more apparent and acceptable. The integration of tissue displacement and hidden scar techniques has become the procedure of choice for surgeons and patients across the globe, subsequently referring to the description of the procedure known as oncoplastic approaches to BCS. The term "oncoplastic" was coined by Dr. Werner Audretsch as a new method to achieve better aesthetic and quality-of-life outcomes than traditional BCS techniques while minimizing morbidity. After these new practices were first popularized in the late 1990s, surgeons began asking, "Are these techniques oncologically safe?" While they were eventually proven to be such, access to this type of training and care is highly variable across the globe.

Breast Conservation Surgery

Definition

Breast conservation surgery was well defined in the aforementioned 2005 international breast conference as "the complete removal of the breast tumor with a concentric margin of surrounding healthy tissue, performed in a cosmetically acceptable manner ("lumpectomy"), usually followed by radiation therapy. While the status of the margins as negative has been agreed upon by all, the definition of negative margins has varying definitions. The American Society of Breast Surgeons (ASBrS), the European Society for Medical Oncology (ESMO), and the NSABP define negative margins as the absence of tumor cells on the ink used to mark the

excised specimen[13,14]. In the case of DCIS, the Society of Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO) consensus statement defines appropriate margins as two millimeters[15].

Eligibility

There are some relative and absolute contraindications to BCS. Intuitively, these are patients with contraindications to radiation therapy or patients with large tumors relative to their breast size that cannot be down-sized by neoadjuvant chemotherapy (NACT) or neoadjuvant endocrine therapy (NET). A large Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that in patients with the same tumor characteristics, 65% of those who received NACT opted for BCS versus 49% of those who received adjuvant chemotherapy (ACT). However, downsizing with NACT was associated with increased local recurrence with no association with distant recurrence or breast cancer mortality[16]. There are also other cancer- and system-related factors that favor candidacy for this therapy.

Tumors that are favorable for BCS include smaller lesions relative to the size of the breast, monocentric tumors, and tumors that surgeons are able to localize[17]. There is no absolute size definition that will rule out BCS candidacy. Cosmetic acceptability should be discussed and plays a major factor in some patients' decisions, as well as their acceptance of the benefit of XRT. Favorable cosmetic results are one of the principal foundations of breast conservation therapy. Each case must be individually tailored to the patient's tumor size relative to breast size, as well as the existing or desired symmetry. In any case, screening imaging leading to early detection can increase eligibility as tumors are usually found at a smaller size when this is utilized. Tumor monocentricity is also important for cosmesis of the breast tissue, as the contour can be challenging to preserve if tumors are removed from multiple quadrants. Tumors are

considered monocentric if there is just one focus of the tumor or if multiple tumors are confined to the same quadrant of the breast. Finally, the cancer must be able to be localized via one of many techniques, which will be discussed in a later section.

Absolute contraindications to BCS include diffuse disease throughout the breast, pregnancy in specific trimesters, or history of XRT to the area. As mentioned above, multicentric disease or a large span of tumor or calcifications can lead to poor cosmesis upon excision if trying to save the breast. Tumors are considered multicentric if there are multiple malignancy foci in separate breast quadrants. If an acceptable cosmetic outcome is achievable, however, some increased risks are still involved with extended radiation boosts or multiple boost fields during adjuvant therapy[18]. Radiation boosts will be discussed in more detail in a separate section. Locally advanced disease may still be eligible for BCS, even with skin or nipple retraction. However, the cosmetic result of excising skin or the nipple must be considered.

Patients with prior chest radiation are not candidates to receive additional radiation treatment, hence discounting their eligibility for BCS. These are most likely patients with a history of another malignancy, such as lymphoma, or of another primary breast cancer for which they already underwent BCT. Mantle radiation for lymphoma encompasses a field including the mediastinum via the anterior chest wall due to the presence of disease in mediastinal lymph nodes. With current technology, the field includes the lateral and upper breasts and the axillary tail, with scatter to the medial, central, and lower breasts[19]. A history of ipsilateral breast cancer with BCS often includes previous radiation to the whole breast. Advancements in partial breast radiation therapy may make it possible to change this from an absolute to a relative contraindication.

Certain stages of pregnancy can exclude a patient from being a candidate for BCT as well. The use of radiation in pregnancy is typically avoided in order to minimize risk to a developing fetus. A typical regimen of 50 Gy to the breasts and chest wall may expose the fetus to about 0.05-0.15 Gy depending on which stage of pregnancy the treatment occurs in. The progression of the fetus may bring him or her closer to the field and increase the dose up to about 2 Gy[20]. Exposure to radiation during the critical periods of organogenesis may have more severe effects than if these same doses were given later in pregnancy. While successful radiation treatment during pregnancy followed by healthy deliveries has been reported, no sufficient data exists for its routine use. Therefore, recommendations remain for no use of BCS in pregnancy's first and second trimesters. BCS can be considered during the third trimester if the adjuvant XRT can be delayed until after delivery, supporting its addition to BCS.

While the histologic subtype of breast cancer does not exclude one from breast conservation, it is generally not a recommended technique for inflammatory breast cancer. In general, NACT is utilized in these situations, and the surgical technique is based on response. If there is a good response to NACT, then BCS isn’t necessarily contraindicated. However, due to its overall rarity, inflammatory breast cancer has been historically treated by modified radical mastectomy when operable after NACT for optimal local control[21]. However, Brezinska et al. demonstrated that locoregional recurrence may only be dependent on the control of a widespread rather than a local process[22]. Further studies are needed before accepting BCS as a standard treatment for inflammatory breast cancer. We do not recommend BCS in patients with inflammatory breast cancer based on available data.

Patient age does not contribute to the selection of this type of treatment. Previously, patients less than 40 years old were considered too high of a recurrence risk to save their breasts. However,

data now supports that there is no increased risk of recurrence if a patient undergoes BCS versus mastectomy solely based on age[23,24]. Young age is now accepted as a prognostic indicator rather than a deciding factor for surgical management.

While no specific size cutoff is set for BCS, it comes as no surprise that early detection can increase the probability of being a candidate for the procedure. In low-middle-income countries (LMICs), screening mammography may not be available. Patients may present with T1 or T2 lesions, and ultrasound can be performed for evaluation. The concordance of these images is established with the clinical exam and any follow-up imaging. By all means, the patient with locally advanced disease can still be a candidate for BCS based on tumor size, axillary evaluation, and availability of a surgeon with appropriate expertise. In many areas, the use of screening mammography may not be available, and the presentation of breast cancer as locally advanced may preclude BCS and lead to a higher risk of local recurrence associated with higher mortality. As alluded to, a significant contributing factor to this is due to the advanced stage at which breast cancer is often diagnosed. LMICs are widely varied in access to resources and goals in screening. In areas where mammography is not widely available, breast self-examination (BSE), done by the patients themselves, and clinical breast examination (CBE), done by a clinician, are promoted as early detection tools. Despite efforts for education, the rates of women undergoing self- or clinically-administered breast examinations remain below 24% (3-24% for BSE[25,26], 12.5% for CBE[27]). Often, providers evaluating patients do not have the resources to look with tools such as ultrasound. Ultrasound can often delineate masses that are solid, cystic or appear suspicious. The ability to look can play a significant role in decision-making and early detection in this setting[28].

Additionally, many LMICs lack unified recommendations. Starting ages for screening mammography vary by over 15 years[29-31]. Availability of mammograms is not the only factor that determines an individual's access to screening and diagnostic mammograms. Large percentages of women in areas where mammography is opportunistically available have never had a mammogram. These women tend to be of lower socioeconomic status and have lower levels of education[29,30]. Within a country or even a region, subpopulations based on socioeconomic class have disparities in BSE, CBE, and mammography[34], which correlates with later diagnosis and higher mortality[35].

Localization Techniques

As mentioned above, one of the main factors in BCS is the ability to localize the tumor. The placement of a marker clip at the time of biopsy is beneficial for the localization of non-palpable tumors as well as confirmation of specimen location. Palpation-guided surgery is a limited technique and is often augmented by the use of other techniques.

Intraoperative ultrasound can be used on its own or as an adjunct to palpation-guided BCS. The Cosmetic Outcome of the Breast After Lumpectomy Treatment (COBALT) trial randomized patients with early-stage palpable invasive breast cancer (IBC) who were planning to undergo BCS to either ultrasound-guided or palpation-guided surgery[36]. One hundred thirty-four patients with comparable tumor characteristics underwent randomization. Resection margins were negative in 97% of patients in the ultrasound-guided group compared to 83% of those in the palpation-guided group, which was statistically significant. Ultrasound reduced the need for further excision and improved cosmetic outcomes. Colakovic and colleagues corroborated these results and demonstrated the usefulness of ultrasound in minimizing acceptable excision volumes[37].

Needle localization (NL) is the most commonly utilized and oldest form of detection for a non-clinically detectable lesion.[38] These are generally mammographically- or MRI-detected lesions that require three-dimensional localization provided by the multiple views given via these imaging techniques. This is their main advantage. There are multiple needle gauges and lengths with different wire hook devices to secure it in place, depending on the manufacturer of the device[39]. A radiologist is generally required for placement due to mammographic guidance, although a surgeon can place the device if a stereotactic setup is available to them. Ultrasound guidance can be used, but in that case, the tumor or biopsy site changes are generally visible on ultrasound, and a needle may not be necessary. Disadvantages of the NL technique include requiring a separate procedure on the day of operation, potentially involving a different department or facility, and displacement or migration of the wire or dislodgement during transport. Other commonly discussed complications are vasovagal reaction during placement, longer surgery time, retained wire fragments, and increased cost to the patient[40].

Many other non-wire devices are becoming more popular due to the previously mentioned disadvantages. However, these are subject to availability in LMICs and the expertise of the surgeon and radiologist for placement. Radioactive seed localization can be performed up to 5 days prior to surgical excision. A 5 mm ^{125}iodine gamma-impregnated seed device is placed within the lesion under radiologic guidance. A specialized hand-held gamma probe is used to guide excision and to confirm no remaining radiotracer within the remaining breast tissue[41]. The major advantage of this is the decoupling of the radiology and surgical appointments, although it still requires them both. The disadvantages are mainly the regulations that come along with radioactive implants and their potential loss or inability to retrieve them, although these may

vary internationally. This localization technique has been demonstrated to be non-inferior to NL with regard to margin negativity and may have the benefit of lower resection volumes[42].

Magnetic seed placement is a technique similar to the radioactive seed, requiring radiologic assistance. However, these seeds can be placed much longer prior to surgery, potentially at the time of the original biopsy, in place of a marker clip. There is no signal decay as seen in radioactive seeds. This 5 mm magnetic seed can be localized with a specialized hand-held detector, which can also estimate the distance between the seed and the probe. This technique has been demonstrated to be non-inferior to NL as well[43]. A major disadvantage of this technique is the inability to use metal instruments due to interference with the signature.

Radiofrequency identification (RFID) is unique as each implantable clip has its own signature. The placement technique is similar to the other seed placements, although the device is larger (1.2 cm), and it can also be done further in advance than the radioactive seed due to lack of signal decay. Again, this technique requires a specialized probe to identify the appropriate lesion or lesions. A significant benefit to this particular technique is that each clip has its own signature. Specific identification of different lesions within the same breast or within the ipsilateral axilla can be easily done. Each one of the seed techniques had advantages over NL, the most important being decoupling from radiologic appointments. However, each also has a distinct extra cost in equipment purchases and training that may outweigh that advantage. Secondary to cost and availability, they are rarely utilized in LMICs.

Ultrasound may not be useful in the identification of non-mass abnormalities, including calcifications. However, it can identify post-biopsy clips or remnants from a biopsy, such as a hematoma or tissue disruption, potentially eliminating the need for the expensive and time-

consuming techniques mentioned above. Hematoma-directed ultrasound-guided (HUG) BCS was shown to be superior to NL with a lower incidence of positive margins[44]. However, the main limitations are available intraoperative equipment and surgeon training.

BCS requires lesion localization, especially in non-palpable tumors. There is no one perfect localization technique. However, accessibility of specialized equipment and potential radiologic consultation can be limiting factors in the availability of BCS across the globe.

Intraoperative and Pathologic Assessment of Margin Status

Margin status has been a widely debated and changing recommendation over the development of breast cancer surgical care and BCS. The current recommendations for IBC suggest that there be no tumor on the inked margins after marking for pathologic evaluation. For DCIS, the majority of experts support the consensus that there needs to be 2 mm of tumor negative margins on all sides of the specimen[45]. The question then becomes how a surgeon can be sure to get the appropriate margins intraoperatively to minimize the need to return to the operating room for a second procedure.

Specimen radiography is the most commonly employed modality to assess adequate removal of lesions and, sometimes, margin status. In addition to being able to visualize a mass or calcifications via this method, the location of the previously placed clip within the specimen can guide the need for further selective margin resection. For example, a centrally located clip may not require further margin excision while a clip located in the periphery of the excised specimen may dictate the need for a more extensive resection (Figure 4).

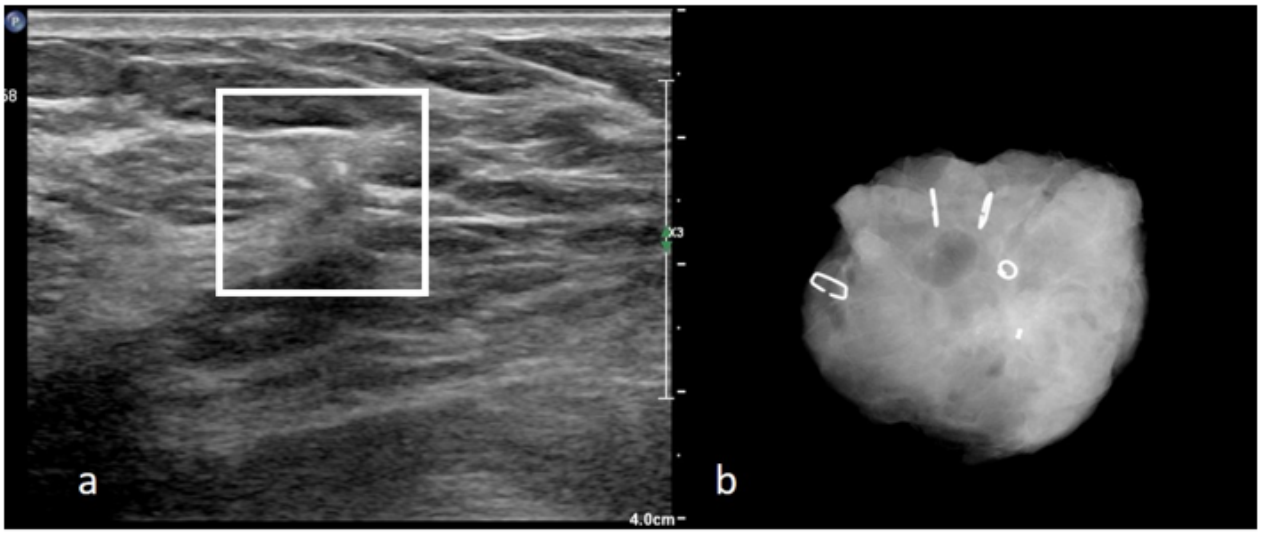

Figure 4. Intraoperative imaging of partial mastectomy specimen. a) Demonstration of the round ultrasound clip visible within the specimen (outlined). The round clip was placed preoperatively to aid in specimen identification. b) Confirmation of biopsy clips in the central portion of the excised specimen away from the margins. Skin staples are used (2 superior and 1 lateral) to orient the surgeon based on the image.

Orientation of the specimen is crucial to this technique for identification of a close margin, which can be done by suture, staples, ink, or any combination of these. Specimen imaging can be done by sending the specimen for an outside radiograph or by using an intraoperative specimen X-ray machine. These can be 2D or 3D images based on the available technology. Newer technologies are being developed to evaluate margins intraoperatively.

Additional cavity shave margins have been studied in depth. These margins are defined as a thin piece of tissue taken circumferentially around the specimen cavity. The use of circumferential shave margins was evaluated by Chagpar et al. This trial showed a significant decrease in the occurrence of positive margins with the use of additional shave margins as well as no significant increase in the tissue resection volume[46].

Overview of Breast Radiation Therapy

Adjuvant XRT is a key feature of most BCS. While there are select cases in which radiation therapy may be omitted, this is generally the exception rather than the rule. In 1976, Fisher et al. began studying the outcomes of total mastectomy versus partial mastectomy alone versus partial mastectomy followed by breast irradiation. The short-term follow-up of five years showed noninferiority of partial mastectomy among the outcomes of disease-free, distant disease-free, and overall survival. The long-term 20-year follow-up demonstrated that the addition of adjuvant radiation therapy decreased the ipsilateral in-breast tumor recurrence (IBTR) rate from 39.2 to 14.3 percent. This outcome was corroborated by multiple other studies[47-49]. The EBCTCG studied over ten thousand patients across 17 trials to determine that "radiotherapy to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth"[50]. Thus, the main benefit of radiation therapy in an adjuvant setting is to decrease the rate of locoregional recurrence (LRR) with a secondary goal of improved survival.

Whole-breast radiation therapy (WBRT) is the most commonly used technique. WBRT consists of the delivery of 1.8 to 2 Gy delivered daily over the course of 4-5 weeks for a total of 45 to 50 Gy. Hypofractionated radiotherapy has been studied in comparison to WBRT. This technique consists of a lower total dose comprised of fewer, larger single doses or fractions. The United Kingdom Standardisation of Breast Radiotherapy (START) trials demonstrated that regimens of 39-41.6 Gy in 13 fractions over five weeks (START-A) or 40 Gy in 15 fractions over three weeks (START-B) are as effective as the standard WBRT dose. Ten-year follow-up showed that the shorter schedule in START-B had significantly lower distant recurrence (12.3% vs. 16%, p 0.014), any breast-cancer-related event (18.3% vs. 22.2%, p 0.022), and all-cause mortality

(15.9% vs. 19.2%, p 0.042). There were similar outcomes for local recurrences (3.8% vs. 5.2%, p 0.10), LRR (4.3% vs. 5.5%, p 0.21), and no worse cosmetic outcomes[51]. Both WBRT and hypofractionated therapy include a boost of therapy to the tumor bed.

Accelerated partial breast irradiation (APBI) is another available modality for adjuvant treatment. Brachytherapy devices, such as intracavitary catheters, balloons, or seeds, are inserted into the surgical bed for delivery of therapy. Devices may be placed in the intraoperative or postoperative setting using a cavity seroma for guidance. These devices are then used to deliver low-dose rate (LDR) or high-dose-rate (HDR) XRT over a shorter period than that required for WBRT. LDR is typically an inpatient procedure, while HDR XRT is delivered twice daily for a 5-day period. The American Society of Radiation Oncology (ASTRO) compiled results from global randomized controlled trials to define suitable criteria for the use of APBI outside of the trial setting. The patients must be over 50 years old, have any invasive subtype or pure DCIS, tumors of 3 cm or less, margins 2 mm or greater, negative nodal status, estrogen-receptor (ER) positivity, and limited lymphovascular invasion (LVI)[52]. These criteria are still developing as new data emerges.

Global Access to Radiation Therapy

Almost all patients who undergo BCS will have the recommendation for radiation therapy. It stands to reason that the availability of BCS is strongly related to the availability of XRT to decrease LRR and increase breast cancer-related survival. Access to radiation therapy varies across the globe. The International Atomic Energy Agency (IAEA) Directory of Radiotherapy Centres (DIRAC) keeps a registry of institutions that maintain the capacity for XRT. As of February 2020, there are 12,227 linear accelerators available across the world, with a population

of over seven billion people. The need for radiotherapy where none is available can be identified by the number of machines per country population.

Access to radiation facilities in LMICs is scarce. The IAEA tracks the availability of radiotherapy machines per million people across the globe and compares the prevalence of these machines with the income status of the countries. Individual countries and availability of varied equipment can be assessed on their website, which is updated regularly[53]. Figure 5 shows the distribution of radiation machines across the globe by population.

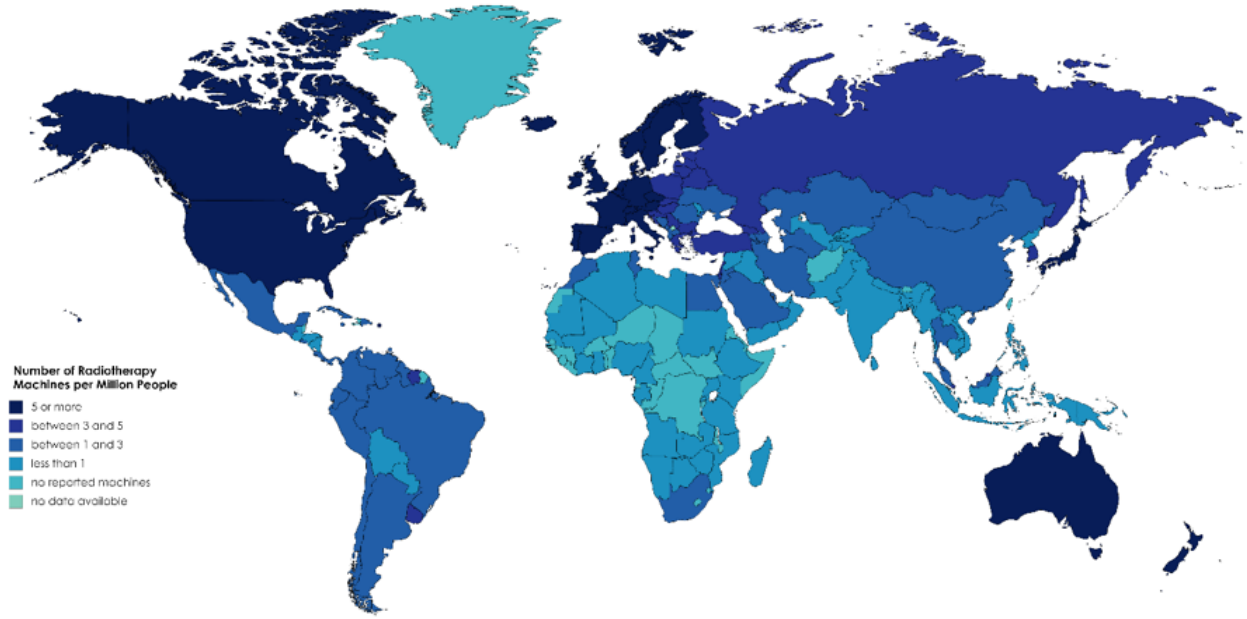

Figure 5. Number of radiotherapy machines per million people. Data for this figure was taken from the IAEA DIRAC[53].

Some regions, such as Latin America, note a linear correlation between gross domestic product (GDP) per capita and population per megavolt machine, whereas African countries have a weaker trend for correlation[54]. This suggests that financial resources are not the only constraint faced by regions such as this. Africa faces challenges to radiation access, such as poor referral systems, low awareness of cancer, social and political instability, and geographic distribution

compared to the travel ability of patients[55]. Access to radiation facilities across in LMICs is far from optimal.

Omission of Radiation Therapy

In LMICs where XRT is not readily available, or in the case that the patient elects not to proceed with radiation therapy, the patients must be counseled on the risk of recurrence. Liljegren et al. studied 381 women with stage I breast cancer to evaluate local recurrence. They were randomized to 184 women who received XRT to the breast and 197 who received no adjuvant XRT. At five years, the local recurrence rate was 2.3% in the group who received XRT and 18.4% in the group who did not. Overall survival did not differ between the two groups[56]. Clark et al. randomized 837 women with node-negative breast cancer following lumpectomy and axillary dissection to receive either adjuvant XRT or no adjuvant XRT. At a median follow-up of 43 months, IBTR was 5.5% in patients who received RT and 25.7% in those who did not. No one group of characteristics could be defined to isolate a population of patients whose risk of recurrence without adjuvant XRT was less than 5%[57]. The Milan III trial compiled three randomized trials with a total of 1,973 patients. Local recurrence at five years was found to be 3.3% in patients who received partial mastectomy with adjuvant XRT versus 11.7% for the same surgical excision without adjuvant XRT[58]. Finally, in the NSABP B-21 trial, Fisher et al. showed that for patients with invasive hormone receptor-positive node-negative breast cancers less than 1 cm, local recurrence with tamoxifen alone is 22.8% versus 4.4% for tamoxifen plus XRT at a mean follow-up of 8 years. There was no difference in overall survival[59]. Table 2 summarizes these studies.

Author	Follow-up (years)	Number of patients	Staging characteristics	Local recurrence		Overall survival	
				XRT	No XRT	XRT	No XRT
Lijegren, et al.[49]	5	381	Stage I	2.3%	18.4%	91.0%	90.3%
Clark, et al.[57]	3.6	837	Any T, N0	5.5%	25.7%	7.9%	9.0%
Veronesi, et al.[1]	5	1973		3.3%	11.7%		
Fisher, et al.[5]	8	1009	< 1 cm, N0, HR-positive	4.4%	22.8%	9.1%	10.1%

Table 2. Randomized controlled trials comparing partial mastectomy with and without adjuvant XRT.

Oncoplastic Techniques for Breast-Conserving Surgery

Background

The goals of oncoplastic breast surgery are better cosmetic and quality-of-life outcomes without sacrificing oncologic outcomes in the process. Once BCS became a common practice, patients and providers noticed contour defects in the breast and visible scars. The cavity was often not closed, and the defects would become apparent as a significant depression as the breast healed and the seroma resorbed. This highlighted the importance of evaluating patients' goals for breast appearance following all treatments and doing their best to reach these goals with a minimal number of procedures. Any localization technique can be used with any oncoplastic technique discussed. Oncologic principles must still be met, and re-excision rates must be proven acceptable and comparable for all methods. These techniques can often be offered to the patient as a substitute for mastectomy while still achieving oncologic goals.

Classification System

A consensus system was created to classify different techniques for oncoplasty, from small volume to extreme oncoplastic techniques[60]. Level 1 includes volume displacement with less than 20% of tissue removed. This level includes thoughtful incision placement as well as the basic glandular flap techniques. This may or may not include skin excision, either overlying the tumor or reducing the skin envelope. Level 2 oncoplasty also includes volume displacement of the breast with 20-50% of parenchymal tissue removed, such as pedicle-based mammoplasties and central excisions. Finally, level 3 oncoplasty includes volume replacement rather than displacement and includes greater than 50% of breast parenchyma excised. Often these are implant-based or autologous tissue reconstructions with skin-sparing methods.

Preoperative Evaluation

We are all aware that the breast is a sexual organ, and we must be upfront in our discussion with the patient about their postoperative expectations. Patients must be clear on the resulting changes in sensation, be aware of the improvement in ptosis, and be accepting of other options. A clear discussion must be initiated that could lead to better remolding of the breast with minimal distortion.

Many factors must be considered in the preoperative planning phase. Imaging is closely examined to evaluate the size of the tumor, the volume to be resected, and the location in the quadrant of the breast. Tumor characteristics are considered, as, for example, lobular tumors may be larger than initially thought, or previously non-suspicious axillae may require a complete dissection. Planning of incision or operative strategy is based on tumor location and size. Clough et al. described a quadrant-based atlas of the breast to aid in technique planning. The breast is divided into the upper pole (11 to 1 o'clock), upper outer quadrant (1 to 3 o'clock), lower outer

quadrant (3 to 5 o'clock), lower pole (5 to 7 o'clock), lower inner quadrant (7 to 9 o'clock), and upper inner quadrant (9 to 11 o'clock). The techniques utilized on a quadrant-based approach gave excellent cosmetic results despite a median tumor size larger than that described in most other studies (25 mm). Each location lends itself to a different optimal surgical strategy[61].

The patient's breasts are evaluated and marked for surgery in the upright position. The size of the breast relative to the tumor is considered. Bra size is measured and recorded, and preoperative images are taken against a plain backdrop in the front- and side-view positions. The ptosis of the breast is assessed. Ptosis is sagging of the nipple-areolar complex (NAC) due to the weight of the breast parenchyma or as fatty replacement of the breast advances with age. Ptosis is graded by distance from the inframammary fold (IMF) to the baseline position of the nipple in a standing position[62]. Grade 1, or mild ptosis, occurs when the nipple is at or slightly below the IMF. Grade 2, or intermediate ptosis, occurs when the nipple is below the IMF but above the lower contour of the breast gland itself. Grade 3, or severe ptosis, occurs when the nipple is below the IMF and at the lower contour of the breast gland (Figure 6).

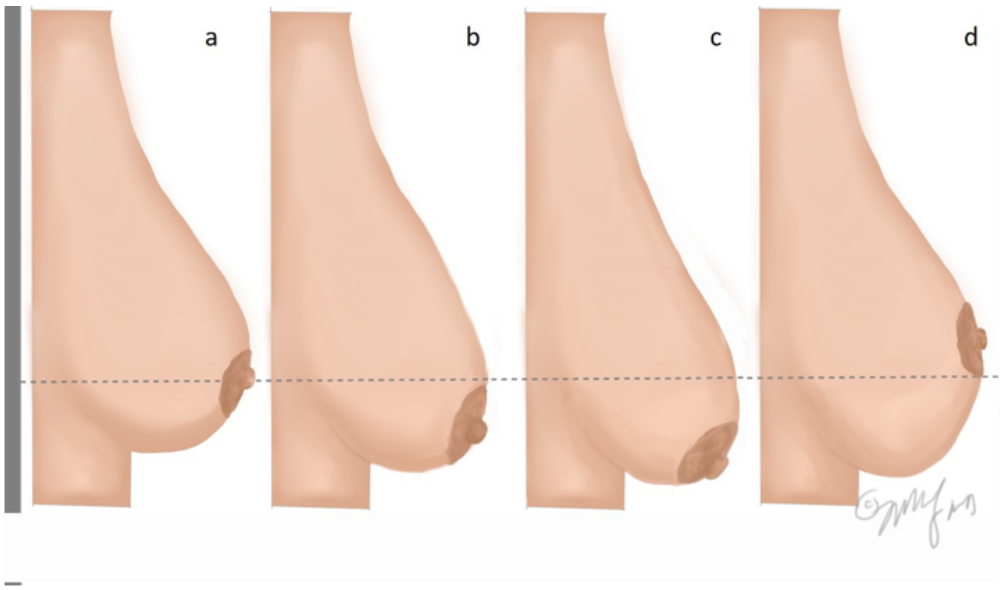

Figure 6. Breast ptosis. a) Grade 1 (mild) occurs when the nipple is at or slightly below the IMF. b) Grade 2 (intermediate) occurs when the nipple is below the IMF but above the lower contour of the breast gland itself. c) Grade 3 (severe) occurs when the nipple is below the IMF and at the lower contour of the breast gland. d) Pseudoptosis occurs when the lower contour of the breast extends below the IMF but the nipple remains above the IMF.

Correction of ptosis must be considered if desired by the patient.

It is also important to consider the timing of oncoplastic procedures. Most can be done in a one-stage fashion at the same time as tumor resection. However, the patient must be counseled on the slight breast changes that may occur with radiation in the postoperative setting. This may contribute to minor asymmetry. Adjuvant chemotherapy, if necessary, may be postponed until wound healing is complete. These factors as well as the availability of surgeons and operative space must all be taken into account when planning oncoplastic BCS.

Minimizing Scar Visualization

Through basic surgical principles of BCS, tumors can be excised with appropriate margins through scars that will not be visible to most no matter what clothing is donned. Previously, incisions were placed directly over the tumor in a radial fashion if below the nipple or in an arcing fashion if above the nipple. In patients with smaller breasts and tumors requiring low excision volumes, basic elliptical excisions can be done without compromising breast shape nor appearance. Multiple incision choices are available for this method. Circumareolar, axillary, or IMF incisions are notorious for healing well with minimal visualization. The circumareolar incision can encompass up to 180 degrees of the areola and can be done at any site on the clock face to access a tumor in any quadrant. The presence of the scar at the border of the pigmented areola and non-pigmented skin provides excellent camouflage. An axillary approach is more advantageous for upper outer quadrant tumors and can often be the same incision used for an axillary staging procedure. IMF incisions are more useful for lower outer quadrant tumors and may tend to be subject to more skin-to-skin contact, which may interfere with healing, depending

on the patient's body habitus. Both IMF and circumareolar incisions typically require a separate incision if axillary staging is pursued (Figure 7).

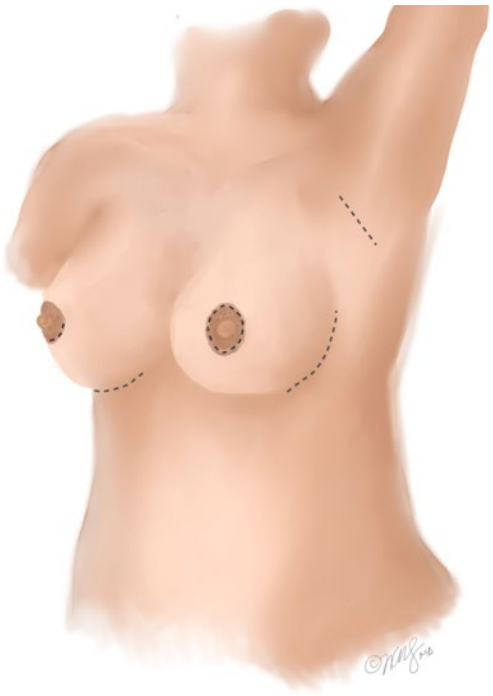

Figure 7. Thoughtful scar placement. This image demonstrates the circumareolar, inframammary, and axillary incisions.

Defect Closure

For the above-mentioned incisions, a parenchymal defect is created that more than likely requires closure to maintain proper breast aesthetic. A skin flap is raised from the incision of choice in the direction of the tumor until the tumor is localized. The breast parenchyma can then be incised with a wide margin around the tumor, ensuring preservation of orientation upon removal. This then leaves the patient with the aforementioned parenchymal defect. The breast tissue must be undermined just superficial to the level of the pectoral fascia to ensure mobility from the chest wall while still maintaining blood supply. It is loosely reapproximated with an interrupted absorbable suture (Figure 8).

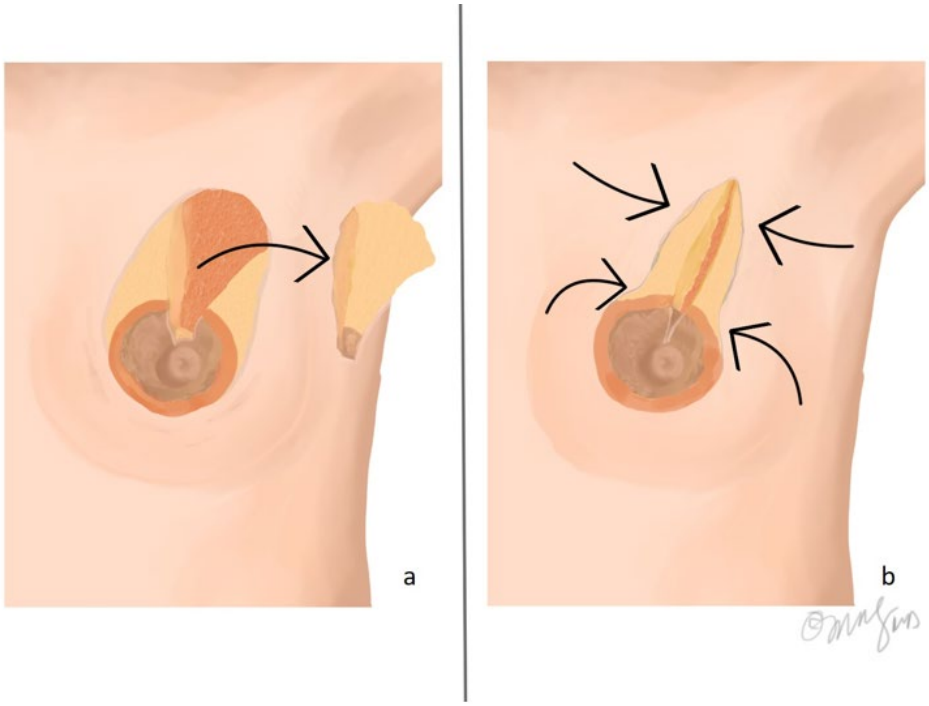

Figure 8. Defect closure. a) A wedge of tissue is removed containing the desired excision specimen. The glandular tissue is elevated off of the chest wall. b) The glandular and fatty tissue is loosely reapproximated to minimize the contour defect upon closure.

These sutures should be in the breast parenchyma if possible. If the breast is mainly fatty replaced, suturing can lead to fat necrosis. The breast can then be evaluated for contour deformity. The dermis can be elevated to minimize this effect if skin wrinkling or dimpling is present.

Techniques for Smaller Breasts with Minimal Ptosis

These methods offer access for a more minor volume resection and correction of mild ptosis. They do often require contralateral surgery when desired for symmetry.

Crescent and Batwing Techniques

This method tends to be more useful in tumors in the upper pole of the breast. At the conclusion, the NAC is moved slightly toward the incised area, so if there is mild ptosis, this can be gently corrected via a superior crescent incision. A 180-degree circumareolar incision is outlined, followed by a concentric crescentic incision about 2 cm superior to that line. The contralateral breast is outlined to match. The skin between the crescent boundaries is de-epithelialized sharply, enabling the breast parenchyma to be entered at the tumor location. On the tumor side, the resection is performed in a similar fashion to the tissue rearrangement mentioned above, with the raising of a skin flap toward the tumor site if needed. The defect created is closed to improve contour (Figure 9). A mirror procedure is performed on the opposite breast, however there is no breast parenchyma removal on that side. Bilateral incisions are closed identically, creating a gentle breast lift to improve ptosis.

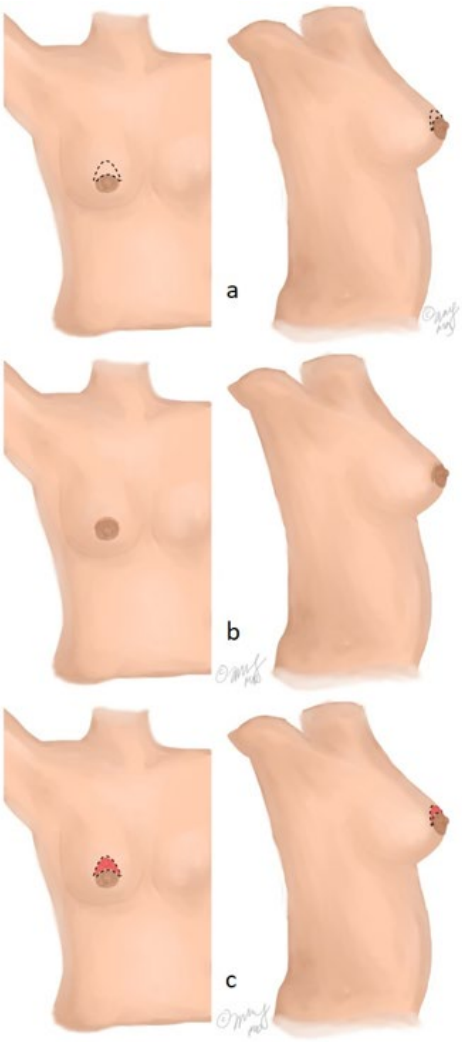

Figure 9. Crescent mastopexy. a) Incision marking with 2 eccentric crescent shapes in the circumareolar area. b) De-epithelialized area within the 2 crescents allows access to the breast parenchyma for specimen excision. c) Closure of crescent with gentle lift of ptotic breast.

If the tumor cannot be reached via the crescent approach, or if additional skin needs to be excised, a batwing or hemi-batwing may need to be extended in order to encompass the appropriate site. A standard crescent incision is drawn and extended either laterally, medially, or both, combining an elliptical excision with a crescent mastopexy. The lower edge of the wing portion of the incision extends along the upper half of the areola (Figure 10). A mirror incision is done on the contralateral breast, with or without the addition of the batwing. The hemibatwing technique is helpful for more posterolateral tumors that may be difficult to reach via the standard crescent or more superficial tumors that require a skin excision but in which the patient with mild ptosis still desires a lift. The batwing addition to the crescent is favorable to tumors of the upper inner quadrant. The breast tissue defect along the wing portion of the incision is closed in a cranial-caudal direction[63].

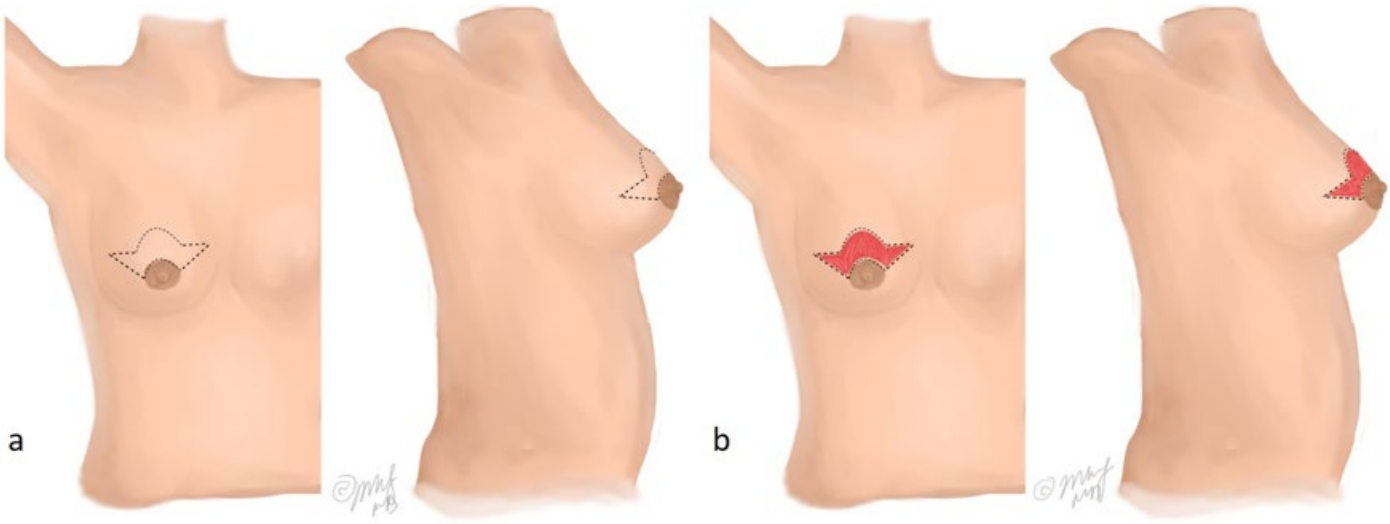

Figure 10. Crescent with batwing. a) Incision marking extension of the crescent incision bilaterally to accomodate different tumor locations. b) De-epithelialized area within the incision allows for access to the breast parenchyma for specimen excision.

Donut (Benelli) Mastopexy

This incision gives 360-degree access to the breast parenchyma, making it ideal for tumors at any location and providing correction for mild ptosis. This is also the best technique for tumors of the upper inner quadrant. The new NAC is outlined with a 38- or 42-mm round cookie cutter centered over the nipple itself, and this is copied bilaterally. Another concentric circle is drawn up to 2 cm outside of that outline, but this circle can be centered slightly above the nipple if correction of ptosis is desired. The skin between the circles is de-epithelialized so that the breast parenchyma can be entered on the tumor side (Figure 11). A pie-slice-shaped wedge of tissue is elevated from the chest wall and excised. The parenchymal tissue is reapproximated gently and re-secured to the chest wall using an absorbable suture. A mirror operation is performed on the contralateral breast without the parenchymal excision unless some volume excision is needed for symmetry. The skin is reapproximated with interrupted absorbable deep dermal sutures followed by a running subcuticular stitch that closes the circle in a purse string fashion[64]. Wrinkling or bunching of the scar will smooth out with healing. Patients should be warned preoperatively that the areola may widen over time.

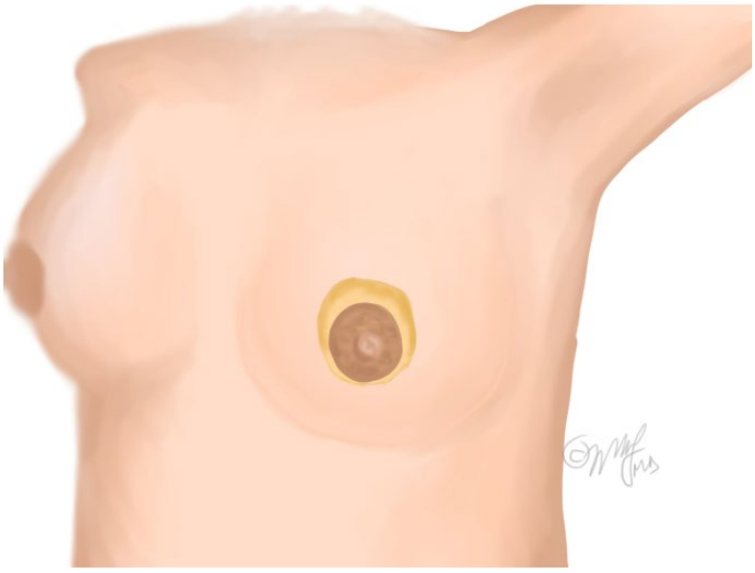

Figure 11. Donut (Benelli) mastopexy. An eccentric circle is drawn around the nipple-areolar complex centered slightly above the nipple. De-epithelialization allows for access to the breast parenchyma in a 360-degree fashion. Closure of this defect provides a gentle lift for mildly ptotic breasts.

Other Techniques

There are multiple other techniques described for this situation in which the breast has minimal or no ptosis. A vertical mammoplasty removes lower pole tumors without elevation of the NAC, leaving a lollipop-shaped or vertical scar (Figure 12). This is best utilized for tumors of the upper pole, lower pole, and lower inner quadrant. A Grisotti mastopexy is useful for when the tumor involves the NAC. The NAC is excised, and skin is preserved over a predetermined area in the inferior lateral portion of the breast.

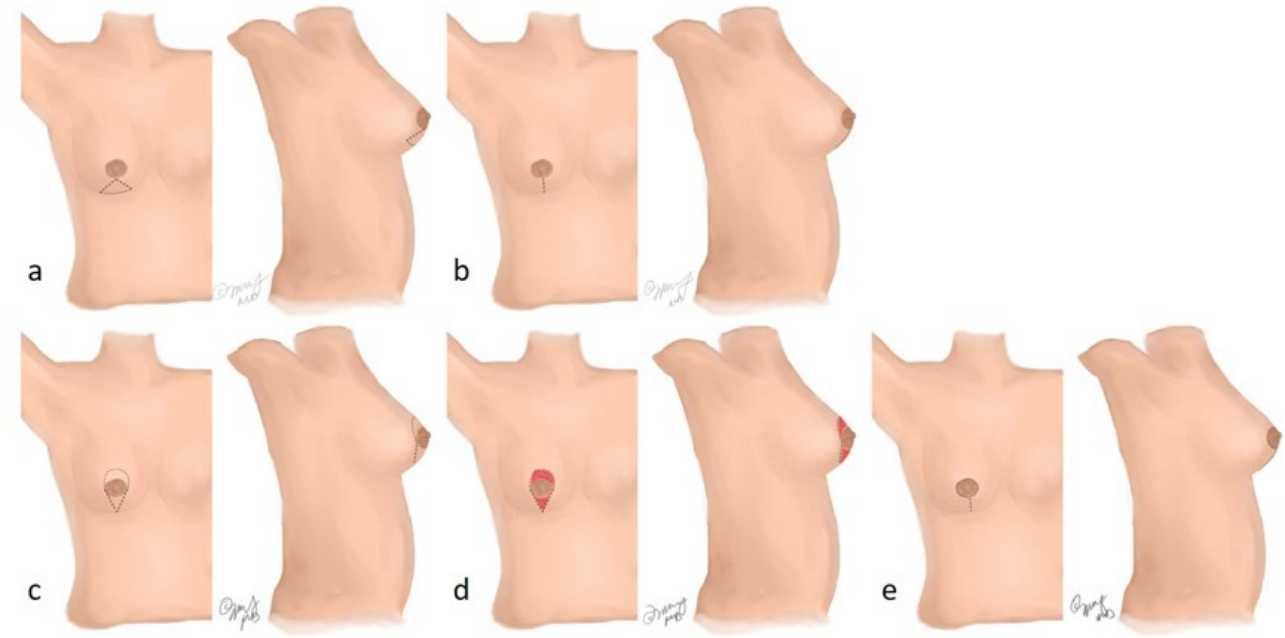

Figure 12. Vertical mammoplasty. a) A wedge-shaped elliptical excision is done in line with the lower pole of the breast. b) The skin is closed in a straight vertical line. c) In the lollipop-shaped approach, an inverted tear-drop is drawn encompassing the NAC. d) The surrounding tissue is incorporated into the incision while the NAC is left in place undisturbed. e) The incision is closed in a circumareolar fashion extending down the vertical midline of the breast.

This preserved area and surrounding de-epithelialized tissue is advanced into the central breast to fill the defect (Figure 13). The nipple can be recreated in a delayed fashion if desired.

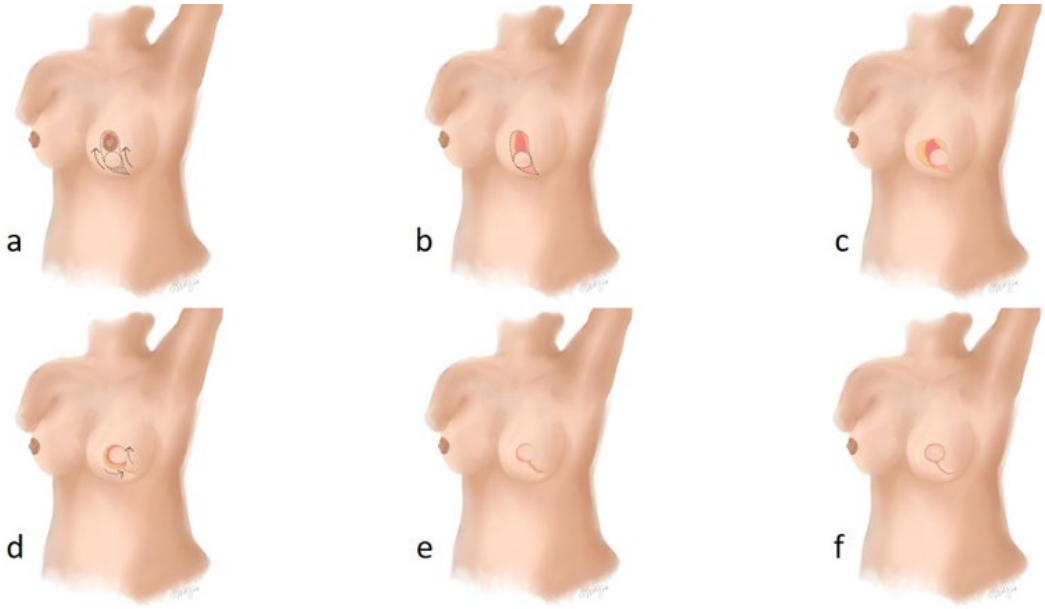

Figure 13. Grisotti mastopexy. a) The nipple-areolar complex is marked and skin is preserved over a predetermined area in the inferior lateral portion of the breast. b) The area is preserved and the nipple areolar complex is excised. c and d) The preserved area tissue is advanced into the central breast to fill the defect. e and f) The incision is closed leaving space to recreate a nipple if desired.

Techniques for Larger Breasts with Ptosis

Pedicle-Based Reduction Mammoplasty

These techniques are exceptionally useful where volume reduction and breast lift are needed. Patients with tumors at any location in any quadrant can be eligible due to the ability to utilize different pedicles. The blood supply to the breast is very redundant from internal mammary, supraclavicular, lateral thoracic, and intercostal perforators. Hence, there are many different components that can sustain the NAC on its pedicle, even with extensive volume resections. The inferior pedicle is the most commonly utilized and is best utilized in tumors of the upper pole and lower inner quadrant.

The patients should be marked in an upright standing position with the surgeon seated. A permanent marker should be used so that the marks are not disrupted at the time of surgical preparation. The anatomic landmarks are clearly marked: the suprasternal notch, the inferior border of the clavicles, the IMF, and the breast midline. The vertical axis of the breast is drawn from the mid-clavicular line (about 7-8 cm from the suprasternal notch) through the nipple and continuing through the IMF. The new position of the NAC is determined and marked unilaterally by placing a finger in the IMF and projecting it forward. This position should typically be at about the mid-humerus. The skin on either side of the NAC is pinched together to ensure a tension-free closure at this point. These pinched edges are marked, and an inverted V can be drawn from these points to the new NAC location. The limbs of this inverted V should measure about 8-10 cm and be equivalent. The marks are continued medially and laterally to meet the exact edges of the IMF. The inferior pedicle itself is marked centered on the vertical axis of the breast as it crosses the IMF. The pedicle base should extend 8 cm in total, 4 cm on either side of the vertical axis of the breast, and continue up vertically to encompass the NAC[65,66]. The contralateral breast is marked in an identical fashion. Completed markings are seen in Figure 1 and Figure 14a. The location

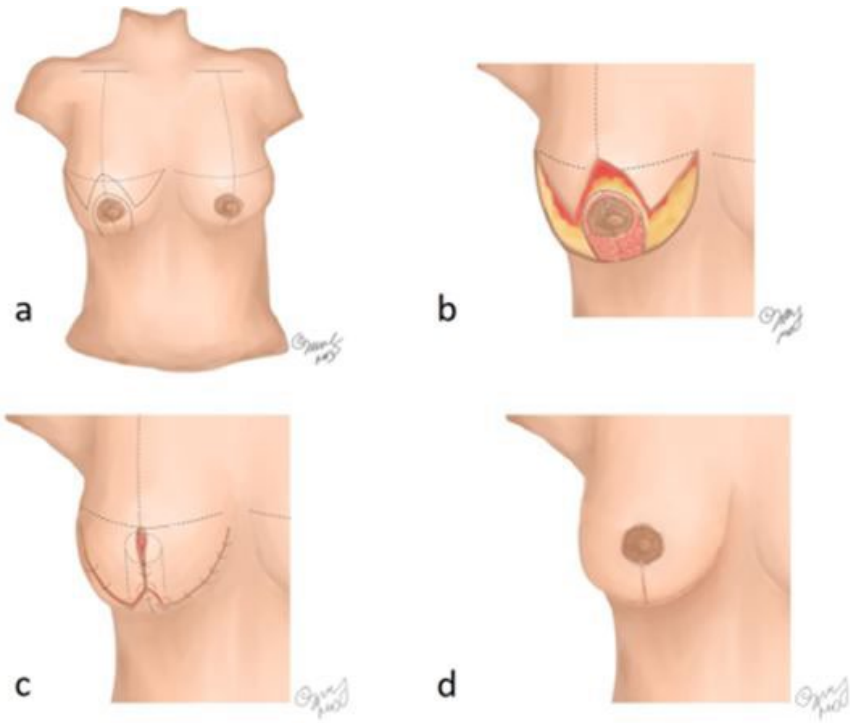

Figure 14. a) Markings for inferior pedicle-based reduction mammoplasty as done in the upright position. b) The inferior pedicle is sharply de-epithelialized and the remainder of the tissue is excised in full thickness. c) The incisions are temporarily closed in a T-shaped fashion and the patient is returned to an upright position intraoperatively to confirm symmetry. D) The NAC is delivered through the incision and secured in place with absorbable suture. The remainder of the incisions are closed in 1 or 2 layers.

of the tumor should be marked at this time to ensure its presence within the excised volume. The pedicle can be adjusted if the tumor should fall in that location. Markings are documented by photography.

Care should be taken while prepping the patient in the operating room so as not to disturb the previously placed marks. The bilateral breasts, axillae, and arms should be included in the surgical field to allow for a full range of motion during the case if needed. A 38 or 42-mm cookie cutter is centered on the nipple to mark the new NAC. The remaining skin of the pedicle is de-epithelialized sharply (Figure 14b). The IMF, inverted V, and connecting incisions are then made with a scalpel. Cautery is used to dissect these tissues down toward the chest wall, being careful not to compromise the skin edges with the cautery. The de-epithelialized pedicle is preserved. The dissection is carried down to the chest wall, but it is not necessary to excise the pectoralis fascia in this case. Care is taken throughout the case to ensure the presence of the tumor in the excision specimen. This can be done with intraoperative ultrasound or any other localization technique. Once removed, the specimen should undergo imaging to confirm the presence of the biopsy clip in the specimen. (Figure 14). The bilateral specimens are weighed for symmetry, and the additional volume can be taken if needed.

After hemostasis and irrigation, drains are typically placed in the excision bed. The corners of the inverted V are brought together at the IMF at the previously marked vertical axis of the breast using an absorbable suture. Staples or sutures can be used for temporary closure of the remainder of the incisions (Figure 14c). The patient's arms are then secured, and the patient is lifted to an upright seated position. The breasts are evaluated for symmetry. Once satisfied, the surgeon marks the new position of the NAC with a 38- or 42-mm cookie cutter. This area is excised in full thickness, and the NAC is delivered through, being careful not to twist or alter the

pedicle. The incisions are then closed in 1 or 2 layers with absorbable suture (Figure 14d). The circumareolar incision should be closed with a longer-lasting absorbable suture. Photographic documentation should be done postoperatively in the immediate period and at each follow-up. Figures 2 and 3 show immediate and 2-week postoperative views.

Central Excision

If a tumor involves the NAC, a central excision can be done in a similar fashion to the aforementioned reduction mammoplasty. A similar set of markings is done around the NAC and can also be done bilaterally for symmetry if desired. The entire volume within the markings is excised in full thickness down to the chest wall and the area is closed in an inverted T fashion. The NAC can be reconstructed at a later date (Figure 15).

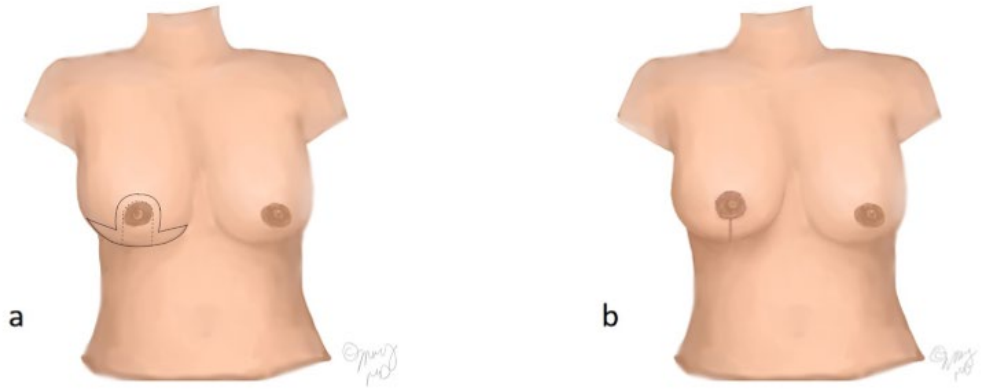

Figure 15. Central excision. a) Markings are done in a similar fashion to the inferior pedicle-based reduction mammoplasty, but these markings encompass the entire NAC. B) The marked area is excised in full thickness and the NAC must be recreated.

Extreme Oncoplasty

Patients with large (≥ 5 cm), multifocal, or multicentric tumors may still desire BCS. Previously thought to compromise cosmesis, BCS can now be offered to these patients who were once told they needed a mastectomy. While little high-level evidence exists to support this practice, smaller studies with short-term follow-up have advocated for its use in favorable cases. Silverstein et al. studied 245 patients with a 96% negative margin rate and a 1.2% 24-month

recurrence rate[67]. Crown et al. evaluated 111 patients and reported a 78.3% negative margin rate and a 1.1% 5-year recurrence rate[68]. Any of the techniques discussed can be used in these cases, with a higher likelihood of requiring contralateral surgery for symmetry. These patients are more likely to require XRT as well, as they are more commonly presenting with locally advanced disease. These extreme cases require multi-disciplinary input for planning.

Pitfalls

One of the most important aspects of BCS is counseling patients in the preoperative setting and assessing the patient's goals. Patients must understand that while the breasts may not appear ideal in the immediate postoperative setting, the remodeling that occurs in the healing process over six months to 1 year will more than likely yield a satisfactory result. Patients who require adjuvant radiation therapy may take longer to complete the process. They also must understand that perfect symmetry is not possible. Common complications of oncoplastic BCS are unsightly scar formation (including "dog ears"), asymmetry, need for re-excision or completion mastectomy, and wound complications. Extensive oncoplasty may also make reading future imaging studies difficult and require multiple re-evaluations for stability.

Summary

Breast conservation has emerged as a safe alternative to mastectomy in nearly all patients with breast cancer, with excellent outcomes. Candidacy depends on tumor characteristics, focality and centricity, ability to localize the tumor, and many other variables. Completion of the therapy often includes XRT. With oncoplastic techniques, the cosmetic results have significantly improved. This has increased the acceptable patient population for this technique.

Salient Points

- Breast conservation therapy has emerged as an oncologically safe option in most breast cancers.
- The recommendation for adjuvant XRT is typically the standard in BCS to reduce local recurrence rates.
- Oncoplastic techniques have broadened the patient population eligible for BCS.
- Based on tumor location, a variety of oncoplastic techniques are available to maximize cosmesis after BCS.

Suggested Reading

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Chapter 23

Axillary Surgical Techniques

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Clinical Case Scenario

46-year-old married women with a rural background presented with a lump in the right breast of 4 months duration. Clinical examination revealed a 3 cm hard irregular mass in the upper outer quadrant of the right breast, and there was no significant axillary lymphadenopathy. She was referred to a nearby medical college for further evaluation. Mammography showed a single BIRADS V lesion in the right breast, and Ultrasonography confirmed mammography findings and also revealed a 1 cm axillary lymph node. The center lacked expertise in axillary ultrasound and guided FNAC. A biopsy of the primary tumor revealed features of the luminal-A type of infiltrative duct carcinoma. Due to the nonavailability of radiation therapy facilities, she was offered a mastectomy. The patient is a manual worker on a farm, and she expressed concerns regarding arm morbidity following axillary lymph node dissection (ALND). Facilities for nuclear medicine were also lacking in the center. However, the treating surgeon was familiar with sentinel lymph node biopsy (SLNB) using blue dye. Since 1% isosulfan blue dye was unavailable surgeon performed a SLNB using methylene blue dye at the time of mastectomy. Final histopathology revealed node-negative stage II luminal breast cancer. The patient was

advised to undergo adjuvant chemotherapy and hormonal therapy, was disease-free at one year, without any clinical evidence of relapse or lymphedema.

Introduction

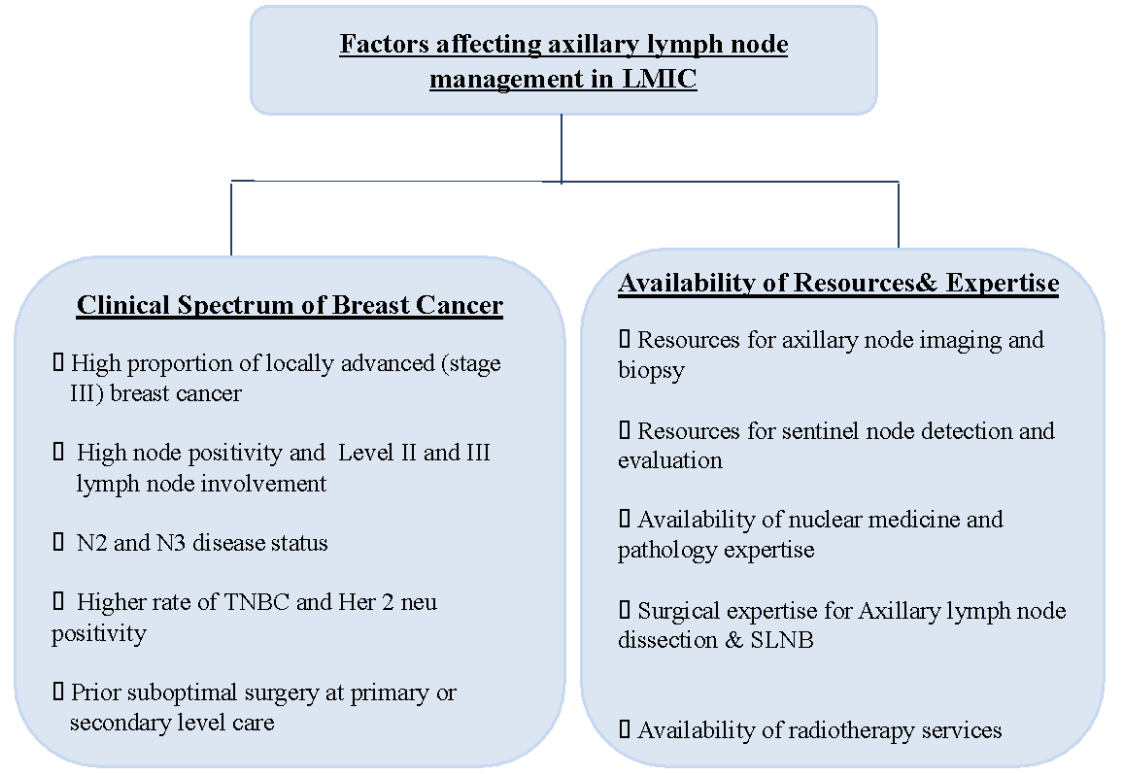
Breast Cancer is emerging as a major public health problem in Low and middle-income countries (LMIC), and as per Globocon 2018 report, Breast Cancer is the most common cancer among women in LMIC (1). Even though the current breast cancer incidence rates of LMIC are relatively lower than the rates reported by High-Income countries (HIC), the overall burden of breast cancer is significantly higher in LMIC due to population size and density. Socioeconomic development, especially in emerging economies of LMIC, is associated with detrimental lifestyle factors and environmental exposures resulting in increased cancer burden (2). Due to limited awareness, lack of universal screening programs, and resource constraints, a significant proportion of breast cancer patients in LMIC present with advanced stage and a high axillary nodal burden (3,4). There are wide variations in the availability and quality of healthcare services in LMIC, with certain geographic regions having state-of-the-art comprehensive cancer facilities and specific geographic locations lacking basic healthcare facilities.

The management of axillary nodes plays a vital role in the overall management of breast cancer. Axillary node management for breast cancer patients has evolved significantly over the last century (5). Lymphatic spread is common in breast cancer, and the predominant site of involvement is axillary lymph nodes. The likelihood of axillary node involvement is related to tumor size, location, histologic grade, and the presence of lymphatic invasion. The presence of axillary metastases is also independently related to intrinsic tumor biology and molecular subtypes. Traditionally, axillary lymph node dissection (ALND) was an integral part of the

surgical management of breast cancer, providing critical staging and prognostic information. ALND also facilitated adjuvant therapy decisions and played a role in controlling the disease in the axillary region. Recently, there has been a paradigm shift towards less extensive axillary surgery in breast cancer patients, mainly to decrease the morbidity of ALND without compromising on oncological outcomes. The main reasons driving the de-escalation of axillary surgery include an increasing proportion of screen-detected early-stage node-negative breast cancer in high-income countries, less dependence on axillary nodal status as a prognostic and predictive factor, decreasing dependence on axillary nodal status for making adjuvant therapy decisions and increasing utilization of neoadjuvant therapy based on molecular and genetic profiling of primary tumors. During the last two decades, the adoption of Sentinel Lymph Node Biopsy (SLNB) in HIC has significantly increased, and rates of ALND are showing a declining trend (6). However, in LMICs, due to the higher incidence of node positivity ranging from 30 to 70% and limited availability of expertise for SLNB and nuclear medicine facilities, ALND continues to be the predominant surgical procedure for axillary node management (7,8). However, in the recent past, surgeons from certain parts of LMICs have adopted SLNB for managing axillary nodes, and some centers are using SLNB with blue dye alone or Axillary Node Sampling (ANS) as an axillary staging procedure. Due to various patients, diseases, and resource-related factors, a pragmatic and feasible approach is needed for the surgical management of axillary nodes in LMIC.

Factors affecting axillary node management in LMIC

- Clinical Spectrum of Breast Cancer
- Availability of Resources & Expertise



Clinical spectrum of breast cancer patients in LMIC from axillary node management perspective

1. Locally Advanced Stage III Node Positive Breast Cancer
2. Locally Advanced Stage III Node Negative Breast Cancer.
3. Patients presenting with prior sub-optimal axillary intervention or unknown axillary status.
4. Patients presenting after Neo adjuvant Chemotherapy
5. Early Stage (I&II) Node Positive Breast Cancer
6. Early Stage (I&II) Node Negative Breast Cancer

Clinical Assessment of Axillary Nodes

Traditionally, axillary nodal assessment and staging are performed by clinical examination only. However, physical examination is neither a sensitive nor reliable method to ascertain the status of the axillary lymph nodes, especially in patients with low-volume disease burden. The positive predictive value of clinical palpation ranges from 60 to 80 percent, while the negative predictive value ranges between 50 to 60 percent (9,10). To overcome significant morbidity associated with ALND, Sentinel lymph node biopsy (SLNB) has been introduced as a minimally invasive staging tool in patients with clinically negative axilla. Subsequently, for clinically palpable or suspicious axillary nodes, axillary ultrasonography (AUSG) along with fine needle aspiration cytology/core biopsy (FNAB) was added to the management algorithm to identify patients who may be candidates for ALND rather than SLNB (11). However, both AUSG and FNAB are highly operator-dependent, and the expertise for assessment of lymph nodes using USG and FNAB may be limited in LMICs. Scaling-up facilities and expertise for ultrasonography and FNAB in LMIC will improve the optimization of patient selection for ALND or SLNB without a significant financial burden. (Figure 1).

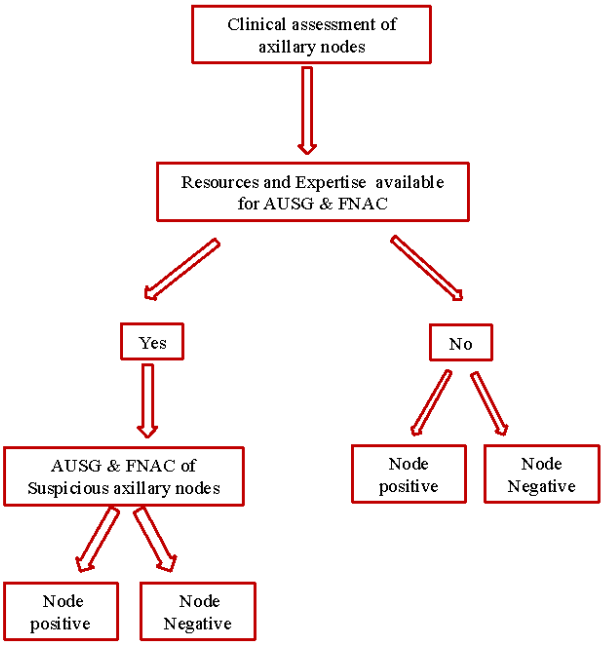


Figure 1: Showing the algorithm for axillary node assessment in LMIC based on the availability of resources and expertise.

Management approach to Axillary Nodes in LMICs

Breast Cancer patients can be grouped broadly into node-negative or node-positive based on the clinical assessment with or without AUSG and FNAC, depending on the availability of expertise. The current standard of care for node-positive patients is ALND, and for node-negative patients, SLNB is recommended. If SLNB expertise is unavailable, Axillary nodal sampling (ANS) is an option for LMICs. A completion ALND is recommended for patients presenting with sub-optimal prior surgical interventions due to high node positivity rates. Managing axillary nodes following neoadjuvant chemotherapy is a challenge in LMIC due to the limited availability of expertise for pre-chemotherapy staging and localization of lymph nodes and restaging of axilla following neoadjuvant chemotherapy, making ALND the default option in the majority of patients. However, SLNB can be offered to node-negative patients following neoadjuvant chemotherapy if expertise is available. Figures 2 and 3 show the axillary nodal management approach for node-positive and node-negative breast cancer patients in LMIC based on the availability of resources and expertise.

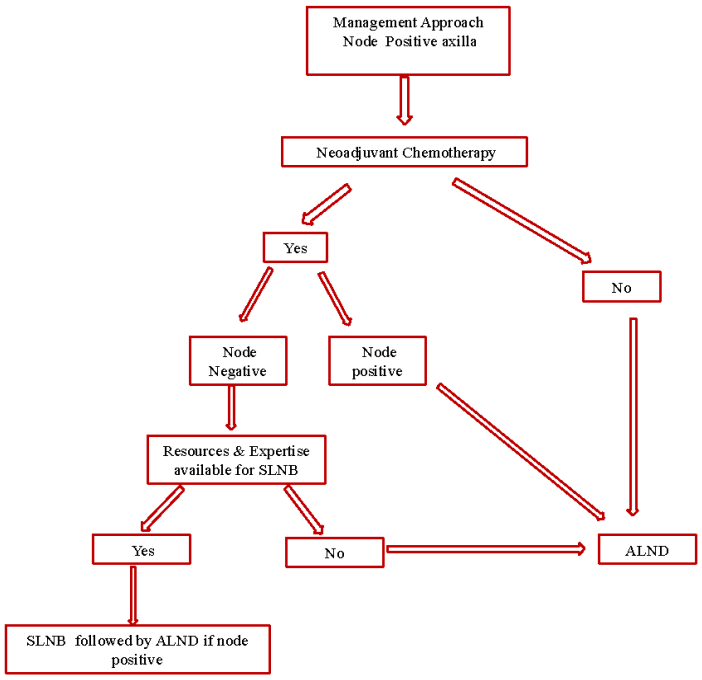


Figure 2: Showing management approach for node-positive patients in LMIC based on the availability of resources and expertise.

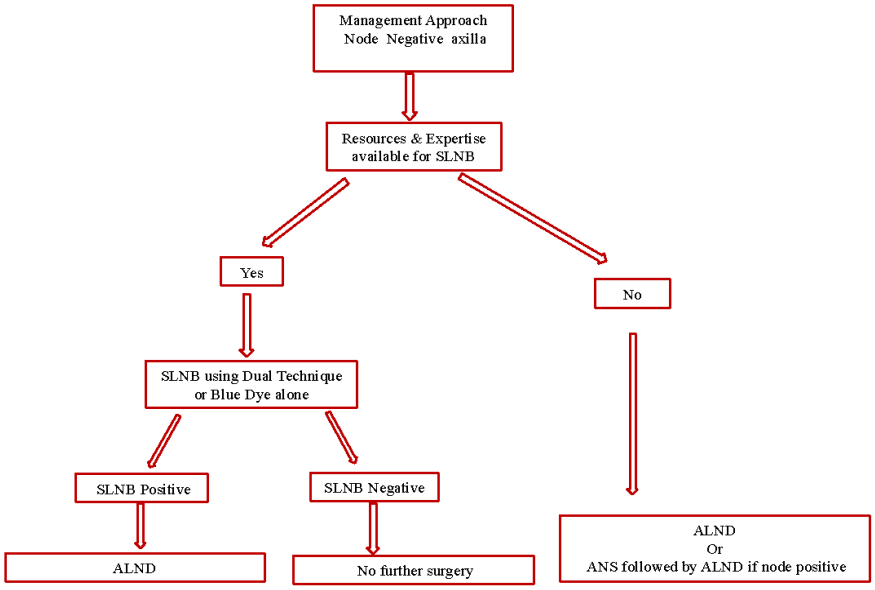


Figure 3: Showing management approach for node-negative patients in LMIC based on the availability of resources and expertise

Axillary Surgical Techniques

Two standard surgical options are available for managing axillary nodes1. Axillary Lymph node dissection (ALND) and 2. Sentinel Lymph node biopsy (SLNB). Axillary Lymph node sampling (ANS) has been described as a third option, but the evidence supporting the utility of ANS is limited in comparison to the evidence base available for ALND and SLNB. However, ANS has potential in LMICs that need more resources and expertise for SLNB. The applied anatomy of the axilla, indications for, and surgical technique of axillary surgical procedures are described below:

Applied Anatomy of Axilla

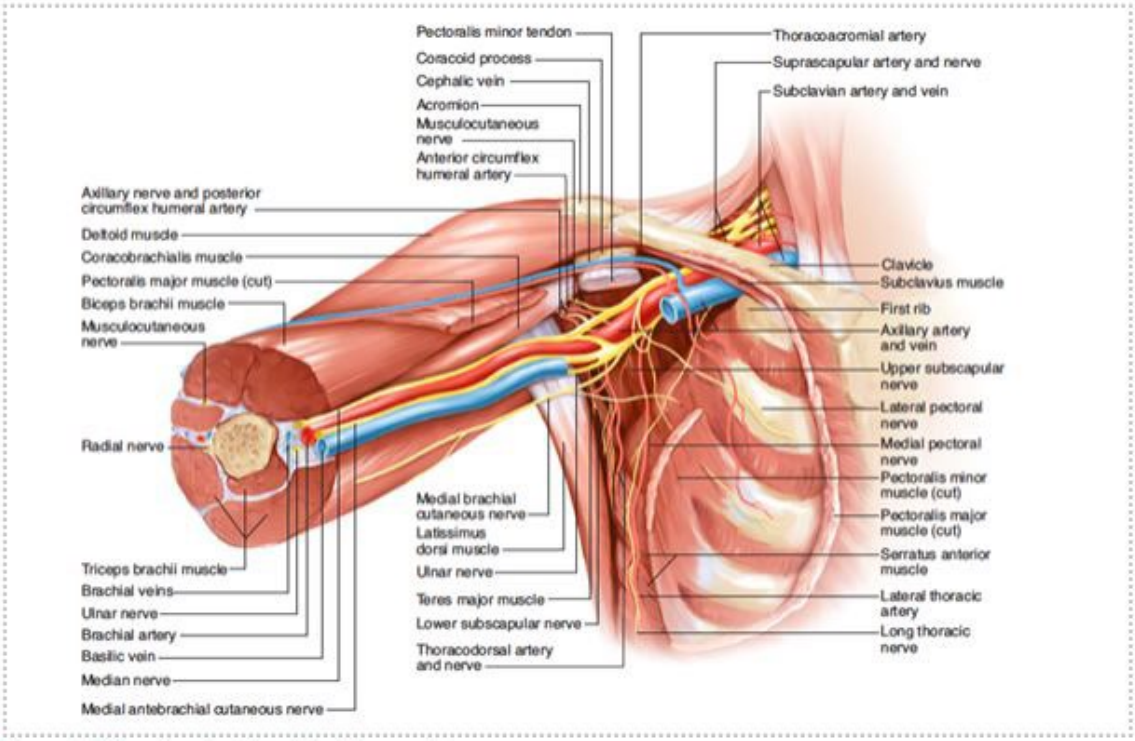


Figure 4: Showing details of Axillary anatomy

The axillary space is a pyramidal compartment with an apex, base, and four walls (Figure 4). The apex of the axilla is formed by the costoclavicular ligament, and the base of the axilla is formed by skin and axillary fascia.

The anterior boundary of the axilla is formed by the pectoralis major and minor muscles, and the posterior boundary of the axilla is formed by the latissimus dorsi muscle. The medial border of the axilla is formed by the intercostal and serratus anterior muscles, and the lateral wall of the axilla is the narrow space on the humerus between the anterior and posterior wall muscles. The axilla fat pad contains lymph nodes, lymphatics, blood vessels, and nerves.

Levels of Axillary Lymph nodes: Axillary lymph nodes are divided into three levels based upon their relationship to the pectoralis minor muscle. Level I - Inferior and lateral to the

pectoralis minor muscle, Level II - Posterior to the pectoralis minor, and Level III -medial to the pectoralis minor muscle, also known as infraclavicular nodes. The rotter nodes or interpectoral nodes are located between the pectoralis major and minor muscles.

Nerves of the Axilla: Functionally important motor and sensory nerves are encountered during axillary dissection**.** Three motor nerves of the axilla encountered during axillary dissection include:

1. The long thoracic nerve (Nerve of Bell) that runs parallel to the chest wall and innervates the serratus anterior muscle. Injury to the nerve during ALND results in winging of scapula deformity

2. The thoracodorsal nerve is located in the deep part of the axilla and innervates the latissimus dorsi muscle. Injury to the nerve results in mild weakness of internal rotation and shoulder adduction

3. The medial and lateral pectoral nerves that innervate the pectoralis minor and major muscles. Injury to these nerves results in atrophy of the pectoral muscles with a cosmetic deformity and restriction of shoulder mobility.

The most functionally significant sensory nerve encountered during axillary surgery is the intercostobrachial nerve which provides sensory innervation to the skin of the axilla and medial and posterior surface of the arm. This nerve exits the chest wall at the second intercostal space. Since the nerves traverse axillary fat, they are at risk of injury during ALND, resulting in clinically significant paraesthesia.

Axillary lymph node dissection: ALND remained the standard of care for managing axillary nodes for almost three-quarters of the last century. Mastectomy, along with the removal of axillary lymph nodes (ALND), was described as a treatment for breast cancer in the late 18th

century, and subsequently, radical mastectomy was widely propagated by William Halstead in the early 19th century. The radical mastectomy procedure laid the foundations for the concept of "radical en-bloc resection surgery for cancers." The goals of ALND are staging, prognostication, and a therapeutic role in controlling axillary disease. The evidence is conflicting regarding the survival benefit of ALND, especially in the era of modern multimodality management (12). ALND is a well-standardized and widely performed surgical procedure for breast cancer and should be part of the curriculum and training in general surgical residency. In LMICs, SLNB is still evolving, and ALND is going to be the mainstay of surgical management for the majority of breast cancer patients.

Indications for ALND

An axillary lymph node dissection is performed along with mastectomy or with the lumpectomy as part of a breast-conserving procedure. ALND can be performed in the following clinical situations.

i. Primary ALND

Clinically node-positive early-stage breast cancer.

ii. Following Neoadjuvant Chemotherapy

1. In Locally Advanced (T4a,b,c) and Inflammatory Breast Cancer patients.
2. In node-positive early breast cancer with residual positive nodes following neoadjuvant chemotherapy.

iii. Completion of Axillary Lymph Node Dissection

1. In node positive patients presenting with incomplete axillary dissection following suboptimal surgery.

2. Following SLNB

    a) In patients with three or more positive sentinel lymph nodes with T1 or T2 tumors.

    b) In patients with any number of positive sentinel lymph nodes with T3 tumors or extranodal extension.

    c) In patients with any number of positive sentinel lymph nodes who will not receive whole breast radiation following mastectomy, patient refusal or non-availability of radiation facilities, and in patients undergoing partial breast irradiation.

    d) Failed SLNB procedure.

    e) Recurrence after SLNB

Surgical technique of ALND

Patient Position: The patient is positioned supine position with the arm on the operated side extended onto the arm board at less than 90 degrees abduction from the chest wall in order to open axillary space for surgery and avoid stretching of brachial plexus and traction injury due to hyperabduction. The arm is draped and kept in the sterile surgical field to facilitate easy access to deeper parts of the axilla, especially for level III clearance.

Incision for ALND:

The incision for ALND will depend on the procedure for primary tumor – mastectomy or lumpectomy. In patients undergoing mastectomy, the lateral extent of the mastectomy incision is utilized for ALND. In patients undergoing lumpectomy, a separate axillary incision is used for ALND in the majority of patients, and a single incision can be used for lumpectomy and ALND if the tumor is located in the axillary tail. Both transverse and longitudinal axillary incisions are

described for ALND, but a curvilinear incision hidden behind the anterior axillary fold gives an optimal exposure and also results in good cosmetic outcomes (Figure 5).

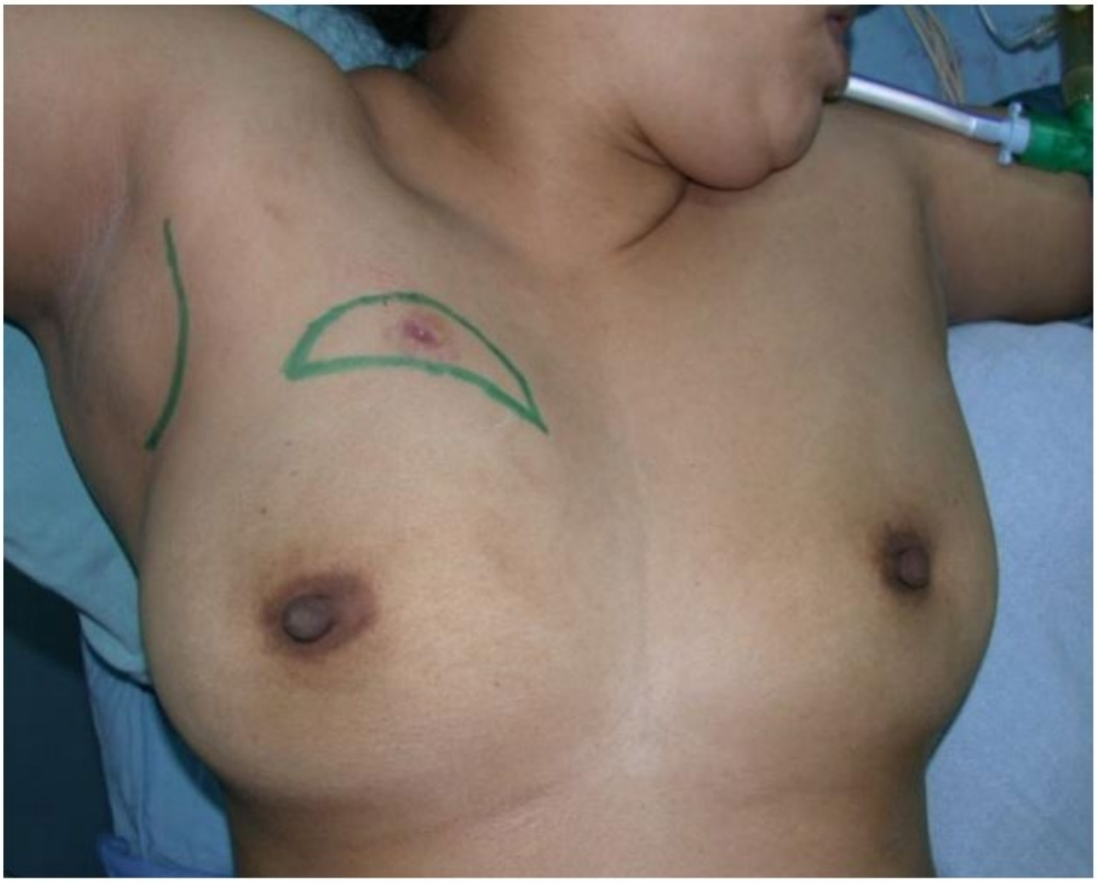


Figure 5: Showing incision for axillary lymph node dissection in a case planned for breast conservation surgery.

Surgical Steps of ALND: In ALND, all fibro-fatty tissue and lymph nodes located between the axillary vein superiorly, thoracodorsal pedicle laterally, and long thoracic nerve medially are removed.

After incising the skin, flaps are raised at the subcutaneous plane with electrocautery or knife. The medial limit for the flap is the lateral border of the pectoralis major, and the lateral limit is the latissimus dorsi. Axillary dissection can be performed from lateral to medial or medial to

lateral fashion. A good energy source, skin hooks, and right-angle forceps are essential tools for a good anatomical dissection. After incising the axillary fascia, the axillary vein should be identified. The plane of dissection should always be below the inferior border of the axillary vein, and avoid stripping the fascia over the axillary vessels to prevent damage to major lymphatic trunks draining the arm. All the lymph nodes containing fibrofatty tissue are meticulously removed using sharp dissection, and minor vascular tributaries can be controlled with diathermy or ligatures. When performing level II and III dissections, necessary steps include delineation of pectoral muscles, preservation of medial pectoral nerve, entering clavipectoral fascia, and looping pectoralis minor muscle. By gentle adduction of the arm and traction of the pectoralis minor, level II and III lymph nodes can be safely removed without the need for division of the pectoralis minor muscle. Care should be taken to identify and protect the long thoracic nerve coursing along the chest wall.

The intercostobrachial nerve is sacrificed to facilitate optimal lymphatic clearance in high-volume axillary disease, and nerve preservation can be attempted in cases with low-volume axillary disease. Identify and preserve the thoracodorsal neurovascular bundle at the lateral limit of ALND (Figure 6). Avoid over-dissection beyond the thoracodorsal pedicle into the proximal arm space to prevent damage to major arm lymphatics unless you encounter gross nodal disease lateral to the thoracodorsal pedicle. In certain clinical situations, you may encounter heavy nodal disease encasing the thoracodorsal pedicle or sometimes the axillary vein. Surgeons in LMIC may also encounter dense fibrosis following neoadjuvant chemotherapy or prior surgical intervention. Attempts should be made to achieve R0 resection, preserving critical structures. Arm care and shoulder exercises to improve range of motion should be recommended routinely

starting from the early postoperative period.

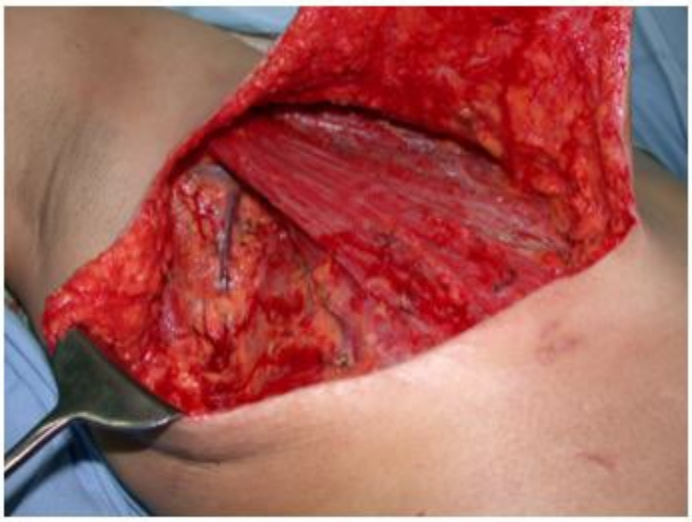


Figure 6: Showing Axillary lymph node dissection.

Types and modifications of ALND: Based on the extent of lymph node dissection ALND can be classified into complete ALND and Level I and II ALND. Complete axillary node dissection involves the removal of all lymph nodes of Levels I, II, and III, whereas with Levels I and II ALND, Level III nodes are spared. Complete ALND is recommended in locally advanced breast cancer with extensive nodal disease due to a higher incidence of Level III involvement (8). ALND modifications revolve around how you handle the pectoralis minor muscle for Level II and III clearance. In the classical description of modified radical mastectomy by Patey, axillary lymph nodes are removed along with the pectoralis minor while preserving the pectoralis major muscle. Subsequently, Auchincloss and Madden described modifications of ALND in which the pectoralis minor muscle is also preserved. A minimum of 10 lymph nodes should be harvested for optimal staging of the axilla using ALND.

Complications of ALND

Apart from routine surgical morbidities like infection, hematoma, and seroma, ALND can be associated with significant morbidity, including lymphedema, neuropathy, and shoulder dysfunction resulting in swelling of the arm, shoulder stiffness, impairment of range of movement, and paresthesias in the upper arm. The incidence of morbidity following ALND ranges from 10 to 50 % and can affect quality of life significantly(12). Significant risk factors for the development of lymphedema include complete ALND, obesity, high axillary disease burden, and postoperative radiotherapy. Prevention and rehabilitation are extremely critical for minimizing the morbidity of ALND.

Sentinel Lymph Node Biopsy (SLNB)

Sentinel lymph node biopsy has been developed as a minimally invasive surgical procedure for staging axilla in breast cancer patients and is a step forward in the overall de-escalation strategy of surgery for breast cancer. This technique was first described by Giuliano in 1994, and subsequently, a number of validation and randomized controlled trials firmly established its role in the surgical management of axillary nodes (12,13). The Sentinel node is the first draining lymph node that receives lymph from the primary tumor, and the rationale for sentinel-node biopsy is that the histology of this first draining lymph node would be representative of the status of the remaining nodes in the axilla. SLNB provides surgeons with information that allows them to avoid unnecessary ALND and its morbidity if the sentinel node is negative. A successful SLNB program involves a multidisciplinary team approach involving nuclear medicine and pathology services. Training and validation of the SLNB technique are mandatory for surgeons planning to initiate SLNB programs. Different SLNB detection techniques are described in the

literature, and blue dye and radioactive tracer-guided techniques are the most widely tried and tested methods. Overall, SLN identification rates range between 85 to 98%, and false negative rates vary between 3 to 10% depending on the surgeon's experience and technique. Patient and tumor-related factors can also influence SLNB detection and false negative rates. Currently, SLNB is well established in HIC and is still evolving in LMICs due to various factors.

Indications for SLNB

I. T1 and T2 breast cancer patients with clinically negative axillary node status.

II. DCIS patients undergoing mastectomy.

III. DCIS patients with suspected invasive cancer.

IV. Patients presenting with negative axillary lymph nodes following neoadjuvant chemotherapy.

Contraindications for SLNB

I. Node-Positive Breast Cancer.

II. Locally advanced and Inflammatory breast cancer.

III. Patients presenting with positive axillary lymph nodes following neoadjuvant chemotherapy.

Special Clinical situations and factors relevant to LMIC

I. SLNB should only be performed if the surgeon is experienced and if necessary resources are available.

II. SLNB may be considered with caution in special clinical situations, including multicentric cancer, prior breast surgery, recurrent breast cancer, pregnancy (only with radioactivity), male breast cancer, and in patients with recurrence in axilla. However, experience in these clinical settings is limited, and the level of evidence is low.

Methods for SLNB Detection: Various methods have been described for SLNB detection, but multiple studies have extensively validated blue dye and radioactive tracer techniques. (14,15) A number of new technologies, including fluorescence imaging, contrast-enhanced ultrasound, and superparamagnetic iron oxide, are under clinical evaluation. The success of radiotracer mapping is superior to that of blue dye, and the success of radiotracer plus dye mapping is superior to that of either method alone. However, the availability of nuclear medicine facilities and gamma detection probes are essential for SLNB using radioactive tracers.

Dye/ Radiotracers used for SLNB

Blue Dye: Six different dyes have been described in the literature for SLNB detection, which include isosulfan blue, patent blue V, methylene blue, Evans blue, indigo-carmine blue, and indocyanine green. However, the most commonly used dyes for SLNB detection are isosulfan blue and methylene blue. Dyes should not be used in pregnant patients.

Isosulfan blue: 1% Isosulfan is the most widely used blue dye for SLNB in HIC, but it is neither freely available nor affordable in LMICs. The advantage of isosulfan dye is its affinity for lymphatics. This dye conjugates with the albumin and stays in the lymphatic channels and sentinel node without any leak into the surrounding tissues. This dye doesn't have major complications; however, anaphylaxis is reported in 0.1% of cases. As makeup contains blue dye, patients with makeup allergies should avoid it. Isosulfan dye can cause bluish discoloration of urine, and patients should be warned prior to the procedure.

Methylene blue: Methylene blue is a water-soluble dye. The major advantage of methylene blue dye is its easy availability and affordability in LMIC. Methylene blue is not associated with anaphylaxis reaction but local reactions such as skin erythema, necrosis, and superficial ulceration are reported in literature following intradermal injection. It can be safely used through a subdermal route. Diffusion into surrounding tissues is more common with methylene blue; hence, injection volume is critical. Studies have shown good outcomes for SLNB detection with methylene blue dye comparable to isosulfan dye (16).

Radioactive Tracer:

The ideal characteristics of a radioactive tracer for SLNB include – the capability for rapid migration and retainment in the draining lymph nodes to facilitate SLN identification, minimal second echelon node spread, low cost, easy availability, and minimal risk of radiation exposure.

Five different radioactive tracers have been used in the detection of SLNB in breast cancer patients, which include technetium Tc 99msulfur colloid, Tc99malbumin colloid, Tc99m dextran, Tc99mrhenium colloid, and Tc99mnanocolloid. The most widely used radioactive tracers are sulfur colloid in the United States and albumin colloid in Europe. Isotopes are available in unfiltered and filtered forms. Larger-sized particles will migrate more slowly, thus visualizing fewer nodes. Smaller-sized particles might migrate too quickly, leading to difficulties in distinguishing between first and second-echelon lymph nodes.

Patient position and anesthesia: SLNB is performed under general, local, or regional anesthesia. Patient positioning is similar to the position used for ALND.

Site, volume, and timing of Injection: Various sites of injection have been tried, and the success rates of SLNB are comparable with peritumoral, intradermal, subdermal, and sub-areolar locations. Due to embryological and anatomical factors, the entire breast parenchyma, including the skin envelope and nipple areola complex drain to a specific group of axillary nodes irrespective of tumor location. Currently, subareola injection before or at the time of induction is the preferred method in most centers practicing SLNB. Generally, blue dye is injected at the time of surgery, and one to two ml of dye is sufficient. Massage of the injection site helps in faster dye migration in lymphatic channels. Radiotracers are typically administered by the nuclear medicine expert a day before surgery or on the day of surgery. The radiation dose used by different investigators ranges between 4 MBq and 120MBq, and the recommended volume of injection is 0.1 to 1.0 ml. Lymphoscintigraphy is not routinely recommended and can be done at the nuclear medicine physician's and surgeon's discretion for specific indications.

Surgical technique

SLNB is a minimally invasive surgical procedure based on principles of navigation and technical expertise is essential for performing a successful SLNB procedure. Familiarity with anatomy and the ability to perform meticulous and precise dissection helps in good functional outcomes. SLNB is mainly performed under general anesthesia, and the patient is positioned in a supine position with extension of the arm at 90 degrees.

SLNB using Radiotracer and gamma probe

A handheld gamma detection probe (Figure 7) is held over the axilla to identify the area of highest radioactivity. A small incision (3 to 5 cm) is made near the area of radioactivity just behind the anterior axillary fold. After opening the clavipectoral fascia, the level I axillary region is entered, and the area between the lateral thoracic vein and the intercostobrachial nerve is evaluated with a gamma probe. The first sentinel node is the node with the highest radioactivity, which is known as the "hot node". Meticulous dissection should be performed for the removal of hot nodes, and over-dissection and damage to critical structures should be avoided. After removal of the node *ex vivo* highest or 10-second count is recorded. All nodes whose radioactive count is 10% of the most radioactive node are considered sentinel nodes and are removed (rule of 10%).

Figure 7: Showing Wireless gamma detection probe and portable display console for SLNB using a radioactive tracer.

SLNB using Blue Dye: After the dye injection and massaging, the axilla is entered through a small (3 to 5 cm) incision behind the anterior axillary fold. After entering the subcutaneous plane surgeon should carefully watch for a blue dye-filled lymphatic tract. The blue-stained lymphatic

is then followed into the axilla until a blue-stained sentinel node is identified (Figure 8).

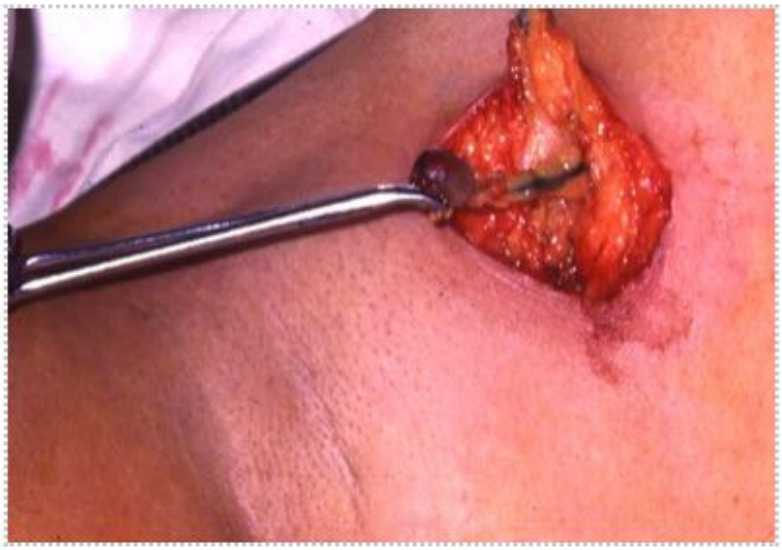


Figure 8: Showing blue stained lymphatic draining into the sentinel lymph node.

SLN biopsy aims to remove “hot” and/or blue nodes and/or palpable and suspicious nodes to accurately stage the axilla. Generally, the number of SLNs varies between one to three, with a median of two nodes in most studies. Staging accuracy does not increase by removing more than three to four nodes.

Histopathology assessment of Sentinel Lymph nodes. The basis of SLNB is to perform a focused and intensive histopathological evaluation of a limited number of lymph nodes. Special expertise is needed for grossing (step sections), frozen section analysis, imprint cytology, and immunohistochemistry. Nodal metastases of sentinel lymph nodes can be categorized as 1. Isolated tumor cells (< 0.2 mm) 2. Micrometastases (0.2 to 2 mm) and 3. Macrometastases (> 2 mm) based on the size of the metastatic focus. In LMICs, conventional histopathology evaluation with H&E staining for identification of macrometastasis can be recommended for routine clinical use.

Complications of SLNB: Many studies have reported significantly lower rates of morbidity rates following SLNB in comparison to ALND. The reported rates of restriction of shoulder movements, neuropathic pain, and lymphedema range between 2 to 10 % following SLNB (17). Various factors, including patient positioning, surgical technique, anatomical variations, and the addition of radiation therapy, can affect morbidity rates following SLNB.

Axillary Node Sampling (ANS)

Axillary Node Sampling (ANS) has been described in the literature as a less invasive surgical staging tool for nodal staging prior to the introduction of SLNB. The primary rationale behind ANS is a sampling of high-risk lymph node stations instead of ALND in early-stage node-negative breast cancer patients. Various techniques of ANS are described including four-node sampling, triple node biopsy, and low axillary sampling depending on the number and lymph node stations targeted (18,19).

Four-Node Sampling: The Edinburgh group described a four-node sample procedure in which the surgeon has to remove by inspection and palpation at least four lymph nodes from the lower axillary fat (level I), and they reported comparable node positivity rates in patients undergoing nodal sampling and clearance.

Triple-Node biopsy: Triple-node biopsy was described by Berg and propagated widely by the Nottingham group. This technique is based on the hypothesis of orderly and stepwise lymphatic spread of breast cancer and provides important prognostic information based on the extent of nodal involvement. In this technique, lymph nodes from three levels - low axillary level, apex of axilla, and internal mammary are removed separately. Triple-node biopsy is technically more challenging than four-node sampling.

Low Axillary Sampling

Vani et al. (19) have described low axillary sampling as an alternative to SLNB for staging axilla in clinically node-negative patients. Their modification of palpation-guided axillary node sampling is a more objective and precise method based on anatomic boundaries, wherein low axillary fat along with a minimum of four lymph nodes are removed between pectoralis major anteriorly, latissimus dorsi posteriorly, serratus anterior medially, and intercostobrachial nerve superiorly.

ANS techniques, especially four-node or low axillary sampling, have the potential to be used as an alternative to SLNB if resources and expertise for SLNB are not available in LMICs. These are simple surgical techniques that do not require expensive resources, and general surgeons can be trained easily.

Summary

The majority of breast cancer patients present with locally advanced stage with high node positivity rates in LMIC. Resources and expertise for axillary nodal staging and SLNB are available in a limited number of centers. ALND is the surgical procedure of choice for node positive patients, and SLNB is recommended for node-negative patients, subject to the availability of resources and expertise. SLNB using blue dye alone or axillary node sampling are reasonable alternatives in resource-constrained settings for managing node-negative patients.

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Chapter 24

Prevention and Management of Breast Cancer-Related Lymphedema

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Introduction

According to the World Health Organization, as many as 170 million people worldwide and 3- 5 million people in the United States suffer from secondary lymphedema. As many and varied procedures have failed to resolve lymphedema, it is our estimation that prevention is the key to avoiding lymphedema, and thus there is a need to optimize breast cancer staging further.

Diagnosis of Lymphedema

Lymphedema is a debilitating condition that is an abnormal swelling due to the accumulation of proteinaceous fluid causing edema. This is an imbalance of the lymphatic interstitial fluid creation rate and lymphatic transport capacity. It is a chronic disease that significantly affects the quality of life for those that it afflicts as it places a financial and emotional burden. Patients with prolonged symptoms have been found to suffer from employment loss, depression, increased medical costs, and difficulty with the ability to perform activities of daily living and recreation.

Breast cancer-related lymphedema is a common complication of breast cancer treatment. The incidence of BCRL increases with combination therapy (surgery, chemotherapy & radiation),

ranging from 25-40%. Lymphedema is staged in 0-3 stages ranging from 0 being subclinical with the absence of clinical edema to 3 being elephantiasis with skin lesions and relapsing infections.

Diagnosis of lymphedema in breast cancer patients is best defined by using objective measurements of the arms. Patients commonly confuse pain of the upper extremity with lymphedema. The National Comprehensive Cancer Network recommends preoperative assessment and ongoing surveillance of bilateral upper extremities to determine in change in size of the affected with the unaffected arm. However, there is no set technique that has been studied and deemed standard of care. A 2-cm increase in circumference or a 10% increase in volume is most commonly used to identify lymphedema. Using multiple points of measurement, arm volumes can be calculated using the formula for a cylinder. There are other methods of measurement, including bioimpedance spectroscopy, tissue dielectric constants, and infrared perometry. These are especially key to the detection of stage 0 or subclinical lymphedema.

Most patients will complain of swelling, pain, heaviness, aching, stiffness, numbness, and impaired arm mobility. However, many patients with clinical lymphedema do not have subjective symptoms. Alternatively, some symptoms, especially pain, may have a root cause in lymphedema. Therefore, all at-risk patients should be screened regardless of symptoms with objective measurement.

It is imperative to measure both clinically reported outcomes as well as patient-reported outcomes. Research on breast cancer-related lymphedema patient-reported outcomes shows that it is multifaceted, including immune dysfunction, swelling, physical impairment, and a psychosocial impact.

One of the most recognized risk factors for breast cancer-related lymphedema is obesity or elevated body mass index (BMI). Additionally, mastectomy (20%) compared with breast-conserving surgical therapy (8%) increases the risk as well as axillary lymph node dissection (ALND) (14%) compared to sentinel lymph node biopsy (SLNB) (8%). This was determined with a 10% relative volume increase as diagnostic criteria. Receipt of radiation therapy increases breast cancer-related lymphedema with an associated higher risk if this was in conjunction with an axillary lymph node dissection. Systemic therapies have also been found to be associated with lymphedema, especially taxane-based chemotherapy.

To reduce risks, patients and clinicians must discuss the risks at the time of diagnosis and before surgical treatment. Post-operatively, avoidance of venipuncture, injection, blood pressure, and compression sleeves for air travel are common but largely unproven ways that patients use to reduce risk. However, pre-operatively patients with high BMI should be counseled on weight loss as well as exercise. The role of exercise for at-risk and affected lymphedema patients is thought to be beneficial and is recommended by the American Cancer Society, Susan G. Komen, and the National Lymphedema Network for at-risk and affected lymphedema patients. Women who use weight-lifting as a part of their exercise routine were found to have relatively less lymphedema as well as less severe lymphedema exacerbations (14% vs 29% in the exercise versus the control group). Care must be taken not to overdo it, as exercise safety is key to adherence and effectiveness in improving lymphedema rates.

Prevention of Lymphedema

The technique of ALND and even SLNB is not standardized, compromising accurate staging and risk of lymphedema. A recent pooled analysis of 6,711 breast cancer patients undergoing SLNB found the incidence of lymphedema to be 6.3% but with a range of 0-23%. A similar

analysis of 5,354 patients undergoing ALND found a pooled incidence of 28% (range 11-57%). (1) Clearly, not everyone is doing the same surgery. Problematic in the de-escalation of surgery is that many times it is replaced with the escalation of radiation to the "undissected axilla," which over time may result in axillary fibrosis and more lymphedema. (2)

Sentinel Lymph Node Biopsy and ALND do not distinguish lymphatics of the breast from those of the upper extremities (UE), as the possibility of mapping the drainage from the UE into the axilla has only recently been published. (3-6) Transection of the UE lymphatics (that can be up to 6mm in diameter) during a lymphadenectomy in patients without significant collaterals, most likely the root cause of lymphedema. Some might say the risk from SLNB is low already (0-13%). However, remember most lymphedema after a SLNB occurs from a SLNB that is pathologically negative. We should strive to lower the risk toward zero of a procedure that ultimately has no benefit to the patient. Unpublished data would indicate that simply reapproximating the afferent and efferent lymphatics after removing the SLN is a simple procedure that should allow reanastomosis of those lymphatics and decrease lymphedema.

Anatomy

Axillary Reverse Mapping (ARM) may be another tool to help us further refine the technique of axillary staging, whether performing SLNB and/or ALND. Klimberg and colleagues have defined the anatomical variations of the drainage of the upper extremity into the axilla. (Figure 1)

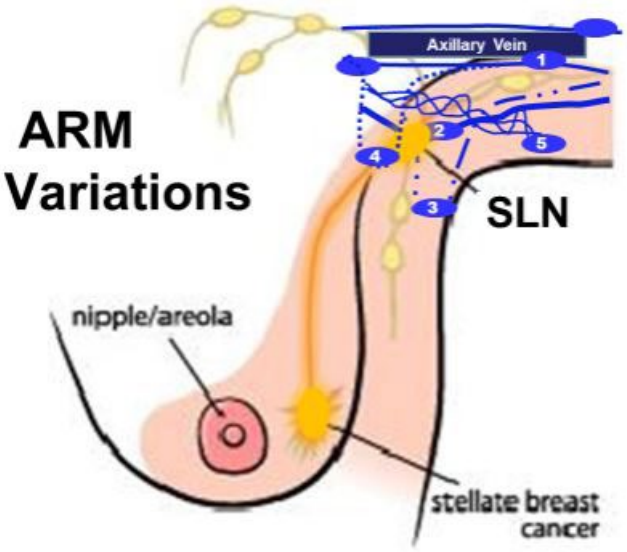

Figure 1: The variations of the lymphatics draining the upper extremity: 1) just below the axillary vein; 2) sling pattern that can dip low into the axilla; 3) lateral apron pattern that can have many nodes but lays over not in the axillary contents proper; 4) medial apron pattern; 5) twine-like pattern or chain of nodes.

Surgical Procedure

In a single institution prospective Phase II trial, 642 patients have undergone 685 ARM procedures with a SLNB and/or ALND (6) Objective lymphedema rates by volume displacement for SLNB and ALND were 0.8% and 6.5%, respectively, with 26-month median follow-up. Blue lymphatics were identified from the SLN incision in 29.2% of patients, meaning they were in harm's way during the SLNB and 71.8% of ALND. Metastases were seen in the blue node, the only node in 4.5% of cases and only in advanced N3 disease. (6) In the subset of patients in the Phase II trial (6) in which an identified blue lymphatic was transected, there was an overall lymphedema rate of 18.7% (9/48) when not reanastomosed/reapproximated, and 0% (0/33) when reanastomosed/reapproximated (p=0.009); this is over an average follow-up of 20 months (range 3-54 months). Similarly, in a randomized pilot trial, Yue and colleagues performed a randomized study in 265 patients undergoing ALND randomized to upper extremity lymphatic mapping (Axillary Reverse Mapping: ARM) versus ALND only. In the control group, 33% developed

lymphedema, and only 6% in the patients with UE lymphatic mapping at 20-month follow-up. (7)

The surgical procedure is demonstrated in this video. (https://youtu.be/v_Ln11PFvVg)

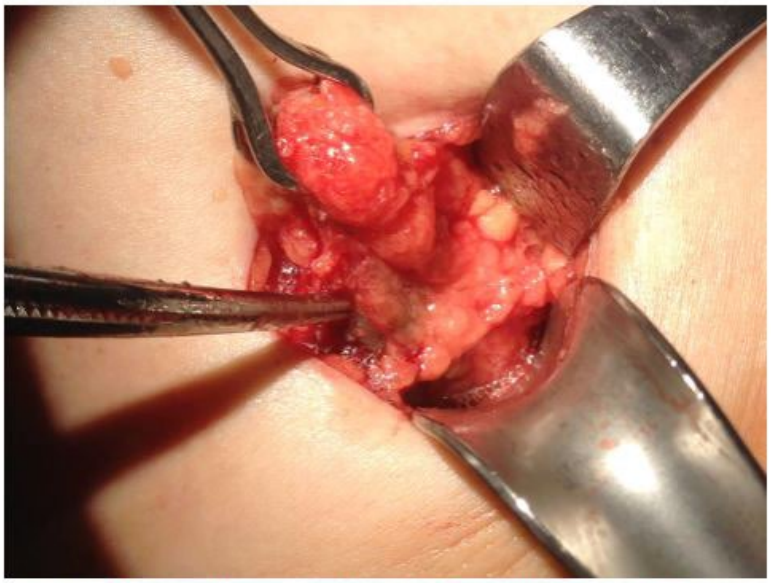

Figure 2: The radioactive node is shown in the Babcock clamp, and the blue node draining the arm is shown at the end of the pointed Cryle clamp.

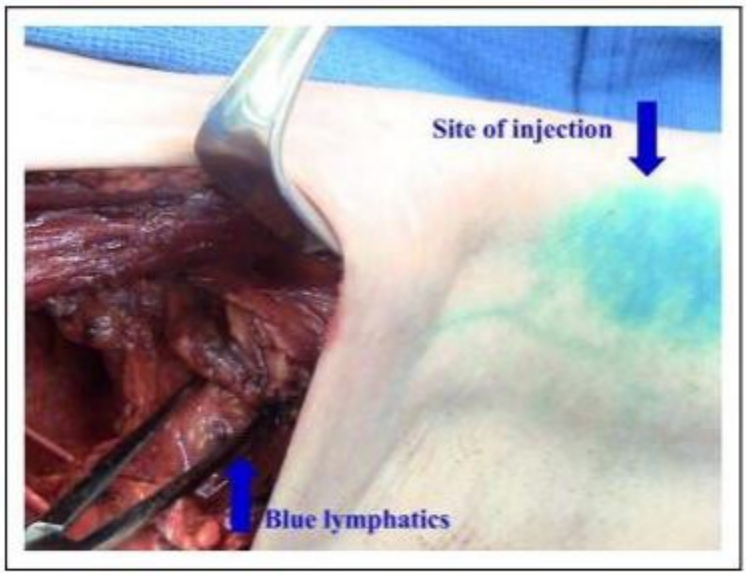

Figure 3: Injection site in the upper inner volar surface of the upper extremity and the blue lymphatics in the pickups.

Radioactivity, ICG, magnetic dye, or carbon can be injected into the breast to find the SLN shown in the Babcock clamp in Figure 2 and blue dye in the upper inner volar surface of the upper extremity, which will demonstrate the blue node and lymphatics draining the arm (shown in Figure 3 at the end of the pickups).

Thus, any surgeon practicing could apply this technique to their practice of lymphadenectomy with minimal training and cost, with a potential benefit to the patient in preventing or mitigating surgical lymphedema. It does not require a microscope and can be done with

loops and a 9.0 prolene, or alternatively, simply tying the lymphatics together with an absorbable suture. If you do not use radioactivity in the breast in your area, you can still use blue dye in the upper extremity in the upper volar surface of the ipsilateral upper extremity. In such a case, it is essential to take any suspicious nodes and reapproximate/reanastomose the afferent and efferent lymphatics as they will reanastomose. (Figure 4)

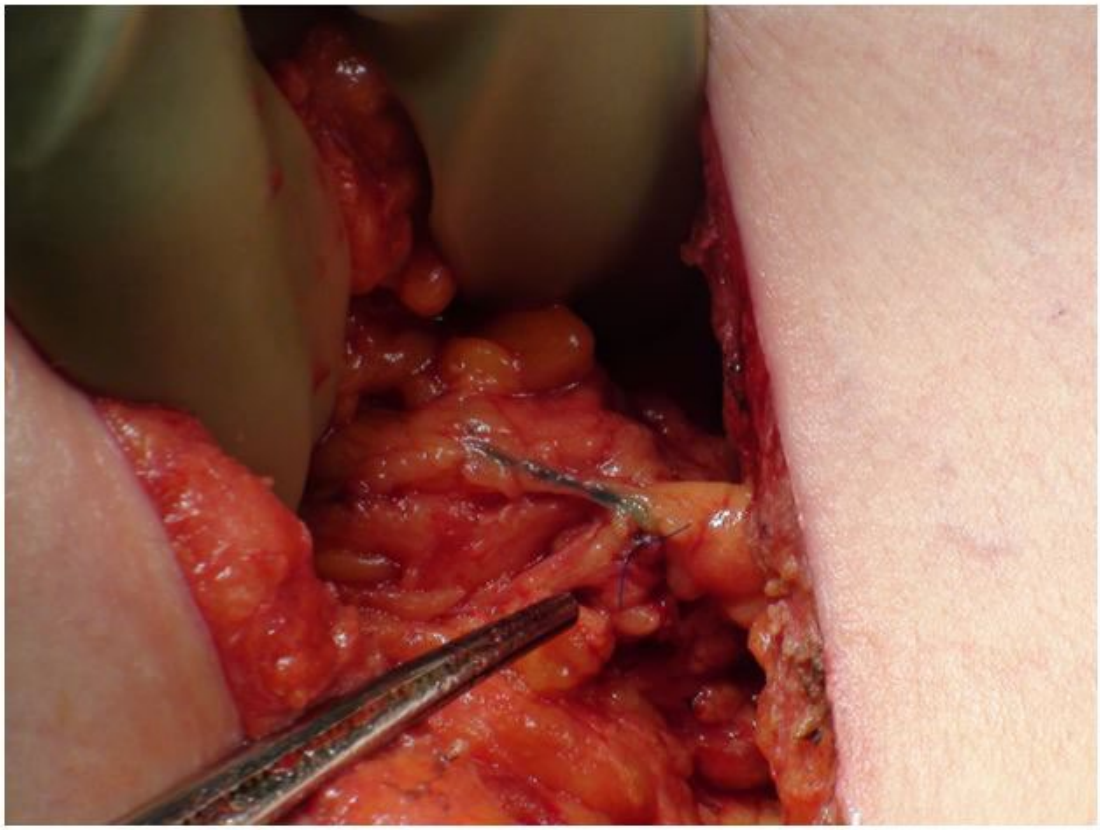

Figure 4: Reanastamoses of afferent and efferent lymphatics.

Treatment of Lymphedema

One in five patients will present with lymphedema after an axillary procedure. Combined decongestive therapy is the accepted standard of care for breast cancer-related lymphedema and other acquired causes of lymphedema. This consists of compression bandaging, physiotherapy (including but not limited to massage and exercises), and skincare. By utilizing these techniques,

patients suffering from lymphedema have reduced limb girth, fibrosclerosis, sepsis risk, and disability due to impaired mobility. This combined decongestive therapy must be employed prior to surgical therapy.

Lymphovenous bypass has been demonstrated to reduce early-stage lymphedema effectively. Lymphatic-venous anastomosis is a procedure that creates multiple proximal new anastomoses using lymphatic collectors below the flow obstruction. The pressure gradient and venous valves promote lymphatic flow. This microsurgical reconstructive procedure must be done in the early stage in order to be able to utilize normal lymphatics before fibroadipose deposition occurs.

Lymph node transfer is an evolving technique. The indications and ideal operative candidates are determined by lymphoscintigraphy as well as indocyanine green fluorescence. The transfer of skin tissue with or without lymph nodes can establish flow across areas of congestion in lymphedema. It can have a simultaneous advantageous effect on scar tissue to treat contractures and accomplish venous stricture lysis that has been found to contribute to lymphedema as well as restore subdermal lymphatics. Lymph node transfer has also been found to increase vascular endothelial growth factor C (VEGF-C) and possible regeneration of lymphatics. Challenges of this technique include the risk of donor-site lymphedema, more likely in the groin and axilla. Reverse lymphatic mapping may aid in reducing this risk by avoiding lymph nodes that drain the extremity. Alternative locations for harvesting include cervical, submental, mesenteric, gastroepiploic, and omental, but these should be weighed with their own risks and associated morbidities.

Liposuction is a debulking technique used in patients with severe late-stage or refractory lymphedema. It removes the accumulated fat and fibrotic tissue but does not address the

underlying pathology. Therefore, these patients will require continuous compression and possible repeated procedures.

Summary

The best approach to breast cancer-related lymphedema is to prevent it by performing SLNB and careful attention paid to reapproximating afferent and efferent lymphatics. The same can be done when an ALND is necessary. Careful attention to protecting the upper extremity may be helpful, especially prevention of infection. When lymphedema does occur, combined decongestive therapy is the first step. If lymphedema is still uncontrolled, lymphovenous bypass or lymph node transfer may be helpful.

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Chapter 25

Management of Non-Invasive Breast Cancer

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Keywords: carcinoma in situ, lobular neoplasia, invasive breast cancer, risk reduction strategies, de-escalation, surgery, chemoprevention

Case Scenario

Management of Ductal Carcinoma In Situ

A 33-year-old woman felt a lump on her left breast two months after stopping lactation. She has no personal or family history. A bilateral mammogram and breast ultrasound (US) was performed. The mammogram showed heterogeneous microcalcifications in an area of 2 cm (Fig.1), and breast US showed multiple cysts with internal echos (Fig.2). An US-guided core biopsy was performed, and the pathology report showed ductal carcinoma in situ, high grade, solid and cribriform. Axillary US showed no suspicious nodes. After discussing treatment options, breast conservative surgery with the oncoplastic procedure (lateral mammoplasty) was decided. (Fig. 3) Pathology showed a high grade of DCIS, 3 cm in size, ER positive, PR negative with negative margins. The patient received whole breast radiation therapy, and Tamoxifen was discussed. No BRCA mutation was identified.

Introduction

Ductal carcinoma in situ (DCIS) is a noninvasive breast cancer that originates from the epithelial cells that line the breast ducts and, by definition, lie inside the intact basement membrane without any basal myoepithelial layer invasion. It ranges from low-grade, intermediate to high-grade tumors that differ in histologic appearance and biological potential, and it can be a precursor to invasive disease. Before screening mammograms, DCIS was primarily diagnosed as a symptomatic disease, usually with a palpable mass or nipple discharge. Nowadays, it is mainly diagnosed as a mammographic finding. In the era of screening mammograms, DCIS can represent up to 25% of new breast cancers and as much as 33% of mammographically detected breast cancers. (1) Nevertheless, this increasing rate of detection has not shown a decline in invasive breast cancer incidence, and this suggests that in some DCIS, overdiagnosis and overtreatment exist. The problem is knowing which patients will have DCIS progress into invasive disease.

Risk factors for DCIS are similar to invasive disease, and they include a family history of breast cancer, being a mutation carrier (BRCA1/2), increased breast density, obesity, and nulliparity or late age at first birth. (2)

Diagnosis

Radiology

Mammography is a highly sensitive diagnostic procedure for detecting DCIS (>90%). Calcifications are the main mammographic finding, with approximately 75% of lesions presenting only as calcifications. (Fig. 1) These are mainly of two types: fine pleomorphic and

fine linear, with a clustered (at least five microcalcifications in a small volume of tissue: <1cc) or linear distribution (ductal extension).

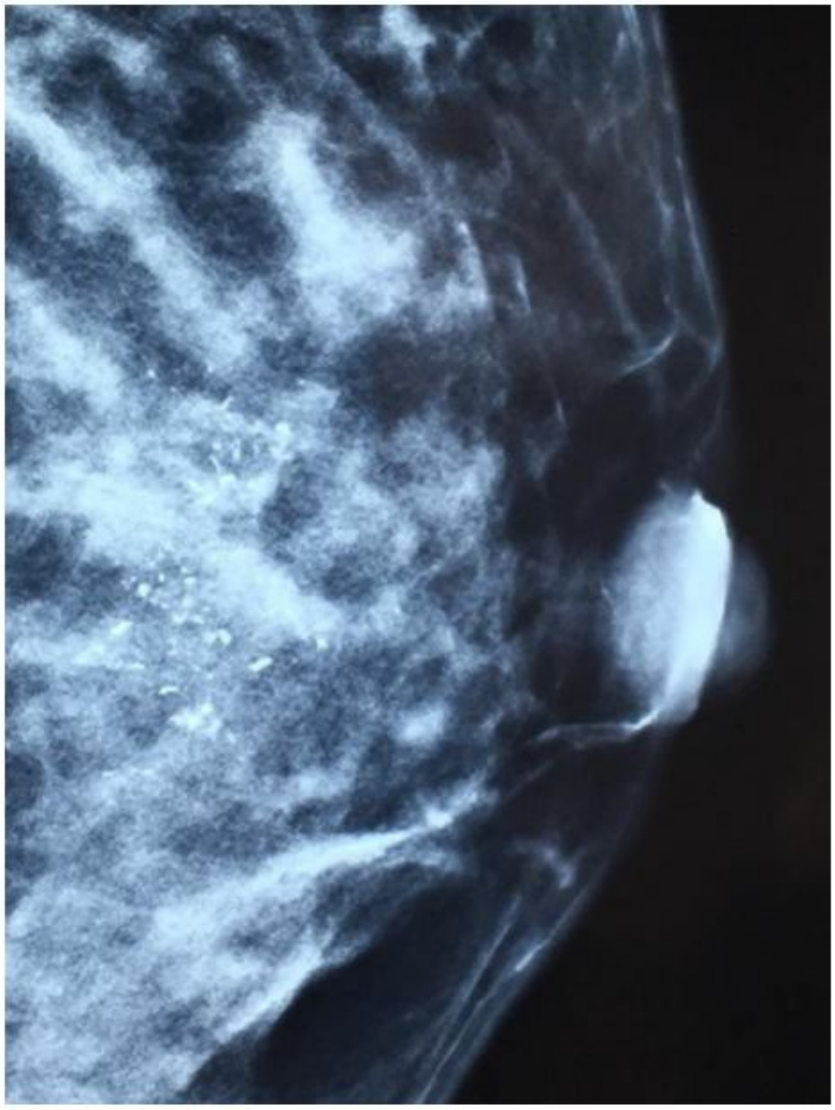

Figure 1: Pleomorphic cluster of microcalcifications highly suspicious for DCIS

The distribution of microcalcifications is commonly used as a guide to assess DCIS size or the dimension of the target zone, but this can involve heterogeneous and omitted areas, which is why DCIS lesions are often underestimated by mammography. The use of digital breast

tomosynthesis has been controversial as the increased detection of DCIS may lead to overdiagnosis and overtreatment. (3)

Breast ultrasound (US) is not standard in the evaluation of mammographically detected calcifications, although the US can visualize microcalcifications associated with DCIS with high-frequency transducers, helping direct US-guided biopsy.

The literature reports that approximately 50% of DCIS lesions are visible on ultrasound, usually as an irregular hypoechoic mass with uncircumscribed margins, parallel orientation complex mixed cystic (Fig.2), and solid mass without posterior features. Also, it can be reported as microcalcifications, architectural distortion, or ductal abnormalities. Some of these findings are indistinguishable from invasive carcinoma.

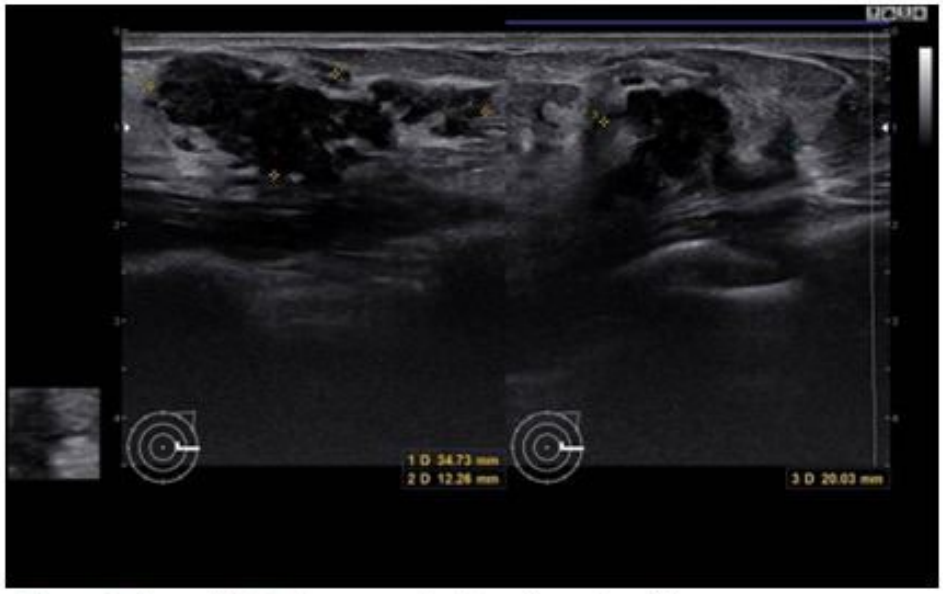

Figure 2: Breast US shows a mixed cystic and solid mass

Several studies support that calcifications, irregular shape, posterior shadowing, distortion, and ductal changes were more frequently associated with high-grade or comedo DCIS.

The role of preoperative magnetic resonance imaging (MRI) in DCIS remains controversial, with diverging results in different studies. Recently, Yoon et al. concluded that preoperative breast MRI showed additional malignancy in US-guided biopsy-confirmed DCIS, diminishing positive surgical margins and repeat surgery rates without affecting the mastectomy rate. However, Fancellu et al. concluded in a meta-analysis that there weren´t significant differences between the proportion of women with positive margins and indicated that patients undergoing preoperative MRI were significantly more likely to have initial mastectomy. (4) Therefore, further research is needed to evaluate the preoperative MRI role in DCIS.

The most common presentation of DCIS on MRI is a non-mass enhancement in a linear or segmental distribution pattern. MRI can miss low-grade DCIS, which is more sensitive for high-grade and intermediate-grade DCIS.

Pathology

There are several architectural subtypes of DCIS: solid, comedo, micropapillary, papillary, and cribriform. DCIS is also classified by nuclear grade and the presence or absence of necrosis. Sometimes, two different types may concur in the same specimen. In the DCIS diagnosis, there are two issues that impact treatment and prognosis. First, distinguishing DCIS from atypical ductal hyperplasia (ADH) is challenging for pathologists. The continuum of lesions that range from ADH to DCIS makes it challenging to differentiate in a core biopsy, and this disparity in diagnosis has been reported in a study where 115 pathologists interpreted breast cases. A high level of diagnostic agreement existed for high-grade DCIS; however, agreement was markedly lower for low-grade DCIS and relatively similar in magnitude to agreement for atypia. (5) Importantly, differentiating clearly between low-grade and high-grade DCIS is crucial to determining the appropriate treatment and reducing overtreatment in DCIS indolent lesions.

Secondly, rates of upgrade to invasive breast cancer in the resection specimens from patients who were primarily diagnosed with DCIS based on a preoperative biopsy have been reported to range from 8–43%. Some of these highly variable numbers can be explained by differences in the size and quantity of biopsies taken as well as by the use of different imaging techniques. In addition, it is essential to be informed about how the biopsy was taken.

Risk Factors and Prognosis

Several reports have identified risk factors that influence DCIS prognosis. Younger age at diagnosis is a consistent adverse prognostic factor for DCIS outcomes. Estrogen receptor positivity has been reported to be linked with a decreased risk of recurrence; usually, low-grade and intermediate DCIS express ER positivity. Her2 positivity is not tested in a DCIS diagnosis, although in some studies, it has been linked to an increased risk of recurrence. There are ongoing trials, such as NSABP B43, on the use of antiHer2 therapy in DCIS that will shed light on the indications and treatment in these cases. Several studies have shown that high-grade DCIS has a higher probability of ipsilateral invasive breast cancer (IBTR) than low-grade DCIS. The study conducted by The Eastern Cooperative Oncology Group (ECOG) with 670 patients with DCIS and excision showed that at a median follow-up of 6.7 years, the low-intermediate group had a 10.5% risk of local relapse, whereas the high-grade group had an 18% recurrence rate, of which 35% were invasive breast cancers. (6)

A positive margin, defined as the presence of ink from the specimen surface on ducts containing DCIS, is associated with increased DCIS and invasive breast cancer recurrence. Controversy has existed regarding adequate margin width for women with DCIS undergoing breast conservative surgery with radiation therapy. Even though it has been shown that around 30.7% of women with DCIS undergoing attempted BCS will undergo additional surgery for margin re-excision,

nowadays, with the improvements in imaging, pathologic evaluation, and hormone therapy treatment, there has been a decline in IBTR.

There is considerable debate, however, regarding whether the width of a negative margin (width of a margin negative for tumor cells) is associated with a decreased risk of recurrence, and classification of the margins makes summary statements difficult. Some of these difficulties have been addressed by the Consensus of the Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ supporting the conclusion that margins of at least 2 mm are associated with a reduced risk of IBTR relative to narrower negative margin widths in patients undergoing WBRT. The evidence does not support the routine practice of obtaining negative margin widths wider than 2 mm. (7) In a study by MD Anderson, it has been shown that since the guideline publication, surgeons are less likely to perform re-excision to obtain a margin greater than 2-mm and more likely to perform re-excision to obtain a 2-mm margin for both pure DCIS and DCIS-M. (8)

Close margins after mastectomy have also been reported as an independent factor for LRR, although rates of close or positive margins occur in a minority of patients. Re-excision of the positive margins or postmastectomy radiation therapy (PMRT) are options for treatment. A large study has shown that as the LRR rate in patients with close margins is low, PMRT is not warranted except for patients with multiple close/positive margins that can- not be surgically excised. (9)

Delayed treatment in breast cancer surgery has always been controversial in the impact on outcomes, with variability in the results. In a recent study, including 123,947 patients with a diagnosis of DCIS, increasing delay to surgery in more than two months was an independent predictor of invasion. Again, a better prediction tool of which subset of DCIS will develop an invasive component is crucial to personalize surgical treatment better. (10)

It is essential to identify risk factors for recurrence after DCIS, as women who develop an invasive ITBR experience an increased risk of death from breast cancer. Nevertheless, there are some cases of DCIS that have an inherent potential for distant metastatic spread without going through the invasive recurrence, and this is the paradox of DCIS. Mortality from DCIS is low, and data have reported 10-year breast cancer–specific mortality rate after a diagnosis of DCIS to be 1.1% and a rate at 20 years to be 3.3%. (11) No significant differences in survival have been found when comparing mastectomy and lumpectomy similar to what is seen in invasive breast cancer.

Treatment

Breast Conservative Surgery/Mastectomy

The indications for BCS in DCIS are the same as for invasive cancer. Excision of DCIS with negative margins and achieving a good cosmetic result are the primary considerations for BCS. BCS, followed by radiotherapy (RDT), offers long-term survival outcomes equivalent to that with mastectomy alone and is an option for many patients, even though, for many years, mastectomy has been the primary option for DCIS. With the increasing use of oncoplastic techniques, some of the indications for mastectomy can be solved with oncoplastic BCS, as some cases of multicentric DCIS and extensive DCIS require a mastectomy and are amenable to skin-

sparing or nipple skin-sparing mastectomy (Fig.3). (12) Other patients desire or benefit from mastectomy, such as cases of unattainable negative margins, large tumor size relative to small breast size, and those BRCA mutation carriers who developed a DCIS.

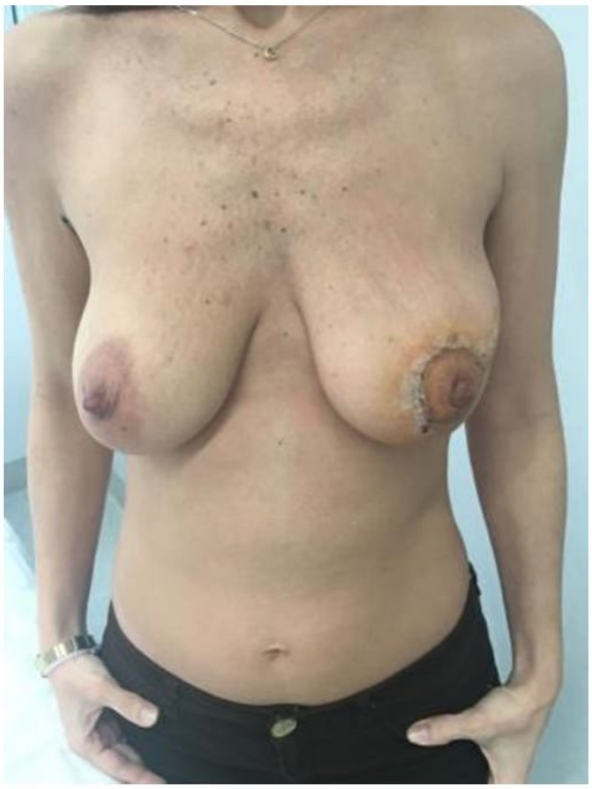

Figure 3: Lateral mammoplasty for extensive DCIS

In the case of mastectomy, nipple-sparing mastectomy plus immediate breast reconstruction is an option that has been proven to be safe and has the lowest local recurrence rate at one to two percent lifetime but the same survival as BCS. Many patients choose to undergo bilateral mastectomies even though rates of contralateral breast cancer in a DCIS diagnosis are very low (For a woman undergoing BCS for DCIS, the 10-year IBTR rate is 2.5-fold higher than the CBC rate), and prophylactic mastectomies have shown not to add any survival benefit. When considering different options, the use of adjuvant hormone therapy, the need for radiation, the survival benefit, and complications should be part of the decision-making process. (13)

Another question has been the benefit of adding whole breast radiation therapy (WBRT) to BCS. Four prospective randomized trials have been published to date comparing excision alone with excision followed by radiation therapy (with or without tamoxifen). These trials treated the whole breast to 50 Gy in 5 weeks without a boost. The NSABP B-17 trial, with a follow-up at 20 years, included patients with localized DCIS with negative margins following excision. The 12-

year data revealed that radiation therapy significantly resulted in a greater reduction in the incidence of invasive recurrences but also significantly reduced noninvasive recurrences (RR = 0.49; *P* = .001). Local failure was significantly increased for patients with questionable or positive surgical margins and for those with marked to moderate comedonecrosis. others have shown (14) Similar results, and a large meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), including 3729 women in four randomized trials of lumpectomy with versus without radiation treatment, have shown that adding radiation treatment after BCS reduced the 10-year rate of local recurrence in the ipsilateral breast from 28.1 to 12.9% ($p < 0.00001$) and reduced the 10-year rate of the subset of invasive local recurrence in the ipsilateral breast from 15.4 to 6.8% ($p < 0.001$). There were no differences in the 10-year rates of breast cancer mortality or mortality from all causes. (15)

Many studies have examined in which patients may WBRT possibly be spared. Most of the trials, even those designed to answer this question, such as the RTOG 98-04 trial (16) closed early due to low accrual. Even when patients were treated with different RDT regimens, the 7-year recurrence rates were 6.7% without radiotherapy vs 0.9% with radiotherapy (*P* = .0003). This trial reinforces the idea that all patients with DCIS (even those with favorable clinical and pathologic features) will have a lower chance of local recurrence with RDT after BCS, but still, the magnitude of the benefit in terms of clinical significance is small in a subgroup of patients, and this needs to be discussed with the patients when considering RDT in this subgroup of favorable prognosis. All the studies show reduced local recurrences with no impact on survival with the use of RDT after BCS. Rates of IBTR are decreased with the use of RDT, regardless of the variable risks of recurrence for every single woman.

Regarding the use of partial breast irradiation (APBI), the American Society for Radiation Oncology (ASTRO) considered that patients with low-risk DCIS should be considered suitable for APBI if they meet all aspects of the definition of "low-risk" DCIS from RTOG 9804, including screen-detected disease, low to intermediate nuclear grade, tumor size ≤ 2.5 cm and surgical resection with margins negative at ≥ 3 mm. The Breast Cancer Working Group of the European Society for Therapeutic Radiology and Oncology (ESTRO) defined three categories for patient selection for accelerated PBI; of these, DCIS was placed in the "intermediate risk" group.

Management of the axilla in DCIS

There is no role for axillary lymph node dissection (ALND) in the surgical treatment of DCIS due to the lack of invasiveness and metastasis. Nodal involvement in DCIS likely represents occult microinvasion that has not been diagnosed due to technical limitations in specimen pathological assessment. Since the introduction of SLN, there has been a controversy over its use. Metastasis to the SLN has been reported to be from 2% to 12%, but the clinical relevance of a positive SLNB in the setting of pure DCIS has not been demonstrated.

One of the reasons for performing a SLN is the rate of upgrade to invasive cancer, which has been reported to be as many as 9% to 33% of patients. (17) Indications vary among breast cancer guidelines and include a solid mass on imaging, extensive calcifications, lesions larger than 25 mm on imaging, a palpable mass, or high-grade DCIS. Nevertheless, it seems that the clearest indication is in patients undergoing a mastectomy since it cannot be performed once the breast has been removed. SLNB should no longer be performed in patients diagnosed with DCIS on core biopsy in the case where they are treated with BCS, as SLNB can still be performed with the same accuracy after BCS if the final pathology reveals invasive breast cancer.

Hormone therapy

The role of tamoxifen has been investigated in two large trials. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial, (18) all women with DCIS received radiotherapy before being randomly assigned to tamoxifen or a matching placebo. After a median of 6 years of follow-up, a significant 37% reduction in breast cancer recurrence was observed with tamoxifen compared with placebo. No significant benefit was seen in ER-negative DCIS. In the UK/ANZ DCIS trial, (19) 1578 women with excised DCIS were randomly assigned to receive tamoxifen with or without radiotherapy. After a median of 12·7 years of follow-up, tamoxifen significantly reduced all new breast cancer events by 29%, with a significant impact on ipsilateral DCIS recurrence and contralateral tumors but no effect on ipsilateral invasive recurrence.

Aromatase inhibitors, such as anastrozole, have been tested in the IBIS II trial in patients with ER-positive or PR-positive DCIS treated by wide local excision with or without breast radiotherapy. (20) The trial did not show the non-inferiority of anastrozole to tamoxifen, nor a significant superiority efficacy.

Anastrozole can be considered another option for postmenopausal women with ER-positive DCIS. Previous patient conditions such as osteoporosis, thrombosis or tolerability should be taken into account when considering the choice between tamoxifen and anastrozole.

Ongoing studies such as the NSABP-37 are examining the comparative effectiveness of tamoxifen and aromatase inhibitors.

Molecular Profiling

One of the main issues in the management of DCIS patients is the ability to determine biomarkers that can separate aggressive from indolent DCIS. Separating both will help in reducing overtreatment for those patients who do not benefit from treatment. Actually, there is only one commercially available multigene expression panel, 12-gene Oncotype DX Breast DCIS assay, which was developed to stratify individual patients with DCIS into groups with different degrees of risk for local recurrence. (21) This assay is supported by two validation trials that used retrospective samples from patients with surgically excised DCIS who did not receive radiotherapy. However, no prospective evidence exists for the Oncotype DCIS Score to demonstrate the validity of changing patient outcomes. Future trials are ongoing to validate the DCIS signature prospectively.

Newer technologies are being developed to identify the DCIS aggressiveness, such as next-generation DNA and RNA sequencing, to identify potential genomic biomarkers that will add or replace current histopathologic risk stratification to classify more accurately low versus high-risk DCIS.

Clinical Trials on No Surgery

With the increasing rates of DCIS diagnosed in screening mammography, a question has been raised on the overtreatment in some patients that may never progress toward invasive breast cancer, particularly low-grade DCIS. Because of these concerns, three prospective randomized clinical trials in the USA and Europe are currently in progress to address de-escalating therapy for patients with newly diagnosed, low-risk DCIS. In the USA, the COMET (Comparison of Operative to Monitoring and Endocrine Therapy; ClinicalTrials.gov identifier NCT02926911) randomizes patients to guideline-concordant (standard) care versus active surveillance. In the

guideline-concordant care arm, the treatment is surgery (lumpectomy or mastectomy) with or without radiation treatment. Only a core biopsy showing DCIS (or incomplete excision) is required in the active surveillance arm. Hormonal therapy is optional in either study arm. (22) In Europe, the two open randomized clinical trials for low-risk DCIS are the LORD (Low-Risk DCIS; ClinicalTrials.gov identifier NCT02492607) study and the LORIS (Low-Risk DCIS; Cancer Research UK [United Kingdom]) study. (23, 24) Both studies randomize patients to standard treatment (including surgery) versus active surveillance. In the standard treatment arm, treatment options are wide local excision (with or without radiation treatment) or mastectomy, and hormonal therapy is optional. In the active surveillance arm, only a core biopsy showing DCIS is required. Despite problems with accrual, results from these ongoing trials will gather evidence to help future patients with low-risk DCIS to choose from standard therapies or active surveillance.

- There are increasing rates of DCIS due to screening mammograms
- A mammogram is the most sensitive method for the detection of DCIS. The use of breast MRI for patients with DCIS is not yet established
- Breast conservative surgery has similar survival to mastectomy. Extensive DCIS can be surgically removed using oncoplastic BCS.
- Whole breast radiation therapy after BCS has been shown to decrease local recurrences with no impact on survival. Local recurrence after mastectomy is lower than with BCS
- SLN is recommended in patients who undergo mastectomy for DCIS
- Hormone therapy decreases the risk of local recurrence and contralateral breast cancer. The benefits and risks of various endocrine therapies need to be discussed.

- Distinguishing between indolent and harmless DCIS is crucial to personalize treatments and avoid overtreatment
- De-escalation of treatments will depend on results from various ongoing trials.

LCIS Case Scenario

Management of Lobular Carcinoma In Situ

A 50-year-old woman, asymptomatic, was referred to our clinic from the breast cancer screening program. No family history of cancer. Mammography revealed three clusters of heterogeneous microcalcifications <1 cm separated by 16 and 28 mm (BI-RADS 4a) (Fig 4). Ultrasound showed no pathological findings at the breast or axilla. Stereotactic vacuum-assisted biopsy was performed on the two most separated clusters, and visible US clips were placed at the biopsy site. Pathology reported microcalcifications with two foci of LCIS, 1.6 and 1.4 mm in size. The patient underwent ultrasound-guided breast-conserving surgery. Final pathology reported LCIS foci in the three clusters of microcalcifications. Chemoprevention was discussed.

Introduction

Lobular carcinoma in situ (LCIS) was first described by Foote and Stewart in 1941 as a rare form of breast cancer originating in lobules and terminal ducts. LCIS is usually an incidental finding in a breast core needle biopsy (or surgical biopsy), so it is difficult to establish the actual incidence. Some studies report rates of 0.5-1.5% of benign breast biopsies and 1.8-2.5% of all breast biopsies. Most of the time, the diagnosis of LCIS is due to mammographic findings; the most common are calcifications (80%), as the case study, or architectural distortion (13%). They usually do not have any sonographic alteration, and on MRI, they may be associated with non-mass-like abnormalities in 71% of the cases. (25)

LCIS usually appears in premenopausal women at a mean age of 49 y/o (median 50 y/o), it is multicentric in 60-80% of the cases, and it may appear in both breasts in 20-60% of patients.

The presence of LCIS is a risk factor and a non-obligate precursor of breast carcinoma. Compared with the general population, LCIS has a seven to 10-fold increase in breast risk. This means an increase in the absolute risk of developing ductal carcinoma in situ or invasive carcinoma ranging from 11 to 28% at 15 years, with a persistent risk over time. (26) Currently, LCIS may be managed with surveillance risk reduction via chemoprevention or with surgery.

Diagnosis

Radiology

Most of the patients diagnosed with LCIS are asymptomatic. In a study by King et al. (26), including 1060 patients with an LCIS diagnosis, the majority (70%) presented with LCIS after a breast biopsy performed by abnormal findings in a mammogram or breast ultrasound. Only 21% of the patients were found to have LCIS for a palpable mass or nipple discharge. Only 4% of the patients were diagnosed after MRI alterations and 3% incidentally after benign surgery like reduction mammoplasty.

LCIS is clinically undetectable, principally detected by suspicious microcalcifications at screening mammography. Calcifications are the main finding of LCIS in mammograms (46-90%). Amorphous clusters or coarse heterogeneous calcifications are the most common morphologies. Less often, they can appear as masses, focal asymmetry, or architectural distortions associated with LCIS. In this case, the patient had microcalcifications on the

screening mammogram. (Fig 4)

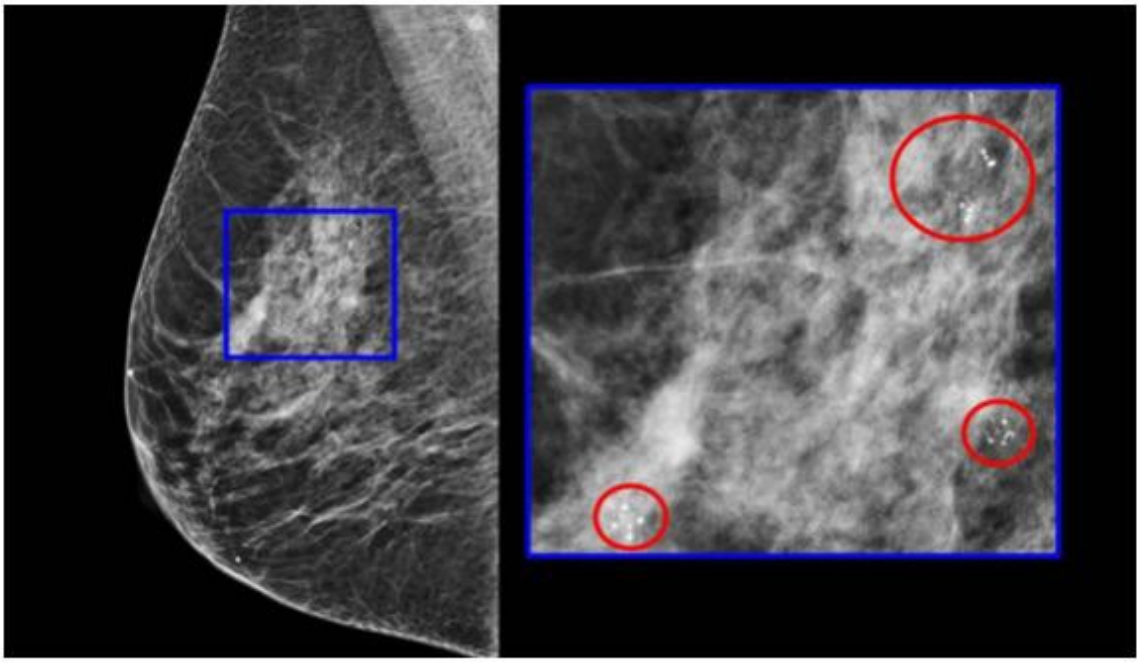

Figure 4: Screening mammogram with three clusters of microcalcifications

Commonly, LCIS is not associated with a mass that can be visualized by breast US unless it shares another diagnosis. In recent years, with the use of a high-frequency transducer by experienced operators, most of the time, it is possible to identify the cluster of microcalcifications by the US, being able to perform ultrasound-assisted breast biopsy, which is faster, cheaper, and more comfortable for the patient than stereotactic-assisted biopsies.

There are very few reports about LCIS findings in MRI. LCIS is described by MRI as an unspecific regional non-mass enhancement with initial fast enhancement and persistent in the delayed phase, or, less frequently, mass enhancement with heterogeneous internal signal. Although a diagnosis of LCIS means a risk factor for developing breast cancer, routine MRI for follow-up in these patients does not result either in increased cancer detection rates nor earlier stage at diagnosis. (27)

Pathology

Microscopically, LCIS is a monomorphic proliferation of non-polarized cells with a round/oval shape. Nuclei are round, small, and located in the center of the cell. (Fig.5) Intracytoplasmic vacuoles are common. Cell borders are indistinct. Usually, mitotic activity is absent. This proliferation happens in the terminal ductal lobular units, filling>50% of the acini. Classically, LCIS is positive for estrogen and progesterone receptors but negative for Her2, though at present, there is no recommendation to test for Her2. There is also complete or partial loss of e-cadherin.

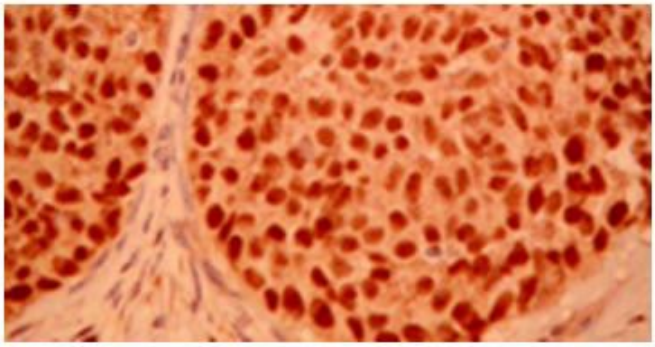

Figure 5: Proliferation of non-polarized cells with round/oval shape

There are variants of LCIS that exhibit different pathologic and prognostic characteristics. Pleomorphic LCIS (P-LCIS) was first described in 1996 by Frost et al and used the term "pleomorphic" due to the similarity to the pleomorphic invasive lobular carcinoma. Histologically, central necrosis and calcifications are common, and mitoses are evident. This variant closely mimics ductal carcinoma in situ, however P-LCIS cells may be differentiated because they are dyshesive, do not have polarity or form secondary lumina, remain negative for e-cadherin and P120 Catenin is located in the cytoplasm. P-LCIS usually is detected in mammograms as an area or calcifications or architectural distortion, and less frequently as a mass lesion (with or without calcifications). In this variant, patients tend to be older compared to classic LCIS and most are postmenopausal.

(28) The most significant difference to classic LCIS is that this variant has a higher risk of upgrade to invasive cancer (20-25%).

Another variant is LCIS with necrosis (N-LCIS) characterized by a massive expansion of the acini and central necrosis. These necrotic foci often harbor calcifications. N-LCIS usually appears in older women and is commonly associated with invasive carcinoma (up to 67% of the cases, mainly invasive lobular carcinoma). (29)

Risk factors and Prognosis

Ispilateral	
Years after LCIS	Risk of breast cancer
5	8%
10	15%
15	27%
20	35%
23	>50%

Contralateral	
Years after LCIS	Risk of breast cancer
10	10%
15	15%
20	25%

Table 1: Cumulative risk of breast carcinoma after LCIS

Some studies have reported that a family history of breast cancer increases the risk for LCIS patients while others have reported that family history does not modify this risk. Other factors that have been considered to modify the risk are age at diagnosis, extent of LCIs or mammographic density, although none of them with convincing results.

In the study by King, including 1060 patients with a diagnosis of LCIS, cumulative risks for developing an invasive carcinoma were around 2% per year after LCIS diagnosis (26) and may

reach up to 50% after 23 years or 25% after 20 years in the contralateral breast. After LCIS presentation, the mean time to cancer diagnosis is 50 months. Subsequent breast carcinoma included ductal carcinoma in situ in 35% of patients and 65% invasive carcinoma (equal proportion of lobular and ductal histologies), with 85% of them being hormone receptor positive. With respect to the distribution of breast cancer, 63% of them are ipsilateral, 25% contralateral and 12% bilateral (around 60% of them synchronous). (26) (Table 1)

In an effort to accurately assess patients and help with the decision making when there is a LCIS diagnosis, multiple models have been developed. One model that incorporates both personal and family history risk factors with personal history of benign breast disease, including LCIS, is the Tyrer–Cuzick TC) model. This model has been applied to 1192 women with a median follow-up of 6 years showing that the TC model is not accurate and may overpredict IBC risk for women with LCIS. (30)

Models are not perfect and one of the interesting findings is that the addition of risk factors, such as family history, among women with atypical hyperplasia and LCIS has not been found to be an additive risk factor among women with high-risk breast lesions and this confirms the idea that all of the risk factors are independent and cannot be simply multiplied together, and this is why the models may overpredict invasive risk.

Because progression to invasive cancer is the key, there is a critical need for better predictors of progression to invasive disease. Several studies have reported that the molecular characteristics of the lesion, including genetic aberrations in important signaling pathways, and alterations in EMT pathways are determining the progression of LCIS. Distinguishing between benign pre

invasive lesions and the harmless ones will allow for better personalized treatments in the LCIS diagnosis. (31)

Treatment

In the last AJCC staging system, LCIS has been removed from the staging and is no longer included in the pathologic tumor in situ (pTis) category. LCIS is treated as a benign entity with an associated risk for developing carcinoma in the future but not as a malignancy capable of metastases. Even the pleomorphic LCIS that partially overlap the features of ductal carcinoma in situ (DCIS), there is insufficient data in the literature regarding outcomes and reproducible diagnostic criteria for this LCIS variant to assimilate it to DCIS in the staging system. (32)

There are two main options for the management of LCIS: Surveillance with or without chemoprevention and surgery.

Surveillance with or without chemoprevention

Current National Comprehensive Cancer Network (NCCN) guidelines (www.nccn.org) recommend counseling on risk reduction strategies to reduce lifetime risk of breast cancer for patients with classic-type LCIS detected on core biopsy or surgical excision. One option is surveillance alone with follow-up, including a physical exam every 6 to 12 months and an annual mammogram considering tomosynthesis (no prior to age 30), and because it places women at high risk, MRI may be added, mainly after 25 y/o. Counseling about chemoprevention with tamoxifen or aromatase inhibitors is highly recommended.

It has been proven to reduce the risk of invasive breast cancer with an HR of 0.27. In the study by King et al. with 1060 patients diagnosed with LCIS, only chemoprevention was significant for

reducing the risk, with a 10-year cumulative breast cancer risk of 7% for women undergoing chemoprevention versus 21% for those who did not. (26) Depending on the menopausal status, Tamoxifen, Raloxifene, or Aromatase inhibitors can be considered. The results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1) show that the use of tamoxifen 20 mg/d for five years reduces the risk of invasive breast cancer by 49%. (18) Raloxifene, at a dosage of 60 mg daily, appears to be less efficacious in risk reduction compared to tamoxifen, but it can be considered in women with intact uterus and poor tolerance to tamoxifen.

The use of aromatase inhibitors (Exemestane or Anastrozole) is not currently FDA-approved for breast cancer risk reduction. This is due to the need for studies comparing their benefits to those of tamoxifen or raloxifene. Nevertheless, they can be an option if there are contraindications to tamoxifen/raloxifene (eg, thromboembolic events). The results from the NCIC CTG MAP3 study show that the use of exemestane reduces the risk of subsequent cancer by 65% at 35 months of follow-up. (33)

Women who undergo chemoprevention need to consider additional age-appropriate gynecological screening if Tamoxifen and bone density if on aromatase inhibitors.

One of the main reasons for not taking chemoprevention is the concern about side effects. It is crucial to establish good communication about breast cancer risk, as well as the risks and benefits of chemoprevention, to facilitate informed decision-making for breast cancer risk reduction.

Surgery

Historically, when LCIS was first described, mastectomy seemed to be the only treatment. This was the option until invasive breast cancer started to be treated with more conservative surgery, and studies showed that the actual risk of breast cancer in women with LCIS was lower than expected.

Nowadays, surgical excision is recommended for all patients with pleomorphic-type LCIS or LCIS that is non-concordant with imaging. Further surgery for classic-type LCIS is not required unless concomitant DCIS or invasive carcinoma is detected.

Surgical excision has been advocated after core biopsy due to the rate of upgrading to invasive or DCIS. In the series by Sen et al. (34) rate of upgrade after LCIS diagnosis was 9.3%, 70% of them presenting as an invasive carcinoma. These authors recommend the excision for all LCIS diagnoses. Nevertheless, other studies claim that after a diagnosis of lobular neoplasia (including atypical lobular hyperplasia and LCIS) in the core biopsy, if there is pathologic-radiologic concordance and lack other indications for excision, then observation may be appropriate. (35) In these cases, the rate of upgrade is 1% - 4.4%.

In the series from King et al., (26), a minority of patients (5%) opted for bilateral mastectomies. The time from LCIS diagnosis to surgery was six months. Women choosing this option were younger and more likely to be premenopausal, had denser breasts, and stronger first-degree family histories. In this group, occult carcinoma was identified in 11% (an equal proportion of invasive and in situ carcinoma).

When discussing different options with women, it is important to improve communication, and in those women considering surgery for risk reduction, all the risks and benefits of this approach

should be considered, as well as the impact that prophylactic surgery may have on their quality of life.

Surgical indications vary for other LCIS variants (pleomorphic LCIS or LCIS with necrosis). With respect to the clinical management of P-LCIS, there has yet to be a clear consensus. Due to the rarity of pure P-LCIS without concurrent invasive carcinoma, there are no randomized prospective trials, though the Alliance group has an ongoing trial. (36) NCCN guidelines recommend complete excision with negative margins, but this may lead to high rates of mastectomy without proven clinical benefit. They also note that evidence on efficacy and outcomes associated with complete P-LCIS excision is lacking. Lately, some authors claim even with close or positive margins, the recurrence risk of invasive cancer appears very low at short-term follow-up. (36) Finally, no data supports radiotherapy in this setting.

There is no evidence of therapeutic benefit from local excision, axillary dissection, radiotherapy, or chemotherapy. Also, mirror biopsy of the contralateral breast, once advocated for treatment of LCIS, remains as historical data but no longer applies.

Improving communication and patient education regarding the natural history and optimal management of LCIS will help in the decision-making process.

- LCIS usually is an incidental finding in a breast core needle biopsy (or surgical biopsy).
- Different models have been used to assess breast cancer risk and help with decision-making accurately.
- Surgical excision is mainly recommended for all patients with pleomorphic-type LCIS or LCIS that is non-concordant with imaging.

- Chemoprevention added to surveillance significantly reduces the risk of developing breast cancer
- Patients who desire bilateral mastectomies should be counseled about the risks and benefits and the impact on quality of life.
- There is a need for better predictors of progression to invasive disease to select treatment better.

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Chapter 26

Breast Reconstruction in Resource-Limited Environments

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Case Scenario

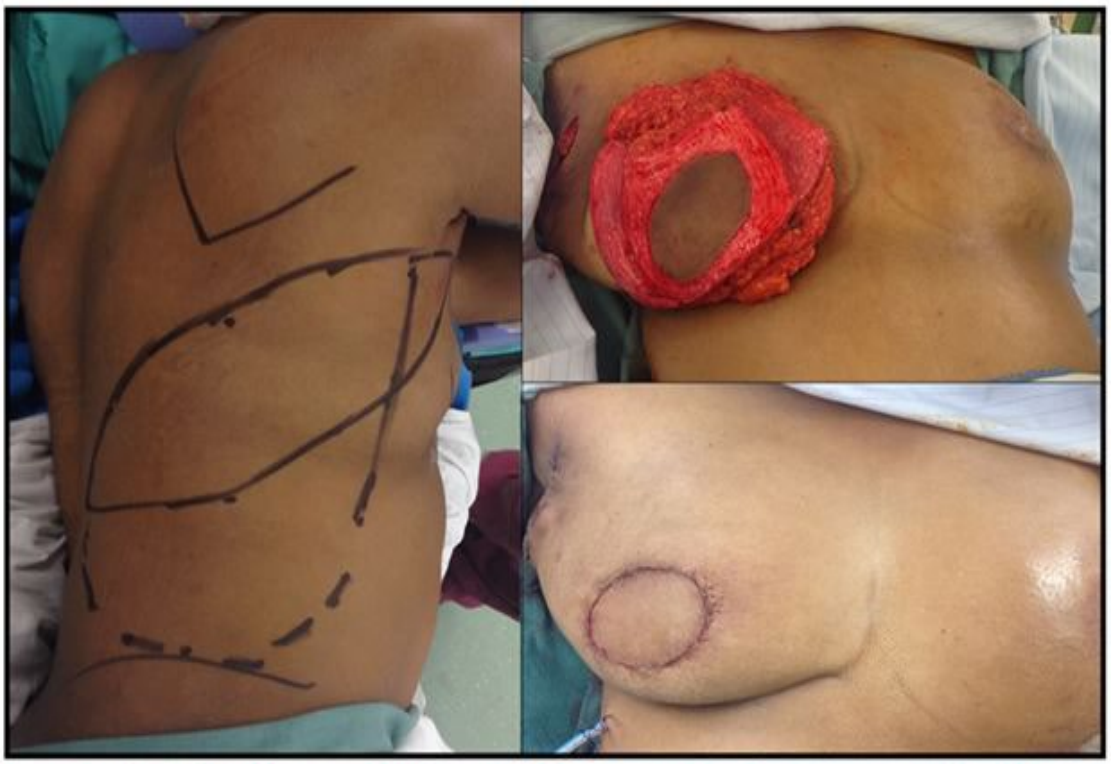

Figure 1. This is a 54 year-old woman who developed right breast cancer. Given the need for XRT, she underwent breast reconstruction (BR) using a latissimus dorsi (LD) myocutaneous flap alone. No implant was needed given the smaller size of her breasts. Photo credit: Donald P. Baumann, MD, FACS

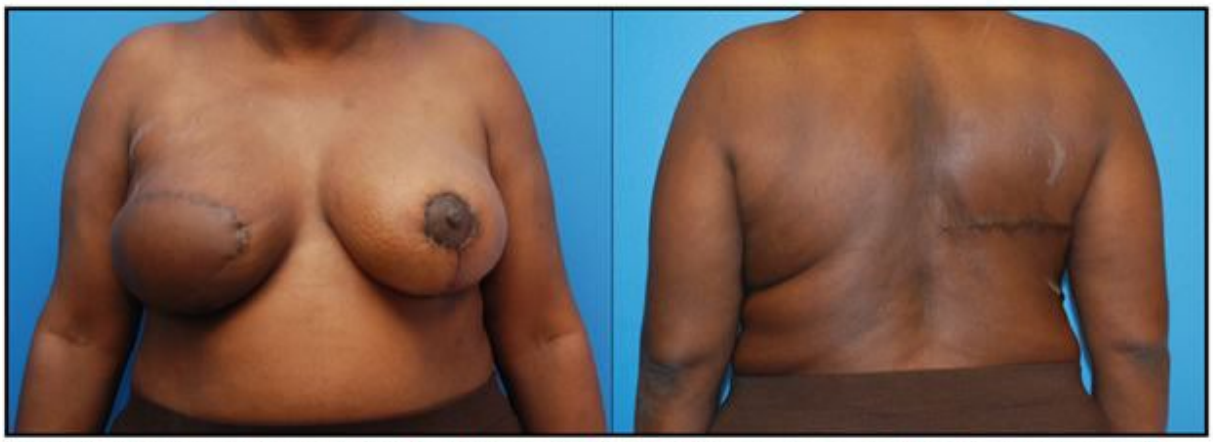

Figure 2. A LD flap with an implant is another option for BR. These postoperative photos represent the donor and recipient sites after XRT. For symmetry, a contralateral reduction was performed. Photo credit: Donald P. Baumann, MD, FACS

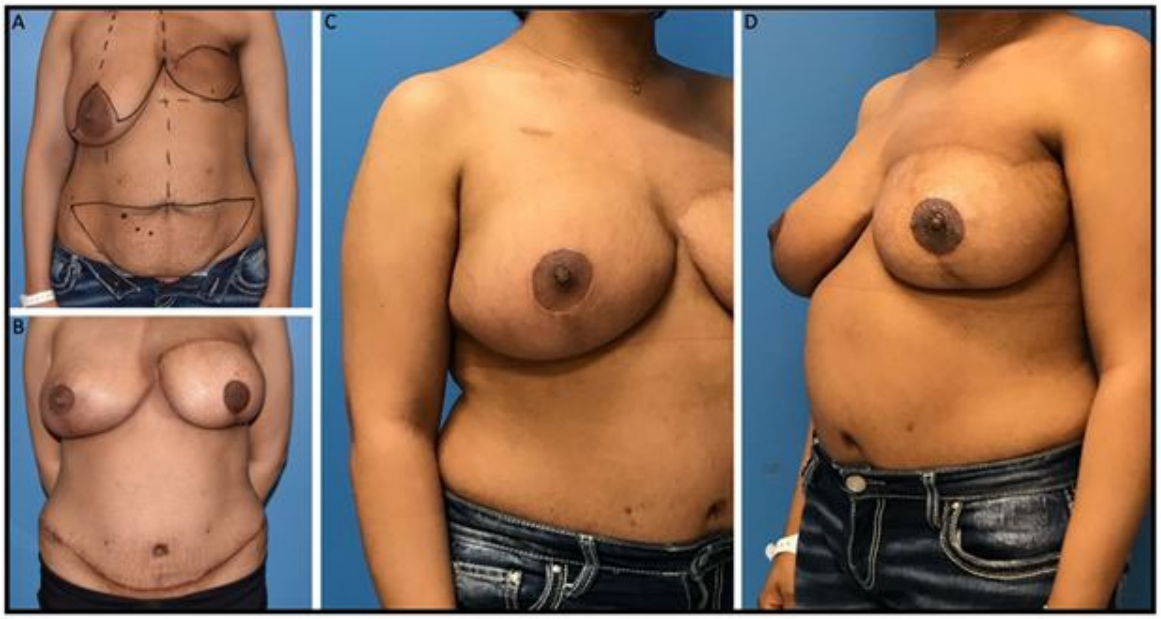

Figure 3. A. This 63 year-old woman underwent left mastectomy with XRT followed by subsequent delayed left BR. Preoperative markings for a left unilateral DIEP flap and right inverted T pattern mastopexy are demonstrated. B-D. In this delayed reconstruction, there is excellent healing of the abdominal donor site. The left breast has subsequently undergone nipple areolar complex (NAC) reconstruction and tattooing to match the right breast NAC. Photo credit: Alexander F. Mericli, MD, FACS

Introduction

With more than one million incident cases each year, breast cancer is the most common cause of cancer-related deaths in women worldwide.[1,2] Although many global and national health agendas

have traditionally focused on the management of communicable disease processes, an epidemiological transition is now occurring in which non-communicable diseases have become more prevalent.[3] Specifically, while over 5 million people died from HIV/AIDS, malaria, and tuberculosis in 2002, more than 7 million people died from cancer during this same time period.[4] Within this context, mortality due to breast cancer continues to rise, particularly in low- and middle-income countries (LMICs).[5,6,7] In contrast to the United States, in which mortality due to breast cancer has consistently decreased by 2% each year since 1990, mortality in LMICs continues to be as high as 88%.[8] While approximately 40% of patients in high-income countries present with low-grade breast cancers, more than 50-70% of patients in low-income countries such as India have locally advanced or metastatic disease at the time of index presentation.[9] Based on current trends, incidence and survival rates of breast cancer will remain unchanged until resources are more effectively invested towards improving care access, correcting lay public misconceptions, and mitigating catastrophic expenditures in low and middle-income countries.[8,10]

Surgery remains a cost-effective method for addressing localized breast cancer. To deliver comprehensive care with optimal outcomes from a surgical perspective, Breast reconstruction (BR) is an important adjunct in cancer care.[11] BR is an established method of restoring form and function to breast cancer survivors. When performed in an immediate or delayed fashion, BR has been shown to significantly improve health-related quality of life, psychosocial functioning, and cosmetic appearance among patients with breast cancer.[12,13] With regard to breast cancer care in low-resource environments, the implementation of BR as a service accessible to all has not yet been established with respect to existing barriers and plausible facilitators. Given the potential to enhance the survivorship experience for breast cancer patients, addressing this deficit is essential.

In this chapter, we present an overview of contemporary methods and outcomes for BR as applicable to low-resource environments and adopt a specific focus on techniques relevant to patients who have received radiation (XRT).

Types of BR

Choosing the "best" BR option for a given patient is ideally borne out of a shared-decision making process and represents one of the most critical preoperative decisions by the treatment team. Two broad categories of reconstruction exist: implant-based or autologous tissue-based techniques. In the absence of XRT, either option can be performed, and in the context of an otherwise healthy patient, this decision is often dictated by a patient's preferences. After XRT, however, complication rates (e.g., reconstruction failure, wound infection) have been shown to rise dramatically in the setting of an implant, and autologous reconstructions are preferred. In patients with comorbid conditions such as obesity, diabetes, and active smoking, the decision is more variable; factors, including surgeon preference, are considered.

The timing of reconstruction is another important consideration. Immediate reconstruction is performed at the time of the mastectomy; healthy patients who do not need XRT are excellent candidates for immediate reconstruction. Delayed reconstruction is commonly performed for patients who require XRT after mastectomy and is safest when performed at least 6-12 months after XRT.[14-19] Interestingly, patients who undergo delayed reconstruction actually demonstrate greater increases in quality of life measures than those who receive immediate reconstruction.[20] For patients presenting with advanced cancer, delayed reconstruction prioritizes the ability to screen for recurrence, which may be salient in resource-limited settings. Additionally, aggressive tumors mandate aggressive resections, which can compromise mastectomy skin quality and

increase rates of flap necrosis and implant exposure. These complications are particularly challenging to manage in the presence of an implant, and minimizing such risks is critical in resource-limited environments.[21,22]

Implant-based Reconstruction

Implant-based reconstruction is the most common surgical approach in high-income countries due to the relative ease, decreased operative duration, relatively shorter time horizon for recovery, and lack of donor site morbidity. This method of reconstruction can be performed in one or two stages. For the one-stage approach, a saline or silicone implant is placed at the time of the skin-sparing mastectomy. While this option seems ideal to avoid multiple procedures, very few women are candidates for this operation as to achieve a satisfactory result in a one-stage approach, the mastectomy flaps must be perfectly viable, and the desired breast size must be the same or smaller than the initial breast mound (i.e., minimally ptotic). Therefore, an expander is a common first step in the process of reconstruction.

During the first stage, an expander is placed beneath the pectoralis major muscle in order to cover the implant with well-vascularized tissue.[23] Total sub-muscular coverage entails the recruitment of the serratus anterior muscle slips laterally and rectus abdominis fascia inferiorly without the addition of acellular dermal matrices. This is the most cost-effective approach, albeit with a slightly increased morbidity for immediate implant-based reconstruction.

The skin is closed as a separate layer from the muscle to optimize coverage, and suction drains (1-2) are usually placed at the primary operation. Patients are admitted to the hospital for overnight observation. As soon as three weeks after the procedure, the expander is filled on a weekly basis with sterile saline to achieve the desired volume based on the patient's preference

for size, volume of the remaining contralateral breast, and according to the dimensions of the chest wall. The filling is complete when the target volume has been surpassed by approximately 20%. Once filling is complete, the tissues are allowed to maintain this stretch for 3-6 weeks. After this time, the expander is exchanged for a permanent saline or silicone implant in a second operation, usually performed on an outpatient basis.

Saline versus Silicone Implants

Although the pros and cons differ between saline and silicone implants, both are considered to be reasonable options for BR. Silicone implants have a more natural feel and appearance but require a larger incision for placement. Silicone implants also require screening for rupture using MRI every 2-3 years, whereas rupture is almost immediately evident in the presence of a saline implant based on a physical exam alone. This is an important consideration if resources for MRI scanners are particularly limited. Importantly, saline implants are considerably cheaper than silicone, another critical consideration for the development of BR programs in low-resource environments.[11] Recent long-term safety data have drawn associations between silicone implants and higher rates of connective tissue disorders (Sjogren's, Rheumatoid arthritis, and Scleroderma).[24] However, this evidence base is inconclusive (aggregate, not risk-adjusted), and prospective registry-based studies are ongoing.

Additionally, at the time of writing, there is mounting evidence of an increased association between textured implants and breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).[25] These are rare T-cell lymphomas that present in a delayed fashion as persistent swelling, mass effect, or pain in the area of a breast implant.[26]

Complications

In the presence of an implant, infection is the most feared complication and occurs in 2.5-3.4% of cases. If detected early, oral or intravenous antibiotics can lead to resolution.[27-34] Commonly, however, surgical explantation is required to address the source of the infection by debriding or washing out the bacterial biofilm on the implant and muscle surface. The implant can be replaced after 3-6 months if the breast pocket remains free of infection.[35,36] An additional complication is implant exposure, commonly due to necrosis of the mastectomy skin flaps. The most effective mediation step for this is avoiding implant insertion in the first place (i.e., deferring implant placement for two weeks to optimize skin flap recovery); therefore, a collaborative relationship with the surgical oncologist is critical.[37] Long-term complications include capsular contracture and rupture, which occur at a rate of 1% per year.[11]

Outcomes with XRT

While many believe that it is possible to perform implant-based reconstruction successfully in the setting of XRT, it is undoubtedly the case that complication rates dramatically increase.[38] In general, XRT induces chest wall fibrosis that leads to erythema, edema, skin desquamation, and muscular atrophy.[38-41] Although this is true regardless of the XRT timing, there is demonstrable variation in the impact on reconstruction outcomes attributable to timing. Lee et al. demonstrated that patients undergoing reconstruction after neo-adjuvant XRT, i.e., pre-mastectomy XRT, experience a significantly higher risk of reconstructive failure [14% rate overall; relative risk, 2.58 (1.86–3.57)], total complications rate [36%; relative risk, 1.89 (1.57–2.28)], and capsular contracture [relative risk, 3.32 (1.36–8.13)].[42] Other studies have demonstrated complication rates as high as 50%.[43]

The likelihood of complications in the setting of post-mastectomy XRT varies based on whether it is the tissue expander or the implant that is undergoing XRT. Lee et al. performed a

systematic review in 2017, which demonstrated that the pooled risk of failure was higher when the tissue expander was radiated compared to the permanent implant (16% vs. 10%). Conversely, the risk of capsular contracture was higher when the implant was radiated compared to the tissue expander (RR, 0.44; $p<0.001$).[44] Others note no difference in complication rates between radiating the tissue expander or implant.[45] Once again, however, timing is critical; the more time that elapses between XRT and reconstruction in either of these settings, the lower the likelihood of complications.[46]

In addition to complications, patient-reported outcomes (PRO) are another important metric to be leveraged in the evaluation of reconstruction outcomes in the setting of XRT. XRT significantly decreases satisfaction in the setting of breast cancer reconstruction.[47-50] Yoon et al. demonstrated that PRO was similar regardless of whether the tissue expander or implant was radiated.[51] Given the unequivocal value of XRT as a means to decrease recurrence, optimizing the likelihood of successful reconstruction in the midst of this necessary treatment is important.[47-50,52-53]

Autologous Reconstruction

Autologous reconstruction has important implications for those in low-resource environments, given the lower long-term cost and complication rate in the setting of XRT.[54] While these operations require a longer recovery with at least 2-5 days in the hospital, autologous reconstructions are associated with significant patient satisfaction, PRO, and quality of life compared to implant-based reconstruction, particularly among radiated patients.[55] One contributing factor is the decreased incidence of complications due to vascularized tissue transfer to the chest wall.

A variety of autologous options, ranging in technical complexity, exist. The latissimus dorsi muscle flap, with or without an implant, is an important cornerstone in the foundation of autologous reconstruction ("workhorse flap"). Transverse rectus abdominis myocutaneous flaps are another option that can be used in a pedicled or free flap fashion. In high-resource environments, microvascular flaps based on small perforators from the rectus abdominis or gluteus maximus muscles are becoming the mainstay of autologous reconstruction. Importantly, however, these cases demand considerable institutional resources (dedicated operating rooms, intensive care unit monitoring, 1:2 nurse staffing ratios) that may not be feasible in low-resource environments that require strict triaging of available capital to life-saving interventions.

Latissimus Dorsi Flap

The latissimus dorsi is an important workhorse flap for BR. It can be performed in one or two stages, depending on whether or not an implant is necessary.[56,57,58] For thin women, the muscle and associated skin paddle alone may be enough to restore form and function. For women with larger breasts, the muscle and skin paddle can be placed over a tissue expander in an immediate or delayed fashion after mastectomy. The expander is inflated in a serial fashion as described above and subsequently exchanged for a permanent saline or silicone implant approximately three months later. Given the reliability and resilience of this flap, it is an excellent option for patients with numerous comorbid conditions. The most common complication is donor-site seroma, necessitating the use of 1-2 closed suction drains at the time of flap elevation.[59,60,61] Other less common complications include partial or total flap loss and implant exposure. Surprisingly, patients uncommonly report functional concerns i.e., shoulder weakness or limited mobility post-operatively. [62,63]

Abdominally-based Flaps

The use of abdominally-based flaps represents another practical option for BR in low-resource environments. The most commonly utilized operations include pedicled transverse rectus abdominis myocutaneous (TRAM) flaps, free TRAM flaps, and deep inferior epigastric artery perforator (DIEP) flaps.

Similar to the latissimus dorsi flap, pedicled TRAM flaps do not require microsurgical expertise. This procedure is commonly performed without an implant in patients with adequate abdominal laxity. An ellipse is designed from above the umbilicus to the suprapubic region to allow for appropriate closure. The skin and subcutaneous tissue can be divided in the midline to accommodate a bilateral BR or can be used for unilateral BR by crossing the midline if more tissue is needed. The tissues are incised, and bovie electrocautery is used to elevate the subcutaneous tissues from the fascia until the medial and lateral row perforating vessels are identified as they exit the fascia. To maintain these perforators, the fascia is incised on either side of the medial and lateral row; care is also required to preserve as much fascia as possible to support a tension-free closure. As the muscle is encountered, it is dissected circumferentially and separated from the posterior sheath. Inferiorly, the deep inferior epigastric vessels are located and divided; the flap's dominant arterial supply is now based on the superior epigastric arteries. The muscle is completely dissected from the pubis and tunneled subcutaneously into the mastectomy space. Care must be taken to make the tunnel at the inframammary fold large enough to prevent venous congestion and flap loss. Additional measures to optimize flap perfusion include a delay procedure i.e., dividing the deep inferior epigastric pedicle 14-21 days prior to complete flap elevation. This can decrease flap necrosis, particularly for patients with a history of smoking, XRT, or obesity.[64,65]

A free TRAM or Deep Inferior Epigastric Perforator (DIEP) flap is another option for abdominally-based reconstruction that obviates the need for delay procedures while maximizing flap perfusion. This flap is based on the deep inferior epigastric system instead of the superior epigastric system. Similar to the pedicled TRAM flap operation, an ellipse is designed from above the umbilicus to the suprapubic area. Instead of dividing the deep inferior epigastric vessels and the inferior insertion of the rectus abdominis, the superior epigastric vessels are ligated, and the superior portion of the rectus abdominis muscle is divided. The deep inferior epigastric vessels, the main source vessel of the flap, are dissected to their origin from the external iliac vessels and clipped. The internal mammary vessels are dissected, and the deep inferior epigastric vessels are anastomosed at this site within the chest using an operating microscope. To safely perform this procedure, facilities for flap monitoring and the ability to return to the operating room for exploration and flap salvage as needed are required.

The distinction between the DIEP and TRAM flap lies in the extent to which one preserves the anatomic integrity of the abdominal wall. In the case of a DIEP operation, either the medial or lateral row of perforators are dissected out in their entirety through the muscle to the deep inferior epigastric system within the pelvis. If the perforators are tightly integrated into the surrounding muscle, a cuff of muscle can be taken to decrease the risk of damage to the perforators.

Additional donor sites include the medial or posterior thigh and gluteal region for patients with limited abdominal laxity to support the tissue required for BR. The perforators are dissected from the adjacent muscle to the source vessels and anastomosed to the internal mammary or thoracodorsal system as in the DIEP flap operation. However, given the variability in the anatomy of the perforating branches, care should be taken before proceeding with these options.

Complications

Complications in the setting of any abdominally based flap include venous thromboembolism, complete or partial flap loss, fluid collections such as hematoma and seroma (donor or recipient site), and dehiscence or wound formation at the abdomen or mastectomy incisions. Complete flap loss is less common for the pedicled TRAM operation, given that the main vascular supply is kept intact throughout. Rates of flap loss in the setting of microsurgical procedures approach 1-5% and are thought to be dependent on the surgeon's technique and experience.

Due to the harvest or manipulation of the rectus abdominis muscle in any of these operations, abdominal wall laxity is a potential major complication. Bulge and hernia are both possible; some authors recommend pre-emptively reinforcing the fascial closure with synthetic mesh (i.e. Prolene mesh) in order to decrease the risk of these complications in particular.[66,67] Unlike those that have undergone a latissimus dorsi flap, patients that undergo the pedicled TRAM flap do note abdominal weakness with flexion. Although controversial, it is thought that the likelihood of abdominal wall laxity or hernia is less in patients who undergo DIEP flap reconstruction.

Outcomes after Autologous Reconstruction

In the setting of XRT, the use of autologous tissue significantly decreases the incidence of reconstruction failure. A systematic review performed by Lee and Mun demonstrated that reconstructive failure was reduced from 33.7% to 6.9 percent when autologous tissue was added to cover an implant compared to an implant alone.[42] Importantly, however, XRT increases the risk of microvascular complications. Therefore, it is important to counsel providers, patients, and families preoperatively and increase the index of suspicion for postoperative complications.[68] PRO are also superior in patients with autologous compared to implant reconstructions at one, two, and eight years after surgery.[12,69,70] In examining differences between the types of flaps

commonly used for BR, patient-reported satisfaction regarding abdominal wall integrity is higher with the DIEP flap compared to pedicled or free TRAM options.[71]

While the use of autologous tissue as the gold standard for reconstruction in the setting of XRT is favored from a complication and patient satisfaction standpoint, the timing of XRT remains controversial. Some surgeons prefer immediate autologous reconstruction despite the potential need to radiate the flap, while others prefer delayed reconstruction to avoid future contracture and fibrosis of the flap. Although some studies have demonstrated an increased likelihood of fat necrosis within the flap after XRT, others demonstrate no clinically significant differences, including the need for revision surgery.[72-76] PRO are also similar to those that undergo XRT before or after reconstruction.[77] The concept of delayed immediate reconstruction has evolved as a means of optimizing the patient's psychosocial well-being by placing a tissue expander at the time of mastectomy to preserve the breast pocket. An autologous reconstruction is performed after the patient completes XRT to prevent XRT-induced alterations of the flap.[78,79]

Oncoplastic Reconstruction

For patients who present with tumors amenable to breast conservation techniques, oncoplastic reconstruction (i.e., displacement, replacement, or augmentation) is an excellent option. Women with larger breasts are candidates for breast reduction techniques for reconstruction after lumpectomy; women with smaller breasts are candidates for volume replacement techniques using the autologous reconstruction options described above, such as the latissimus dorsi flap.[80] Common designs for mastectomy incisions include circumvertical, periareolar, crescentric, L-shaped incision, or an inverted T (Wise) pattern. Standard designs to ensure perfusion to the nipple-areolar complex include superior, superomedial, and inferior pedicles.[80] These operations can be performed by the breast surgeon alone or in conjunction with

the plastic surgeon. Studies have found no significant difference in locoregional recurrence, local control rates, and progression-free and overall survival with or without immediate oncoplastic reconstruction.[81] Given the ability to perform tumor resection and reconstruction in one operation without the need for implants or frequent postoperative monitoring, oncoplastic reconstruction is a technique that is readily applicable to low-resource environments.[80]

BR in Low-resource Settings

Difficulties in achieving equitable access to BR persist in both developed and developing countries. Concerns regarding transportation, cost, social support, and education appear to be among the main considerations that span from rural parts of the United States to Kumasi, Ghana to India.[10,82] From a health systems standpoint, funding is a critical consideration. While BR clearly improves psychosocial well-being, many are not able to sustainably allocate resources towards this end given resource constraints. As such, BR is often a service accessible only in private settings and associated with a cosmetic surgery fee structure. Ensuring stable sources of funding for BR on a government or foundation level is one of the most critical steps in increasing access to this intervention. To this end, governments must also consider that the costs of reconstruction might be offset by increased economic productivity attributable to higher survival rates among breast cancer patients and improved psychological function among survivors. Amidst all of these challenges, successful breast cancer care will not occur without improving societal perceptions and awareness regarding the treatment of this pathology, particularly among younger patients with more aggressive disease processes. Given that barriers to care cannot be generalized amongst different regions and cultures, different approaches may be needed to provide effective care to individual nations on a global scale.

Gaps in Knowledge and Future Directions

BR has yet to be universally available in any region across the world. Whether in resource-limited environments or not, there are barriers to the availability and accessibility of this service. One of the first gaps in knowledge that must be addressed is the contextual (e.g., perception of reconstruction as cosmetic) and infrastructural (e.g., lack of plastic surgeons, outdated technologies) barriers to BR in LMICs. Although we know that reconstruction improves health-related quality of life among women in high-income countries, the extent that these outcomes are reproducible in LMICs has yet to be studied in great detail. The interest and experience level of providers and trainees in performing BR is another consideration. If patients and providers believe in the value of BR, funding and resource allocation is the next challenge. Ensuring that governments understand the non-cosmetic nature of BR, and emphasizing the link between plastic surgery and oncology is critical. To this end, including plastic surgeons and BR services within the multidisciplinary team is critical.[83] Improving communication between oncology and BR teams facilitates this process. Decision support tools, educational materials, and longitudinal programs for patients are also important. Implementing funding programs that account for economically disadvantaged populations will allow for widespread access. Gaps in knowledge regarding supply chain management of the resources required for autologous and implant-based reconstruction must also be addressed to make reconstruction as affordable as possible.

Conclusions

The opportunity to improve access to reconstruction is contingent upon expanding access to breast cancer care. Although epidemiological indicators of breast cancer have stabilized in the

US, the burden of disease continues to rise in LMICs. As plastic surgeons, this provides the opportunity to strengthen our presence on the global stage with the ultimate goal of expanding opportunities for reconstruction worldwide. Whether using autologous or implant-based forms of reconstruction in an immediate or delayed fashion, implementing cost-effective, reliable, and evidence-based approaches to BR is a significant challenge that must be addressed by those committed to women's health.

Salient Points

1. BR is best performed in a multidisciplinary fashion in conjunction with surgical oncologists, XRT oncologists, medical oncologists, and skilled nursing staff.
2. For patients with a history of XRT or who will undergo XRT as part of treatment, autologous tissue is best for reconstruction to decrease complication rates and optimize patient satisfaction.
3. Implant-based reconstruction using a tissue expander followed by the permanent implant is best utilized in patients who do not need XRT or for patients who have too many comorbid conditions to tolerate the operative duration of autologous reconstruction.
4. Oncoplastic reconstruction is a cost-effective and safe operation for women undergoing breast conservation therapy.
5. Future studies must examine sustainable approaches to funding BR and evaluating patient-reported outcomes after mastectomy in low-resource environments.

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Chapter 27

Breast Cancer in Elderly Patients

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Case Scenario

70-year-old Kenyan woman who presented with a new lump in her left breast, with biopsy and imaging subsequently finding invasive ductal carcinoma of the breast, initial staging of cT2N1M0, grade 2, ER+, PR+, HER2-. She is able to complete most activities of daily living (ADLs) and instrumental activities of daily living (IADLs), although she does not go shopping anymore because she does not have the energy to walk several blocks to the market. Her BMI is 22. The mental status exam shows no significant deficits.

Introduction

Breast cancer remains the most common cancer diagnosis and cause of cancer-related deaths among women globally. It is also a disease of aging, with approximately 50 % of breast cancer occurring in women aged 65 and older [1]. Despite this high frequency, elderly women tend to be underrepresented in clinical trials, resulting in a lack of evidence to inform the management of this population. Treatment decisions are generally based on retrospective studies and the extrapolation of study results from younger patients. Treating the elderly in low- and middle-

income countries (LMIC) represents an even greater challenge given significant deficiencies in professional and technical resources, in addition to limited available data to guide treatment decisions at the extremes of age. In general, chronologic age alone should not dictate treatment decision-making. Instead, each patient's risks and benefits should be assessed, considering their performance status, life expectancy, comorbidities, personal preferences, and potential treatment barriers.

Breast cancer in older women is more likely to have favorable tumor characteristics, such as estrogen receptor (ER) positivity, a low proliferative index, and a lower incidence of human epidermal growth factor receptor 2 (HER2) overexpression. Despite exhibiting less aggressive tumor characteristics, women over the age of 70 diagnosed with breast cancer have significantly lower 5-year survival than younger patients [2]. Older women often receive less aggressive treatment than younger patients and are less likely to be treated according to established guidelines, leading to a higher risk of disease recurrence [3].

Previous guidelines have been published that address diagnostic and management strategies in resource-deficient settings, including the Breast Health Global Initiative (BHGI) and, more recently, the NCCN Framework for Resource Stratification of the NCCN Guidelines (NCCN Framework), which will prove to be valuable references for clinicians [4, 5]. In the current review, we present and discuss the standard of care for the management of breast cancer in older and elderly individuals as would take place in a high-resource setting while highlighting important considerations and alternative approaches for limited-resource settings.

Surgery

Surgical therapy is the cornerstone of management for early-stage breast cancer and is arguably the most readily accessible therapy in LMICs. In the older adult, chronologic age alone is a poor predictor of surgical morbidity and mortality; rather, multiple other factors, including the presence of pre-existing comorbidities, pre-operative nutritional status, and measures of "frailty", among others, more strongly impact outcomes. Indeed, surgical mortality is negligible among healthy older individuals with breast cancer (<1%) [6]. Numerous tools are available to aid in determining an optimal management strategy (i.e., ability to tolerate surgery and/or chemotherapy), with one of the more thorough methods being the comprehensive geriatric assessment (CGA), which assesses function, comorbidities, nutrition, medications, socioeconomic issues, and geriatric syndromes. (*Table 1*)

Demographics and social status	Marital status, living situation, financial resources
Comorbidities	Patient's other medical problems
Functional status	Independent, caregiver, performance status
Cognitive function	Mini mental state examination
Nutritional status	Body mass index, weight loss
Polypharmacy	Medications that may affect therapy
Geriatric syndromes	Dementia, delirium, incontinence, osteoporosis

Table 1. Domains of the Comprehensive Geriatric Assessment

[7]. The Preoperative Assessment of Cancer in the Elderly (PACE), which incorporates a CGA, can be used to evaluate whether an older individual is an appropriate surgical candidate [7]. Given that the CGA is time-consuming and generally is performed by a geriatrician, practical considerations, especially in LMICs, may limit its broad applicability. Therefore, an abbreviated

assessment may be employed to screen for those individuals who would benefit from a full CGA. The G8 assessment is one such tool that has been prospectively validated and is utilized by the European Organization for Research and Treatment of Cancer (EORTC) for their clinical trials. (*Table 2*) [8, 9].

Items		Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake 1 : moderate decrease in food intake 2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg 1 : does not know 2 : weight loss between 1 and 3 kgs 3 : no weight loss
C	Mobility	0 : bed or chair bound 1 : able to get out of bed/chair but does not go out 2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression 1 : mild dementia or depression 2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m^2)	0 : BMI < 19 1 : BMI = 19 to BMI < 21 2 : BMI = 21 to BMI < 23 3 : BMI ≥ 23
H	Takes more than 3 medications per day	0 : yes 1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good 0.5 : does not know 1 : as good 2 : better
I	Age	0 : >85 1 : 80-85 2 : <80
	Total score	0 - 14 = presence of a geriatric risk profile > 14 = absence of a geriatric risk profile

Table 2: G8 Health Status Screening Tool

Another method is the abbreviated comprehensive geriatric assessment (aCGA), which has been retrospectively validated [10].

If a patient is medically fit and clinical criteria are met, older individuals should be offered the same surgical options as their younger counterparts [11]. In many LMICs, the standard of care will be a total mastectomy plus level I/II axillary dissection, given lack of access to radiotherapy. Where available, the standard of care remains breast-conserving surgery (BCS) plus whole-breast radiotherapy (WBRT) or mastectomy followed by postoperative radiation if indicated. While older women may be more likely to be treated with mastectomy rather than BCS, evidence suggests that older women can comparably tolerate BCS compared to mastectomy and have fewer functional limitations [12, 13]. Furthermore, they are more likely to choose BCS over mastectomy if offered the choice and report a better body image with BCS [14]. For those with ER-positive tumors and comorbid conditions that preclude surgery (or for those who refuse surgery), primary endocrine therapy alone may be prescribed. Primary endocrine therapy (in contrast to neoadjuvant endocrine therapy) refers to the administration of endocrine therapy as the sole treatment approach for ER-positive early-stage breast cancer. A meta-analysis published in 2007 by Hind et al. showed no significant difference in overall survival when surgery (with or without endocrine therapy) was compared to endocrine therapy alone in women over the age of 70 [15] However, primary endocrine treatment is inferior to surgery in terms of local control and PFS, and should only be offered to patients with ER-positive disease with a short life expectancy (<2-3 years).

Older patients with large cancers who are not good candidates for BCS may be offered preoperative systemic therapy to allow for less aggressive surgery to be performed at a later date. Fit older women may benefit from chemotherapy, while patients with ER-positive disease may

respond to neoadjuvant endocrine therapy with the intent of downsizing the tumor and allowing for less extensive surgery [16]. In LMICs, the benefits of BCS in early-stage disease may not be realized due to a lack of access to radiation facilities or to screening mammography (resulting in more advanced presentation). In this case, mastectomy may be the only available approach. Modified radical mastectomies are indeed performed more often than BCS in LMICs for these reasons [17]. In patients with locally advanced disease, screening for metastatic disease is especially critical, given that mastectomy would not generally be indicated in the presence of metastatic disease.

Management of the axilla in older adults is an active area of investigation. In clinically node-positive patients, axillary lymph node dissection (ALND) remains the standard of care and continues to be recommended in fit elderly individuals. On the other hand, the management of clinically and radiologically node-negative axillas in older adults is evolving. The current standard of care is sentinel lymph node biopsy (SLNB), and in those with positively identified sentinel lymph node disease, completion ALND. Multiple studies, however, have called into question the necessity of axillary lymph node sampling in some contexts. Three randomized trials have reported that selected older women with clinically negative axilla who will receive adjuvant endocrine therapy may safely avoid axillary surgery without a negative outcome. For example, women over 70 with T1, ER-positive cancers, and clinically negative axilla have excellent overall survival when treated with lumpectomy and tamoxifen, with or without radiation [18].

Similarly, in the International Breast Cancer Study Group Trial 10-93, older women (>60 years) who were to be treated with tamoxifen and had a clinically node-negative axilla were randomly assigned ALND or no ALND, with results showing comparable disease-free survival and overall

survival [19]. The Society of Surgical Oncology (SSO), partnering with the Choosing Wisely campaign, supported to “not routinely perform SLNB surgery for women older than 70 years with hormone-receptor-positive (HR)+) breast cancer. Selected women with 1 or 2 positive sentinel nodes may also safely avoid an ALND. The American College of Surgeons Oncology Group Z0011 trial assessed outcomes in women with T1 or T2 breast cancer and 1 or 2 positive sentinel nodes randomized to completion ALND or no ALND. All patients were treated with whole breast radiation. Although the trial was concluded prematurely, similar outcomes were reported for distant recurrence and overall survival [20].

In some cases, staging information gained from SLNB will influence future treatment decisions. However, in situations where this information would not impact treatment, such as patients who are poor candidates for adjuvant chemotherapy, one could argue that lymph node assessment may not be warranted if outcomes and treatment strategies were not impacted. In LMICs, lymph node staging via SLNB may not be available, and consequently, complete level I and II axillary dissection is performed more often than not in these settings [21]. Therefore, while ALND or SLNB with completion ALND, if indicated in otherwise healthy women, remains the standard of care in high-resource environments, determining the value of lymph node assessment in early-stage disease may be especially relevant to those with limited resources and could minimize potentially unnecessary morbidity associated with ALND.

Adjuvant radiotherapy

Access to radiation facilities is more limited in LMICs, and therefore, distinguishing the clinical contexts in which it is essential and those in which it may provide little to no benefit is especially important. Radiotherapy remains a key BCS element for young and healthy older individuals. As

with surgery, age alone should not preclude patients from irradiation, as older women generally tolerate it well with reasonable cosmetic outcomes [22]. Nevertheless, even if well-tolerated, adjuvant radiation is associated with toxicity, burden to the patient, and significant cost, making the identification of individuals who may safely avoid it of significant interest. As both the risk of local recurrence and the relative benefit of RT after BCS decrease with age, some women may be safely treated without adjuvant radiation [23]. Three large randomized trials have examined the omission of radiation in selected older women with early-stage breast cancers who plan to take endocrine therapy. The Cancer and Leukemia Group B (CALGB 9343) trial randomized women ages 70 or older with stage I ER-positive tumors (<=2 cm) on tamoxifen to lumpectomy with or without adjuvant RT. Although increased local recurrence was observed in the no-RT arm, breast cancer-specific survival and overall survival were comparable, with most deaths occurring independently of the cancer [24]. Similarly, the PRIME II randomized trial, which involved women 65 and older, and the Swedish Breast Cancer Group randomized trial (SweBCG 91 RT) both found increased risk for local recurrence with no-RT arm but minimal difference in 5-year and 15-year survival, respectively [25, 26]. Given this data, some older women with early-stage, ER-positive breast cancer may choose not to receive adjuvant RT.

Clinical trials have demonstrated that post-mastectomy RT is associated with improved overall survival and decreased local recurrence in patients with high-risk disease; however, whether this could be generalized to older women is less clear, as that population was not adequately represented in these trials. Nevertheless, large cohort studies in older populations have corroborated this general finding. In a large cohort study of women 70 and older, post-mastectomy radiotherapy (PMRT) was associated with improved survival in those with T3/4 or N2/3 disease, whereas lower-risk T1/2, N0 or N1 disease did not have this same benefit [27]. In

another study of older women who underwent mastectomy but received no PMRT, the risk of local recurrence was only associated with large tumors (>5 cm) or ≥ 4 positive nodes [28]. Thus, PMRT should be recommended in older women with high-risk diseases, while its utility in those with lower-risk disease remains to be further evaluated.

Adjuvant systemic therapy

Systemic therapies have dramatically impacted outcomes in high-resource settings, although they can have limited availability in LMICs. Furthermore, proper application of systemic therapies generally requires access to pathological services, which also may not be readily available, to determine important tumor features such as hormone receptor and HER2 statuses. The National Comprehensive Cancer Network (NCCN) does not have an upper age limit set for the utilization of chemotherapy Therefore, we must acknowledge that several factors need to be taken into account when making systemic treatment decisions, including life expectancy, comorbidities, and performance status. Several tools have been developed to predict the risks and benefits associated with chemotherapy in older individuals, including Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), Cancer and Aging Research Group (CARG), and PREDICT tools [29-31]. The CRASH score was developed in a population of patients aged 70 and older and predicted risk for Grades 3 and 4 non-hematologic toxicities and Grade 4 hematologic toxicities. The CARG score was developed for those 65 and older and predicted risk for Grades 3-5 toxicities from systemic chemotherapy. Both utilize clinical, laboratory, and functional variables in addition to cancer-specific and regimen-specific variables.

The PREDICT model is a valuable tool that incorporates patient, tumor, and treatment-specific variables to predict the benefits of systemic therapy. It includes estimates of the benefits of

endocrine therapy, chemotherapy, and trastuzumab. One limitation of the model is a lack of adjustment for comorbidity, an important issue in older patients. This validated instrument can be a valuable adjunct for decision-making in this population.

Adjuvant chemotherapy

Two large international randomized clinical trials; CASA [Chemotherapy Adjuvant Studies for Women at Advanced Age] and ACTION [Adjuvant Cytotoxic Chemotherapy in Older Women]), aimed to evaluate the risks and benefits of adjuvant chemotherapy in older women, closed prematurely because of insufficient accrual [1]. However, other clinical trials that enrolled women from all age groups showed that elderly women in good health benefitted from systemic chemotherapy as well as younger adults. A prospective, randomized clinical trial enrolled women aged 65 years and older and randomized them to receive combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) versus doxorubicin and cyclophosphamide (AC) versus capecitabine alone. Results of this study showed that patients treated with capecitabine alone were twice as likely to have cancer recurrence and almost twice as likely to die compared to patients assigned to standard chemotherapy. This was especially seen in the hormone receptor-negative subgroup of women (hazard ratio [HR], 2.62; P=0.001) [32, 33]. Despite an obvious benefit to receiving chemotherapy, older patients tend to experience a higher frequency of treatment-related toxicities, as seen in retrospective studies [34]. While an anthracycline-based chemotherapy regimen was shown to benefit older breast cancer patients at high risk of recurrence [33], it has been associated with a higher rate of hematologic and non-hematologic toxicities [35]. Anthracycline-related cardiac toxicity was a major issue seen in elderly patients, and an age-related effect of this toxicity has been reported [36].

Additionally, a higher incidence of acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) has been noted in the elderly population [37]. These data suggest that standard adjuvant chemotherapy has a role in the treatment of fit older women. However, the choice of adjuvant chemotherapy is critical. For many older women with lower-risk cancers or for those with contraindications to anthracyclines, regimens such as cyclophosphamide, methotrexate, 5-fluorouracil (CMF) or docetaxel cyclophosphamide (TC) can offer benefit without the risk of anthracycline toxicities, reserving the anthracycline-taxane regimens for fit older women with high-risk disease. Studies of TC in older breast cancer patients have shown acceptable toxicity (with prophylactic GCSF) and tolerability [38]. Although standard regimens are always preferred, weekly paclitaxel has activity in breast cancer and may be an option for a patient who is unlikely to tolerate multiple chemotherapy agents. Consideration of the risks and benefits of chemotherapy must be carefully weighed prior to treatment.

Adjuvant anti-HER2 therapy

HER2-positive (HER2+) breast cancer affects older women nearly as frequently as younger women. In many LMICs, pathologic assessment of HER2 status is not possible, and targeted therapies are not available. If feasible, adjuvant trastuzumab in these patients reduces relapse by 40% and mortality by a third; however, a chief concern with trastuzumab is its effect on cardiac function, particularly in combination with anthracyclines, as it is associated with increased risk of cardiomyopathy by five-fold and double risk of decline in left ventricular ejection fraction (LVEF) in anthracycline-trastuzumab combinations. In particular, elderly patients tend to have higher rates of cardiovascular comorbidities, making toxicity from therapy more likely [39]. Therefore, careful consideration is needed prior to committing to anti-HER2 treatment, and a particular preference for non-anthracycline-based regimens is recommended in this population.

Healthy older patients with HER2+ early-stage breast cancer and normal left ventricular ejection fraction should be offered trastuzumab in combination with chemotherapy. The combination of docetaxel, carboplatin, and trastuzumab (TCH) is an option but is associated with significant toxicity in the older population. The combination of adjuvant paclitaxel and trastuzumab has been shown in a general population of patients to have a low risk of cancer recurrence (< 2% at three years) and a low risk of heart failure at 0.5% in patients with node-negative HER2+ breast cancer [40]. This is an attractive option for many older women with HER2-positive disease because of the risk-benefit ratio and is often used in women with higher-risk diseases who would be unlikely to tolerate more intensive regimens. Although there is insufficient evidence to recommend single-agent trastuzumab in patients who are not candidates for chemotherapy, the 2011 St Gallen consensus states that it might be reasonable in certain cases where chemotherapy risks outweigh benefits [39].

Access to trastuzumab is often limited in LMIC, and HER2-directed adjuvant therapy lasting less than one year has been investigated in several trials, including FinHer, SHORT-HER (9 weeks vs. one year), and PERSEPHONE (6 months vs. one year) [41-43]. While FinHer and SHORT-HER failed to show the non-inferiority of a shorter duration of trastuzumab, PERSEPHONE did find that six months of trastuzumab was non-inferior to 12 months. All these studies showed a lower rate of cardiac toxicities in the shorter-duration arms. Therefore, adjuvant trastuzumab treatment duration may be adjusted according to prognostic factors, especially in health systems with limited resources.

Adjuvant endocrine therapy

In high-resource settings, adjuvant endocrine therapy is routinely offered in ER-positive breast cancers larger than 5 mm, regardless of age, given the demonstrated benefit to disease-free and

overall survival and its low toxicity profile. Therefore, pathology services that can evaluate estrogen receptor status by immunohistochemistry are especially critical resources to aim to make available in LMICs. Aromatase inhibitors (AIs), in particular, are generally recommended over tamoxifen in post-menopausal women, given they are associated with a lower risk of endometrial cancer, thrombosis, and increased disease-free survival. For example, the Breast International Group 1-98 trial demonstrated improved disease-free survival in those receiving adjuvant letrozole over adjuvant tamoxifen, including those over 75 [44]. The National Cancer Institute of Canada Clinical Trials Group MA. 17 trial found statistically significant benefit to disease-free survival only in those under 60 who received letrozole over placebo following five years of tamoxifen therapy [45]. No interaction between age and treatment was noted, however, and no differences were observed in toxicity or quality of life, suggesting that endocrine therapy is a reasonable strategy for older women.

On the other hand, bone loss and increased fracture risk are also more strongly associated with AIs than tamoxifen, which may be an issue in older women who have a higher prevalence of bone density loss and osteoporosis [44]. Thus, a priority in providing AI therapy in this population is mitigating these side effects with close monitoring of bone density and supplementing vitamin D, calcium, and antiresorptive therapies where indicated. An additional concern with AI therapy is its high cost relative to tamoxifen, so it may not be widely accessible in LMICs. For this reason, tamoxifen is more commonly offered in LMICs [17]. Thus, while AIs are regarded as superior in several respects, tamoxifen is nonetheless a reasonable alternative if toxicity or cost/availability is an issue.

Management of metastatic breast cancer

In many LMICs, the majority of breast cancer cases present with metastatic disease [46]. In general, older individuals with advanced disease are expected to have similar benefits from treatment in comparison to younger women; nevertheless, balancing treatment and quality of life in those of advanced age is a priority [1]. As with adjuvant therapy, treatment strategies in the metastatic setting are similarly guided by tumor characteristics and the patient's individual clinical condition and preferences. In LMICs, timely and accurate pathology evaluation for ER and HER2+ status (where available) by immunohistochemistry is critical to providing appropriate targeted therapy and improving survival. For hormone receptor-positive tumors, endocrine-based therapies are the mainstay of treatment. Endocrine therapy with tamoxifen is affordable and widely available in LMIC. However, aromatase inhibitors are generally preferred to tamoxifen in high-resource settings, as multiple trials have shown improved outcomes/toxicity relative to tamoxifen in elderly individuals with metastatic disease [47, 48]. Although availability may be limited in LMICs, endocrine therapies in combination with CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have recently been shown to have survival benefits in the first-line setting and are generally well tolerated in the elderly population[49].

For those with HER2+ disease, first-line management in resource-rich countries consists of dual HER2 blockade with trastuzumab and pertuzumab combined with taxane-based chemotherapy. Barriers to accessing HER-2 targeted biological therapy are multifactorial and include issues related to drug funding and high treatment costs in LMICs [50]. A study done by Debiasi et al. showed that access to trastuzumab and pertuzumab significantly improves survival and prevents premature deaths in women with metastatic HER2-positive breast cancer in Brazil [51]. The availability of safe and effective biosimilars might increase access to trastuzumab and allow greater use of anti-HER2 therapy in LMIC [52]. In those who are hormone receptor-positive and

HER2+ and are not candidates for chemotherapy, combined endocrine therapy and HER2-targeted therapy is an option. A recent retrospective study analyzed data from patients with hormone receptor-positive (HR+) and HER2+ disease, showing that patients receiving hormonal therapy plus anti-HER2 had improved overall survival compared to chemotherapy plus anti-HER2 (HR: 0.74, p = 0.004) [53].

For those with triple-negative disease, hormone-refractory, or rapidly progressing disease, chemotherapy is recommended. Sequential single-agent chemotherapy agents with favorable toxicity profiles, such as weekly taxanes or capecitabine, are generally preferred. Combination chemotherapy regimens are more toxic and only provide a minimal survival benefit in this setting; therefore, should generally be avoided in the elderly [49]. Many of the treatment regimens recommended in resource-rich countries can be cost-prohibitive in LMICs. In these cases, roles remain for basic anthracycline-based chemotherapy, such as Adriamycin or classical CMF (cyclophosphamide, methotrexate, and 5-FU), in the absence of viable alternatives.

Palliative Care

All patients with metastatic breast cancer will benefit from a prompt referral to palliative care services where they are available. Palliative care focuses on relieving symptom burden and maintaining the best quality of life possible for patients with advanced cancer. It is best delivered in concert with anti-cancer therapy early in the trajectory of illness. If a patient is not a candidate for cancer therapy, a palliative care referral can help manage symptoms and maintain quality of life for as long as possible.

Conclusion

Most elderly patients in LMIC can benefit from a multidisciplinary treatment approach with surgery, chemotherapy, targeted therapies, and endocrine therapy, depending on their tumor biology. Obtaining a complete and timely histopathological review is a very important step in the treatment approach, although this may represent a challenge in LMIC, given the lack of access to high-quality tissue processing facilities and prognostic marker evaluation. Breast cancer treatment in elderly patients should be aimed at improving quality of life in addition to maximizing the survival benefit. Therefore, a comprehensive assessment of patients' functional capacity and comorbidities and tumor characteristics is needed before committing to any therapy.

Clinical Scenario Conclusion

The patient given in the clinical scenario elected to undergo a modified radical mastectomy, as the benefits of breast-conserving surgery were limited by the lack of access to a radiotherapy facility in her region. Her Cancer and Aging Research Group (CARG) score predicts her risk for chemotherapy toxicity of 44%, and adjuvant chemotherapy would only increase her 5-year survival from 88% to 89%, according to the PREDICT tool. Based on this high toxicity risk and limited benefit, she only received adjuvant endocrine therapy. Although an aromatase inhibitor would generally be preferred in the postmenopausal setting, only tamoxifen is available in her region and is relatively affordable.

Key Points

- A multidisciplinary treatment approach is preferred in elderly patients.
- A comprehensive assessment of a patient's functional capacity and comorbidities is essential in determining the risks and benefits of therapy in older adults. Multiple tools are available online for this purpose.

- Fit older patients with breast cancer tolerate many cancer therapies well.
- Breast cancer treatment in elderly patients should be aimed at maintaining quality of life in addition to maximizing the survival benefit.
- In the metastatic setting, prompt referral to palliative care services can help manage symptoms and maintain quality of life.

Items		Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake 1 : moderate decrease in food intake 2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg 1 : does not know 2 : weight loss between 1 and 3 kgs 3 : no weight loss
C	Mobility	0 : bed or chair bound 1 : able to get out of bed/chair but does not go out 2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression 1 : mild dementia or depression 2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m^2)	0 : BMI < 19 1 : BMI = 19 to BMI < 21 2 : BMI = 21 to BMI < 23 3 : BMI ≥ 23
H	Takes more than 3 medications per day	0 : yes 1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good 0.5 : does not know 1 : as good 2 : better
I	Age	0 : >85 1 : 80-85 2 : <80
	Total score	0 - 14 = presence of a geriatric risk profile > 14 = absence of a geriatric risk profile

Table 2: G8 Health Status Screening Tool

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Chapter 28

Breast Cancer in Young Women

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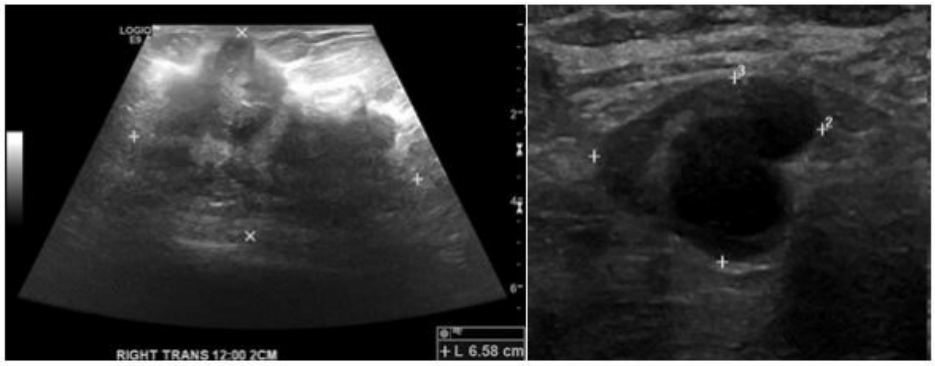
Clinical Scenario

A 32-year-old woman presents with a palpable breast mass. There are no skin changes or nipple discharge. She denies any systemic symptoms and has no significant family history. Physical examination reveals a 6 cm firm mass and palpable ipsilateral axillary lymph nodes. Ultrasound of the breast and axilla confirms a 6.8 cm solid breast mass and an abnormal appearance of the lymph node (Figure 1). Core needle biopsy shows triple negative invasive ductal cancer, and the lymph node was positive for malignancy.

What is your next step in management? Does it change if you are in a country with limited resources? What special considerations should you take, given the patient's age?



Breast *Axillary*

Figure 1: Breast Ultrasound and Axillary Ultrasound -BIRADS 5

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death in women globally. In 2018, there were nearly 2.1 million new breast cancer diagnoses worldwide, accounting for 11.6% of all new cancer diagnoses and 6.6% of all cancer-related deaths [1]. While breast cancer risk increases with age, ~7% of all breast cancer diagnoses occur in women younger than 40 years old, 2.4% being under the age of 35, and 0.65% more youthful than 30 years old [2, 3]. Breast cancer is the leading cause of cancer-related death in women of this age group, with survival rates in young women being lower than their older counterparts [4, 5]. This has been attributed to several factors, including younger patients presenting with larger tumors and more lymph node involvement (higher stage), delay in diagnosis due to lack of screening and low clinical suspicion for cancer, as well as more aggressive tumor biology with more triple negative and HER2+ cancers [2, 4, 5]. Incidence of breast cancer in young women also varies by race, with breast cancer being twice as common in African American women under the age of 35 than in their white counterparts despite the overall incidence of breast cancer being higher among white women [6]. African Americans are also more likely to have hormone receptor-negative disease, basal-like phenotype, and be diagnosed at a more advanced stage than white women; however, survival by stage of disease is equivalent [5, 6].

These trends hold true in Low- and Middle-Income Countries (LMICs), where breast cancer is the most commonly diagnosed cancer and leading cause of cancer-related death among women (with the exception of Sub-Saharan Africa, where cervical cancer is the leading cause of cancer-related death) [1]. Breast cancers in these regions also tend to present at more advanced stages and have worse outcomes. This is likely due to a lack of breast cancer screening programs, limited access to care with fewer medical centers and medical specialists, poor availability of

medicine or equipment, and less education/awareness of the disease [7]. In fact, according to a paper by Magrath et al., 80% of Africans have no access to radiotherapy or certain medical specialists, including pathologists, oncologists, pharmacists, etc. [7]. These limitations have a significant impact on cancer treatment and contribute to the disparity seen in mortality rates between High-Income countries and LMICs.

Compounding these issues are the special considerations that must be taken into account when treating young women with breast cancer. These include pregnancy, fertility, and the psychosocial and economic impacts on family and society. This chapter will review the management of breast cancer in young women with a specific focus on management strategies in LMICs.

Diagnosis and Work-up

Screening

In most High-Income Countries (HICs), breast cancer education and awareness are prevalent, and routine screening programs are well established. The highest rate of breast cancer diagnosed in women younger than 40 years old occurs in Europe and North America, while the lowest rates of breast cancer occur in Eastern and Southern Africa [2]. Some may attribute this difference in incidence to a lack of screening programs in LMICs. However, routine screening does not typically occur under 40 years old [2]. In the U.S., for example, routine screening for average-risk women begins at 40 years of age with an annual mammogram and clinical breast exam (CBE) with or without the addition of breast self-exams (BSE). In patients who are younger than 40 years old, the recommendation is for CBE every three years with optional BSE though no studies have shown a significant impact on cancer-related outcomes with BSE. The use of

routine imaging for screening is not recommended in this young population. Dense breast tissue makes mammography less sensitive than in older patients, and even when young women do undergo annual mammography, diagnosed cancers are more likely to present as interval cancers [3]. MRI (Magnetic Resonance Imaging) is only used in screening in patients with a 20-25% lifetime risk of breast cancer or in those with prior chest irradiation for Hodgkin's Lymphoma before the age of 30 [6].

Given the lack of routine screening, most women younger than 40 years old detect their own breast abnormalities or present with breast complaints [8]. This can often lead to a diagnosis delay due to inadequate awareness of the disease or low suspicion of cancer on the part of the patient and practitioner, given the patient's young age. In LMICs, other causes of delay can be related to lack of resources or access to healthcare facilities or personnel. The combination of presentation delay and absence of screening exams leads to more patients presenting with symptomatic and higher-stage cancer, which portends worse outcomes [3, 8].

Evaluation

Once a young woman presents with breast complaints, further evaluation is required with CBE and imaging studies tailored to the breast complaint. As mentioned, mammograms are less sensitive in younger patients due to the higher density of breast tissue. Ultrasound is a good alternative as it can distinguish solid from cystic masses. MRI is not typically indicated despite it being more sensitive in dense breast tissue. [3, 6]. MRI may be helpful in situations such as a palpable mass without finding on mammogram or ultrasound, or where there is a significant discrepancy in tumor size between physical exam and other imaging, or to evaluate the extent of residual disease after neoadjuvant chemotherapy in patients who want breast-conserving therapy [9]. Routine axillary ultrasound should be performed to evaluate abnormal lymph nodes. In

LMICs, however, these imaging resources may not be available. Ultrasound is likely the imaging modality of choice as it is cheap, portable, and more readily available.

In patients whose physical exam or initial imaging studies show signs of locally advanced disease (large tumors (T3), extensive skin or chest wall involvement (T4), inflammatory cancer, or fixed/matted axillary lymph nodes), metastatic workup is indicated. [9]. In limited resource settings, this evaluation may consist of basic labs, CXR, and abdominal ultrasound as bilateral mammograms, PET scans, bone scans, and CT abdomen/pelvis may not be feasible [10].

Pathology

All suspicious lesions should be biopsied for definite diagnosis and to determine hormone receptor status, which includes estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) if possible. Core needle biopsy (CNB) is the method of choice where available. Pathology should report the cancer type and hormone receptor status to aid in management decisions. This may be difficult in LMICs where resources are limited. For example, some LMICs may not have access to CNB or pathologists. Fine needle aspiration (FNA) is a simpler and cheaper procedure that requires less equipment and histologic material. Although FNA may be able to diagnose cancer and help avoid long delays in diagnosis, it is unable to differentiate invasive vs non-invasive cancer. CNB is preferred to determine invasion as well as obtain hormone receptor status [10].

Abnormal axillary lymph nodes on physical examination or imaging should undergo percutaneous biopsy, with FNA or CNB, to evaluate for axillary nodal involvement to guide staging and surgical procedure. This may be more difficult if resources are limited.

Management

The treatment sequence of a newly diagnosed breast cancer will depend on the stage and operability of the cancer. In non-metastatic breast cancer, the initial step is to determine if the cancer is operable. Non-operable situations include inflammatory breast cancer, extensive skin involvement with ulceration or satellite skin nodules, fixed or matted axillary lymph nodes, fixation to the ribs or sternum, involvement of neurovascular structures of the axilla, or lymphedema in the ipsilateral arm. These clinical situations should prompt imaging to evaluate distant metastatic disease and further define the extent of locally advanced breast cancer. Ideally, systemic therapy is given first to reduce tumor burden and increase the resectability of non-operable disease [9]. This may not be possible in LMICs where access to systemic therapy may be limited, and thus more extensive surgery may be required.

Neoadjuvant endocrine therapy is another option for downstaging disease. Aromatase inhibitors are preferred to tamoxifen in postmenopausal women with clinical stage II-III breast cancer who are hormone receptor-positive (high ER expression), and HER2 negative. It typically takes 4-6 months of neoadjuvant endocrine therapy to see significant tumor regression, and complete pathologic responses are not commonly seen. Unfortunately, there is no established role for neoadjuvant endocrine therapy in premenopausal women. [11, 12] Patients presenting with stage I and II disease are generally operable and can typically have the tumor resected first. The treatment algorithm in Figure 1 shows key decision points and management based on the stage, as discussed next.

Surgery

As mentioned, young women with stage I or II breast cancer can usually undergo surgery first. They have the same surgical options as their older counterparts – either mastectomy or breast-conserving surgery (BCS) with adjuvant radiation. Some exceptions to this are noted later in the special considerations section of the chapter. These options are well established with equivalent survival outcomes. Several studies, however, have shown that younger women have higher local recurrence rates after BCS than older women [5, 6], making margin status important. Contraindications to BCS include disease that cannot be resected to negative margins with acceptable cosmetic outcome, diffuse suspicious or malignant appearing calcifications on imaging, patients who cannot receive postoperative radiation therapy (see contraindications below), and those who are pregnant at cancer diagnosis [9]. In these situations, mastectomy is the procedure of choice in young women. In LMICs where radiation therapy may not be available or logistically feasible, mastectomy remains a standard and commonly employed accepted surgical treatment even for early-stage breast cancers [13].

Patients with invasive breast cancer with clinically negative axillary lymph nodes should also undergo sentinel lymph node (SLN) surgery for axillary staging. SLN surgery done with dual tracers detects the sentinel lymph node(s) in 97-99% of patients [9]. The results of SLN surgery predict the status of the remaining axillary nodes in >95% of cases [9]. Exceptions to performing routine SLN are in older women (such as women over age 70 with early-stage hormone receptor-positive, HER 2 negative disease and no palpable lymph nodes) or those with comorbid conditions precluding them from receiving systemic therapy as nodal information would not change management in these patients.

This point is illustrated in the 2016 Society of Surgical Oncology Choosing Wisely Guidelines which aim to question the necessity of certain tests or procedures in select patient populations. The guidelines state that routine use of SLN surgery in clinically node-negative women ≥70 years old with early-stage hormone receptor-positive, HER 2 negative breast cancer should be avoided as the omission of this procedure does not result in increased rates of locoregional recurrence and does not impact breast cancer mortality [14]. This statement was formulated based on two important papers. First, a 2013 study by Hughes et al. compared lumpectomy plus tamoxifen with or without radiation therapy and showed no benefit of radiation therapy after lumpectomy plus tamoxifen in women over 70 years old in terms of overall survival or distant disease-free survival (though small improvement in locoregional recurrence) [15]. The second, a 2011 paper by Marelli et al., showed elderly patients with early-stage breast cancer and clinically negative nodes (T1N0) did not benefit from axillary dissection (compared to observation) in terms of cancer mortality and thus supports that SLN surgery could also be omitted due to low incidence of axillary disease seen in this age group [16]. Based on these results, axillary staging can be individually considered only if the result may impact decisions on systemic therapy.

The American College of Surgeons Oncology Group (ACOSOG) Z0011trial randomized patients with clinical T1-2 N0 invasive breast cancer with 1 or 2 positive lymph nodes on SLN surgery to completion axillary dissection or no further axillary surgery. The two groups had no difference in local recurrence, nodal recurrence, or overall survival. Based on these results, it has been accepted that no further axillary surgery is needed in patients who fit Z0011 criteria. Completion axillary lymph node dissection is indicated in patients with three or more positive sentinel lymph nodes and in patients who are found to have matted lymph nodes intraoperatively. Exceptions to this are patients undergoing mastectomy, those who received neoadjuvant therapy, and patients

treated with partial breast irradiation. In LMICs where SLN surgery is not available, axillary lymph node dissection for staging is indicated.

Radiation

After breast-conserving surgery, whole breast irradiation (WBI) reduces the risk of ipsilateral breast cancer recurrence and improves survival [3]. Adjuvant radiation therapy is especially important in younger women with breast cancer since their absolute risk of local recurrence is higher than their older counterparts. The typical treatment regimen is 50 Gy in 2.5 fractions on a daily basis over 5-7 weeks. This is followed by a boost of 10 Gy to the tumor bed [9]. Studies show that a boost to the tumor bed leads to improved local control in all age groups, but the largest absolute risk reduction is seen in patients younger than 40 years old [13]. Leaving surgical clips in the tumor bed at the time of BCS helps guide the area to boost with radiation. Accelerated partial breast irradiation (APBI), where radiation is targeted to a limited area of breast tissue surrounding the tumor cavity, has only been studied in women over 45-60 years old and is not currently recommended for young women with breast cancer [3]. In fact, the American Society of Breast Surgeons recommendations for the use of APBI require a minimum age of 45 years along with several other factors, including tumor size <3cm, adequate margins, and negative nodes. [17] Hypofractionation delivers larger fractions over a shorter period of time, thus reducing the number of treatments needed to approximately three weeks. Though this shorter regimen would be beneficial in LMICs where access to radiation therapy is scarce, hypofractionation is only recommended in women over 50 years old, according to the American Society of Radiation Oncology guidelines [3, 9].

Current standard adjuvant radiation therapy after BCS therefore consists of whole breast irradiation with standard fractionation. Radiation therapy delivery should not be delayed

postoperatively, and interruptions should be avoided. Delays of more than three months are associated with decreased survival [13], and interruptions of more than one week during postoperative radiation therapy after BCS are associated with worse local control and overall survival [13]. This may be very difficult in LMICs, where delays and interruptions may be caused by a myriad of logistical factors.

Post-Mastectomy Radiation Therapy (PMRT) is targeted to the chest wall and regional lymph nodes, reduces the risk of local recurrence, and improves overall survival [13]. PMRT is indicated for primary tumors >5cm, positive margins, and≥ 4 positive lymph nodes. PMRT can be considered in 1-3 positive lymph nodes, but in LMICs where resources may be scarce, PMRT should be reserved for >4 positive lymph nodes. Adverse factors that may prompt consideration of PMRT include close surgical margins, lymphovascular invasion, grade 3 disease, premenopausal status or if systemic therapy is not available. The typical PMRT regimen is 46-50 Gy in fractions of 1.8-2 Gy to the chest wall, surgical scars, and drain sites [13].

As mentioned above, contraindications for radiation therapy include prior chest wall irradiation, including mantel radiation for Hodgkin's Lymphoma, pregnancy, and the presence of connective tissue disorder or collagen vascular disease [9]. In these situations, mastectomy is often preferred over BCS since adjuvant radiation cannot be delivered. Similarly, if adjuvant radiation is not available, mastectomy may provide the best oncologic control.

Chemotherapy

Trials across all age groups have shown benefits from adjuvant chemotherapy in terms of local recurrence and overall survival in patients with breast cancer. This is especially true for young women. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a meta-

analysis evaluating the benefit of adjuvant chemotherapy in women younger than 50 years old compared to women aged 50-69. They found anthracycline-based chemotherapy combinations had a larger impact on the annual breast cancer death in the younger age group decreasing it by 38% irrespective of hormone receptor status, nodal involvement, tamoxifen use, or other tumor characteristics compared to a 20% reduction in the older age group [3, 5]. There was also a benefit in recurrence rates. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B30 trial had a secondary aim which showed overall survival is also significantly improved in premenopausal women who have chemotherapy-induced secondary amenorrhea for at least six months after therapy regardless of chemotherapy regimen or hormone receptor status [6]. Preferred chemotherapy regimens in patients with breast cancer generally consist of a combination of anthracyclines and taxanes [3].

Patients with cancers that overexpress human epidermal growth factor receptor -2 (HER2) should also receive biologic therapy with HER2-targeted therapy such as trastuzumab (Herceptin) as part of their adjuvant (or neoadjuvant) systemic therapy. Large randomized trials [3] have shown improved overall survival with trastuzumab regardless of patient age. Pertuzumab is approved in combination with trastuzumab and chemotherapy for HER2+ cancers in the neoadjuvant and advanced-stage settings [3]. These agents are expensive, and access may be limited in LMIC.

Hormonal Therapy

Women with stage I-III hormone receptor-positive cancers should receive adjuvant hormonal therapy. In premenopausal women, this is most commonly with tamoxifen which has been shown in an EBCTCG meta-analysis to improve annual breast cancer death rate by 1/3 as well as decrease the risk of recurrence by 50% regardless of patient age [3, 5]. Initially, tamoxifen was

recommended as adjuvant therapy for five years, however the Adjuvant Tamoxifen: Longer Against Shorter Trial (ATLAS) showed ten years of treatment was more beneficial in terms of recurrence risk and overall survival than five years of treatment, particularly in premenopausal women [5]. Tamoxifen is cheap and has relatively low side effects in young women.

In premenopausal women with hormone-sensitive breast cancer, adjuvant ovarian suppression may also be used to help prevent recurrence. Ovarian suppression may be achieved with tamoxifen plus a luteinizing hormone-releasing hormone (LHRH) agonist. In LMICs where LHRHs may not be available or are cost prohibitive, surgical oophorectomy, tamoxifen, or aromatase inhibitors are other options [18]. Although the prognosis for premenopausal women who achieve chemo-induced amenorrhea is more favorable than for those who do not, the therapeutic value of ovarian suppression is not clear [3].

Locally Advanced Breast Cancer (LABC) - Stage III

Locally Advanced Breast Cancer (LABC) includes patients with large primary tumors (>5cm, T3), tumors with chest wall or skin involvement (T4), inflammatory breast cancer, and extensive clinical node involvement (N2 and N3) [10]. In developing countries, 40-60% of newly diagnosed breast cancers are locally advanced at presentation. The majority present with stage III or IV disease with a 5-year survival of 50% [19]. This is likely due to delays in presentation, diagnosis, and treatment in these LMICs with limited resources and access to care. In a retrospective case series from Pakistan over a 3-year period, 112 of 172 (65%) newly diagnosed breast cancers were LABC at presentation, with 11.6% presenting with metastatic disease. 91.9% had tumors $\geq$ 5cm (63.6% T3; 36.6% T4), 76.7% had lymph node involvement, and 19.6% had chest wall involvement. The mean age at diagnosis was 52 years old. Neoadjuvant therapy was given to all patients in order to downsize the tumors. However, only 6.1% were able

to undergo BCS, while 86.9% had modified radical mastectomy, and 7% required either radical mastectomy or toilet mastectomy (11.6% were metastatic and not operated on) [19]. Though this is only a small case series, it illustrates the burden of disease common at presentation in LMICs and how this affects management decisions.

Management

In countries with limited resources, surgery is the primary treatment for operable LABC, with most patients undergoing modified radical mastectomy (MRM). Where more resources are available, however, neoadjuvant chemotherapy should be given first, followed by surgery and subsequent adjuvant therapy. This approach allows for potential downstaging of cancer after a good clinical response and can convert inoperable cancers into operable ones or allow for BCS rather than mastectomy. It also helps assess the efficacy of systemic therapy on that cancer [10]. Postoperatively, all patients with locally advanced breast cancer, regardless of surgical techniques, should be referred for adjuvant chemotherapy and radiation therapy, and all hormone receptor-positive patients should receive tamoxifen or an aromatase inhibitor, as discussed earlier.

LABC that is inoperable at presentation due to direct invasion into the ribs or intercostal muscle, skin edema or ulceration, satellite skin nodules, or inflammatory breast cancer should have neoadjuvant chemotherapy. If the cancer remains inoperable after chemotherapy, the patient should be referred for radiation therapy, where a 46-50Gy total dose is applied to the breast and regional lymph nodes. If the cancer is still inoperable following that radiation dose, then additional radiation may be used [13].

Metastatic Cancer Breast Cancer - Stage IV

Presentation with metastatic breast cancer is not uncommon in LMICs. In fact, it is estimated that 20-30% of patients in LMICs present with metastasis. This is in stark contrast to HICs where only 3-6% of patients are metastatic at presentation. [20]. In young women aged 25-39 there has also been an increased incidence in metastatic breast cancer diagnoses from 1.53 to 2.90 per 100,000 patients from 1976 -2009 [3]. This is especially concerning in the young population as young age is an independent risk factor for poor prognosis [3].

Management

Metastatic breast cancer is difficult to manage in resource limited countries where access to care may be restricted and medications and medical specialists may be lacking. The mainstays of treatment are systemic chemotherapy as discussed above and palliative radiation therapy. Surgery of the breast primary generally does not play a therapeutic role and is mainly performed for symptom control with a toilet mastectomy. The role of surgical resection of the breast primary in Stage IV breast cancer is controversial. In a registry trial in the US, there was no survival advantage from surgical resection of the breast primary. In a prospective trial in Turkey of 274 patients, there was no improvement in survival at 36 months of follow up, however with longer study follow-up (median 40 months) surgery was associated with a survival advantage. A prospective trial in India of 746 patients showed no survival advantage from resection of the breast primary in patients with metastatic breast cancer at initial presentation who responded to front-line chemotherapy.

Key to mitigating the impact of metastatic breast cancer in LMICs is to invest in education and screening programs to allow for earlier detection leading to clinical downstaging and therefore better prognoses and outcomes.

Special Considerations in Young Women

Breast Cancer in Pregnancy

Breast cancer is the most common cancer diagnosed during pregnancy with an incidence of 1.5%. Pregnancy at time of diagnosis poses a challenge to standard breast cancer treatment due to potential harm to the fetus at various stages of development. Patients presenting with breast complaints while pregnant should undergo diagnostic mammography with shielding of the fetus, ultrasound, and CNB. Staging work up is dictated by clinical stage at presentation as in non-pregnant women, however, CT scan, X-ray, and nuclear medicine expose the fetus to radiation and need to be considered carefully and are usually avoided. MRI is contraindicated due to the gadolinium required. In LMICs where these more complex imaging studies are not available, management is more straight forward [3].

Surgery is safest during second trimester of pregnancy, but can be performed in all trimesters. For women presenting with breast cancer in their second or third trimester, both mastectomy and BCS are acceptable operative approaches, however, timing of adjuvant radiation therapy must be carefully considered. In patients who require chemotherapy, partial mastectomy can be performed first, followed by adjuvant chemotherapy with radiation delayed until the postpartum period. In cases where the patient is diagnosed in the first trimester and chemotherapy is not indicated, mastectomy is recommended [9]. Chemotherapy can be given in the second and third trimesters and can be used in either the adjuvant or neoadjuvant setting. Cytotoxic and endocrine

therapies are contraindicated in the first trimester. For axillary staging, SLN surgery with low dose radioisotopes can be done during pregnancy, but methylene blue and isosulfan blue are contraindicated (class C) [3]. In LMICs with limited resources, MRM is likely the procedure of choice. Chapter 27, Pregnancy Associated Breast Cancer, further discusses this topic.

Fertility

A unique feature of breast cancer management in young women is the impact of treatment on fertility. Risk of infertility varies with a patient's age, reproductive reserve, and various aspects of treatment including the duration of treatment, chemotherapy agent used, dose administered, etc. The rates of infertility are not clearly defined, and it is hard to predict who will have issues with fertility. Patients should therefore be referred to onco-fertility specialists to discuss fertility preservation prior to starting chemotherapy. Options for fertility preservation include embryo, oocyte, or ovarian tissue cryopreservation and ovarian suppression with luteinizing hormone-releasing hormone (LHRH) agonists [3]. Administration of Gonadotropin-releasing hormone (GNRH) agonist during chemotherapy have also been used for ovarian protection and have shown to reduce the risk of premature ovarian failure in women under age 50 from 22% to 8% [9]. As these resources are likely not available in most LMICs, the specifics are beyond the scope of this chapter, however, being aware of the risk and having frank discussions with patients regarding fertility is prudent.

Psychosocial Factors and Economic Impact

Young women with breast cancer are especially prone to psychosocial distress after cancer diagnosis. They have increased feelings of anxiety and are more likely to be worried about beauty and attractiveness, fertility and family planning, and sexual function than their older

counterparts [3]. Similarly, they may be more concerned about sustaining their careers or education, raising young children, and have fear of cancer recurrence. In LMICs, young women are vital to the socialization, education and maintenance of health among their children. When these women are taken out of that role by breast cancer diagnoses there are societal impacts [21]. In some countries, young women also make up a sizeable part of the work force and their absence during treatment can results in economic and financial impacts as well. The fact that young women present with more advanced stage disease, have more aggressive tumors, and worse outcomes in LMICs increases these burdens as more aggressive and extended treatment regimens are required compared to treatment of earlier stage breast cancers. Further investment in cancer awareness/education and screening may help mitigate these effects and enable diagnosis at an earlier stage.

Summary

Breast cancer in young women is a global problem, with the highest incidence of young women being diagnosed in HICs, but the highest mortality rates being seen in LMICs. Young women tend to present with higher-stage disease and with more aggressive tumors making management of breast cancer in young women more difficult, especially in resource-limited settings. Special consideration must also be given to the unique features of cancer treatment in young women that differ from their older counterparts. Despite this, breast cancer in young women is very treatable. With improved education and awareness, along with clinical screening programs to aid in earlier detection in LMICs, better outcomes are possible. Figure 2 is our algorithm for managing young women with breast cancer.

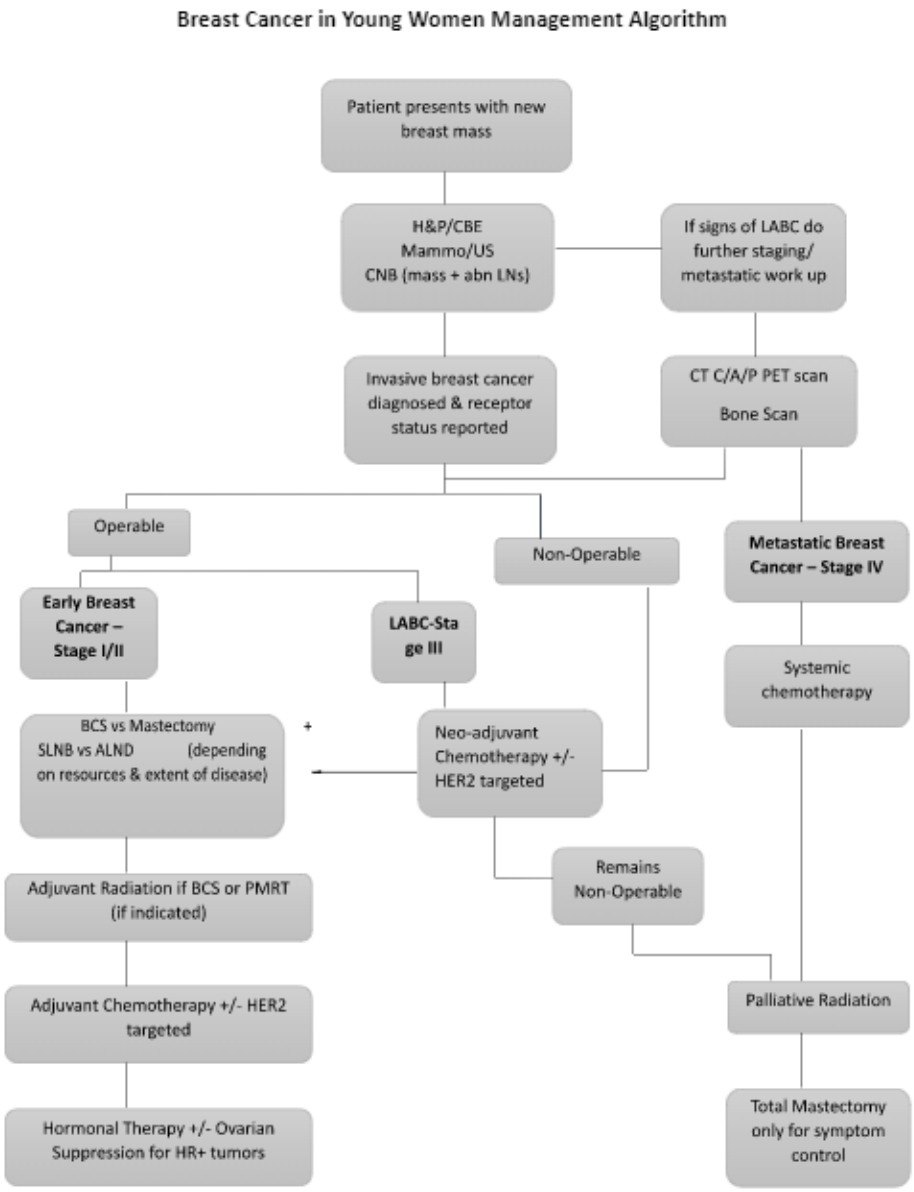


Figure 2: CBE: Clinical Breast Exam; CNB: Core Needle Biopsy; LNs: Lymph Nodes; BCS: Breast-Conserving Surgery; SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; PMRT: Post-mastectomy Radiation Therapy

Clinical Scenario Conclusion

The patient had a negative metastatic workup and underwent neoadjuvant chemotherapy. Imaging after neoadjuvant chemotherapy showed an excellent response with mass now measuring 1cm and radiographically negative axilla. She underwent lumpectomy and SLN surgery with localization and removal of the clipped positive node. Three sentinel nodes were negative for malignancy. She received adjuvant radiation.

Key Points

- Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death in women globally, and survival rates in young women are lower than their older counterparts.
- Breast cancers in LMICs tend to present at more advanced stages and have worse outcomes in part due to delays in diagnosis and limited resources for management.
- Most young women detect their own masses or present with breast complaints due to a lack of screening in this age group.
- All new breast complaints should have a History & Physical, clinical breast exam, and imaging as available, and any mass or suspicious lymph nodes should be biopsied for pathologic tissue diagnosis and hormone receptor status.
- New cancers can be divided into those that are operable and those that are non-operable, as well as by stage to help with management decisions. Most early-stage breast cancers can proceed straight to surgery, while locally advanced and non-operable cancers should have neoadjuvant systemic therapy where possible.
- Surgical management consists of BCS vs mastectomy and SLN surgery vs ALND (if SLN surgery is not available). There is a limited role for surgery in metastatic cancer except for symptom control.

- Patients should be referred for adjuvant radiation therapy, chemotherapy, and hormonal therapy based on surgical pathology/stage and hormone receptor status. Hormone receptor-positive patients may also benefit from ovarian suppression.

- Special considerations in young women with breast cancer include pregnancy, fertility, and psychosocial issues, and relevant referrals should be made to address these issues.

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Chapter 29

Pregnancy-Associated Breast Cancer in Low-Resource Settings

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Clinical Scenario

A 29-year-old female in Kigali, Rwanda, initially presented to the medical clinic at 32 weeks' gestation with a right breast lump that was thought to be a developing milk duct. Subsequently, at 39 weeks, she had an uncomplicated vaginal delivery. She then returned to the clinic several weeks after delivery when she noticed that the right breast lump had grown. On exam, the mass was palpable in the upper outer breast with clinically palpable right axillary lymph nodes; the left breast and axilla were unremarkable. She was sent for a breast ultrasound that revealed an 8 cm mass and multiple enlarged axillary lymph nodes in her right axilla.

Differential Diagnosis

The finding of a breast mass in a pregnant patient should be addressed quickly and assumed to be pregnancy-associated breast cancer (PABC) until objective clinical evidence suggests otherwise. The differential diagnosis for a breast mass includes benign lesions such as phyllodes tumor or

fibroadenoma. Also, depending on the clinical scenario, an abscess or a galactocele could be the cause of a breast lesion during pregnancy.

Pregnancy-associated breast cancer

Definition

Pregnancy-associated breast cancer (PABC) is an entity defined by the diagnosis of an invasive breast cancer during the perinatal period. This time period also includes the first 12 months after delivery. The diagnosis of PABC necessitates providers caring for pregnant patients to have a high level of clinical suspicion and a low threshold to evaluate any breast-related concerns. Providers must also counsel and educate pregnant women on breast-related signs and symptoms that warrant a clinical evaluation. Providers must also give patients information about access to care: when and how the patient can notify her provider if a breast complaint arises. *A multi-disciplinary approach is paramount for successful management.*

Incidence

In the United States, the annual incidence of PABC is estimated to be low ~ 0.2-3.8% [1-3]. The National Cancer Institute estimates PABC to occur in ~1 in every 3000 pregnancies. Despite this low incidence, PABC represents one of the most common cancers diagnosed in young women [4]. Close to 20% of the invasive breast cancers diagnosed in women between 30 to 40 years old are associated with pregnancy [2]. While the lifetime risk for invasive breast cancer increases with age, it follows that the incidence of PABC may also increase as more women delay childbearing to later ages.

The incidence of PABC in developing nations needs to be better described and documented. In these nations, cancer registries are increasing in number. However, the ability to detect, refer,

and appropriately treat complex patients is highly variable. The World Health Organization (WHO) surveyed 177 of the 194 member nations and found “significant deficits in cancer diagnosis and treatment…particularly in low-income countries, where less than 30% of countries have generally accessible services” [5]. More effort in data collection is required to identify the incidence of PABC in low-income nations.

Prognosis

A point of controversy exists regarding PABC and associated worse prognosis/outcomes when compared to non-PABC. The conclusions vary in the literature on this topic. Patients with PABC tend to be diagnosed with locally advanced invasive ductal carcinoma of larger size, often also involving the axillary lymph nodes. It is more common for these cancers to be estrogen receptor (ER) negative, progesterone receptor (PR) negative, and HER-2/neu receptor negative or triple-negative [6]. However, this subtype is also more common in younger women with breast cancer, regardless of pregnancy status; therefore, some studies suggest that the features of breast cancer at a younger age, and not the physiology of pregnancy, portends worse outcomes. For patients with PABC and a median follow-up of 61 months, Langer et al. found a favorable overall survival rate of 81.8% at five years in their single institution cohort [7]. These results were similar to other studies in the United States [8, 9] and Europe [10, 11] comparing pregnant and nonpregnant age- and stage-matched controls (control groups varied across studies).

Conversely, numerous analyses support the conclusion that there are worse outcomes among PABC patients [12-14]. A multi-institutional study by Bonnier et al. found that the five-year overall survival of the PABC group was 68% compared to 77% for nonpregnant patients [12]. Furthermore, a large meta-analysis of 41 studies analyzed by Hartman and Eslick estimated that

for patients diagnosed with breast cancer during or after pregnancy, the overall risk of death was higher than controls who were not pregnant (hazard ratio of 1.46) [15].

In line with the limited data on the incidence of PABC in developing nations, there is a lack of data on the disease-specific mortality for PABC. Nevertheless, available data on breast cancer mortality can be used to inform an understanding of PABC mortality. In 2008, using data from the WHO International Agency for Research on Cancer (IARC), Shulman et al. calculated the number of breast cancer deaths as a percentage of incident cases by four gross national income groups. For low-income countries, the rate of death was 48%. The rate of death was 40% in low-middle-income countries, 38% in high-middle-income countries, and 24% in high-income countries [16]. These disparities in outcomes can, in part, be explained by differences in the nations and regions that support population health services, including comprehensive early disease detection programs, in contrast with those nations unable to access higher quality screening and comprehensive patient care [17].

It has been considered in recent years that the ‘westernization’ of developing nations’ economies and lifestyles has started to close the observed breast cancer mortality gap [18]. In 2018, the WHO IARC database estimated the number of breast cancer deaths for women in low-income countries to be 14.7 per 100,000, 14.9 for low-middle-income countries, 10.7 for middle-high-income countries, and 12.9 for high-income countries. [19].

Identification and work-up of a pregnancy-associated breast mass

A woman’s physiology and breast findings change significantly during pregnancy. For this reason, breast changes associated with a cancer diagnosis may not be perceived as concerning. Importantly, it is imperative that pregnant women are counseled regarding breast cancer signs

and symptoms, in addition to when and how to alert providers in the event that a breast complaint arises.

PABC does not occur more often in one trimester than another. Pregnant patients should notify the clinical team when unexpected or unilateral breast changes occur during any trimester. These changes can include palpable findings, bloody nipple discharge, mastodynia, skin dimpling, erythema, swelling, or edema. Additionally, it is critical for women in the post-partum period who are breastfeeding or undergoing post-lactational involution to have breast concerns evaluated. A high degree of suspicion is imperative, as breast changes that occur secondary to malignancy may be misinterpreted as more commonly encountered lactational sequelae, including mastitis and breast abscesses.

A patient should feel comfortable alerting her treating providers whenever she is concerned about her health. Typically, given the dynamic nature of breast changes during pregnancy, new and suspicious findings present for two weeks or longer may be more concerning than those findings present for a shorter period of time. Notably, findings that are progressive and/or refractory to conservative management (i.e., antibiotic therapy, percutaneous aspiration) herald a more concerning etiology.

Imaging

The imaging modalities used to evaluate breast concerns during pregnancy and lactating or post-partum women include diagnostic ultrasound and 2-D or digital mammography. Data has shown that the combination of mammograms and ultrasound to work up a concern for PABC is sensitive and specific [20, 21]. Diagnostic ultrasound is considered first-line imaging and is

preferred in low-resource settings. New, palpable lesions or bloody nipple discharge can also be assessed with ultrasound.

Diagnostic mammograms should be used to evaluate subtle findings when a physical exam is suspicious, but ultrasound is negative [22]. Otherwise, diagnostic mammograms are considered a supplement for suspicious findings on ultrasound. Mammograms can adjunctively assess for microcalcifications that would not otherwise be seen on ultrasound.

Radiation exposure associated with mammography has been well studied. According to an assessment of the safety of radiation dosing, the American College of Radiology (ACR) concluded that mammograms are not contraindicated during pregnancy. Also, there is low exposure to the developing fetus in the setting of radiologic exams that are not directly performed on the abdomen. According to the ACR, a fetus's radiologic dose during a mammogram is as low as <0.03 mGy. At this level no teratogenic effects would be expected. When adding abdominal and pelvic shielding, exposure is even further reduced [22,23]. Magnetic resonance imaging (MRI) without contrast can play a role in the workup for breast concerns in pregnant patients. The ACR recommends against the use of gadolinium in pregnant women, and gadolinium is considered a teratogen, as exposure to gadolinium during pregnancy is linked with several adverse events, including inflammatory changes, stillbirth, and neonatal death [22, 24].

Diagnosis/Pathology

Tissue diagnosis is needed to diagnose PABC and is typically obtained with the assistance of radiologists and guided by imaging. This is best done with core biopsy rather than fine needle aspiration (FNA). Core biopsy provides a more robust sample of tissue to complete

histopathologic assessment. Treatment options can be heavily guided by the information gleaned from histopathology (i.e., receptor status). Cytology, completed after FNA, is insufficient for receptor analysis and at times, may not yield sufficient data to obtain a diagnosis. When image-guided core biopsy is not accessible or feasible, pursuing percutaneous or excisional biopsy is acceptable. *If an excisional biopsy is completed, efforts should be made to obtain adequate tissue for analysis and appropriately orient the specimen for pathologic analysis.*

Staging

In the existing literature, PABC is associated with more aggressive subtypes and advanced stages of disease. [7-9, 12, 25]. In a study by Langer et al., a majority of PABC patients had more regional disease, including larger tumor size and more lymph node involvement [7]. In the absence of suspicious signs and/or symptoms (e.g., headaches, changes in vision, bone pain, etc.), breast and/or axillary evaluation alone is a reasonable staging work-up [26]. In cases where tumors are categorized as T2 or greater, axillary ultrasound should also be employed. Ultrasound is a low-cost exam with no radiation exposure. We advocate for limited testing to assess for metastatic disease unless indicated by advanced disease stage and patient signs and symptoms. When employed, staging requires a balance of added risk associated with further interventions and cumulative addition of radiation exposure to the fetus.

However, the discovery of metastatic disease can significantly alter management plans. For patients with ≥ T3 disease with clinically positive axillary lymph nodes, it is sufficient to order a chest x-ray to assess thoracic anomalies (with abdominal shielding), serum laboratory testing (including complete blood count with differential, as well as renal and liver function labs) and a liver ultrasound to assess for concerning liver lesions. MRI without contrast to assess the spine should also be obtained when available. Some data show that low-dose radionuclide bone scans

could be considered if the patient is kept well hydrated throughout the procedure with a Foley catheter to monitor hydration status. There is limited data on whole-body assessments, with MRI or PET, to make a robust recommendation in pregnant women [27-29].

Treatment

Surgical Options

It is paramount that PABC patients begin anticipatory discussions and initiate treatment as soon as possible. A multi-disciplinary approach is ideal but may not be feasible in all settings. The management of PABC follows a similar paradigm to that of non-PABC, though the timing of all therapies must be thoughtfully considered. *While sensitive to discuss, patients have the option to terminate the pregnancy.* When appropriate, it should be explained to the patient that different therapeutic options may be implemented if the patient is not pregnant. However, it is important to state that pregnancy termination is not necessary for treating breast cancer.

Regarding surgical management of PABC, the local extent of the disease is an important consideration along with the patient's pregnancy trimester. Anesthesia is considered safe in all trimesters, with slightly higher risks associated in the first trimester, including the risk of thromboembolism and miscarriage [30]. In the first trimester, the preferred surgical management of the breast is mastectomy and axillary lymph node assessment. Because radiation therapy is an absolute contraindication during pregnancy [26], breast-conserving surgery (BCS) is not an ideal option in the first trimester. To this end, at the time a patient diagnosed in the first trimester would reach full term (37 weeks), scheduling for adjuvant radiation therapy (RT) would be outside the recommended timeline (≤ 12 weeks post-breast conservation).

In the second and third trimester, BCS and mastectomy may be potential options in appropriately selected patients. Again, in the BCS setting, ideally, RT initiation should be planned for no more than 12 weeks post-surgery. RT may not be necessary post-mastectomy. Surgical treatment considerations (i.e., tumor-to-breast ratio, multi-centricity, etc.) can be applied during the second and third trimesters. Surgical evaluation of the axilla is dependent on preoperative status. For clinically positive axillary lymph nodes, i.e., those that are palpable or have a positive cytologic/histologic diagnosis, axillary lymph node dissection (ALND) is the standard of therapy. According to the National Comprehensive Cancer Network (NCCN) guidelines, when axillary lymph nodes are clinically negative, options for management include ALND or sentinel lymph node biopsy (SLNB). To identify the appropriate axillary lymph node(s) during a SLNB, technetium Tc-99m sulfur colloid may be utilized during pregnancy. Blue dye (e.g., isosulfan blue or methylene blue) is considered contraindicated in pregnancy due to the risk of anaphylaxis and unknown teratogenic risk [26]. If technetium Tc-99m sulfur colloid is not institutionally or regionally available, ALND should be employed.

Reconstruction after mastectomy in PABC is felt to be best suited in the delayed setting. A concern is the potential added risks and/or complications that reconstruction interventions may pose intraoperatively and postoperatively. An additional concern for PABC patients undergoing reconstruction in the immediate setting includes the understanding that the physiologic changes of the postpartum breast tissue are unpredictable, making symmetry more complex to achieve. Nonetheless, immediate reconstruction is not contraindicated in PABC. In fact, in a few modern small series, reconstruction was shown to be feasible without negatively impacting maternal or fetal outcomes [31-33]. *When undertaken in the immediate setting, tissue expander placement may allow for the least additional operative time and associated risks.* Coordination with

reconstructive surgeons, if available in low-resource settings, can be challenging despite these considerations.

Systemic chemotherapy

During the second and third trimester, pregnancy is not considered a contraindication to chemotherapy. Given the association with pregnancy loss, chemotherapy is avoided in the first trimester [34]. After the first trimester, the risks of fetal malformations in exposed patients were found to be similar to untreated patients. If possible, chemotherapy should not be given within 3 weeks of a planned delivery or after 35 weeks gestation in order to give the patient time to recover from the hematologic toxicities of treatment prior to the onset of labor. During treatment with chemotherapy, adjustments for weight gain and change in body-surface area must be made as pregnancy progresses.

The most common chemotherapy regimens for the treatment of breast cancer include FAC chemotherapy (5-fluorouracil 500 mg/m2 IV days 1 and 4, doxorubicin 50 mg/m2 by IV infusion over 72 hours, and cyclophosphamide 500 mg/m2 IV day 1). Another common regimen is AC (doxorubicin + cyclophosphamide) therapy which does not include the 5-FU portion. Safety studies of taxane use during pregnancy have been limited, and the use of taxanes, such as paclitaxel, is currently implemented on a case-by-case basis. Emerging data on taxane safety during pregnancy indicate that this treatment could be considered after the first trimester when anthracyclines are contraindicated [35]. Most anti-emetic therapies are considered relatively safe in pregnancy, including ondansetron, dexamethasone, lorazepam, promethazine, and prochlorperazine.

According to the NCCN, several breast cancer therapies are contraindicated in pregnancy. Anti-HER-2 monoclonal antibodies such as trastuzumab and pertuzumab are currently contraindicated throughout pregnancy due to reports of fetal oligohydramnios, pulmonary hypoplasia, and intrauterine fetal demise. Ideally, these drugs should be delayed until the postpartum period when indicated for HER2-positive disease. Endocrine therapy is also contraindicated during pregnancy, as these drugs are known teratogens.

Obstetric Considerations

The impact of pregnancy on the patient's decisions regarding treatment for breast cancer can be significant. Some patients may consider forgoing therapy to spare the fetus treatment-related exposure, while other patients may decide to terminate a pregnancy. *Therefore to help guide patients in their treatment decisions, it is important for physicians to be highly knowledgeable and informed regarding the data existing about this complex issue.* It is also important to have confirmation of gestational age, as the timing and types of treatment will vary significantly by trimester. An obstetric ultrasound should be used to confirm the stated gestational age to help guide treatment.

Consideration of elective termination

There is currently no evidence that termination of pregnancy improves survival from breast cancer [36]. However, some patients may find it difficult to proceed with treatment while pregnant. Future fertility should also be discussed, as treatment with chemotherapy can affect a patient's ability to conceive in the future. Importantly, the patient's choice should be supported by the patient's treatment team.

Surgical considerations

Miscarriage rates from surgical interventions are slightly higher in the first trimester due to the stress of surgery and the effects of general anesthesia [37]. *If surgery is pursued in the first trimester and early second trimester, fetal heart tones should be checked and documented before and after surgery.* When a patient reaches a gestational age, at which point an obstetrician would intervene and/or a neonatal team would resuscitate a viable fetus in the event of preterm delivery, a non-stress test with fetal heart rate and contraction monitoring should occur before and after surgery. The gestational age when these interventions are implemented can vary from facility to facility, depending on the availability of obstetrical and neonatal specialists and associated technology.

Chemotherapy risks

The majority of chemotherapy safety data is in anthracycline and alkylating agents. As stated previously, the risk of fetal malformations in the second and third trimesters is similar to unexposed pregnancies. The main risks from chemotherapy exposure are preterm delivery and intrauterine growth restriction (IUGR) [37]. Chemotherapy regimens can cause pancytopenia, and delivery exposes patients to additional risks for the development of infections and acute hemorrhage. Recovery of red blood cells, platelets, and white blood cell counts is important prior to delivery. *Therefore, the recommendation has been made to stop chemotherapy by 35 weeks if term induction is planned or three weeks prior to a planned preterm delivery if indicated for standard obstetrical indications.*

Obstetrical delivery timing

Fetal well-being should be balanced with maternal well-being during treatment as much as possible to permit the best outcomes for the patient and the developing fetus. *Efforts should be made to delay delivery until term at 37 weeks, as accurate gestational age dating may not always be possible.* This is especially important in low-resource settings, as access to neonatal specialists and equipment can also be limited. Due to the risk of IUGR, when chemotherapy regimens are used, fetal growth ultrasounds are recommended every four weeks, starting at 24 weeks, with subsequent performance of umbilical artery dopplers if IUGR occurs. Early delivery may be indicated if the fetus has an improved chance of survival after preterm delivery with the resources available. Prior to 34-37 weeks, intrapartum steroids, including intramuscular betamethasone or oral dexamethasone, can be used when appropriate to aid in fetal lung maturity.

Breastfeeding

The implications of breast cancer treatment on breastfeeding are especially important in developing nations, where breastfeeding until two years of age is the norm, attributed to both cultural beliefs and nutritional necessity. Therefore, the impact of treatment on breastfeeding is critical, and thoughtful shared-decision making must be undertaken to support the well-being of the mother and the infant. If breastfeeding is considered unsafe in conjunction with an indicated treatment, it must be ensured that the patient has access to alternative forms of nutrition for her child.

Breastfeeding is considered safe in the contralateral breast if the patient is not undergoing chemotherapy or endocrine therapy. Most cytotoxic therapies are excreted in the breast milk, and unless under strict guidance from an oncology pharmacist, breastfeeding is contraindicated for

patients treated with chemotherapy. This is also true for anti-HER2 therapies [37]. Lactation can occur after breast radiation though patients may have a decreased milk supply.

Consideration for subsequent pregnancies

Generally, it has been recommended that women wait until two years after completion of treatment of their breast cancer to attempt to conceive. Long-acting contraception, including hormone-free copper intrauterine devices, can be considered to provide adequate and safe birth control during this time frame. If long-acting contraception is unavailable, patients should be counseled about family-planning considerations and other forms of available and affordable contraception.

Psychosocial and cultural implications

The importance of psychosocial and cultural factors for patients with PABC cannot be underestimated. According to WHO, 90% of patients' health outcomes are attributable to psychosocial factors [38]. In fact, Anderson and colleagues specifically studied the barriers to guideline implementation in breast health in low-income countries [39]. A common factor associated with the lack of breast cancer care is the construct of fatalism – the idea that the disease is fatal, and the outcome cannot be changed. This concept was found to be especially common in Middle Eastern and sub-Saharan African cultures. A similar belief is an idea that fate will decide the outcome – 'what will be will be.' Patients are also skeptical of surgery and may erroneously believe that operating on the breast will cause harm or spread the disease. Some patients believe the diagnosis will bring shame to their family; members of the community may consider something to be wrong with a family when a relative is diagnosed with breast cancer. In some societies, husbands may divorce their wives diagnosed with cancer as these women are

considered damaged, leading to loss of home and socioeconomic status for the affected patient. Similarly, unmarried women or women with daughters may be considered unmarriageable, removing this opportunity for success within the culture. These ideas are especially damaging to women with PABC, who are in a particularly vulnerable position within their society and medical decision-making community.

It is important to note that women desiring medical care may not have access to the needed support. Frequently, women need more resources, including transportation or financial support. In the study by Anderson [39], it was shown that many patients did not receive adequate care merely because they were not referred for either treatment with chemotherapy or radiation. This may have been secondary to a lack of resources, such as the fact that in 2008, Uganda only had four mammogram machines for ~6-7 million eligible women and a radiologist-to-patient ratio of 1:300,000, making early identification of breast cancers a tremendous challenge [40]. There can also be authoritarian actions by the physician such that the physician may choose not to disclose a patient's cancer diagnosis secondary to the belief or concern that knowledge of the diagnosis could lead to self-harm. For these reasons, it is critical to support education about treatment options and prioritize consideration of each patient's circumstances and beliefs when recommending treatment.

Recommendations for developing nations

Table 1 includes recommendations for diagnosing and caring for patients with PABC when resources are minimal. Consideration for the nuanced recommendations made in the preceding sections can be used when the different treatment modalities and trained healthcare providers are

Table 1. Recommendations for PABC in developing nations with limited resources	
Identification	CBE at 1st obstetric, 28-week, and postpartum visits
	Ultrasound for clinically identified breast mass
Diagnosis	Core-needle biopsy
Surgery	Mastectomy + ALND
Delivery	37 weeks
Postpartum treatment	Tamoxifen for ER+ or PR+ disease
Abbreviations: ALND – axillary lymph node dissection; CBE – clinical breast exam; ER – estrogen receptor; PR – progesterone receptor.	

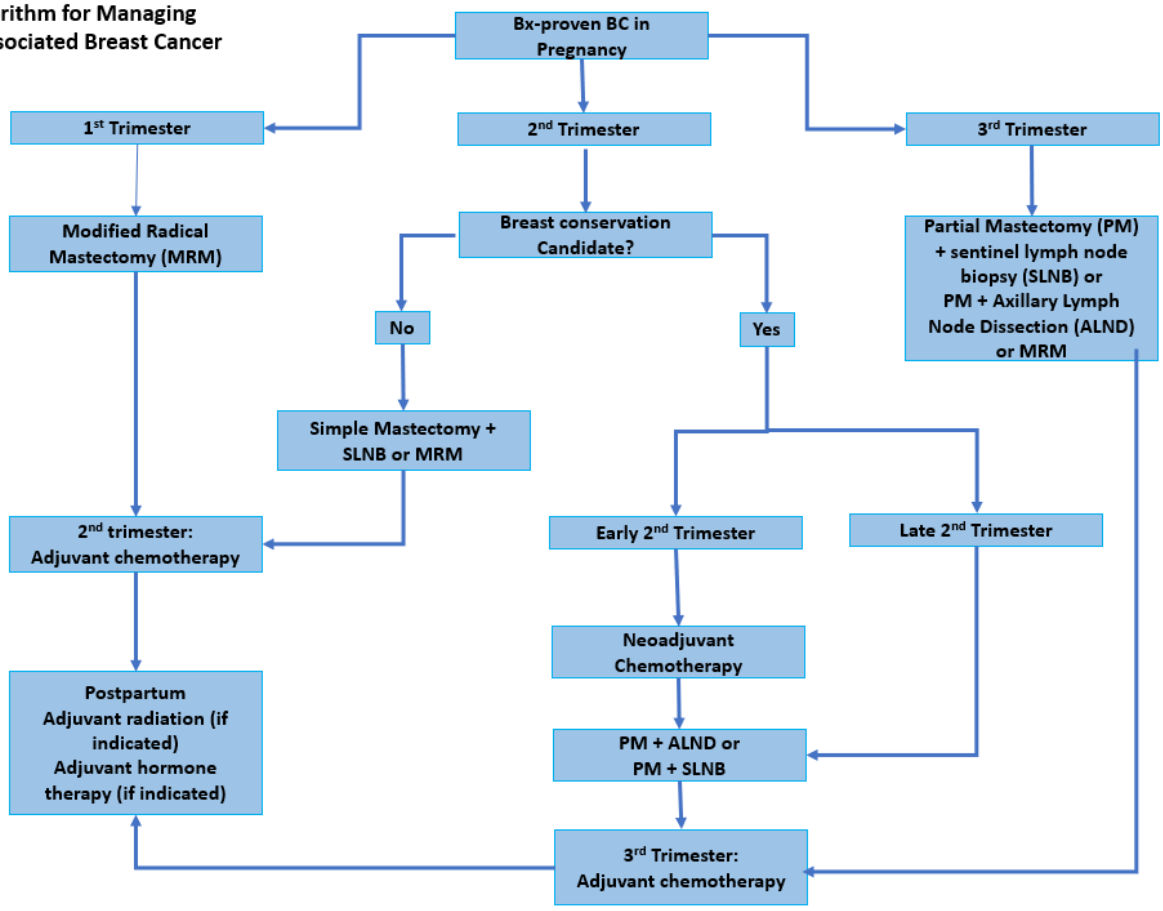
available, but the course of action found in Table 1 should be considered when resources are lacking.

A mainstay of the diagnosis of PABC is the clinical breast exam (CBE). It is straightforward to train non-physician/nurse community healthcare workers in the identification of a breast mass. In order to identify PABC in a timely matter, CBE should be performed at the first obstetric appointment, in addition to being repeated at the 28-week visit and postpartum exam. Ultrasound can be used to follow up on any identified findings, frequently using the same machine for obstetric exams. With or without ultrasound, core needle biopsy is also easier to learn for healthcare workers with less training than excisional biopsy.

Upon diagnosis of a PABC, referral to a cancer center in the region is preferred but not always practical due to large travel distances, family obligations, and financial constraints in developing nations. Thus, treatment for many breast cancers is performed in a nearby community. Because radiation treatment is not available in many low-resource environments, mastectomy with ALND is the mainstay of surgical management for PABC in these settings. This surgery should be relatively safe to perform in any trimester and also adequately control the disease. Chemotherapy may be indicated as well, but some patients do not have the resources to undergo chemotherapy. Therefore, tamoxifen may be the drug of choice for hormone receptor-positive disease in the postpartum period. Tamoxifen also has the benefit of being an oral drug that is relatively inexpensive.

Implementation of these recommendations should help to improve the outcomes for women in developing nations diagnosed with PABC. Consideration for the patient's family planning desires and obstetrical implications must also be accounted for in the multidisciplinary treatment plan. Figure 1 highlights an algorithm for managing pregnancy-associated breast cancer.

Figure 1. Algorithm for Managing Pregnancy-Associated Breast Cancer



Clinical Scenario Conclusion

A core biopsy was performed of the patient's breast mass, and she was diagnosed with locally advanced triple-negative breast cancer. The patient completed neoadjuvant chemotherapy and stopped breastfeeding. She had a favorable response to chemotherapy, the breast mass was no longer palpable, and the axilla was clinically negative. The patient subsequently underwent a right mastectomy and axillary lymph node dissection (modified radical mastectomy); radiation services were not available.

Key Points

- Diagnosis of breast cancer in pregnancy requires high suspicion and low threshold
- Treatment of breast cancer is safe in pregnancy- Treatment will vary upon the availability of resources
- Surgery can safely be done in any trimester
- Mastectomy and axillary lymph node dissection are the mainstay of surgical treatment, especially when radiation therapy is not available
- Chemotherapy is contraindicated in the first trimester
- If possible, chemotherapy should not be given within three weeks of delivery
- Endocrine therapy, anti-HER-2 monoclonal antibodies are contraindicated during pregnancy
- Plan for delivery should be at 37 weeks' gestation or later, pending obstetrical indications for earlier delivery.
- It is not necessary to terminate pregnancy with a diagnosis of PABC

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Chapter 30

Management of Hereditary Breast Cancer for Low- to Middle-Income Countries

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Clinical Scenario

A 37-year-old G2P2 female presents to a women's health clinic in a low-income country with a breast mass. She undergoes a workup and is diagnosed with breast cancer. The physician notes that she has a mother and sister diagnosed with breast cancer at the ages of 55 and 42, respectively, and a maternal aunt with ovarian cancer in her 40s. The physician arranges for surgery and adjuvant treatment for her breast cancer but is concerned that there may be a genetic mutation running in the family. What would be the next steps in her care?

Introduction

This chapter aims to outline the current guidelines for managing hereditary breast cancer in unaffected and affected carriers for providers in low and middle-income countries (LMIC) and to provide practical strategies for their care. According to the World Bank, low-income countries are defined as those that have a national income per person of $1,025 or less, and middle-income countries have a national income per person between $1,025 and $3,995. Since data on the

management of hereditary cancer in LMICs is often lacking in many areas, we have used studies on non-Caucasian races as a proxy for LMICs.

Identifying Gene Carriers in Low to Middle-Income Countries

Genetic mutations account for 5-10% of breast cancer cases worldwide. Genetic testing for high-risk individuals is the standard of care in most high-income countries. However, gene panel testing, and genetic counseling are not readily available resources in most LMICs. In addition, most of the research done on surveillance and treatment strategies for mutation carriers has been done in high-resource settings, so it may be difficult to extrapolate these results to areas that lack significant resources. These factors underscore the difficulty in identifying gene carriers in LMICs. The United States (US) is not considered a LMIC, but some areas in the US are low-income areas and can be used to understand how to increase genetic testing access for patients. Studies conducted in the United States in low-income areas have shown that telephone surveys, systems-wide surveys, and a screening tool used at mammography centers have all shown increased access to genetic testing for the low-income and specific racial/ethnic minority populations of women (1). These interventions could serve as models to increase access to genetic testing in LMICs.

Nonetheless, even in high-income countries at centers with access to genetic testing, there is racial disparity in who actually undergoes testing. In a case-control study of 408 women with a family history of breast or ovarian cancer, African American women were nearly 80% less likely to undergo BRCA testing than white women despite socioeconomic status and patient risk perception and attitudes about testing (2). The authors postulated that mistrust of the healthcare

system worries about racial discrimination based on genetic testing results, and physician bias may all contribute to the racial disparity in genetic testing.

There are many barriers to genetic testing that are specific to LMICs and not high-income countries like the US. These include the cost of testing endorsed by the patients and their family members, overall poor health literacy, and many countries just not prioritizing access to genetic testing. Most of these countries do not have well-established genetic clinics or even breast clinics to provide ongoing high-risk assessment and surveillance. An international consortium of medical centers created the GenTEE (Genetic Testing in Emerging Economies) project to understand genetic testing services in other parts of the world and how to improve access to these services. There were eight emerging economies that were involved in the GenTEE project: Argentina, Brazil, China, Egypt, India, Oman, Philippines, and South Africa. Their research has demonstrated that countries with emerging economies have significant financial barriers to patients receiving genetic testing, as they are usually only offered as commercial and out-of-pocket services and are not covered by private or social insurance. In addition, there are geographical barriers, as genetic testing is usually only offered in urban areas. Many laboratories and hospitals with testing facilities lack quality assessment and standard operating procedures (3,4). With assistance from the European Union, the project aimed to stimulate the development of guidelines and training procedures to develop more genetic testing centers and improve access to high-quality and affordable testing services.

The social and cultural issues that arise with the use of genetic testing in middle and low-income countries also need to be addressed. Many LMICs will need more resources or finances to provide patients with a genetic counselor or geneticist, and physicians will need education and training to provide genetic testing. Even in the US, national guidelines state that other healthcare

professionals can provide genetic testing provided they are educated on who needs genetic testing, pre and post-test counseling, and how to manage the results (5,6). A positive test result will also significantly impact the patient's family members, which will need to be considered. Surveys in LMICs have also discovered that several patients may not want to have genetic testing due to their worry about stigma and discrimination based on the results. There are some reports of individuals fearing experiencing social isolation or inability to find a partner to marry based on genetic testing results (7). Understanding how to overcome these barriers could help improve access to genetic testing. While countries such as the United States have legislation that prohibits any type of discrimination based on genetic testing results (The Genetic Information Nondiscrimination Act of 2008), other countries in emerging economies do not have any protections for patients undergoing genetic testing. These countries may also lack laws that protect the confidentiality of their results.

There are several validated risk assessment tools that providers can use in the clinic to help identify women who have an increased likelihood of having a mutation in a breast cancer susceptibility gene (8). These include the Ontario Family History Assessment Tool, the Manchester Scoring System, the Gail Model, the Breast Cancer Surveillance Consortium (BCSC) risk calculator, and the International Breast Cancer Intervention Study instrument (Tyrer-Cuzick). These tools are publicly available and can be used by physicians or other trained professionals to assess a patient's short or long-term risk of breast cancer. However, many of these tools were developed primarily in Caucasian populations and, therefore, may not perform well in other races. However, the BRCAPRO, which predicts the likelihood of a BRCA mutation, has been examined in non-Caucasian populations. A study of nearly 300 minority families showed that BRCAPRO predicted mutation status fairly accurately in other races

besides just white patients, although accuracy was highest in Hispanics compared to African Americans, Asians, and other races (9).

Genetic Testing Guidelines

Guidelines for genetic testing continue to evolve over the years. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines still recommend genetic testing primarily for patients diagnosed with breast cancer under the age of 50 and/or patients with first-degree relatives who are diagnosed with breast cancer under the age of 50. However, a recent study of nearly 1000 patients from 20 community sites showed that the prevalence of pathogenic/likely pathogenic variants was no different between those patients who fulfilled NCCN criteria and those who did not fulfill criteria (10). Recently, the American Society of Breast Surgeons (ASBS) published updated consensus guidelines on genetic testing for hereditary breast cancer (6). The society recommends that breast surgeons and other medical professionals who are knowledgeable in genetic testing provide genetic testing education, make recommendations, and arrange testing. In addition, the society recommends that genetic testing be offered to all patients with newly diagnosed or a personal history of breast cancer and that testing should be made available to patients without a personal history but a strong family history in first or second-degree relatives, including breast cancer at younger than 45 years of age, ovarian cancer, male breast cancer, and pancreatic cancer. While many LMICs may not currently have the resources to provide genetic testing to all breast cancer patients, these newer guidelines suggest that, when available, genetic testing should not be restricted to only young patients, those with a strong family history, or those without access to a genetics clinic.

Multi-gene Panel Testing

In 2012, many genetic testing companies began offering multigene panel testing. Multigene panel testing involves testing other genes besides BRCA 1/2, such as *PALB2, ATM, CHEK2*, and *CDH* (Table 1). NCCN guidelines recommend multigene panel testing when more than one gene can explain an inherited syndrome or if a negative test is found and there is still a high suspicion of an inherited syndrome (5). It is important to note that many genes detected on a multigene panel may not be clinically actionable. NCCN guidelines do warn about the higher risk of variants of uncertain significance (VUS) with multigene panel testing and that clinical management should not be based on VUS findings. The prevalence of VUS can vary from 18% up to 37% (11–13) and has been shown to be higher in African Americans and Asians compared to Hispanics and Caucasians (14).

Direct-to-Consumer Testing

Since the United States Supreme Court ruled that genes and the information they encode cannot be patented, genetic testing companies have proliferated. As expected, many more people have access to genetic testing by going directly to these companies and ordering a genetic test-now commonly referred to as "direct-to-consumer testing." The number of people undergoing direct-to-consumer testing has dramatically increased even in the past few years. A report from the Massachusetts Institute of Technology (MIT) predicted that in 2017, 1 in 25 people in the United States had undergone direct-to-consumer testing. It is now felt that companies that provide direct-to-consumer testing perform genetic testing in twice, if not three times, the number of patients that the genetic testing companies provide. However, it is important to note the limitations of direct-to-consumer testing. For example, 23andMe, a company founded in 2006, tests only for founder BRCA mutations and sells kits for $99 to $499. Founder mutations

account for approximately 81% of Ashkenazi Jewish BRCA mutations but only for 6% of non-Ashkenazi Jewish BRCA mutations. Direct-to-consumer testing is also associated with false positive results, which can occur up to 40% of the time (15). Clinical guidelines do recommend confirmatory testing for those patients who test positive for a founder mutation and even in those who test negative, but there is a high clinical suspicion for an inherited syndrome. As this technology continues to become more accessible, accurate, and affordable, direct-to-consumer genetic testing may become an essential resource in LMICs.

Prevalence of BRCA and Other Pathogenic Genetic Mutations by Race/Ethnicity

The exact prevalence of *BRCA 1/2* mutations worldwide is unknown, and most studies looking at frequency in different ethnic groups are done in high-income countries. Many smaller studies in the past have shown that there is variation in prevalence among other ethnic groups. In a recent study of breast cancer patients from the Northern California site of the Breast Cancer Family Registry, there was an estimated prevalence of *BRCA1* mutations in 3.5% of Hispanics, 1.3% of African Americans, and 0.5% of Asians versus 2.2% in nonwhites and 8.3% in Ashkenazi Jewish patients (16). However, when younger patients with breast cancer were examined, the prevalence of *BRCA1* was 16% amongst African Americans compared to 7.2% in white patients. In a study of 35,000 women who had breast cancer, the prevalence of pathogenic variants was 9.3%, and approximately 50% of these variants were non-BRCA genes (17). Prevalence rates were 11.2% in Latin Americans, 11.2% in Near/Middle Eastern versus 8.8% in Asians, and 9.0% in Western/Northern Europeans. As we move toward more population-based genetic testing, we will better understand the true prevalence of not just *BRCA* but also other pathogenic variants across different races and ethnicities.

Management Options for Unaffected Gene Carriers in Low to Middle-Income Countries

Many of the management options for gene mutation carriers in LMICs will be based on guidelines used in high-income countries because few studies have examined these options in LMICs. There are three management options for unaffected documented gene carriers: surveillance, chemoprevention, and prophylactic surgery. We will review these three options and how they can be best applied to women in LMICs.

Surveillance

In women who do not have a familial risk of breast cancer, randomized trials have shown that annual mammographic screening from the age of 50 to 70 years has a significant survival advantage. However, in women younger than 30, mammography may not be the most sensitive tool. Younger women likely have denser breasts, which makes it difficult to detect tumors with mammography. In addition, studies have shown that screening mammography may be less sensitive in *BRCA* mutation carriers due to the high growth rate of tumors, and they may have tumors with histopathological characteristics that may make them more inconspicuous (18).

Annual magnetic resonance imaging (MRI) is now the recommended standard of care for screening for young women with a familial or genetic predisposition to breast cancer. The first prospective study to examine the efficacy of MRI for women with a familial or genetic predisposition to breast cancer was published in 2004. This study showed that MRI had superior sensitivity for cancer detection compared to mammography. Approximately 40% of cancers detected were under 1.0 cm in the MRI arm compared to 14% of mammography alone patients. A subsequent study showed that over 70% of BRCA carriers undergoing annual MRI cancers were under 1.0 cm compared to approximately 30% in the screening mammography arm alone (19). Likewise, the proportion of node-positive tumors was about 40% in the MRI group

compared to 13-14% in the mammography group in both studies. Other subsequent screening studies in either *BRCA* carriers or those with suspicious family history have also shown that MRI detects more cancers than mammography and at an earlier stage (20,21). However, the Dutch MRISC Screening Study did show that tumor size at diagnosis, diagnosis at a young age, and interval cancers were worse in *BRCA 1* carriers compared to *BRCA 2* carriers, two cohorts of patients with high to moderate cumulative lifetime risk (22). Another recent randomized controlled trial from the Netherlands in women with a familial risk (but do not have *BRCA1/2* mutations) showed that the addition of annual MRI to mammography was able to detect tumors at an earlier stage (23). At the same time, the impact of MRI on overall survival in *BRCA* carriers is unknown since no randomized studies of MRI exist and many MRI studies in *BRCA* carriers do not have long enough follow-up. A prospective screening study of *BRCA* carriers, some of which did have cancer in the past, showed that over 80% of unaffected airlines who had been diagnosed with cancer were still alive at eight years of follow-up (20).

Women in LMICs may not have access to MRI surveillance, and as discussed above, these women may be at higher risk of a node-positive larger tumor than if they were able to undergo MRI. Although approximately 30% of patients with a >20% lifetime risk of breast cancer undergo routine MRI amongst five Breast Cancer Surveillance Consortium registries, the prevalence of MRI use in LMIC is largely unknown (24). In a study of an international database of *BRCA* carriers, approximately 72% of *BRCA* carriers were undergoing MRI surveillance. However, this study collected data from countries not typically considered LMICs: Austria, Canada, China, France, Israel, Italy, Holland, Norway, Poland, and the United States (25). Assuming the MRI is largely unavailable in LMICs, other management options, such as chemoprevention or prophylactic surgery, may be more feasible in these countries.

Chemoprevention

There have been several clinical trials that have demonstrated the benefit of using selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) as chemoprevention in women at increased risk of developing breast cancer. These studies have all examined five years of chemoprevention, and there are currently no studies looking at chemoprevention beyond five years. The IBIS-1 trial compared the effect of five years of tamoxifen treatment to placebo in women with greater than two times the relative risk of breast cancer and found a 31% risk reduction in ER-positive cancer but no risk reduction for ER-negative cancer. The NSABP-P-1 trial compared five years of tamoxifen with placebo in patients with a >1.6% 5-year risk of developing breast cancer and demonstrated a 67% risk reduction in ER-positive breast cancer. The Study of Tamoxifen and Raloxifene (STAR) trial compared the two drugs in postmenopausal women with a >1.6% 5-year risk and found that raloxifene is 24% less effective but had a more favorable side effect profile (26). A randomized, double-blind study of an AI, exemestane, versus placebo in post-menopausal women with an increased risk of breast cancer demonstrated a 65% relative reduction in the annual incidence of invasive breast cancer (27). Despite the promising results of these studies, chemoprevention is typically underutilized in high-income countries.

Many women are fearful of the side effects of tamoxifen, including hot flashes, sexual dysfunction, endometrial cancer, and thromboembolic events (28). In addition, there is little data on the efficacy of chemoprevention in gene carriers. King *et al.* performed a retrospective review of the NSABP-P1 Breast Cancer Prevention Trial to look at the effect of tamoxifen vs placebo in *BRCA* carriers. Of the eight women with *BRCA1* mutations who developed breast cancer, three were in the placebo group, and five were in the tamoxifen group (RR 1.67; CI 0.32-

10.70). Of the 11 women with *BRCA 2* mutations who developed breast cancer, eight were in the placebo group, and three were in the tamoxifen group (RR 0.38; CI 0.06-1.56) (29). While this data is limited by the retrospective nature and the sample size, it suggests that tamoxifen chemoprevention may be beneficial in women with *BRCA2* mutations but not *BRCA1* mutations. Providers should present the risks and benefits of chemoprevention to high-risk patients to help them decide on utilization. Nonetheless, chemoprevention in LMICs may not be feasible given the lack of resources and physicians who are comfortable prescribing the medication and following patients.

Prophylactic Surgery

Prophylactic surgery may be the most viable option for gene carriers in LMICs. The NCCN has recommended that providers and patients who are carriers of *BRCA, p53,* and *PTEN* mutations consider the benefits of bilateral prophylactic mastectomies (PM) (Table 1). However, the guidelines state there is insufficient evidence to recommend prophylactic mastectomy for genetic mutations of moderate penetrance (Table 1).

Gene Mutations with Known Increased Risk of Breast Cancer	Management Guidelines for Breast Cancer Risk
BRCA1	• Annual Screening MRI screening from 25-29, annual mammogram, and consider annual breast MRI screening from age 30-75. • Discussion of risk-reducing mastectomy.
BRCA2	• Annual Screening MRI screening from 25-29, annual mammogram, and consider annual breast MRI screening from age 30-75. • Discussion of risk-reducing mastectomy.
TP53 (Li Fraumeni Syndrome)	• Annual Screening MRI screening from 20-29, annual breast MRI screening and mammogram from age 30-75. • Discussion of risk-reducing mastectomy.
PTEN (Cowden Syndrome)	• Annual mammography with consideration of breast MRI starting at age 30-35 or 5-10 years before the earliest known breast cancer in the family . • Discussion of risk-reducing mastectomy.
ATM	• Annual mammogram and consider breast MRI starting at age 40.
PALB2	• Annual mammogram and consider breast MRI starting at age 30.
CHEK2	• Annual mammogram and consider breast MRI starting at age 40.
NBN	• Annual mammogram and consider breast MRI starting at age 40.
NF1	• Annual mammogram and consider breast MRI starting at age 30 and consider breast MRI from 30-50.

Table 1: NCCN Guidelines for the Management of Patients with High-Risk Breast Cancer Mutations

While there have been no randomized clinical trials to study if there is a survival advantage of PM, there are several observational studies, and modeling studies that suggest PM can achieve a significant reduction in risk for breast cancer and improve survival (30). It has been reported that PM can reduce the risk of the development of breast cancer by over 90%, with studies reporting a 0-2% rate of breast cancer after PM (Table 2) (31–34).

Authors, year, ref	N	Results	Conclusions
Meijers-Heijboer 2001 (31)	139	Incidence of breast cancer: • 0% : Prophylactic group • 2.5% : Surveillance group	• Prophylactic mastectomy reduces incidence of breast cancer
Hartmann 2001 (32)	26	Incidence of breast cancer: • 0% : Prophylactic group	• Breast cancer risk reduction in prophylactic group: 90-100%
Rebbeck 2004 (PROSE) (33)	483	Incidence of breast cancer: • 1.9% : Prophylactic group • 49% : Surveillance group	• Breast cancer risk reduction in prophylactic group: 90% • No impact on OS
Domchek 2010 (34)	2,482	Incidence of breast cancer: • 0% : Prophylactic group † • 5.8-8.1% : Surveillance group §	• Prophylactic mastectomy reduces incidence of breast cancer

Table 2: Selected Series of Impact of Prophylactic Bilateral Mastectomy for BRCA -1/2 Mutation Carriers
PROSE: Prevention and Observation of Surgical Endpoints
OS: Overall Survival

†: incidence was zero for those who did and those who did not have prior or concurrent prophylactic salpingo-oophorectomy (PSO)

§: incidence was 8.1% for those who have prior or concurrent PSO and 5.8% for those who did not have prior or concurrent PSO

(Courtesy of Quyen D. Chu. Cassidy M, Mendez J. In Chu QD, Gibbs JF, Zibari GB (eds). Surgical Oncology, A Practical and Comprehensive Approach. New York: Springer 2014:141-61).

A 90% risk reduction in breast cancer with surgery is significant given that the lifetime risk of breast cancer with BRCA 1 is 60-80% and with BRCA 2 is 40-60% (30). However, consideration of PM can be complex, as surgically removing both breasts can have significant psychological effects on women, and there are complications associated with bilateral PM. Breast reconstruction, either through implants or autologous flaps, entails further surgical risk and may not be available in LMICs. Nevertheless, PM can be an attractive option to *BRCA* mutation carriers and others with a strong family history of breast cancer who do not want to undergo yearly surveillance.

Kurian et al. used computer simulation models and data from previous studies to compare PM with breast screening in mutation carriers (Table 3).

	% Survival by 70 with PO at 40 years old	% Survival by 70 with PO at 50 years old	% Survival by 70 without PO
No screening, no PM	68	61	53
Screening, no PM	74	69	59
Screening, PM at 50 yo	75	71	61
Screening, PM at 40 yo	77	74	64
Screening, PM at 30 yo	79	76	66
PM at 25 yo	79	76	66

*Table 3: Survival Analysis for BRCA 1 mutation carriers by Age 70**
**Data from Kurian et al (28).*
PM: Prophylactic Mastectomy; PO: Prophylactic Oophorectomy

They found that the survival probability by age 70 of BRCA1 mutation carriers with no intervention is 53%, and with just screening, it is 59%. However, prophylactic surgery could potentially significantly improve survival over a no-screening approach. A prophylactic oophorectomy at 40 years would improve survival from 53% in those with no interventions to 68%. Moreover, a prophylactic mastectomy at 25 years old would improve survival from 53% to 66%. However, their results show that prophylactic oophorectomy (PO) by the age of 40 is the most important factor in improving the overall survival of *BRCA1* carriers. The highest survival advantage was PO at age 40 combined with PM at age 25, with an overall survival of 79% (30). PO performed in premenopausal women has been shown to reduce the risk of breast cancer by approximately 50% but has no impact on breast cancer risk if performed in postmenopausal women.

Other studies have looked specifically at the impact of prophylactic bilateral salpingo-oophorectomy (PBSO) in premenopausal women when looking at breast and other gynecologic cancers (Table 4) (34–38).

Authors, year, ref	N	Results	Conclusions
Kauff, 2002 (35)	170	Proportion who are disease-free from breast or gynecologic cancers: • 94% : PBSO group • 69% : Surveillance group	• PBSO decreases risk of breast & gynecologic cancers
Eisen, 2005 (36)	3305	Breast cancer risk reduction following oophorectomy: • BRCA1: 56% • BRCA2: 46%	• Oophorectomy significantly reduces risk of developing breast cancer for BRCA 1/2 carriers • Risk reduction is higher if oophorectomy was performed before age 40
Finch, 2006 (37)	1828	Incidence of gynecologic cancers: • 0.22% : PBSO group • 1.0% : Surveillance group	• PBSO reduces risk of ovarian and fallopian tubes by 80% • Substantial risk for peritoneal cancer remains following PBSO
Kauff, 2008 (38)	1079	Risk reduction following PBSO: • 85% for BRCA1 associated gynecologic cancers • 72% for BRCA2 associated breast cancers	• PBSO significantly reduces gynecologic cancers in BRCA1 carriers and breast cancers in BRCA2 carriers • PBSO did not significantly impact on BRCA1 associated breast cancer or BRCA2 associated gynecologic cancers
Domchek, 2010 (34)	2482	Incidence of ovarian cancer with no personal history of breast cancer: • 1.3% : PBSO group • 5.8% : Surveillance group Incidence of ovarian cancer with personal history of breast cancer: • 1% : PBSO group • 6% : Surveillance group Incidence of second diagnosis of primary breast cancer: • 11.1% : PBSO group • 13.7% : Surveillance group	• Reduces risk of ovarian cancer • Reduces risk of breast cancer †† • Reduces risk of ovarian cancer • Does not reduce risk of second diagnosis of primary breast cancer

Table 4: Impact of Prophylactic Bilateral Salpingo-Oophorectomy (PBSO) for BRCA-1/2 Mutation Carriers
PBSO: Prophylactic Bilateral Salpingo-Oophorectomy
†† Breast cancer risk reduction was observed in women aged < 50 years but not in those aged> 50 years. (Courtesy of Quyen D. Chu. Cassidy M, Mendez J. In Chu QD, Gibbs JF, Zibari GB (eds). Surgical Oncology, A Practical and Comprehensive Approach. New York: Springer 2014:141-61).

Some studies demonstrate a different risk reduction for the incidence of breast cancer when comparing BRCA1 to BRCA2 patients who received a PBSO (36,38). The risk reduction in gynecologic cancers, such as fallopian and ovarian, has been reported to be 80-94% in patients with BRCA 1 or 2 mutations who undergo PBSO (35,37).

For those BRCA carriers who have already been treated for ovarian cancer, there may still be some advantages to undergoing PM. McGee et al. demonstrated that women with *BRCA* mutations over the age of 50 who have already been diagnosed with stage III/IV ovarian cancer have a less than 2% survival advantage by the age of 80 after PM. Therefore, they recommended that in BRCA carriers who have been diagnosed with ovarian cancer, PM should only be offered if they were diagnosed with stage I/II ovarian cancer at or before the age of 50 (39).

For women who are interested in having surgery, nipple-sparing mastectomy (NSM) allows for a superior cosmetic outcome and reconstruction options. More importantly, several studies have shown that nipple-sparing mastectomy (NSM) is a safe oncologic outcome for *BRCA* carriers. One multi-institutional study of 150 *BRCA* carriers who underwent NSM, and a mean follow-up of 32.6 months demonstrated only one occurrence of primary breast cancer, which occurred six years after her prophylactic surgery and did not involve the nipple-areolar complex (40). While there is a paucity in the literature about long-term outcomes, the St. Callen International Expert Consensus panel, which comprises representatives from more than 20 countries, has endorsed NSM as an option for *BRCA* mutation carriers as long as there is a careful pathologic review of the retro-areolar tissue (41).

Depending on the surgical specialty resources available, reconstruction after PM should be offered. An international study from Semple et al. demonstrated that 69.1% of women with a

BRCA1 or *BRCA2* mutation had breast reconstruction after PM. However, they found that women were more likely to have reconstruction after prophylactic surgery than if they were having surgery for the treatment of breast cancer (79.7% vs 62.9%). In addition, age was an important factor as *BRCA* carriers who were over the age of 45 were 64% less likely to undergo reconstruction. There was a large discrepancy in the percentages of reconstruction by country, ranging from 50% of women in China to 85.7% of women in France (42). Although the countries in this study were not considered low or middle-income, it is important to understand that many women would wish to have reconstruction after prophylactic surgery.

Several studies have shown that the risk of occult malignancy in PM specimens is <2%. Therefore, it is not recommended to perform a sentinel lymph node biopsy at the time of surgery.

Management Options for Affected Gene Carriers in Low to Middle-Income Countries: The Role of Contralateral Prophylactic Surgery

Women with BRCA mutations who develop breast cancer have been shown to have no significant difference in distant recurrence and overall survival compared to women with sporadic cancer (43,44). However, women with BRCA mutations have a much higher cumulative lifetime risk of developing contralateral breast cancer, with reports ranging from 20-83% at 10-20 years. While contralateral prophylactic mastectomy (CPM) has not been shown to have a significant survival advantage in cases of sporadic cancer, several retrospective studies have shown that affected *BRCA* carriers may benefit from CPM (Table 5).

Study, year, ref	N	Median follow-up	Survival benefit to CPM
Sprundel et al, 2005 (46)	148	3.5 years	• HR 0.35 (95% CI: 0.09-1.39)
Evans et al, 2013 (47)	718	8.5-9.6 years	• HR 0.37 (95% CI: 0.17-0.80)
Heemskerk-Gerritsen et al, 2015 (45)	583	11.4 years	• HR 0.49 (95% CI: 0.29-0.82)
Metcalfe et al, 2014 (48)	390	14.3 years	• HR 0.52 (95% CI: 0.24-0.93)

Table 5: Survival Benefit of Contralateral Prophylactic Mastectomy (CPM) in Affected BRCA Carriers Demonstrated Through Retrospective Studies
HR: Hazard Ratio
CI: Confidence Interval

For example, a Dutch multicenter cohort study showed an adjusted hazard ratio of 0.49 (95% CI 0.29-0.82) for women who underwent CPM compared to those who did not (45). Other studies have shown similar findings, but all the failings of this study are retrospective in nature; many patients were not undergoing MRI surveillance, and in some cases, patients did not know they were *BRCA* carriers until many years after their cancer diagnosis (46–48). Nevertheless, national guidelines recommend CPM consideration for affected *BRCA* mutation carriers (5,49). In addition, when paired with prophylactic oophorectomy, CPM has been found to be the most cost-effective prevention strategy when compared to surveillance alone (50). Especially in settings where women may not have access to robust surveillance programs, physicians should discuss the benefits of CPM with *BRCA* mutation carriers who are diagnosed with breast cancer.

The contralateral breast cancer (CBC) risk for carriers of other non-*BRCA* mutations is largely unknown, although studies have shown that *CHEK2* 1100delC and *PALB2* mutations are associated with increased CBC risk (51). Studies have also shown that ATM carriers do not

necessarily have an increased CBC risk (52). With this lack of data, there are no recommendations for CPM for non-*BRCA* carriers. Despite this, studies have shown that about 69% of patients who receive CPM do not have a known significant genetic risk for breast cancer, suggesting that the decision to have a CPM likely stems from other psychosocial factors, such as age <50, white race, college or higher education, and receiving genetic testing, with either a positive or negative result (53).

Conclusion

In conclusion, many challenges remain for the management of hereditary breast cancer in LMICs. First, the identification of gene carriers is particularly challenging given the low number of resources in LMICs. Second, once a genetic mutation is detected, managing that patient is challenging for the aforementioned reasons. Given the fact that most LMICs will not have the resources to start a high-risk or genetics clinic, education of primary care physicians about genetic testing becomes crucial to increasing access to genetic testing for patients. Reducing the cost of testing through government-funded programs or other programs will also help access. At the same time, limited resources may make surveillance and chemoprevention nonviable options for gene carriers in LMICs. Therefore, prophylactic surgery may take precedence. Most LMICs will have resources to provide surgical care, although reconstruction is not always readily available. In general, we do not recommend prophylactic surgery without a positive gene test unless there is a strong family history, overwhelming suspicion of the patient having an underlying genetic mutation, and a compelling reason why the patient cannot undergo testing and the patient's insistence on pursuing prophylactic surgery. In such cases, thorough counseling with the patient is of utmost importance.

The field of genetic testing and management of hereditary breast cancer continues to evolve and change. In high-income countries over the past 20 years, the cost of genetic testing has dropped dramatically, testing has expanded from one gene to many genes, and the long-term outcomes of surveillance and prophylactic surgery are becoming more clearly defined. With these rapid changes in the field, it is hoped that patients in LMICs will reap the same benefits over time as patients in high-income countries.

Case Conclusion

The patient obtained access to genetic testing and tested positive for a BRCA1 mutation. She elected to undergo a bilateral prophylactic mastectomy with sentinel node biopsy on the affected side. Her nodes were negative. She did not wish to pursue reconstruction at this time and was referred to a gynecologist to consider a salpingoophorectomy.

Key Points

- Genetic testing for breast cancer genes is the standard of care in high-income countries but may not be available in LMICs.
- High-risk individuals can be identified using validated risk-assessment tools.
- MRI is superior to mammography for surveillance of patients with a significant family history of breast cancer or known mutation carriers.
- Women with hereditary breast cancer/*BRCA* mutations can be offered bilateral prophylactic mastectomy. Younger women may have a more significant survival benefit.
- Management Options for Unaffected Gene Carriers include (1) Surveillance, (2) Chemoprevention, and (3) prophylactic surgery (mastectomies and oophorectomies)

- Prophylactic oophorectomy in premenopausal women provides the greatest survival advantage to women with *BRCA* mutations.

- Retrospective studies show a survival benefit to contralateral prophylactic mastectomy in affected gene carriers, but prospective longitudinal studies are needed to determine if CPM does afford a survival benefit to these women.

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Chapter 31

Occult Primary Breast Cancer with Axillary Metastases

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Case Scenario

60-year-old healthy female presents with a two-month history of bulky right axillary adenopathy but otherwise normal breast exam and no other symptoms. She is a non-smoker and has no family history of cancer.

Mammogram: no suspicious breast masses or microcalcifications.

Ultrasound: Confirms two adjacent morphologically abnormal appearing right axillary lymph nodes, not fixed to each other or to axillary vasculature/brachial plexus. Four-quadrant breast ultrasound negative.

Sono-guided core needle biopsy: adenocarcinoma, immunohistochemistry positive for estrogen receptor; negative for progesterone receptor and HER2/*neu*.

Breast MRI: Confirms suspicious right axillary adenopathy; negative for suspicious breast lesions.

Introduction

Breast cancer presenting as axillary metastatic disease with unknown primary was first described by Halsted in 1907[1] as three cases of "cancerous axillary glands with non-demonstrable cancer of the mamma." Undoubtedly, many of the early cases of occult breast cancer were actually cases

of node-positive disease associated with small or subtle breast lesions camouflaged by dense breast tissue. Fortunately, breast imaging has evolved substantially over the past several decades, and small tumors can be detected with high sensitivity. Yet despite this improved ability to identify non-palpable breast tumors, the clinical presentation of axillary metastases secondary to occult breast cancer has persisted. This presentation is typically assumed to result from a microscopic focus of disease embedded within the breast[2], but it has also been postulated to originate from ectopic breast tissue within an axillary lymph node[3]. Of the nearly two hundred thousand cases of invasive breast cancer that are diagnosed in the United States every year, approximately 0.3%-1.0% continue to present as clinically overt metastatic adenopathy in the axilla with an occult breast primary[2,4]. As with breast cancer in general, the overwhelming majority of patients are female, but occurrence in men has been reported[5]. Worldwide incidence rates for this disease pattern are unknown but are likely to be higher in low- and middle-income countries (LMIC) where mammographic screening, as well as diagnostic imaging, are not widely available and breast cancer stage distribution tends to be more advanced.

Despite the relative infrequency of this pattern of disease, it is an important topic for review because of the associated diagnostic and therapeutic questions that arise. Effective (and potentially curative) locoregional and systemic treatments for node-positive breast cancer are available. Patients with clinically evident axillary metastases and an occult breast primary are candidates for these treatment strategies. It is, therefore, essential that they be evaluated and managed appropriately. Node-positive breast cancer is an example of a high-risk disease that typically benefits from chemotherapy as an essential component of multidisciplinary treatment. This chapter will focus on the diagnostic and locoregional therapeutic options for occult breast

cancer presenting as axillary metastatic disease; these patients must also receive appropriate phenotype-specific targeted systemic therapy as well as chemotherapy.

Differential Diagnosis

Benign, reactive hyperplasia is the most common cause of axillary adenopathy. Other etiologies include sarcoidosis and tuberculosis. If the axilla can be successfully pulled into the mammography field, then the mammographic appearance of central lucency and/or an ultrasound image of fatty hilum will favor benignity. However, it is essential to pursue tissue diagnosis (with tissue sent fresh to the laboratory) via percutaneous needle biopsy or open excisional biopsy if there is any doubt regarding the nature of adenopathy. Once a histopathologic diagnosis of malignancy is established, a work-up to identify the primary is indicated. While breast cancer is the most likely cause of axillary metastases, other potential causes include neoplasms originating from lymphoma, melanoma, thyroid, lung, renal, ovarian, pancreatic, gastrointestinal, and colorectal tissue. Adenocarcinoma cells on histology will rule out lymphoma and melanoma. Occasionally it will be difficult to distinguish a primary breast tumor located in the axillary tail from a true axillary lymph node. Nodes that are completely replaced by metastatic disease and primary tumors that are adjacent to axillary lymph nodes may contribute to this dilemma. The patient with a prior history of contralateral breast cancer presents yet another diagnostic challenge, as the possibility of axillary cross-metastases also exists. In LMIC, where advanced-stage breast cancer is more common, it is also important to rule out new contralateral breast cancer with regional metastases extending to bilateral axillary nodal basins.

Diagnostic Evaluation

A careful history and physical exam (with attention to other nodal basins, breasts, skin lesions, and scars from previously resected skin lesions) is essential. In LMIC, it is common for patients

to have undergone resection of a breast tumor in the past without definitive pathology available; if the resected lesion was malignant and the cancer left incompletely treated, then progression of disease may result in subsequent clinical presentation as nodal metastases.

Standard diagnostic workup should include a chest X-ray, mammogram, and breast ultrasound. If a primary tumor in the breast is identified, then this lesion should be targeted for biopsy. It should be noted that mammography will not necessarily capture clinically evident adenopathy, as the axilla (especially level 2 or 3) can be challenging to include in the field. Routine histology with hematoxylin and eosin staining of a needle biopsy from the axillary node(s) will usually be adequate in characterizing lymphoma, melanoma, or adenocarcinoma as the primary pattern of disease. Core needle biopsy using a 14- or 16-gauge device is preferred over a fine needle biopsy so that adequate tissue is available for basic histology and immunohistochemistry studies. If needle biopsy is unavailable, or is non-diagnostic, then surgical excisional biopsy should be pursued.

If the axillary biopsy reveals adenocarcinoma on histology, then further evaluation should include immunohistochemistry for estrogen and progesterone receptor studies and HER2/neu. Hormone receptor expression is strongly consistent with a diagnosis of breast primary and will influence the selection of adjuvant systemic therapy. Unfortunately, however, these studies may be negative in one-third to one-half of breast cancers, and primary tumors of the abdominopelvic organs as well as melanoma, may display hormone receptor positivity. HER2/*neu* expression is a prognostic marker of an inherently more virulent disease, but its high responsiveness to targeted anti-HER2 therapy can result in excellent outcomes. When the histologic pattern is in doubt, other markers such as mammaglobin, CEA, mucicarmine, and lactalbumin will support a

diagnosis of metastatic adenocarcinoma[6,7] Among axillary lymph node cases revealing adenocarcinoma histologically, more than 90% of cases result from a primary breast malignancy.

If adenocarcinoma is confirmed histologically and the patient has no symptoms suggesting a gastrointestinal or pulmonary site of primary disease, then extensive body imaging work-up to look for non-breast primaries is usually a low-yield endeavor. However, a meticulous breast evaluation to localize the intramammary primary tumor is essential. Initial efforts include meticulous scrutiny of diagnostic mammogram images, and bilateral breast ultrasound scanning is necessary. Magnetic resonance imaging (MRI) has become widely accepted as the next most useful modality, and MRI can identify the breast primary in more than half of cases.[8-12] When the MRI findings are suggestive of the breast primary, a repeat targeted breast ultrasound is indicated. The follow-up/second-look ultrasound, guided by the MRI findings, is frequently successful in identifying the tumor, and an ultrasound-guided percutaneous biopsy can then be readily performed[11,13,14]. When available, MR-guided core needle biopsy or MR-localized surgical biopsy can also be considered; CT-guided biopsy of breast lesions detected on MRI has also been described[15,16]. Less commonly, PET Scans[17-19], nuclear medicine imaging with technetium-99m sestamibi scans[20,21], and computerized tomography[22] have also been reported as successfully identifying otherwise occult breast tumors.

Patients in LMIC are less likely to have access to breast MRI evaluations, and there is little screening and diagnostic mammography services; PET, nuclear medicine, and CT scanning are also limited. Details about the international availability of these imaging modalities are beyond this chapter's scope and have been described by others. Because of these resource constraints, breast ultrasound has been advocated as a reliable primary imaging modality for both breast cancer screening (whole breast ultrasound) and diagnostic evaluations (targeted ultrasound)[24].

Patients with node-positive breast cancer are more likely to harbor distant organ micrometastases, underscoring the importance of these patients receiving systemic therapy in addition to locoregional treatment. Patients presenting with bulky axillary disease may benefit from body imaging at the time of diagnosis to assess for overt evidence of Stage IV disease, especially if confirmation of disease will alter management. Careful questioning to ascertain symptoms of brain metastases or osseous metastases to weight-bearing skeletal structures are examples of disease spread requiring special attention. For the asymptomatic patient presenting with mobile and clinically resectable axillary metastases, extent-of-disease body imaging needs are scheduled at the discretion of the oncology treatment team. Routine body imaging can be obtained via CT scanning of the chest/abdomen/pelvis coupled with bone scan, or PET-CT total body imaging can be performed. As noted previously, resource constrained LMIC may have to rely on alternative imaging modalities, and the triad of chest X-ray, hepatic ultrasound, and bone scan may be utilized as more cost-efficient and accessible options to assess the organs most commonly involved with metastatic spread from breast cancer.

Treatment

Historically, mastectomy with axillary lymph node dissection (i.e., modified radical mastectomy), followed by adjuvant systemic therapy and post-mastectomy radiation therapy (PMRT), has been the standard management approach for patients presenting with axillary metastases and an occult primary[25-27]. Older series involving mastectomy reported broad variation in the frequency of identifying a primary tumor in the breast specimen, ranging from 12-67%[4,26,28,29]. Advances in preoperative breast imaging, including the frequent use of MRI to evaluate a breast tumor appropriate for resection, have resulted in lower rates of identifying a lesion in mastectomy specimens from these patients. Furthermore, contemporary-era node-

positive breast cancer is often treated with preoperative chemotherapy, which can yield a complete pathologic response. For patients treated in LMIC healthcare facilities, chemotherapy may not be readily available or affordable. In these circumstances, if the patient presents with operable disease, then proceeding directly to modified radical mastectomy for locoregional control, followed by systemic therapy (if feasible) and consolidation of locoregional treatment with PMRT, remains a reasonable treatment plan.

			Local Recurrence			Survival			
Study, year, ref	N	Median followup	Breast Tx: Observation *	Breast Tx: XRT*	Breast Tx: Mastectomy	Breast Tx: Observation*	Breast Tx: XRT*	Breast Tx: Mastectomy	Tumor identified in breast specimen among cases treated by mastectomy or breast tissue sampling
Ellerbroek, 1990 (28)	42	131 mos	N=13 LR 57%	N=16 LR 17%	N=13 LR Not reported	5-yr OS 75% in breast conservation patients		5-yr OS 68% in mastectomy patients	12%
Kemeny, 1986 (29)	18	Not reported	N=5 LR Not reported	N=2 LR Not reported	N=11 LR Not reported	0/5 deaths at 2-9 yrs f/u	1/2 deaths at 10 mos f/u	4/11 deaths at 2-13 yrs	36%
Baron, 1990 (4)	35	53 mos	N=1 LR Not reported	N=6 LR Not reported	N=28 LR Not reported	5-yr OS 65% in breast conservation patients		5-yr OS 77%	67%
Vlastos, 2001 (41)	45	7 years	N=7 LR 29%	N=25 LR 8%	N=13 LR 15%	5-yr OS 43%	5-yr OS 91%	5-yr OS 75%	15%
Foroudi, 2000 (42)	20	73 mos	N=6 LR 83%	N=12 LR 25%	N=2 LR 0%	Median OS 56 mos	Median OS not reached; 1/12 deaths at time of report	N/A; only 2 mastectomy patients	Not reported

Table 1. Early studies of outcomes in patients presenting with axillary metastases and an occult breast primary managed by mastectomy versus breast conservation.
LR= local recurrence; mos=months; OS=overall survival; N/A=not applicable
**Selected patients in the breast observation category (with and without XRT) had open tissue biopsies*

Studies dating back to the 1980s have confirmed the safety of breast-conserving approaches in this patient population. Table 1 summarizes results from older studies that have explored breast

conservation, demonstrating that survival is not compromised by breast conservation but that locoregional radiation, as opposed to breast observation alone, will optimize rates of disease control.

When breast conservation is contemplated, all efforts should be made to identify the primary tumor in the breast so that it can be targeted for resection via lumpectomy, leaving only microscopic, low-volume disease in the breast for control via radiation. Ideally, these efforts would include mammography, breast ultrasound, and breast MRI. However, it should be noted that the earliest studies of breast conservation in the setting of an occult breast primary presenting with axillary metastatic disease occurred in an era that pre-dated applications of breast MRI and whole-breast ultrasound. Physicians in LMIC who have access to the full spectrum of breast imaging technologies do not have can, therefore, still consider offering breast conservation to these patients, but only if they are confident regarding access to whole-breast radiation.

Preoperative chemotherapy is a valuable treatment strategy in this breast cancer scenario. Patients with bulky and/or inoperable disease that is fixed and matted to major axillary vasculature or to the brachial plexus should always be triaged to neoadjuvant chemotherapy in hopes of improved, safer resection after downstaging. Axillary ultrasound imaging and breast MRI can be useful in assessing the extent of axillary disease. Following a percutaneous core needle biopsy establishing a diagnosis of metastatic breast cancer, a reasonable treatment sequence involves proceeding onto chemotherapy as the next step, followed by axillary lymph node dissection and consolidation of treatment with breast and possibly regional radiation (depending on the extent of nodal disease). This approach offers the benefits of in vivo tumor response monitoring, with the opportunity to cross the patient over to an alternative chemotherapy regimen in patients found to have resistant disease.

					Outcomes	
Study, year, type, ref	Sample size, followup	Frequency Breast MRI Use	Frequency ALND performed	Breast Treatment*	Local Recurrence	Survival
Varadarajan, 2006, Single Institution (43)	N= 10 Median f/u 57 mos	70% (pts with positive MRI excluded from outcome analyses)	100%	XRT only: 80% Mast: 10% PM: 10%	0%	100%
Walker, 2010, SEER (44)	N= 750 10-year outcomes reported	NR	79.5%	XRT only: 29% Mast ± XRT: 39% Observation: 32%	NR	10-year OS: Mast or Breast XRT: 64.9% No Breast Tx: 58.5%
Barton, 2011, Single Institution (45)	N= 55 (pre-MRI) N= 48 (post-MRI) Median f/u 68 mos	36% (MRI identified primary tumor in 7/20 pts)	81%	Mast alone: None XRT alone: 73% Observation: 27%	LRR: Breast XRT: 14% Observation: 27%	5-year OS: Breast XRT: 84% Observation: 85%
Masinghe, 2011, Single Institution (45)	N= 53 Median f/u 9 yrs	13% (pts with positive MRI excluded from outcome analyses)	47% (45% had axillary excision and 8% had axillary sampling)	Mast alone: None XRT alone: 77% Observation: 23%	5-year LR: Breast XRT: 16% Observation: 36%	5-year breast cancer specific survival: Breast XRT: 73% Observation: 58%
Fayanju, 2013, Single Institution (45)	N= 7 Median f/u 86 mos	86% (MRI correlation with breast primary unknown)	100%	Mast alone: 43% XRT alone: 43% Observation: None Mast + XRT: 14%	One LR in pt treated by breast XRT and ALND	No deaths at 86 mos
Sohn, 2014, Korean Breast Cancer Society (46)	N= 142 Median f/u 78 mos	NR	100%	Mast alone: 9% Mast + XRT: 15% Observation: 5% XRT alone: 45%	NR	OS not affected by choice of surgery (mast vs no mast)
Rueth, 2015, Single Institution (47)	N= 36 Median f/u 64 mos	92%	92%	Mast + XRT: 25% Observation: 3% XRT alone: 72%	No LRR at 64 mos median f/u	One pt with distant metastatic disease and mortality in pt treated by breast XRT and ALND
McCartan, 2017, Single Institution (48)	N= 38 Median f/u 7 yrs	100%	100%	Mast alone: 18% XRT alone: 66% Observation: None Mast + XRT: 16%	LR: Breast XRT: 8% Mast: 0%	No survival difference in mast vs breast XRT groups
Hessler, 2017, NCDB (30)	N= 1231 8-yr OS endpoint	NR	100%	Mast + XRT: 48% XRT alone: 28% Observation: 25%	NR	XRT alone + ALND independent predictor of improved survival on multivariate analysis (mortality HR 0.509; 95% CI 0.321-0.808; p=0.004)
Johnson, 2019, SEER (40)	N= 353 Median f/u 66 mos	NR	100%	Mast alone: 27% Mast + XRT: 29% XRT alone: 43%	NR	5-yr OS: Mast: 88% Breast XRT: 86%
Kim, 2020, Korean Radiation Oncology Group (49)	N= 66 Median f/u 82 mos	100% (pts with positive MRI excluded from outcome analyses)	100%	XRT alone: 95% Mast: None	LRR: 14%	5-Yr OS: 93% 5-Yr DFS: 92%

Table 2: Contemporary studies of locoregional treatment and outcomes in occult breast cancer presenting with axillary metastases.

*ALND= axillary lymph node dissection, XRT= radiation, Mast= mastectomy, PM= partial mastectomy, SEER= Surveillance, Epidemiology and End Results Program, NR= not reported, f/u= follow-up, LRR= locoregional recurrence, LR= local recurrence, OS= overall survival, NCDB= National Cancer Data Base.*Percentages do not add up to 100% in selected studies because of rounding and unknown/unreported data.*

As shown by more contemporary studies of locoregional management and outcomes in patients with axillary metastatic disease and an occult breast primary tumor in Table 2, rates of breast-conserving management have increased substantially over time. Comparable to the older studies, breast radiation reduces local recurrence rates, and one large national study demonstrated a survival advantage in cases managed with breast preservation/breast radiation[30]. Of note, nearly all patients in these contemporary series underwent axillary lymph node dissection regardless of the breast management, and the majority received chemotherapy and targeted therapy (endocrine treatment and/or anti-HER2 therapy) as indicated by the biomarker profile. Rates of neoadjuvant versus postoperative/adjuvant chemotherapy and use of postmastectomy radiation varied within and between studies. The impact of treatment sequence on outcomes is, therefore, less well-defined. Similarly, delivery of postmastectomy radiation and/or regional nodal radiation has varied in the reported series, but this decision is based on the extent of nodal metastases identified in the ALND (Axillary Lymph Node Dissection) specimen.

As noted above, more recent studies have reported outcomes for patients who have had an ALND included in their management. Patients receiving neoadjuvant chemotherapy for node-positive breast cancer today will often be offered the option of a targeted sentinel lymph node dissection as a strategy to avoid an ALND. The targeted sentinel node dissection typically involves dual-agent lymphatic mapping (blue dye and radioisotope tracer injections) as well as resection of the originally biopsied/clipped metastatic axillary node. If these nodes are negative for metastatic disease, then complete pathologic response in the axilla can be safely assumed, and additional axillary surgery can be omitted.[31,32] Lymphatic mapping for sentinel lymph node biopsy may not be feasible in LMIC, so ALND is likely to remain an important component of surgical care for patients in these settings.

Prognosis

The low incidence of this disease pattern makes it difficult to assess prognosis definitively. Several older studies have suggested that patients with occult breast cancer and axillary metastases had improved survival compared to the majority of node-positive breast cancer patients[25,26,29,33-36]. However, other investigators from the same era[37,38]. have disputed this contention, finding similar outcomes compared to other patients with axillary metastases. Today, breast cancer prognosis is most accurately defined by disease phenotype because of the prognostic value of individual biomarkers as well as their ability to predict response to targeted therapy. Patients presenting with axillary metastases and an occult breast primary tumor have a spectrum of biomarker profiles, and their disease phenotype carries comparable prognostic and therapeutic value as seen with other breast cancer patients. Montagna et al.[39] conducted a case-control study of eighty occult breast cancer patients from the European Institute of Oncology presenting with axillary metastases matched to node-positive breast cancer patients presenting with a clinically evident T1 breast tumor (up to 2cm in size). For both patient subsets, 58% were hormone receptor-negative; 25% were HER2/neu-overexpressing; triple-negative breast cancer and more than four metastatic lymph nodes were the strongest determinants of worse outcome. Johnson et al.[40] also found estrogen receptor negativity and volume of nodal metastases to be independent predictors of worse outcomes among patients with occult breast cancer presenting as axillary metastases identified from the United States' National Cancer Data Base.

Key Points

- Breast cancer presenting as axillary metastases with an occult primary is uncommon, accounting for fewer than 1% of cases in screened populations; frequency in LMIC is not well-documented

- Initial diagnostic evaluation should include bilateral mammography and breast ultrasound, with either core needle biopsy of the axillary disease (sono-guided when feasible) or surgical biopsy if needle biopsy is not available

- In LMIC, a thorough history and physical should include an assessment of any prior breast biopsies that might have been malignant but for which the patient may not have had pathologic information

- If adenocarcinoma is confirmed on axillary biopsy and no primary tumor is evident on mammography or ultrasonography, then a breast MRI should also be performed to look for a primary breast

- Body imaging to look for clinically significant distant organ disease should be done in symptomatic patients but is otherwise offered at the discretion of the treating team and should be tailored to the resources available to the individual healthcare community.

- Treatment for occult breast cancer presenting as axillary metastases includes multidisciplinary management, including chemotherapy; locoregional management; and targeted, phenotype-specific systemic therapy as indicated.

- Treatment options include:

    - Systemic therapy: chemotherapy, which can be offered in the neoadjuvant sequence or postoperatively in patients that have operable axillary disease and when chemotherapy is not available/affordable

    - Surgery should include axillary lymph node dissection. In communities where neoadjuvant chemotherapy is available, and if the patient has a strong clinical response, a targeted sentinel lymph node biopsy can be performed, and ALND may be avoided if a complete pathologic response in the axilla is confirmed.

    - Local therapy to the breast can be in the form of mastectomy or whole breast radiation, with comparable outcome results. Postmastectomy radiation should be strongly considered in these high-risk/node-positive breast cancer patients.

Targeted endocrine and/or anti-HER2/*neu* therapy should be delivered in cases of hormone receptor-positive and/or HER2-*neu* overexpressing disease, respectively.

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Chapter 32

Management of Phyllodes Tumor, Paget's Disease, and Male Breast Cancer

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Case Scenario

A 40-year-old woman presented with a 10-year history of a small fibroadenoma in the upper outer quadrant of her right breast prior to presentation. The mass began to increase in size over the preceding 18 months slowly and was associated with pain for the past month. Clinical exam demonstrated a 12 cm mobile mass with no associated adenopathy (Fig. 1). Mammogram was suggestive of a phyllodes tumor (Fig. 2). Core needle biopsy was consistent with a phyllodes tumor. The patient underwent a total mastectomy with negative resection margins. The final pathology showed a benign phyllodes tumor.

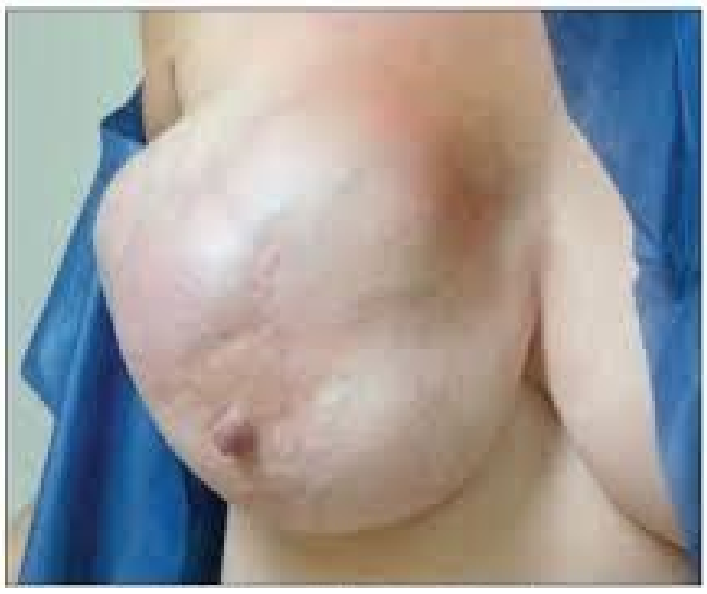

Figure 1: Patient with Large Palpable Mass

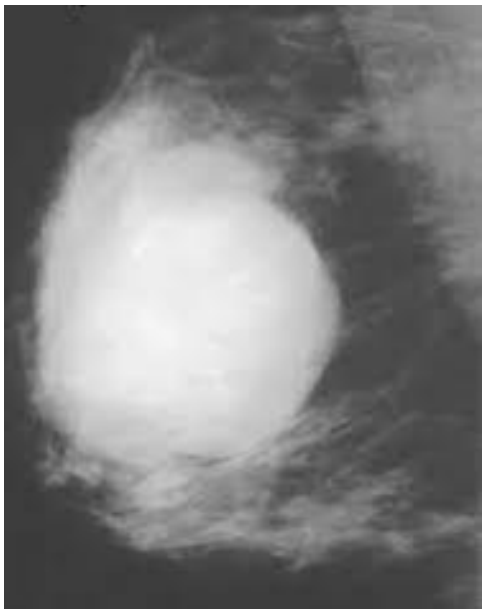

Figure 2: Mediolateral Mammogram of Phyllodes Tumor

Epidemiology

Phyllodes tumors, the most common breast sarcoma, are rare, accounting for 0.3% to 0.5% of breast tumors and 3-5% of fibroepithelial tumors. This tumor occurs more commonly in Asian, white, and Latin American populations [1]. Phyllodes tumors most commonly occur in women 35-45 years of age which is 20 years later than fibroadenomas. Rarely is it diagnosed in adolescents, the elderly, or men.

Presentation and Pathology

Patients usually provide a history of a longstanding breast mass that has slowly increased in size over the prior 6-12 months or, less commonly, increases in size over a short time. Patients frequently have a history of fibroadenomas. These stromal tumors present as a palpable, nodular, unilateral, painless solid mass and most often occur in the upper outer quadrant. Rarely they may be bilateral. The average tumor size is 3-4 cm. Tumors 10 cm. or more in diameter are classified as giant phyllodes tumors and can be as large as 40 cm. Large tumors may have skin discoloration and associated overlying dilated veins, although nipple retraction is rare. The clinical features are similar to those of smaller tumors, and they are often fungating.

Although fifteen to twenty percent of patients can present with palpable axillary nodes, only 1% will have true nodal metastasis. However, among patients with malignant phyllodes tumors, 15% will have axillary metastasis. The differential diagnosis includes fibroadenoma, adenoma, breast sarcoma, hamartoma, lipoma, juvenile papillomatosis, carcinoma and metastasis.

Pathology

On pathologic examination, phyllodes tumors are lobulated, unencapsulated, have a nodular surface, lack a true capsule, and may invade into the surrounding breast tissue. On sectioning, small tumors have a uniform white consistency and resemble fibroadenomas. Larger tumors are grey yellow in color and often have associated clefts filled with bloody fluid or jelly-like material. The solid component may have focal hemorrhage, necrosis, or cystic changes. Invasive ductal and invasive lobular cancers, as well as DCIS and LCIS, are rarely found either within the tumor or near the fibroepithelial component. In rare cases the fibroblast component can dedifferentiate into cartilage, smooth or striated muscle cells and portends a poor prognosis.

There are three pathological subtypes of phyllodes tumors, benign, borderline, and malignant. Approximately two-thirds of phyllodes tumors are benign or borderline while one third are malignant. Young women are more likely to have benign tumors [2]. The WHO classification divides phyllodes into benign, borderline, or malignant subtypes based on the degree of stromal atypia, mitotic activity, tumor margins, and interstitial cell hyperplasia (Table 1) [3]. Tumor grade is a significant predictor of incomplete tumor excision [Guillot]. Differentiating benign phyllodes from fibroadenomas and borderline from malignant phyllodes tumors can be challenging.

Table 1: Characteristics of Phyllodes Tumors (WHO)

	Pathological Features			
	Stromal Cell Atypia	**Interstitial Cell Hyperplasia (Fibroblasts)**	**Mitoses/HPF***	**Tumor Margin**
Benign	Mild	Mild	<4	Negative
Borderline	Moderate	Moderate	4-9	Negative or Positive
Malignant	Severe	Severe	≥ 10	Positive

**HPF-high power field*

Diagnostic Evaluation

Ultrasound, mammography, and core needle biopsy are the preferred methods for diagnosis. On ultrasound, the mass will appear bulky, and lobulated, with solid hypoechoic echoes and clear boundaries. Mammography will demonstrate well-circumscribed oval or lobulated densities with smooth edges (Fig. 2). A radiolucent halo due to adjacent compression of normal tissue and coarse benign calcifications may also be seen. Larger tumors can appear lobulated but still have clear borders. MRI can be useful in distinguishing benign and malignant variants.

Either core needle or excisional biopsy offers similar diagnostic accuracy. However, a core needle biopsy can yield an accurate diagnosis while preserving treatment options and is the preferred biopsy method. Core biopsy has a 93% negative predictive value. The accuracy of fine needle aspiration is 0-20% and should not be used. The final diagnosis should be based on the pathological findings in the post-operative specimen due to the frequent coexistence of benign, borderline, and malignant features within the same tumor.

Treatment and Outcomes

Surgery is the primary treatment modality for primary and recurrent disease. Patients should have clinical follow-up every six months for three years following definitive treatment.

A diagnosis of benign, borderline, or malignant phyllodes tumor following core needle biopsy should be managed with excision with >1cm. margins. Phyllodes tumors, unlike fibroadenomas, should never be shelled out due to high recurrence rates. Thus, re-excision should be performed to obtain 1 cm margins. Benign phyllodes tumors may be an exception since only 1-4% recur although there has yet to be a consensus on this approach.

Definitive surgical excision with >1 cm. margins is the preferred treatment and can include either partial or total mastectomy [4]. In cases where 1 cm. margins cannot be obtained, positive margins are associated with 30% recurrence, while margins >2mm and 1-2 mm are associated with 10% and 12.5% local recurrence, respectively [5]. Partial mastectomy combined with oncoplastic techniques as well as total and nipple and skin-sparing mastectomy, can be employed when indicated without increasing local recurrence. Total mastectomy is usually performed for large tumors and is dictated by patient preference and tumor-to-breast ratio considerations. Lymph node involvement is rare as the tumor metastasizes by the hematogenous route. Axillary treatment is not indicated unless there is a nodal enlargement or direct extension of the tumor into the nodal bed. In the presence of adenopathy or direct extension into the axilla, limited axillary surgery should be considered.

Large phyllodes tumors uncommonly involve the chest wall. However, if the chest wall is involved, the muscle should be removed en bloc with 1 cm margins. Immediate breast reconstruction can be performed with implants, autologous tissue, or a combination of techniques without increasing local recurrence as long as adequate surgical margins are achieved.

Ten to 40% of phyllodes tumors recur. Local recurrence occurs in 15-20% of cases and is associated with inadequate excision. The overall reported recurrence for malignant, borderline, and benign tumors is 27%, 25%, and 17%, respectively [1]. While benign tumors can be treated with local excision with low recurrence, borderline and malignant tumors are more likely to display local and distant recurrence. A recent study of recurrence following re-excision of benign phyllodes tumors reported residual tumors in 9% of patients with close margins and 8.8% with positive margins. At 35.5 months of follow-up, only 1.9% of patients developed a second

recurrence. There was no difference in recurrence for patients with positive and close margins following the excision of benign phyllodes tumors [6].

Borderline and malignant phyllodes tumors are more likely to recur locally as well as distant. A recent study reported a 10-year locoregional recurrence for borderline/malignant variants of 12% [7]. The factors that increase local regional recurrence are age less than 40 and close or positive margins. Margin status is the only independent predictor for recurrence, and tumor size does not affect local recurrence.

Distant recurrence occurs in 6% of all patients with phyllodes tumors. However, metastasis occurs in 0-3% of benign, 0-11% of borderline and 10-50% of malignant tumor subtypes [8]. Among malignant and borderline phyllodes subtypes, rates as high as 50% have been reported. However, a recent study of 124 patients with borderline and malignant phyllodes tumors from Memorial Sloan Kettering Cancer Center identified subgroups of patients with borderline/malignant phyllodes who had a survival advantage [9]. This study reported 100% distant recurrence among 25 patients whose tumors had poor prognostic features (marked stromal cellularity, stromal overgrowth, infiltrative borders, and ten or more mitosis per 10 high-power fields). However, patients with tumors that lacked poor prognostic features had a 10-year disease-specific and overall survival of 100% and 94%, respectively. Conversely, those whose tumors had poor prognostic features had a 10-year disease-specific and overall survival of only 66% and 57%, respectively. The preferred sites of metastasis are the lung (66%), bone (28%), brain (9%), and rarely liver and heart. Metastasis is related to tumor biology rather than the extent of surgery and carries a poor prognosis with no long-term survival.

Evaluation of patients with suspected recurrence should include history and physical exam, mammography for women over 30 years of age, ultrasound, and core needle or excisional biopsy to confirm the diagnosis. Chest CT (Computed Tomography), with and without a contract, and CXR should be considered to assess the extent of the disease. If no metastatic disease is identified, re-excision of the recurrent tumor with >1 cm. margins should be performed. Axillary treatment is not indicated. Post-operative radiation should be considered in patients with close margins (< 1 cm.). In patients with close margins, radiation therapy can decrease local recurrence by 57%, although there is no consensus regarding its use. While it can reduce local recurrence, it has no impact on disease-specific or overall survival. Chemotherapy is indicated for recurrent or metastatic disease. Chemotherapy, using regimens for sarcoma, does not improve outcomes in patients with malignant phyllodes tumors and offers no survival advantage.

Key Points

- Phyllodes tumors comprise 0.3-0.5% of breast cancers and occur most frequently in Asian, white, and Latin American populations.
- Core needle biopsy is the preferred diagnostic method, and fine needle aspiration should not be used.
- Surgery, consisting of partial or total mastectomy without axillary treatment, is the preferred approach for both primary and recurrent disease.
- Radiation and chemotherapy have limited roles in the management of this disease.

Case Scenario

A 48-year-old woman presented with a one-year history of pruritis and erythema of the right nipple that she has intermittently treated with topical steroids. Two months prior to presentation, she developed oozing and crusting of her nipple and associated pain (Fig. 3).

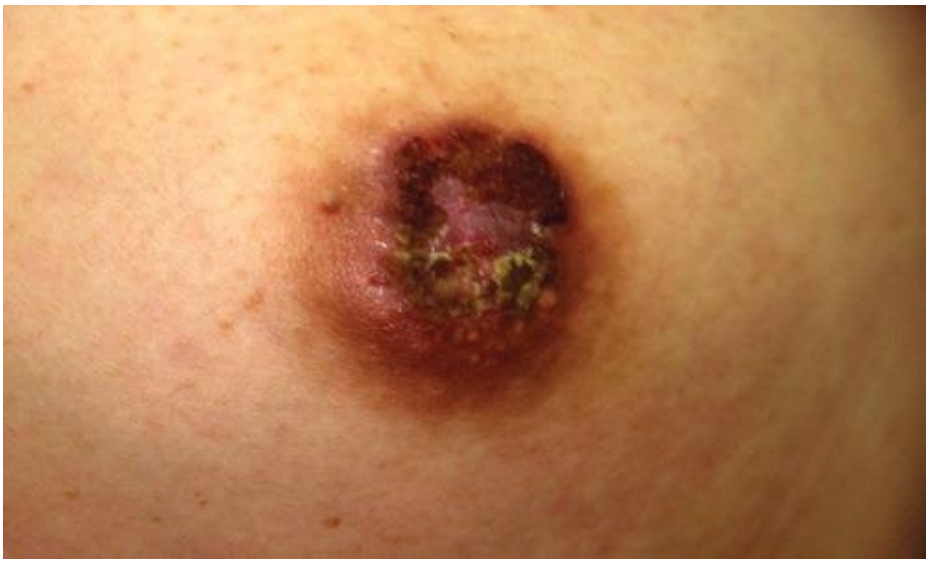

Figure 3: Paget's Presenting as a crusted ulcerated NAC

Clinical breast exam revealed a subareolar areolar mass, associated thickening, and no axillary adenopathy. A mammogram showed areolar thickening (arrowhead) and a 1 cm. subareolar mass with associated pleomorphic microcalcifications (Fig. 4). A biopsy was performed and showed high-grade, ER/PR negative invasive ductal carcinoma. The patient was treated with central excision, sentinel node biopsy, radiation, and adjuvant therapy.

Epidemiology

Paget's disease of the nipple, a rare breast cancer, accounts for 1-4% of breast cancers. It primarily affects women aged 50-60 years but can be found in women less than 30 years. The

time from symptom onset to treatment is usually 6-12 months, and the nipple-areolar complex changes precede the appearance of cancer by 1-2 years.

Paget's disease in males is extremely rare, with approximately 40 cases reported worldwide. Onset in men occurs at a mean age of 61 and has the same clinical features and biological behavior as that found in women. However, 5-year survival is only 20-30% due to delayed diagnosis [10].

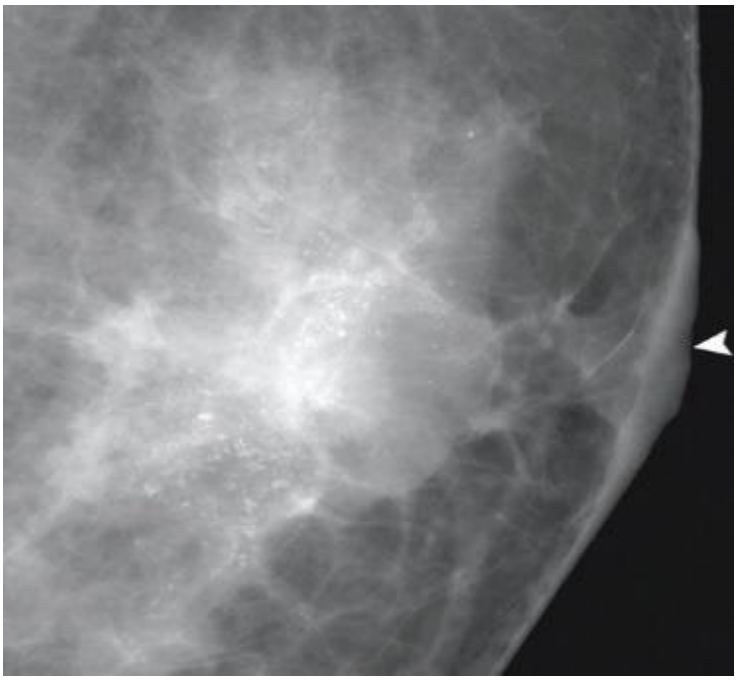

Figure 4: Mammogram demonstrating BIRADS 5 Calcifications. The arrow indicates the nipple.

Paget's disease is associated with an underlying in situ or invasive cancer in 85-90% of cases and occurs alone in 10-15% of cases [11]. Sixty percent of associated cancer will either be located centrally beneath the nipple-areolar complex or within 2 cm. of the areolar border. The remaining 40% are located elsewhere in the breast, with the upper outer quadrant being the most common peripheral location.

Presentation and Pathology

Patients present with a history of persistent eczematous dermatitis associated with pruritis or pain, erythema, scaling, oozing, or crusting. Early nipple changes precede the cancer by 1-2 years. They are frequently mild and attributed to dermatitis, which frequently results in a diagnostic delay of 6-12 months. Bloody or purulent discharge or an inverted nipple may also be present. Early-stage disease presents as nipple scaling and erythema while in advanced stages,

the lesion presents as a thickened, well-demarcated oval plaque that may involve the entire nipple/areolar complex. Rarely Paget's Disease may manifest as a cutaneous horn.

Paget's disease usually presents as a unilateral lesion. However, it can be bilateral and in the nipple of accessory breasts. Approximately 50% are associated with palpable mass beneath the nipple, and 20%-60% are distant from the nipple-areolar complex. Paget's disease without a palpable mass occurs in 20% of patients. Palpable masses are usually associated with invasive ductal carcinoma, while DCIS is associated with nonpalpable masses. Axillary adenopathy is associated with palpable tumors. The associated ductal cancers may be unicentric or multicentric and are more commonly located in the central portion of the breast although ectopic variants have been described most often in the upper outer quadrant.

The differential diagnosis includes atopic/contact dermatitis, chronic eczema, psoriasis, mammary ductal ectasia with chronic nipple discharge, syphilitic chancre, benign intraductal papilloma, basal cell carcinoma (Bowens Disease) and superficial spreading melanoma.

Paget's disease arises from malignant cells that have migrated from an underlying cancer to the epidermis. It is associated with an underlying in situ or invasive ductal cancer in 96-100% of cases. Approximately 2/3 of patients will have an associated invasive and 1/3 an associated in situ cancer; 25-30% will have multifocal disease.

Paget's cells are located in the basal region of the epidermis and appear as single cells or gland-like clusters (Fig. 5; arrows).

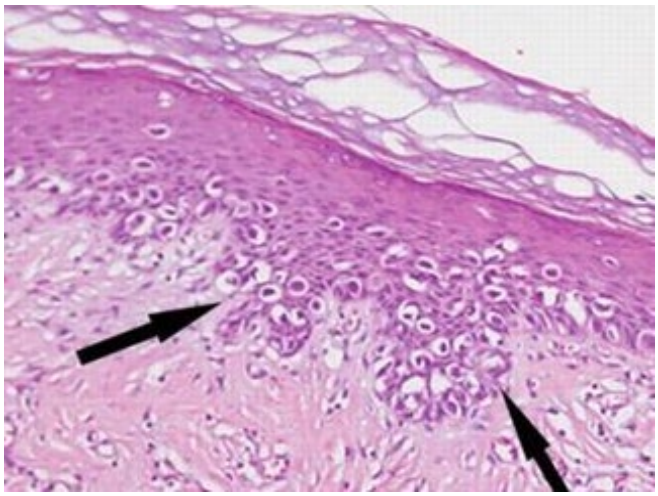

Figure 5: Arrows point out Paget's cells in an H&E Stain

They are hyperchromatic, pleomorphic nuclei with pale clear cytoplasm that sometimes contain melanin. On immunohistochemical exam, the cells can express low molecular weight cytokeratins, carcinoembryonic antigen, epithelial membrane antigen, mucins or melanocytic antigens, and Ki 67. The cells may also express ER, PR, or HER-2-neu. However, the absence of hormone receptors does not rule out Paget's disease. Invasive ductal carcinomas associated with Paget's disease are more commonly high grade and ER/PR negative when compared to invasive ductal carcinomas without associated Paget's disease.

Diagnostic Evaluation

Initial diagnostic evaluation should include a thorough history, breast exam, biopsy of the skin of the nipple/areolar lesion, bilateral mammogram, and ultrasound. Mammography may demonstrate a mass with or without architectural distortion, malignant microcalcifications, skin and nipple/areolar thickening, and/or nipple retraction. Ultrasound findings are nonspecific and include hypoechoic areas, masses, dilated ducts, or skin thickening. Fifteen to 65% of patients with a negative mammogram will have an underlying malignancy. MRI should be considered in patients with a negative mammogram and ultrasound examination to identify an underlying carcinoma or to assess the extent of known disease and guide surgical treatment.

A wedge biopsy of the nipple-areolar complex is the preferred biopsy method since it encompasses the entire thickness of the epidermis. Punch biopsy is suboptimal as it may not yield adequate epidermis, and shave biopsies should not be performed due to inadequate tissue sampling.

Treatment and Outcomes

Surgical treatment is guided by whether Paget's disease is confined to the nipple-areolar complex and whether it is associated with invasive or in situ ductal cancer. There are three surgical treatment options for breast management: central excision with or without peripheral lumpectomy, central lumpectomy with or without sentinel node biopsy, and total mastectomy with or without breast reconstruction or sentinel node biopsy [12]. Patients treated with central excision with or without peripheral lumpectomy should receive adjuvant radiation. Excision alone is associated with local recurrence of 33-40% within six years and should not be performed.

Historically, mastectomy was considered the treatment of choice for patients due to the high prevalence of multicentricity and false-negative mammography. However, contemporary evidence has demonstrated that breast conservation (lumpectomy and radiation) and mastectomy with or without an associated malignancy offer equivalent survival advantages when adjusted for tumor size and nodal status [13,14,15]. Central excision consisting of complete excision of the nipple-areolar complex followed by radiation for patients with DCIS is associated with a 5% recurrence after six years [14]. Despite the evidence supporting equivalence, mastectomy remains the most common surgical treatment. The standard treatment for men is mastectomy, sentinel node biopsy with further axillary treatment as indicated, and adjuvant therapy as indicated based on tumor and nodal characteristics [10].

Sentinel node biopsy should be performed in all patients undergoing treatment for Paget's Disease without palpable adenopathy [16]. It is both safe and effective, with reported localization of 96% when both dye and isotope are used. The sentinel node will be the only positive node in

75% of cases. Axillary clearance should be performed for positive sentinel nodes or in the presence of palpable adenopathy.

Survival is 5-10% lower for stage-matched patients with Paget's disease compared to non-Paget's associated infiltrating ductal cancer [15]. The prognosis of patients with Paget's disease is adversely affected by the presence of a palpable mass, adenopathy, tumor histology, and age <60. The 5-year relative survival of patients with Paget's disease is 82.6% compared to 87.5% for invasive ductal cancer. Ten-year disease-specific survival for node-negative patients is 93% and 47% with node-positive disease. Survival is excellent for patients with Paget's disease associated with an underlying DCIS. Among men, the overall 5-year survival is 20-30%, and they may have a higher incidence of associated invasive disease than women [10].

Paget's confined to the nipple-areolar complex or associated with DCIS carries an excellent prognosis. A multi-institutional study reported 15-year local control, disease-free survival, and overall survival of 87%, 97%, and 90%, respectively, among patients with Paget's disease confined to the nipple-areolar complex [17]. A recent SEER (Surveillance, Epidemiology, and End Results) study reported 15-year survival of 92 and 94% among women with Paget's disease alone or with associated DCIS treated with central lumpectomy and radiation or mastectomy [15]. Survival among women with invasive disease was 87% for central lumpectomy and radiation and 60% for mastectomy. The 15-year breast cancer-specific survival was 61% among women with Paget's disease associated with invasive ductal cancer, 94% among those with associated DCIS, and 88% for women with Paget's disease alone. Tumor size > 2cm. and nodal status were the only independent prognosticators of disease-specific survival.

Adjuvant chemotherapy and hormonal therapy should be based on tumor and nodal characteristics of the associated in situ and/or invasive cancer. The reader is referred to the National Comprehensive Cancer Network (NCCN) guidelines as well as the discussions in earlier chapters to inform tailored adjuvant treatment recommendations for invasive and in situ breast cancer [13].

Key Points

- Paget's disease accounts for 1-4% of breast cancer cases. It is most commonly diagnosed in women aged 50-60 years of age but has been reported in men.
- Early symptoms of a pruritic eczematoid nipple or areolar rash may precede the diagnosis by 1-2 years.
- Almost all cases of Paget's disease are associated with an underlying DCIS or invasive ductal cancer, and breast evaluation is essential.
- The current evidence supports the equivalence of breast conservation and mastectomy in patients with Paget's disease.
- Sentinel node biopsy should be performed in all patients undergoing definitive surgical treatment.

Male Breast Cancer

Case Scenario

A 57-year-old male presented with a 3-month history of a left breast mass associated with nipple retraction. He palpated the enlarging mass while showering but stated that he noticed the nipple

retraction two years ago. A clinical breast exam revealed a firm 4 cm mass in the left upper outer quadrant without associated lymphadenopathy. A left diagnostic mammogram and ultrasound showed a 3.6 cm irregular subareolar mass (Fig 6). An ultrasound-guided core biopsy was performed of the left breast mass, which revealed a high-grade, ER+/PR+/HER2neu -, invasive ductal carcinoma.

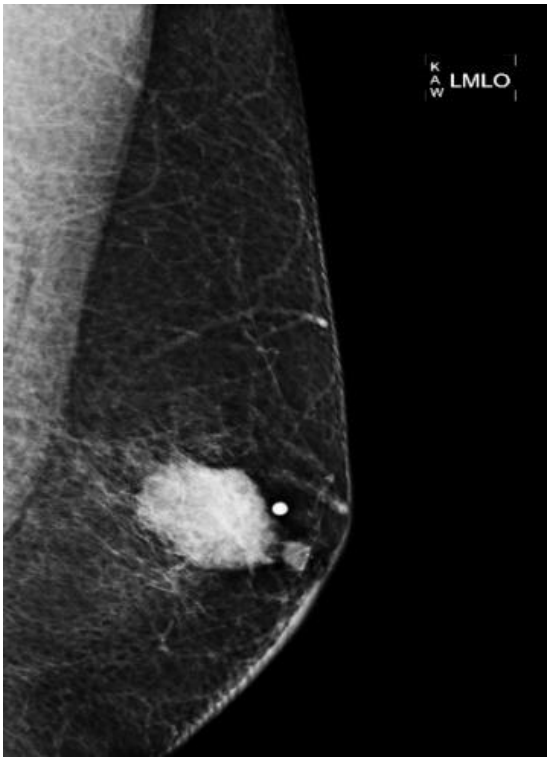

Figure 6: Mammogram demonstrating a 3.6cm subareolar mass.

Epidemiology

Male breast cancer (MBC) represents approximately 1% of all breast cancers. The average age of diagnosis is 60-70 years of age. The risk factors for the development of male breast cancer include family history of breast and ovarian cancer, Afro-Caribbean heritage, inherited genetic mutations (BRCA1/BRCA2, CHEK2, PALB2, ATM), and exposure to chest wall radiation. Diseases causing hormonal imbalance, such as obesity, liver cirrhosis, and testicular abnormalities (mumps orchitis, undescended testes, or testicular injury) predispose men to develop breast cancer. Exogenous estrogen usage, as seen in prostate cancer treatment or in men undergoing gender reassignment, increases risk. Other rare disorders that lead to excess estrogen, such as Klinefelter's syndrome (XXY) are risk factors for the development of male breast cancer.

There is limited clinical trial data and research available on male breast cancer, as clinical trials have experienced difficulty with recruitment. Most of our data and management of male breast

cancer is extrapolated from clinical research on women, despite the fact that MBC has distinct clinicopathological features distinct from female breast cancer (FBC) [18,19].

The incidence of newly diagnosed MBC has increased by approximately 25% globally. The Global Burden of Disease (GBD) 2017 database from 1990 to 2017 revealed an increase in incidence from 8,500 to 23,100. Low, moderate, and high-resource countries experienced increases in diagnosis, most pronounced in men aged 15-49 [19, 20].

Presentation and Pathology

The initial clinical finding of breast cancer in men is often a painless, unilateral, palpable subareolar breast mass or nipple retraction. Male breast cancer commonly presents at a more advanced stage compared to women with larger tumor size and palpable ipsilateral lymph node involvement. Approximately 50% of men present with distant metastasis at the time of initial diagnosis. The later stage of initial diagnosis can be attributed to a lack of awareness of male breast cancer by the patient and clinician and the rare incidence of disease [21, 22].

Invasive breast cancer is found in the majority of male breast carcinomas, with in situ cancers only representing 10% of diagnosed MBCs. *In situ*, carcinomas often present as a bloody nipple discharge without a palpable mass. MBCs are typically of ductal origin and are almost exclusively estrogen and progesterone receptor positive. They are also androgen receptor positive. Her2/neu amplification is less frequent in male breast cancer. Triple-negative MBC is exceedingly rare. Invasive lobular carcinoma is rare due to the lack of terminal lobules in male breast tissue. Estrogen is required for terminal lobular differentiation, and invasive lobular carcinoma is rarely seen with MBC when there is increased estrogen exposure. Other

histological subtypes of breast cancer, such as medullary, tubular, or neuroendocrine tumors, are unusual in men [18, 19, 21].

Diagnostic Evaluation

Mammography, breast/axillary ultrasound, and core needle biopsy are the mainstay of the diagnosis of male breast cancer. The mammogram will reveal an irregular or spiculated mass. An area of architectural distortion may be visualized on the mammogram. Microcalcifications are uncommon in males. Characteristic ultrasound findings include an irregular appearance and hypoechoic mass with posterior shadowing. Examining the axilla with ultrasound with particular attention to enlarged axillary lymph nodes, loss of fatty hila, and thickened cortices can indicate axillary involvement. If axillary lymph nodes appear abnormal, an ultrasound-guided fine needle aspiration or core needle biopsy should be performed, and clip placement is advised. CT scan of the chest, abdomen, and pelvis with bone scan or PET scan is indicated for MBC staging similar to women. Genetic counseling and genetic testing, when available, should be considered in all MBCs as approximately 13-20% carry an identifiable inherited genetic mutation [18, 21 22].

Treatment and Survival

Surgery, radiation therapy, endocrine therapy, and chemotherapy are the cornerstone treatments of MBC in developed countries. In low-resource countries, surgical intervention is the mainstay of treatment, as other treatment modalities may be cost-prohibitive. Historically, the most common surgical treatment for male breast cancer is mastectomy. Men are more likely to prefer mastectomy due to the paucity of breast tissue and the central location of the tumor. These factors often lean towards mastectomy [21, 23].

The trend in treatment for FBC has evolved toward breast-conserving surgery (BCS). We have not observed a similar trend in surgical management of MBC. BCS with oncoplastic technique and nipple-sparing mastectomy can be used with careful case selection and is utilized in 3-15 % of cases. The patient satisfaction that accompanies a good cosmetic outcome is a crucial factor when weighing surgical options for both men and women. Systematic literature reviews demonstrate that BCS in men is feasible and oncologically safe, with similar local recurrence rates and disease-free survival intervals as FBC. Considerations for BCS and, in men are similar to FBC, considering the breast size to tumor volume ratio. Neoadjuvant chemotherapy can be considered in men who prefer BCS to decrease the tumor burden and make BCS more practical if desired. Men with cancers that do not involve the nipple-areolar complex can be considered for nipple-sparing mastectomy [21, 24, 25, 26, 27].

Axillary nodal status is a key prognostic factor for staging, treatment, and survival in MBC. While data is limited, sentinel lymph node biopsy can be successfully performed in MBC and has increased accuracy with the combination of a radiotracer and blue dye. Sentinel lymph node biopsy should be considered for men with a clinically negative axilla [28].

Patients with hormone receptor-positive MBC should receive a 5-10-year course of adjuvant tamoxifen. Tamoxifen is also the first-line endocrine treatment for metastatic MBC. However, significant side effects with tamoxifen, such as hot flashes, decreased sex drive, visual disturbances, and cognitive changes, have affected compliance with hormonal therapy, as seen with FBC. Aromatase inhibitor as single agent usage is discouraged due to inferior outcomes versus tamoxifen alone. If tamoxifen is contraindicated, a gonadotropin release in hormone analog (GnRH) plus an aromatase inhibitor can be used.

Indications for chemotherapy and radiation are similar to those indicated in female breast cancer (FBC) when accounting for tumor size, hormone receptor status/Her2 status, and axillary lymph node involvement. Preoperative axillary ultrasound demonstrating abnormal appearing lymph nodes and subsequent metastatic nodal involvement based on FNA or CNB can aid the decision for using neoadjuvant chemotherapy. Molecular assays with the 21 gene recurrence risk score have limited data showing prognostic benefit in MBC. Systemic therapy for advanced MBC is similar to that in women [29].

Surveillance for early-stage MBC does not require routine mammography according to NCCN guidelines, although an ipsilateral mammogram should be considered in men undergoing BCS[5]. NCCN 2020 guidelines recommend bone density assessment at baseline and every two years for men who receive adjuvant GnRH analog therapy [22, 29]. The reader is referred to earlier chapters in this book for additional guidance.

Overall, 5-year survival for MBC is lower (82.8%) than for FBC (88.5%), according to SEER Data. There is a significant need for increased outreach and awareness of screening, diagnostics, research, and treatment/surveillance options targeted towards MBC [30].

Key Points

- Male breast cancer represents 1% of all breast cancers. The average age of diagnosis is 60-70 years of age.
- Male breast cancer commonly presents at a more advanced stage and is typically hormone receptor positive.
- Mammography, breast/axillary ultrasound, and core needle biopsy are used to diagnose MBC.

- Breast conservation is feasible and safe in appropriately selected men.
- Sentinel lymph node biopsy is feasible and spares morbidity of an axillary dissection similar to women.

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Phyllodes Tumor

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Chapter 33

Breast Cancer Training

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Case Scenario

A fellow's perspective on the value of specialized breast cancer training

As a Breast Surgical Oncology fellow, the additional year of focused training enhances your technical skills, complex surgical decision-making, knowledge of clinical trials/research and multidisciplinary management of breast cancer patients. It builds on the skills acquired in general surgery residency, where dedicated time is not always available to learn the complex multidisciplinary aspects of breast cancer. Fellowship provides an opportunity to refine and mature operative techniques while broadening clinical management and research knowledge and facilitating career advancement with lifelong mentors. Important components of an ideal Breast Surgical Oncology fellowship program for prospective fellows are outlined in Table 1.

Table 1. Components of an ideal Breast Surgical Oncology fellowship training program from the fellow's perspective.

High clinical and operative volume exceeding Society of Surgical Oncology minimum training requirements
Exposure to broad and complex breast cancer disease
Graduated autonomy in clinical breast cancer care
Expertise among multidisciplinary spectrum
Faculty commitment to teaching
Comprehensive didactic curriculum and conferences/tumor board
Opportunities and support for clinical research
Dedicated mentorship and career development
Leadership development and opportunities
Supportive environment focused on optimizing fellow's education and opportunities

Introduction

The contemporary management of breast cancer is centered on the understanding of invasive breast cancer as a systemic disease requiring a multidisciplinary approach to curative therapy. Initially approached as a surgical disease, it is now well recognized that improved clinical outcomes have been driven by the introduction and advancement in medical therapies, including chemotherapy and targeted therapy, the adoption of radiation therapy, and advancements in reconstructive techniques. This transformative change in management has resulted in a renewed focus on personalized care with an emphasis on limiting long-term surgical morbidity, given improvements in life expectancy, particularly in early-stage disease. Furthermore, a sophisticated understanding of tumor biology and the differential response of tumor subtypes to systemic therapies has rapidly driven clinical practice.

This evolving management paradigm has shifted the role of the breast surgical oncologist. Still highly regarded as the leader of the multidisciplinary team, the breast surgical oncologist is uniquely positioned to guide the patient through the complicated matrix and management course facilitating their understanding of treatment options and their advantages and disadvantages in

the context of the patient's goals and values. For this reason, the breast surgical oncologist needs to not only have expertise in the surgical management of breast cancer but also multidisciplinary decision making.

Breast surgical oncology fellowship training in the United States

Recognizing the intricacies in the management of breast cancer and the need for subspecialty training, focused fellowship training in breast surgical oncology was born. [1] Leaders in the surgical oncology and breast surgical societies and Susan G. Komen Breast Cancer Foundation championed this effort culminating in breast surgical oncology fellowship programs with the explicit intention of building upon general surgical training with dedicated multidisciplinary instruction in breast cancer management. [2]

By all standards this effort has been a tremendous success and even more relevant with the rapidly changing breast cancer treatment paradigms. Starting in 2003, the fellowship programs have grown from 26 to 53 approved programs and produced over 700 fellowship trained breast surgical oncologists. The impact of fellowship training has been well recognized in improved surgical outcomes and patient satisfaction. [3-6]

The need for fellowship training in breast surgical oncology is becoming more necessary as the field advances and general surgery residency programs face competing interests resulting in less than robust comprehensive breast cancer training. Several studies evaluating the experience of general surgery residents have shown decreased exposure to complex breast surgical cases including modified radical mastectomy and decreased self-efficacy with multidisciplinary management. [7-10]

The composure of breast surgical oncology fellowship programs

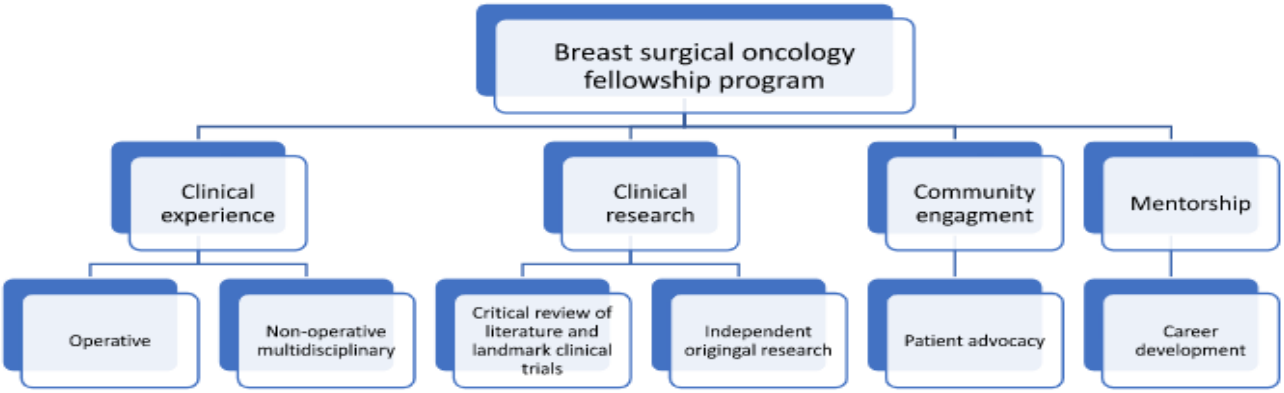

Figure 1. Essential pillars of a Breast Surgical Oncology Fellowship Program

A Breast Surgical Oncology Fellowship Program are outline in Figure 1.Fellows typically rotate on multidisciplinary services including breast medical oncology, radiation oncology, breast imaging, breast pathology, plastic and reconstructive surgery, high-risk genetics and cancer screening and prevention. Table 2 is an example of breast surgical oncology fellow rotation.

	1	2	3	4	5	6	7	8	9	10	11	12
1	BSO	CSP	BSO	BSO	BMO	BSO	Vacation	BSO	BSO	Vacation	BSO	Plastic Surgery
2	BSO	CSP	BSO	BSO	BMO	BSO	DI	BSO	BSO	Pathology	BSO	Plastic Surgery
3	BSO	Genetics	BSO	BSO	Radiation	BSO	DI	BSO	BSO	Pathology	BSO	Elective
4	BSO	Vacation	BSO	BSO	Radiation	BSO	DI	BSO	BSO	Community	BSO	Elective
		Research			Research		Research			Research		Research

Table 2: Rotation Schedule

Community outreach and patient advocacy has been a core of the fellowship programs since their inception. Specialized instruction in breast surgical oncology management with mastery of advanced techniques such as nipple and skin sparing mastectomy, complex breast conserving surgery with oncoplastic reconstruction, targeted axillary dissection and axillary dissection with axillary reverse mapping. Additionally, fellows acquire skills in determining treatment plans and advising patients on treatment options focused on their goals and values, promoting survival and preserving quality of life.

In addition to the rigorous and comprehensive clinical experience, fellows are expected to advance the field with investment in clinical research. Perhaps more than any other specialty, breast surgical oncology has a long tradition of clinical trial driven evidence-based practice. Fellowships should include instruction on these landmark and contemporary clinical trials which provide the foundation for current practice and push the envelope towards the future.

National breast surgical oncology fellowship training requirements

A survey of former breast surgical oncology fellows from 2005 to 2009 found that despite being well prepared for clinical practice, fellows were less confident in imaging modalities, including ultrasound and imaging guided biopsy. [11] From this experience, it was clear that there was a need to provide a standardized experience for all fellows. The Society of Surgical Oncology (SSO) subsequently designed the Fellows Institute, a content and skills-based workshop for fellows across the United States to provide similar exposure and training.

Understanding the variability across training programs and in an effort to continue to ensure a baseline proficiency and curriculum for all breast surgical oncology fellows, the SSO established

a national training curriculum with defined minimum training requirements. Initially adopted in 2015 and updated in 2019, this curriculum is outlined based around topics commonly encountered in breast surgical practice to those which are more specialized. [12] It also defines operative and non-operative exposures with a minimum number required to be considered proficient and also classified based on the likelihood of encountering them in practice.

This curriculum was revolutionary, allowing for flexibility within each training program while also allowing for a minimum standard with which to ensure the quality and exposure of graduating fellows to the comprehensive experience across the breast cancer spectrum. Furthermore, it provides fellows with a metric with which to achieve and measure their exposure and fellowship experience.

Accreditation and program management

The SSO and American Society of Breast Surgeons (ASBrS) provide leadership and accreditation for the fellowship training programs. Through interval site visits, representatives of these organizations ensure that individual fellowship programs advance the education and support the careers of their fellow fellows. This includes providing robust clinical operative and non-operative experience, rotations with multidisciplinary services, didactic curriculum, clinical research opportunities, and completion of the minimum training requirements. Essential non-clinical educational components of a breast surgical oncology fellowship program are outlined in Table 3.

Program and rotation goals and objectives
Reading list of landmark studies
Routine evaluation of fellow clinical performance
Routine evaluation of faculty teaching
Weekly didactic curriculum
Involvement in conferences and tumor board
Independent original clinical research
Mentorship and career guidance

Table 3. Essential non-clinical educational components of a breast surgical oncology fellowship program

Additionally, these reviewers ensure that fellows are supported in their careers and throughout the fellowship year. The fellowship program directors are also invited to participate in a subcommittee of the SSO, which enables a shared vision, facilitates collaboration, and provides alignment across programs.

Mentorship and career development

Breast surgical oncology fellows are adult learners gaining mastery and advanced skills in treating breast cancer. A critical component of fellowship is the nurturing and development of a life-long career in breast surgical oncology. This requires strong mentorship from training faculty who are well-equipped to provide clinical, research, and career guidance, thereby allowing fellows to mature into independent practitioners and leaders. The critical importance of mentorship in surgical careers has been well established and is within this supportive environment that the next generation of breast surgical oncologists will grow and develop themselves into mentors for future fellows. [13]

Conclusion

There are many lessons learned from the United States experience that may inform breast cancer training in low-middle-income countries. The first is that advanced multidisciplinary training is paramount for the breast surgical oncologist. Programs should provide fellows with both operative and non-operative exposure, critical review and understanding of practice-changing clinical trials, involvement in clinical research, and community outreach. The creation of a national curriculum encourages a minimum standard of proficiency across training programs. A thoughtful and periodic review and evaluation of fellowship programs and these training requirements will ensure the programs are leading into the future in a rapidly changing field.

Effective mentorship will enable fellows to gain critical skills and leadership to carry into their upcoming careers as they impact the lives of countless men and women with breast malignancy.

Key points

- Dedicated instruction in breast surgical oncology, building upon foundational general surgical principles, is optimal in developing the contemporary breast surgical oncologist.
- Breast surgical oncology training requires mastery of the surgical management of breast cancer as well as multidisciplinary treatments and considerations.
- Critical breast surgical oncology training components include a comprehensive operative and non-operative multidisciplinary experience, clinical research, and community outreach.
- The national curriculum and training requirements provide a standard experience for fellows across fellowship programs.
- Mentorship is important to develop fellows equipped for future practice and leadership within the field.

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Chapter 34

Cancer Surveillance in Low- and Middle-Income Countries

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What is a Cancer Registry?

Cancer registries serve as a database about a group of patients regarding their medical history and their social history, including age, gender, and race. The registry provides specimens correlating radiographic imaging, treatment, and outcomes for each tumor in a deidentified, publicly available forum.

Cancer in Low- and Middle-Income Countries

When it comes to the epidemiology of disease, it is well established that low- and middle-income countries face much greater risks of morbidity and mortality from communicable diseases. These numbers have significantly declined with the advent of vaccines and better hygiene practices. Yet, care remains incomplete: understanding how non-communicable diseases, such as cancer, are trending in these nations. The current method of data collection for cancers worldwide includes each country reporting their cases to the World Health Organization (WHO), which then accounts for these tumors and provides basic statistics. The number of countries participating in this outreach has steadily increased over the years, yet not all countries participate. The quality and uniformity of data for each country varies significantly, with low-income countries having

disproportionately poor data quality. Based on current figures, stomach, esophageal, and liver cancers are at much higher rates in low- and middle-income countries. Cancers that have an infectious origin are also found to be of greater prevalence in developing countries, including malignancies from HIV, HPV, and hepatitis.[4] Though current sources show that the greatest number of cancer cases are in developed nations, the incidence and mortality rates are greater in less developed countries.[5,6] The rates of mortality of cancer have significantly decreased in developed nations, further strengthening that proper research, funding, and infrastructure can improve patient and population-related outcomes.[7]

There are a multitude of reasons for the discrepancies in care, of which access remains one of the leading causes. The availability of resources in developing nations is exceptionally low. Estimates show that developed nations have 12 times more operating rooms than low income countries.[2] Some studies estimate four mammograms per 7 million women in developing nations, while others have found that only 5% of women have been screened for cervical cancer, despite many wanting to be screened for these conditions.[8,9] The limitation of medical resources and availability of strong healthcare plays a significant role in accessing proper treatment, yet it is crucial also to recognize that these individuals face a poor understanding of disease and warning signs, cultural barriers and stigma, financial constraints, and lack of healthcare.

In addition to increased risk of mortality, increased incidence of cancer significantly impacts each country's economic profile and indirectly affects measures such as economic income, GDP, and productivity loss from morbidity. In the United States alone, it is estimated that the national cost of cancer care was $157 billion in 2010.[10] It is evident that each country loses productivity and resources when its people are affected by cancer, with those within developing countries facing an increased burden of this financial pressure.

The Importance of Cancer Registries

The Surveillance, Epidemiology, and End Results (SEER) Program was established in 1973 by the National Cancer Institute in an effort to understand the burden of cancer in the United States. This program collected data directly from hospitals for all cancer types and sought to understand the epidemiology of the disease from both a basic science and public health perspective. It provided the backbone for the increased effort placed on cancer research and established that each malignancy is unique in its risk factors, presentation, and response to treatment.

One of the greatest ironies of healthcare reform is that discrepancies in care cannot be realized without data, yet establishing a source of data becomes a large task. With the dynamic changes in populations at both an international and national level, it becomes imperative that resources exist that allow for trends, associations, and risk factors to be established to help aid efforts toward stronger populations. Though each country has its own standards of care, analyzing data across nations allows for recommendations to be established with greater evidence-based support.

The greatest disadvantage that low- and middle-income countries have in gaining attention to this increased area of mortality is the need for more data and understanding of disease burden. For that reason, an international cancer registry focusing on low- and middle-income countries is imperative. Without a centralized organization that streamlines tumor-related pathology, it becomes impossible to assess the true burden of disease in each country. The establishment of a registry has many benefits, the greatest of which is illustrating the disease burden across populations and sub-populations. By utilizing both basic science values as well as demographic information, registries are equipped to understand the incidence and prevalence of different diseases and their associated risk factors. As each institution varies in its population

demographics, combining data points can make conclusions supported by greater statistical power and consequently have a more significant impact on further research and medical management. In addition to understanding the epidemiology of disease, registries provide information regarding changes over time. It is essential to note how the disease changes over the years and if interventions such as policymaking have proved to be effective.

Registries also aid with the identification of high-risk populations and help target public health and interventions accordingly. By providing legislators and healthcare workers with the data to support additional funding, manpower, and equipment, countries with increased risk of disease have a better chance of obtaining funding and associated resources.

What Has Already Been Done

The problem of a lack of central structure is not unique to cancer, yet the impact that it has can affect millions in the future. Several efforts have been made over the years to minimize the differences and better understand these countries' disease pathology.

Global Cancer Observatory (CGO or GLOBOCAN)

GLOBOCAN serves as the WHO’s primary medium of conveying statistical information regarding cancer to an international audience. In addition to providing global cancer statistics, it also aims to equip researchers by providing them with estimates of epidemiological information for the current state, the future, as well as address the extent that risk factors play in leading to cancer. Released in 2018, it is one of the newest tools currently available to help determine the discrepancies of cancer risk by socioeconomic status. This tool provides statistics for 36 types of cancer from 185 countries worldwide. Working in conjunction with the International Association

of Cancer Registries, GLOBOCAN provides epidemiological data for each country and tumor type on a fact sheet. Statistics are pre-analyzed, and the data is publicly available.

Statistics from GLOBOCAN 2018 show that there was a total of 18.1 million new causes in 2018 alone, with lung cancer being most commonly diagnosed in both males and females. Variability is seen in terms of the incidence of cancer and the most common cause of death based on the country and its correlating level of development.[11] At an international level, lung, breast, and colorectal cancers contribute to the greatest number of cases. Differences in incidence and prognosis arise when looking at the lesser common cancers. Data shows that regional differences and cultural variations in lifestyle and diet do contribute to the epidemiology of disease

International Association of Cancer Registries (IACR)

Founded in 1966, IACR remains one of the leading organizations to confront the battle of cancer at a global level. With the aim of collecting data from populations all over the world, this registry contains information regarding each case's tumor type, pathology, and follow-up care. It works in accordance with the WHO and has also been a partner in the efforts to establish GLOBOCAN. IACR works to also provide guidelines on population-based cancer registration, particularly in less economically developed nations and has strived to demonstrate how data can be collected from less-resourced areas. Through efforts such as IARC Regional Hubs, natives are trained in the collection of data and technical assistance to better help their communities. These regional sites are connected with networks and provided with administrative support, allowing them to feel supported and collaborate with surrounding communities.[12] Currently, only about 8% of Asia and 11% of Africa are represented by the International Association of Registries (2006), compared to 99% of North America and 57% of Europe.[1]

National Program of Cancer Registries (NPCR)

The NPCR serves as one of the CDC's long-term efforts to collect national-level data about cancer statistics around the United States. Established in 1992 as a rest of the Cancer Registries Amendment Act. Data collected includes the type of cancer, grade and stage, treatment and outcomes.

NPCR collects data from 45 states, including the District of Columbia, accounting for over 95% of the United States population. Data collected from this registry has helped track cancer trends across the nation and helped support legislation, funding, and research efforts towards cancer.

SEER

SEER is another cancer registry for the United States; however, it is a program of the National Cancer Institute. SEER includes data such as age, sex, race, and other geographic information for each tumor that is submitted. Data is then made publicly available for other researchers to use. This registry currently includes about 28% of the US population, including 20 US geographic areas and five states. The database is organized from insurance data and is based on diagnosis codes and other cancer registries that use hospital data.

Next Steps

Registries require expertise from a variety of individuals, and it is imperative that they are carried out in a way that not only benefits those providing samples but also those using the collected data.

What the Registry Should Include

As with any data-collecting process, the variables chosen are of utmost importance. From including demographics, genetics, medical workup, treatment, and outcomes, variables must be

well thought out to identify causation and association and better illustrate trends across different geographic locations. Demographics should not only include statistics about age and sex but should inquire deeper into socioeconomic status by asking about the level of education, insurance status, and income bracket.

Currently, most registries do not emphasize collecting information regarding risk factors in their process of tumor procurement. As the data related to both lifestyle and cancer is strongly correlated, it is vital that a registry at an international level focuses on these aspects. Whether it be asking about alcohol and substance use, dietary preferences, or the history of HIV, registries can be further strengthened.

It is easy for clinicians and researchers to study data based on known risk factors and scientifically based knowledge, yet when working in foreign nations, it is crucial to understand the role that culture plays in a patient's presentation. When procuring data surrounding cancers, questions surrounding why and how patients sought care are particularly important to consider. A better understanding of why they presented, what barriers they faced in meeting with a physician, or what their understanding of the disease is will help better guide future practices. It cannot be taken for granted that patients who are presenting fully understand their disease process, and it becomes the role of the healthcare professionals to ask pertinent questions so that medical awareness and the understanding of the culture surrounding the disease increases.

Prevention

International registries are not only able to provide information regarding current malignancies but have the power to also further assist with increasing efforts towards cancer prevention. Screening has been repeatedly shown to have dramatic reductions in morbidity and mortality of

cancers worldwide. It is unfortunate that access to such programs is disproportionately greater in more developed countries, and the awareness surrounding cancer screening is not as prominent in middle- and low-income countries. Future registries should additionally focus on asking questions regarding whether the patient was ever screened if they were given an opportunity for screening, and if they thought screening would be beneficial.

How to Make This a Standard of Care

Though international and national registries hold tremendous power in influencing efforts for greater care, participation is highly variable. Whether it be a lack of manpower or initiation, not all geographic areas participate in these efforts. Methods to change this include requiring tumor registries to be part of the standard of care for any patient. Legislation must be stringent that patients presenting with malignancies must be automatically enrolled in these databases so that holistic and higher-quality data may become available.

Another method of making cancer registries more part of day-to-day life is by educating the public about these initiatives. By the public becoming aware of these efforts, their understanding of cancer increases, and they are also educated about the resources available to them if they experience abnormal symptoms. Public health efforts are the most effective when met with community support, and it is essential that regardless of the endeavor taken, their support is procured by working with them and community leaders.

Data Collection and Distribution

Perhaps one of the most important factors surrounding the creation of a cancer registry includes how the data is collected, how it is stored and maintained, and what procedure is in place for distribution to third parties for analysis.

In 2015, the CONCORD program established global surveillance of cancer survival for the first time, publishing trends in survival over the 15-year period of 1995-2009.[13] The database included 67 countries that included two-thirds (4.8) billion of the world's population with 40 countries the data had 100% national population coverage. This study, known as CONCORD-2, provided centralized quality control, and analyzed data for 25,676,887 patients diagnosed with one of 10 common cancers, representing 63% of the global cancer burden in 2009. The 279 population-based registries covered a combined total population of 896 million people.

The US Centers for Disease Control and Prevention (CDC) described CONCORD-2 as the beginning of global surveillance estimates "that can be compared, so scientists can begin to determine why survival differs among countries. This could lead to improvements in cancer control programs".

CONCORD-3 updates worldwide surveillance of cancer survival trends to include patients diagnosed up to December 31, 2014. Follow-up on registry patients from 2000-2009 is included in the database. CONCORD-3 includes data from patients diagnosed during 2000-2014 with one of 18 malignancies that represent 75% of the global cancer burden, with additional data included on tumor grade and first course of treatment. CONCORD-3 covers almost one billion people worldwide. It includes 15 common cancers in adults and three common cancers in children. Data quality has improved. The results are timely: published within three years of the end of follow-up. CONCORD-3 updates the worldwide surveillance of cancer survival to 2014. It includes data for over 37.5 million patients diagnosed with cancer during the 15-year period 2000–2014. Data were provided by over 320 population-based cancer registries in 71 countries and territories, including 26 countries of low or middle income; 47 countries provided data with 100% population coverage. {13}

The CONCORD Working Group includes members from 27 countries and provides a strict data protocol to participating registries defining standardized data structure/content, file transmission procedures, and statistical analyses. Standardized quality control methods were used, and identified errors were corrected by the registry involved. Five-year net survival estimates were age-standardized with the International Cancer Survival Standard weights.

The WHO Executive Board in 2106 recommended strengthening health systems for cancer patients. Subsequently, the World Assembly followed up with a resolution on cancer control in May 2017, including strategies to reduce late presentation, reduce mortality, and improve quality of life.

Funding

Funding is at the core of the establishment of an international cancer registry and should be a collaborative effort between multiple nations. The HIV/AIDs epidemic is a prime example of how government efforts are at the core to public health success. The HIV/AIDs epidemic came to the spotlight in the early 1980s when trends in similar disease patterns began arising in homosexual men across the nation. Slowly, the NCI and CDC began to work on better understanding the disease and targeting their efforts, leading to legislation changes beginning in 1982. From then on, research was exponentially increased, and the government procured millions of dollars towards better care for these patients. 30 years later, in 2010, the first patient cured of HIV was confirmed, and today, being diagnosed with HIV is no longer considered an end to life. A smaller number of people are dying of AIDs, and medications are better addressing the immunosuppression that was once feared.

This is just one example of how the combination of public health efforts, legislation, and medicine can be combined to achieve superior outcomes. For the full effort to be placed on understanding and battling cancer, governments from all over the globe will have to contribute to the joined efforts. In addition to monetary support, governments can aid by placing incentives for participating in screening and quitting smoking. By placing taxes on industrial companies that use teratogens, governments can also indirectly support efforts to decrease cancer incidence.

In addition to securing funding, when budgeting for a registry, it is important to consider costs for each tumor acquired. Costs associated with this include the price for registration, the price for administration, labor costs, and the price of storage. Estimates show that registering a tumor in a low- or middle-income country will cost anywhere from $4 to $16 (based on 2013 monetary value), depending on the exact location of the registry.[14]

Perceived Problems

Failure mode and effects analysis is the idea that prior to initiating a project, it is always good to anticipate hurdles that may arise and possible solutions. With such a large international endeavor, it is natural that lines of communication may get lost and that uniformity in documentation and tumor procurement could be variable. To decrease the chances of this, it is essential that leadership not only keep in constant contact but that there is a strong sense of structure within the organization. Responsibilities should be clearly demarcated, and a line of hierarchy should be established for when questions arise.

In addition, it is essential to note that cultural barriers and religious sensitivities are considered. Attitudes towards cancer, seeking medical treatment, and the usage of alternative medicines is not fully understood, yet play a significant role in patient compliance with treatment and

management. This knowledge can only be gained from working in the field but should be noted of in case changes need to be made.

Alternatives to an International Registry

An international registry is recommended. However, there are other options. It is possible to have registries at smaller levels, and it is important to note the positives and negatives of each of these choices.

Maintaining a state-level or national registry

An alternative to using an international registry is to maintain one at the state or national level. Though the parameters would be similar, it would be critical that nations maintain standards of procedure. Many low- and middle-income countries need more funding and infrastructure for such projects. It becomes even more important that countries are confident that they will be able to sustain themselves and obtain the data needed to make the maximum impact.

Using Hospital Data

Another method of obtaining data is by directly working with hospitals to acquire tumors and associated records. By working with hospitals directly, researchers are able to talk to the teams procuring and collecting tumors. Problems arise because there are too many healthcare centers to be in contact with, and due to this, it is possible much of the quality of data can be lost.

Salient Points

Data collection and registries have improved with the advent of international registries. However, there remain gaps in resources in low- and middle-income countries, hindering statistical analysis and longitudinal data acquisition. The goal of a cancer registry is to facilitate

data collection to support national and international endeavors in providing high-quality care. Low- and middle-income countries are at a disadvantage when procuring adequate infrastructure in part due to a lack of statistics available for stakeholders and legislation; however, by providing a uniform data set, countries will more appropriately be able to allocate resources and set standards of care.

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Chapter 35

Survivorship Care

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Introduction

Globally, breast cancer 5-year relative survival rates range from 80 to 90% in high-income countries (HICs), to 60% in middle-income countries, to below 40% in low-income countries (1). These differences have been attributed to a myriad of factors, including disparities in early detection, type of breast cancer, access to treatment, type of treatment, and social and cultural barriers. For this chapter's purposes, breast cancer survivor is defined as a breast cancer patient who has completed the treatment (2).

The concept of survivorship as a distinct phase of cancer treatment is evolving and not fully defined. In 2006, the Institute of Medicine (IOM) issued a milestone comprehensive report, *From Cancer Patient to Cancer Survivor: Lost in Transition,* which highlighted the importance of surveillance, health promotion, and assessing and managing the physical, psychological, and spiritual, social, and practical long-term needs and side effects faced by cancer survivors after completion of active treatment. The IOM divides survivorship care into five principal areas: 1) Surveillance for cancer recurrence or new cancers, 2) management of symptoms that persist after the treatment ends, 3) evaluation of risk and prevention of late treatment side effects, 4) assessment of psychosocial needs and 5) counseling of patients on lifestyle modifications for

prevention and improved quality of life (3). Four of the ten recommendations regarding cancer survivorship by the IOM, the issues receiving the utmost attention to date, have been the provision of a summary of diagnosis, treatment received (treatment summary), future follow-up care plans, and healthy lifestyle recommendations. (4). The optimal and more effective approach to survivorship care must focus on patient and provider education. Patient education on the long-term sequelae from the cancer treatment, breast cancer recurrence, adherence and compliance to the treatment recommendations, lifestyle modifications, and cancer prevention. Provider education on treatment side effects, screening and management of psychosocial distress, and communication with the cancer team (5). As such, survivorship needs to be changed over time. Survivorship programs need to address these changes effectively as one size does not fit all. We must move towards more tailored survivorship programs that target individual needs in an age and culturally sensitive manner.

In low- and middle-income countries (LMICs), focusing on survivorship is especially challenging, and awareness of the long-term issues affecting cancer survivors is low. Breast cancer patients in LMICs are often younger, present at more advanced stages, and have more aggressive disease (6). Radiotherapy for breast conservation and sentinel lymph node biopsy for minimally invasive axillary staging are often unavailable in LMICs (7), leading to more extensive surgical approaches such as mastectomy and axillary lymph node dissection with higher rates of long-term complications such as body image changes, and loss of arm mobility and lymphedema. Breast cancer survivors in LMICs may experience greater effects from chemotherapy-induced early menopause, infertility, and impairments in sexual function and body image and may have an increased risk of recurrence as well as a sense of isolation due to social and cultural conditions. Unfortunately, supportive care services are frequently limited in LMICs;

program development for survivorship care and long-term follow-up appropriate for LMICs has not been well addressed (2).

Given the limited resources in LMICs, it is challenging to focus on breast cancer survivorship. In many countries, breast cancer screening and awareness are still not a priority, let alone survivorship. The Breast Health Global Initiative (BHGI), at its 5th Global Summit consensus statement in 2013, identified nine key resources for appropriate survivorship care and developed resource-stratified recommendations for healthcare systems to provide supportive care services based on the available resources (2). Three key elements are evident as you analyze survivorship care globally and, more specifically, in LMICs: First, resource identification, stratification, and allocation are critical. Hence, it is important to provide a foundation of the basic services and the bare minimum necessary to meet the breast cancer survivor's most essential physical and psychological needs. Second, survivorship care must be tailored to its patient population, considering age, socioeconomic, and cultural factors. Third, survivorship care spans a long time after the completion of the cancer treatment. As such, the survivors' needs and expectations change over time, and the care plan must be responsive and provide appropriate support.

Survivorship care is not an exact science but an integral component of care as breast cancer patients transition to survivors. As mentioned earlier, survivorship care must focus on the patients and the health care providers. Key recommendations include health professional education focusing on managing physical and psychosocial long-term treatment complications. Patient education can help survivors transition from a provider-intense cancer treatment program to a post-treatment provider partnership and self-management program and should include education on recognizing disease recurrence or metastases; management of treatment-related

sequelae, and psychosocial complications; and the importance of maintaining a healthy lifestyle. Increasing community awareness of survivorship issues was also identified as an important part of supportive care programs. Other recommendations include screening and management of psychosocial distress; management of long-term treatment-related complications, including lymphedema, fatigue, insomnia, pain, and women's health issues; and monitoring survivors for recurrences or development of second primary malignancies. Breast cancer survivors should implement healthy lifestyle modifications, including physical activity, and maintain a healthy weight where possible. Health professionals should provide well-documented patient care records that can follow a patient as they transition from active treatment to follow-up care (2).

In 2016 the American Cancer Society (ACS) and American Society of Clinical Oncology (ASCO) published the Breast Cancer Survivorship Care Guideline to provide recommendations to assist primary care and other clinicians in the care of female adult survivors of breast cancer. A multidisciplinary expert workgroup with expertise in primary care, gynecology, surgical oncology, medical oncology, radiation oncology, and nursing conducted a systematic review of the literature and was tasked with drafting the Breast Cancer Survivorship Care Guideline (8). 1073 articles met inclusion criteria; after a full-text review, 237 were included as the evidence base. The clinical practice guideline addresses five key areas of breast cancer survivorship to provide recommendations on best practices in the management of adult women after breast cancer treatment, focusing on the role of primary care clinicians and other clinicians who care for post-treatment breast cancer survivors. The five areas covered include 1) surveillance for breast cancer recurrence, 2) screening for second primary cancers, 3) assessment and management of physical and psychosocial long-term and late effects of breast cancer and treatment, 4) health promotion, and 5) care coordination and practice implications. As stated in

the guideline, patients should undergo regular surveillance for breast cancer recurrence, including evaluation with a cancer-related history and physical examination, and should be screened for new primary breast cancer. Data do not support performing routine laboratory tests or imaging tests in asymptomatic patients to evaluate for breast cancer recurrence. Primary care clinicians should counsel patients about the importance of maintaining a healthy lifestyle, monitor for post-treatment symptoms that can adversely affect quality of life, and monitor for adherence to endocrine therapy.

The risk of physical long-term and late effects after therapy for breast cancer is associated with several factors, including (a) type of treatment, (b) duration and dose of treatment(s) (increasing cumulative dose and duration of therapy increase the potential risk), (c) specific type of chemotherapy, (d) receipt of any type of hormone treatment, and (e) age of patient during treatment (8). Hence, the potential physical and psychosocial long-term and late effects associated with these therapies need to be targeted as part of the survivorship care. In this chapter, we will focus on the survivorship issues of lymphedema, women's health, and lifestyle modifications in the LMICs.

Lymphedema

The incidence of lymphedema among breast cancer survivors varies widely (9), although it is estimated that over 40% of survivors will experience lymphedema to some degree. (10-11) The risk of lymphedema is much lower with sentinel lymph node dissections than with the full axillary lymph node dissection previously performed in all cases (12). Lymphedema may occur immediately after treatment or develop after many years. Radiation treatment may cause or exacerbate lymphedema, especially radiation to the supraclavicular lymph nodes or axilla.(13)

Managing lymphedema and shoulder morbidity can be a major concern for breast cancer survivors in LMICs. Patients should be encouraged to self-report upper extremity limb changes and simple arm and shoulder exercises that can be part of their daily activities. Monitoring for lymphedema can be done using basic circumferential measurements of limb girth (14), as more advanced monitoring strategies, such as perometers may not be available (15). Limb compression supplies, such as non-custom sleeves] or stretch tubing, may be helpful in controlling lymphedema, whereas physical therapy (PT) or occupational therapy (OT), including the more intense lymphedema treatment of complex-decongestive therapy (CDT), will require significant expertise to provide. The best strategy against lymphedema is prevention and early detection. Early introduction of lymphedema therapy, including arm exercises and lymphatic massage, has been associated with a lower incidence of lymphedema compared to controls (16). Patient and family education on simple range of motion exercises is inexpensive and easily accessible. Ideally, it is recommended that primary care clinicians (a) should counsel survivors on how to prevent/reduce the risk of lymphedema, including weight loss for those who are overweight or obese (LOE = 0); and (b) should refer patients with clinical symptoms or swelling suggestive of lymphedema to a therapist knowledgeable about the diagnosis and treatment of lymphedema, such as a physical therapist, occupational therapist, or lymphedema specialist (LOE = 0). (8)

Women's Health Issues

Breast cancer survivors experience unique issues such as early menopause, body image, and sexual health. Early menopause may be a long-term treatment effect in LMIC as the majority of women receiving chemotherapy are premenopausal. Providers need to recognize the symptoms of early menopause and manage the patients accordingly (17-18). Furthermore, in LMIC

sociocultural factors need to be addressed, and the women need to be informed and counseled on contraception, early menopause, infertility, fertility preservation, and sexuality. In all settings, breast cancer survivors need to address body image issues that affect their sexual life after treatment. As providers, it is critical that we address these issues in a culturally sensitive and patient-centered way.

Lifestyle modifications

Lifestyle guidelines for breast cancer survivors in high-income countries may be adapted to LMIC settings (19-20). These lifestyle recommendations need to be tailored to the patient's comorbidities and physical performance status and, most importantly, need to be culturally, socially, and economically appropriate. Optimal nutrition to avoid obesity and weight gain as associated with hormonally sensitive breast cancer should be part of the strategy. Physical activity is associated with decreased breast cancer-specific and all-cause mortality. Recommended physical activity (e.g., 150 min/week of moderate-to-vigorous physical activity and resistance exercise at least twice a week) can be modified to accommodate community and cultural habits and conducted independently of the health care system (e.g., at home, with relatives, or friends, or in the community). General lifestyle recommendations for breast cancer survivors should follow general healthy living advice associated with chronic disease prevention, as breast cancer survivors are susceptible to chronic diseases (e.g., cardiovascular disease) and often die from them. Disease prevention aspects of care should not be ignored due to a history of cancer (21).

Other concerns beyond the scope of this chapter include bone health, cognitive impairment, cardiotoxicity, musculoskeletal health, pain, and neuropathy.

Breast cancer care is multidisciplinary and thus requires shared patient care records. As survivors transition from oncology-focused care to primary care or community-based care, a detailed diagnosis and treatment summary should follow the patient and include primary tumor biology, stage of disease, and sequence of given treatments. Recent literature reviews found that many primary care providers did not receive adequate documentation regarding a patient's diagnosis and treatment when the patient transitioned to their care (22). The interface between primary and oncology specialty care: treatment through survivorship is an important component of survivorship care (23). In HICs have identified treatment summaries as helpful and preferred information resources (24). Simple patient care documentation strategies include hospital discharge reports or outpatient treatment summaries. More advanced documentation can include treatment summaries and survivorship plans.

As patients in LMICs continue to have improved breast cancer survival rates, quality of life issues (25). The experiences and expectations of multiethnic women with breast cancer vary regarding post-treatment care and expectations (26). Survivorship care models need to be culturally and linguistically adapted to meet these diverse needs and the limited available resources.

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Chapter 36

Breast Cancer Staging

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Breast Cancer Staging

Assessment of the extent and biologic nature or "stage" of a cancer is the foundation of treatment planning and understanding the cancer's potential long-term outcome or prognosis. Staging systems are tools to record and communicate this information among providers and to people with cancer. These systems also are used to design clinical research studies of the treatment of similar cancers and to understand changes in cancer presentation and outcome for populations of people over time.

The TNM staging system, first proposed in the 1940s by Pierre Denoix, has been widely adopted and endorsed by the American Joint Committee on Cancer (AJCC) and the International Union of Cancer Control (UICC) as the foundation of cancer staging.[1] A TNM "Stage Group" is derived from information on the extent of the tumor (T), the involvement of regional lymph nodes (N) and the presence or absence of distant metastases (M). Because knowledge about cancer treatment and outcomes evolves over time, TNM staging undergoes periodic revision.

Revisions have occurred every 6 – 8 years. The most recent version of TNM stage is the 8th Edition released in 2016. [2-4]

The foundation of TNM staging is anatomic information on the tumor, regional lymph nodes and metastases. However, increasingly it is understood that the prognosis of a cancer and the impact of treatment is affected by measurable non-anatomic biological factors. Therefore, more recent revisions of TNM staging use key biologic factors as modifiers of anatomic data to define a stage group. Limited use of non-anatomic factors in stage determination dates back many decades. More recently, the use of non-anatomic factors in staging has expanded. The AJCC TMN 7th Edition prostate cancer staging effective in 2010 used prostate specific antigen (PSA) and Gleason's Score in addition to T, N and M to define stage groups[4]. In the most recent edition, the 8th Edition published in 2016, the AJCC included tumor grade and the expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 in breast cancer staging [3-4].

The inclusion of non-anatomic factors in staging has generated substantial debate and impacts the use of staging worldwide. For all situations where the AJCC has incorporated non-anatomic factors in staging, it starts with the anatomic T, N, and M and adds the non-anatomic factors as modifiers to define prognostic stage groups. Therefore, regardless of the ability to obtain non-anatomic biologic markers, the purely anatomic stage can be recorded on all cancers and be universally communicated to allow comparisons of cases from all settings irrespective of levels of resources.

Where the AJCC incorporates these to define stage groups, the UICC primarily considers these as "prognostic factors" to be used to complement anatomic stage groups to help clinicians and patients to define the prognosis of the cancer and its treatment. However, the UICC has long

recognized the importance of non-anatomic prognostic factors and has published a handbook of prognostic factors going back to 1995 that is now in its third edition.[5]

For breast cancer, the anatomic extent of the cancer remains a key feature impacting prognosis and treatment. However, breast cancer is a biologic heterogenous group of diseases with distinct behavior and response to treatment. The biologic subtypes of breast cancer are broadly defined by the expression of estrogen receptor, progesterone receptor and HER2. The most widely used classification consists of four molecular subtypes. Luminal A tumors are hormone receptor positive, HER2 negative, and lower grade. Luminal B tumors are hormone receptor positive and HER2 negative or positive but higher grade. Triple negative or basal-like are higher grade tumors that do not express any of the three receptors. HER2 enriched tumors typically also have a higher grade and do not express estrogen or progesterone receptors. Anatomic factors being equal, with surgery alone, patients with hormone receptor positive cancers have a distinctly better prognosis than those with estrogen negative disease.[6] The biologic subtype also dictates optimal adjuvant systemic therapy. Anti-estrogen endocrine therapy improves survival with hormone receptor positive cancers. In some cases, cytotoxic chemotherapy modestly improves survival for patients with estrogen positive disease over and above the impact of endocrine therapy. [7] It is even more effective for those with triple negative cancers and HER2 positive cancers.[8] Supplementing chemotherapy with anti-HER2 drugs in HER2 positive cancers dramatically improves prognosis.[9,10] Because of these differences in prognosis and the impact on the choice of treatment, the AJCC determined that these markers should be obtained on all invasive breast cancers whenever possible. Further, clear differences in survival among the breast cancer subtypes led the AJCC to add these markers to anatomic T, N,

and M to define stage groups. The AJCC also included tumor grade as defined by the modified Bloom-Scarf-Richardson or Nottingham grading system, in defining stage group.

These changes were based on the analysis of outcomes on large populations of patients. The analysis was performed with the American College of Surgeons National Cancer Data Base (NCDB). The NCDB includes cancer registry staging, biomarker, treatment, and survival data on about 1,000,000 people with cancer diagnosed annually in the United States. This is about 70% of all new cancers in the US. These analyses assign stage groups based on the survival of patients for different combinations of T and N, ER, PR, HER2 and grade.[4] All patients with metastases at diagnosis (M1) remain classified as Stage IV. Separate staging systems were created for clinical and pathological stage. "Clinical prognostic stage" is based solely on clinical information and "pathological prognostic stage" on clinical information plus surgical pathology findings. Table 1 shows a portion of the table for clinical prognostic staging. The full clinical and pathological prognostic stage tables are available along with the AJCC 8th Edition Breast Staging Chapter free of charge at https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx[4].

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

Table 1: Representative section of the table for AJCC 8th Edition Breast Cancer Clinical Prognostic Staging. The complete tables for clinical and pathological prognostic staging are available at https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx *3*

The complexity of these stage groupings makes it impossible to commit to memory and therefore the clinician must use the tables or a computerized stage calculator. The AJCC has licensed several vendors who produced mobile device apps available on app stores for iOS and Android devices and incorporated staging into electronic health record systems. Although the 8th edition staging scheme was developed with unpublished NCDB data, several studies have subsequently validated the accuracy of the staging system, addressing various ethnic groups, subtypes including HER2 positive disease, younger patients, and those with locally advanced breast cancer.[11-21]

Prognostic staging groups for a given T and N combination differ from stage groups assigned with the prior anatomic TNM system in a high proportion of patients. Figure 1 shows

the proportion of cases with stage group changes from the anatomic staging of the AJCC 7th Edition to the AJCC 8th Edition Prognostic Staging. The major changes were the downstaging (to a lower number stage group) of ER/PR positive and HER2 positive cancers; and the upstaging (to a higher number stage group) of triple negative cancers and those tumors with higher grade. This reflects the different impact of treatment on outcomes, especially with the use of trastuzumab and other anti-HER2 drugs with chemotherapy for HER2 positive cancers.

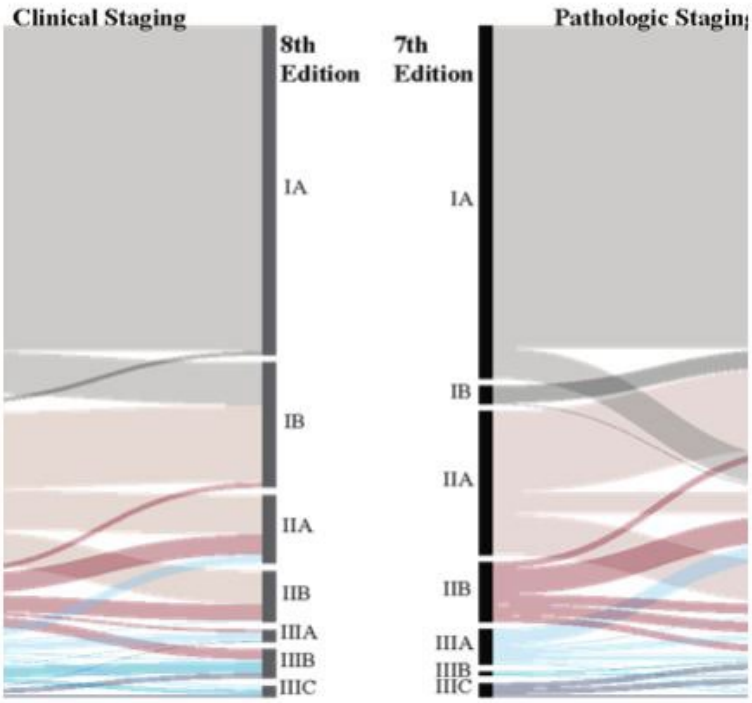

Figure 1: The figure depicts the changes in distribution of stage groups between the 7th and 8th Editions of the AJCC Staging Manual. The width of each bar or line depicts the frequency of that particular stage. Lines or bars that go from left (7th edition) to the right (8th edition) depict changes in stage distribution with stage ascending from top to bottom. Changes are shown separately for clinical staging and pathological staging. As an example, both clinical and pathologic Stage IB represent a small percentage.

Prognostic staging assumes that patients are offered appropriate systemic therapy based on the extent of disease and biologic sub-type – chemotherapy with anti-HER2 therapy for HER2 positive cancer, chemotherapy for triple negative cancer, and endocrine therapy with or without chemotherapy for hormone receptor positive cancer.

In the United States, it is expected that prognostic staging including ER, PR, HER2 and grade will be used in staging all invasive breast cancers. However, in many settings worldwide resources are limited and access to rapid pathological evaluation and assessment of biomarkers may not be available. Therefore, in these areas it may not be possible to determine the prognostic stage. Further, as discussed elsewhere in this book and in practice guidelines directed at regions with limited resources, more expensive drugs such as the trastuzumab and other anti-HER2 drugs may simply not be available. In lower resource regions when biomarker information is not available, stage group using only anatomic information should be assigned. The AJCC and UICC provide in their 8th Editions of TNM the table for stage groups based solely on T, N and M anatomic information termed "anatomic stage" (Table 2). These stage groups are unchanged from the AJCC 7th Edition but will likely evolve with future versions.

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Table 2: Anatomic Stage Group Table – AJCC 8th Edition Breast Cancer Staging: to be used in low and middle resourced regions where biomarkers are not readily available.[3]

Cancer care in resource limited regions is advancing, and the availability of pathology services and biomarker testing, and of lower cost HER2-directed drugs may improve. The prognostic stage reflects the prognosis of a cancer assuming appropriate therapy. However, even if biomarkers cannot be readily obtained, surgeons should recognize the potential value of commonly available endocrine and chemotherapy drugs for all breast cancer subtypes. Women with more advanced tumors especially should be considered for systemic therapy if at all possible.

Recording the anatomic extent of a cancer and staging is important in the care of breast cancer patients to plan therapy and communicate with other physicians and with patients. In addition, recording stage allows a cancer registry to collect information on large populations to help understand how cancer may present in a country or region. American registries collect the anatomic and prognostic information as discrete data elements (T – size in millimeters; N – number of positive nodes; grade; and status of ER, PR and HER2). The cancer registry system assigns prognostic stage. However, the discrete data in the registry can be used to assign anatomic stage group thus making possible worldwide comparisons. For regions in the world where ER, PR, HER2, and grade are not available, recording anatomic stage information is equally important. Anatomic information and stage group are the key factors used to determine both local and systemic therapy as discussed thoroughly in this book.

Clinical stage should be recorded on all patients based on history, physician examination and any imaging obtained to guide therapy. Note that no imaging is needed or required by AJCC or UICC to assign clinical T, N, and M and clinical stage group. The clinical stage may be the only stage available in all cases. Pathological stage should be recorded based on clinical findings supplemented by surgical findings. Recording T, N, M, and anatomic stage group and reporting

this information to a cancer registry are also critical for assessment of the patterns of breast cancer presentation and outcomes in a clinic, hospital, region or nation.

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Chapter 37

BI-RADS

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Keywords: BI-RADS, mammography, ultrasound, MRI, reporting, radiology, imaging

Case Scenario

A 50-year-old female patient with no past medical history presents to her primary care physician with a clinical complaint of a two-week history of a palpable lump in her right breast. She has no family history of breast cancer. She has never undergone screening mammography. On physical examination, there is a palpable lump in her right breast at 5 o'clock. There is no adenopathy on palpation of the right axilla. Diagnostic mammography (Case Figure 1) and ultrasound (Case Figure 2) were performed, which reported an assessment of BI-RADS 5. An axillary ultrasound was normal. The patient then underwent ultrasound-guided biopsy, yielding a pathologic diagnosis of grade 3 ER+, PR+, HER2+ invasive ductal carcinoma.

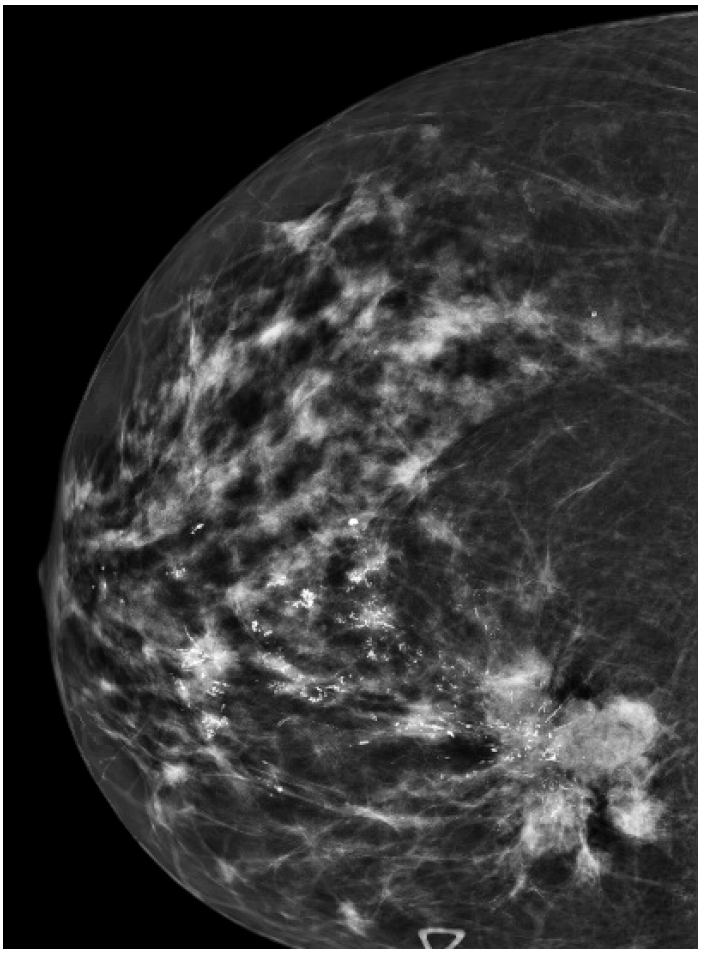

Figure 1: Right CC view full-field mammogram demonstrates an irregular high density mass with spiculated margins indicated by a triangular palpable marker. On this CC view, the mass can be seen in the medial breast at posterior depth. In addition, there are extensive segmental coarse heterogeneous microcalcifications involving nearly the entire medial breast.

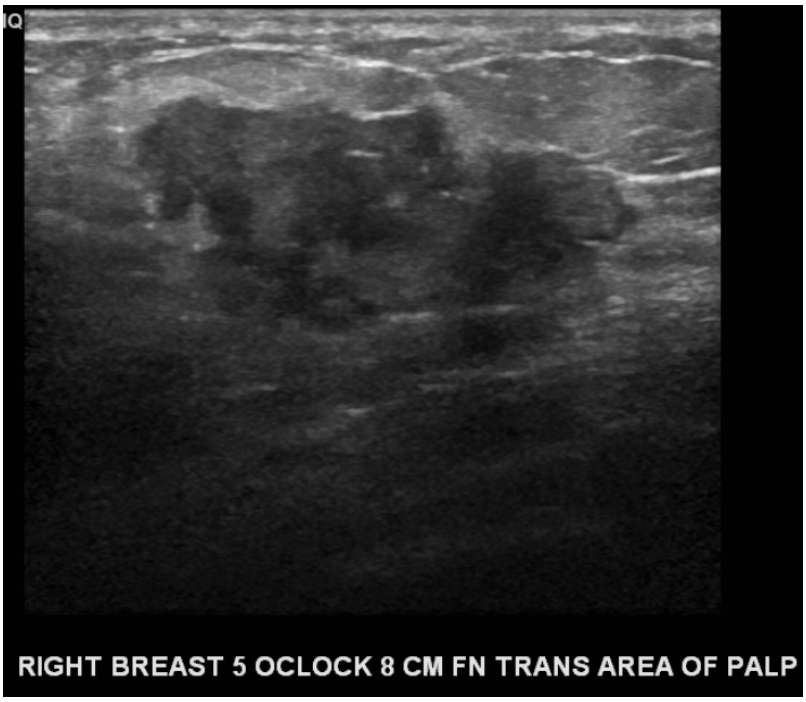

Figure 2: Grayscale B - mode ultrasound imaging in the transverse plane of the right breast at 5 o'clock 8 cm from the nipple taken during diagnostic evaluation demonstrates an irregular hypoechoic mass with microlobulated and angular margins. There are calcifications within the mass, also seen on concomitant mammography and malignant in etiology.

Introduction

Originally designed in 1993, the Breast Imaging Reporting and Data System (BI-RADS) atlas was developed to improve breast radiology descriptions for more clear and concise documentation. Since that time, several revisions have been issued, including additions from 1995, 1998, and 2003. The most recent revision to the BI-RADS atlas was issued in 2013. This chapter will present the BI-RADS assessments, recommendations, and terminology of breast lesions across imaging modalities. For more thorough description and classification, one should refer to the BI-RADS atlas in its entirety [1].

The main modalities of breast imaging are mammography and ultrasound. Both modalities have been used as screening (evaluating an asymptomatic patient population) and diagnostic (evaluating both asymptomatic patients with abnormal screening exams and symptomatic patients) tools. Magnetic resonance imaging (MRI), contrast-enhanced mammography (CEM), breast specific gamma imaging (BSGI), molecular breast imaging (MBI), and breast computed tomographic (CT) imaging are some of the advanced imaging tools utilized in breast evaluation. MRI is the most widely used of this cohort and is discussed thoroughly in the BI-RADS atlas; however, it may be unavailable in many countries due to cost and accessibility. A brief overview of MRI will be presented in this chapter [1].

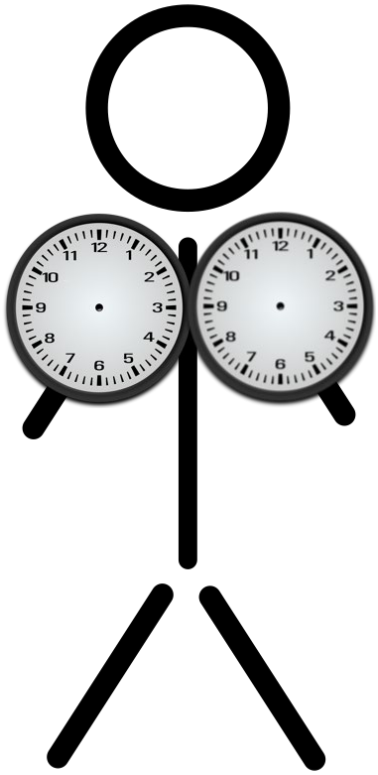

Figure 3: Stick figure with clock faces superimposed on the location of each breast, illustrating the appropriate location descriptions.

In addition to understanding the main modalities of breast imaging, lesion location descriptors are provided for standardization. Lesion locations in each breast are reported in terms of a standard clock-face position. The 12 o'clock and 6 o'clock locations in both breasts are superior and inferior, respectively. In the right breast, 9 o'clock is lateral and 3 o'clock medial. In the left breast 9 o'clock is medial and 3 o'clock is lateral. Figure 3 provides an illustration of a stick figure with the standard clock position of each breast. Quadrant locations are also utilized as descriptors, including the upper outer, upper inner, lower outer, and lower inner quadrants.

On mammography, the depth of a lesion is described in terms of anterior, middle, and posterior depth.

On ultrasound, lesions are more often described in terms of centimeters from nipple. The most common viewing protocol for mammograms directs the nipple of the right breast toward the left side of a screen or film, which is shown in Figures 4 and 5. The opposite holds true for the left breast [1].

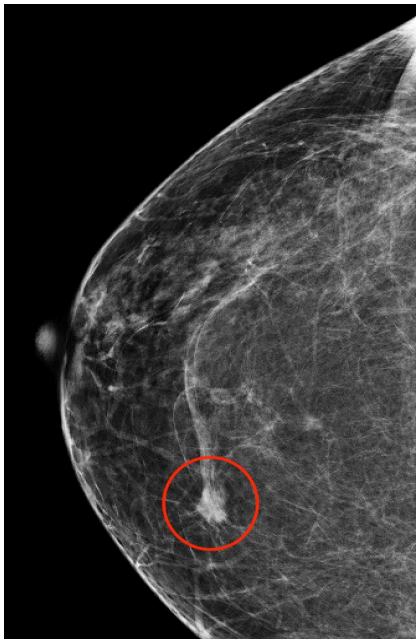

Figure 4. Right CC full - field 2 -D digital mammogram demonstrates an irregular mass in the right breast which appears in the medial breast and at middle depth on this CC view. With the MLO view, the finding can be seen in the 3 o'clock location. The assessment was BI-RADS 0:Additional imaging evaluation recommended.

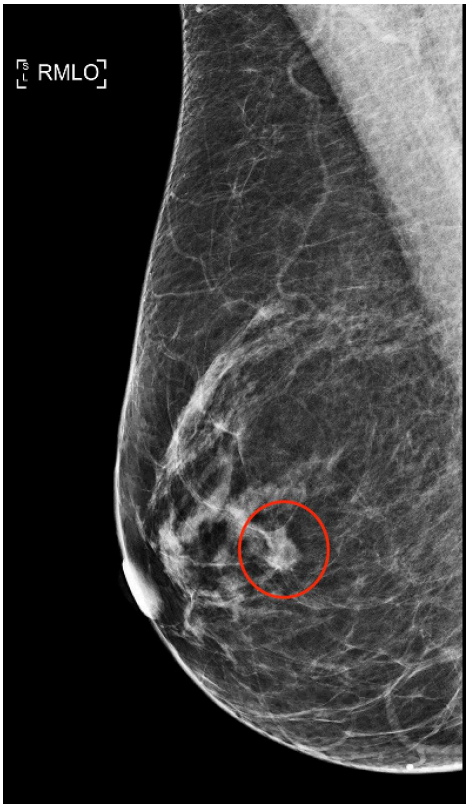

Figure 5: Right MLO full-field 2-D digital mammogram demonstrates an irregular mass in the right breast that appears at the nipple level on the MLO view. With the CC view, the finding is at the 3 o'clock location. The assessment was BI-RADS 0: Additional imaging evaluation recommended.

Assessment Categories

For each breast imaging study, the interpreter renders an overall assessment of the exam. Regardless of whether one or both breasts are imaged, a single assessment is made. Before

outlining the imaging findings, the assessment categories and their implications must be understood. The BI-RADS assessments range from 0-6. The hierarchy of abnormality in assessment categories is (from most abnormal to least abnormal) the following:

$$5 \rightarrow 4 \rightarrow 0 \rightarrow 6 \rightarrow 3 \rightarrow 2 \rightarrow 1$$

For example, if a patient has a mass in her right breast that appears very likely malignant and the left breast is normal, the right breast will have a BI-RADS 5 assessment, whereas the left would be assigned a category 1. The category 5, which is described in this chapter and carries the highest likelihood of malignancy, will trump the category 1 and will be reported as the overall assessment. Whether there are multiple findings, findings in both breasts, or a combination of benign-appearing and suspicious-appearing findings, each should be managed appropriately. Note that the assessment categories are separate from the recommendations on breast imaging reports. While they typically coincide (ie a BI-RADS 2, or benign, assessment will likely accompany a recommendation of continued screening), in a case where a patient has a palpable lump or a positive margin that is imaging-occult, an assessment of BI-RADS 2 may be concomitant with a recommendation for clinical evaluation or surgical excision, respectively [1].

a. BI-RADS 0: An assessment of ‘0’ means that the exam is incomplete and additional imaging is needed. This could be for various reasons, typically due to a need for additional mammography or ultrasound. Examples of the most common findings that are given a ‘0’ assessment include masses, asymmetries, architectural distortion, and calcifications. Figures 4 and 5 show an example of a screening mammogram with an irregular mass in the right breast at 3 o’clock middle depth assessed as BI-RADS 0 on screening mammography. Other reasons for which a ‘0’ assessment may be used include technical repeats or waiting for prior

exams (prior exams are not required for interpretation). This assessment is primarily given at the time of screening mammography to indicate a detrimental change since the prior exam or a questionable finding on a baseline mammogram. If this assessment is rendered before obtaining previous imaging exams and the prior exams (which provide evidence that the finding of interest shows long-term stability) arrive after a report is issued, an addendum is typically issued to indicate that no further imaging is needed. An assessment of '0' is not recommended for diagnostic mammography, ultrasound, or MRI [1].

b. BI-RADS 1: An assessment of '1' indicates that there is no finding of interest to address on the mammography exam, and the exam is read as negative. This assessment is given only if the exam has no specific descriptions. A '1' assessment should not be rendered if there are any findings in either breast that are described by the reader, even if such findings are benign. For example, one may choose to describe benign post-surgical changes in the right breast of a patient who underwent lumpectomy several years ago. Although describing these findings does not change the management recommendations, the assessment would no longer be a '1.' Annual screening mammography is the typical recommendation issued for such an assessment [1]. Figure 6 shows a mammogram that was assess as BI-RADS 1.

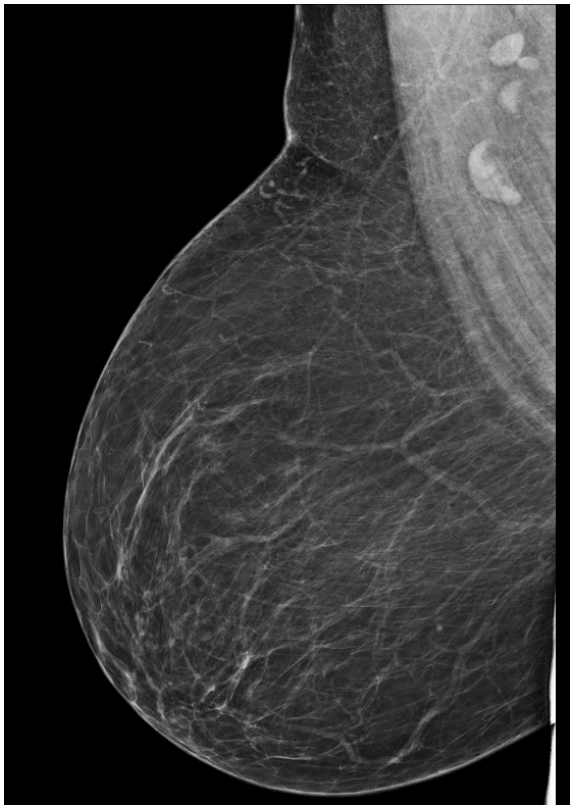

Figure 6: Right breast MLO view demonstrates normal fatty tissue. There is no finding to describe in this image. This is assessed as BI-RADS 1: Negative.

c. BI-RADS 2: An assessment of '2' means that the exam is benign. The difference between categories '1' and '2' is that with a category '2' there is a benign finding being described in the report. In diagnostic imaging cases, this is often assigned due to the need for explaining symptoms or describing previously reported findings. As discussed above, a '2' assessment may be rendered in cases where an actionable symptomatic or pathologic diagnosis (i.e. lump or positive margins) is nevertheless required. In this setting, the BI-RADS 2 assignment would be accompanied by a recommendation for the appropriate steps in managing the clinical issues [1]. Figure 7 is a CC-view mammogram in a patient who has undergone a lumpectomy. There is expected distortion (circle) and nipple retraction (arrow) from lumpectomy but no suspicious finding. This warranted a BI-RADS 2 assessment.

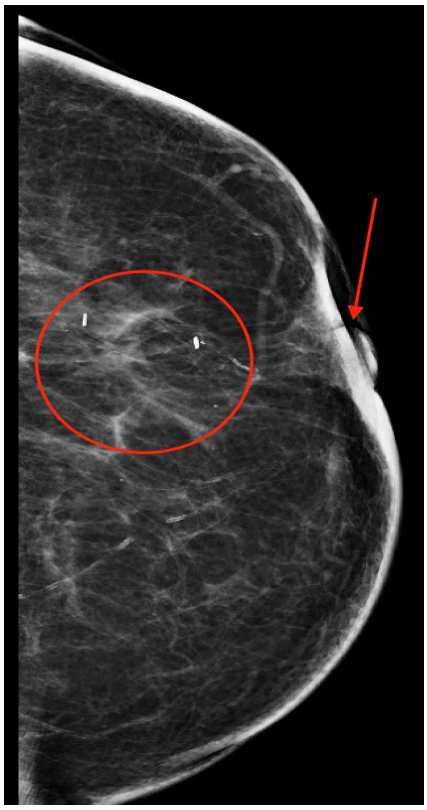

Figure 7: Left breast CC view mammogram demonstrates post-surgical changes of distortion with associated surgical clips(circle)and nipple retraction(arrow). This is expected surgical change, described in the report with an assessment of BI-RADS 2: Benign.

d. BI-RADS 3: This assessment, which is described as probably benign, should be less commonly assigned, and there are specific indications for its use. BI-RADS 3 is not recommended for use in screening mammography, only after complete diagnostic work-up. It is ideally used for baseline (first breast imaging exam ever performed) findings; however,

some unique situations combined with interpreter experience may appropriately warrant a probably benign read. Mammography, ultrasound, and MRI all have guidelines for appropriate utilization of a category '3' assignment. There have been numerous publications regarding this assessment for each modality, and mammography has the most robust data support for the current recommendations [1].

This exam category also has a specific time regimen for follow-up, typically with an initial short interval evaluation at 6 months. The second evaluation is then recommended 6 months later, which should coincide with the patient's bilateral mammography exam. At this time, if the finding of interest is unchanged, having been evaluated with specific imagine twice, stability will have been demonstrated for one full year. After stability is documented for one year, a final assessment is recommended one year later to prove two years of stability. This timeline for management is most accepted for mammography and ultrasound. The BI-RADS atlas discussion of BI-RADS 3 for MRI suggests a similar management strategy for this modality, recognizing the limitations of less literature available for guidance. Based on available data, a BI-RADS 3 assessment is thought to carry >0% but ≤ 2% likelihood of malignancy. A summary of the indications for use of BI-RADS 3 is detailed below.

Mammography [2]:

a. Nonpalpable, noncalcified, and circumscribed mass on a baseline exam with no suspicious features on additional mammographic imaging and no sonographic correlate (Figure 8)

b. Focal asymmetry (noncalcified, nonpalpable) on a baseline exam with no suspicious features on additional mammographic imaging and no sonographic correlation.

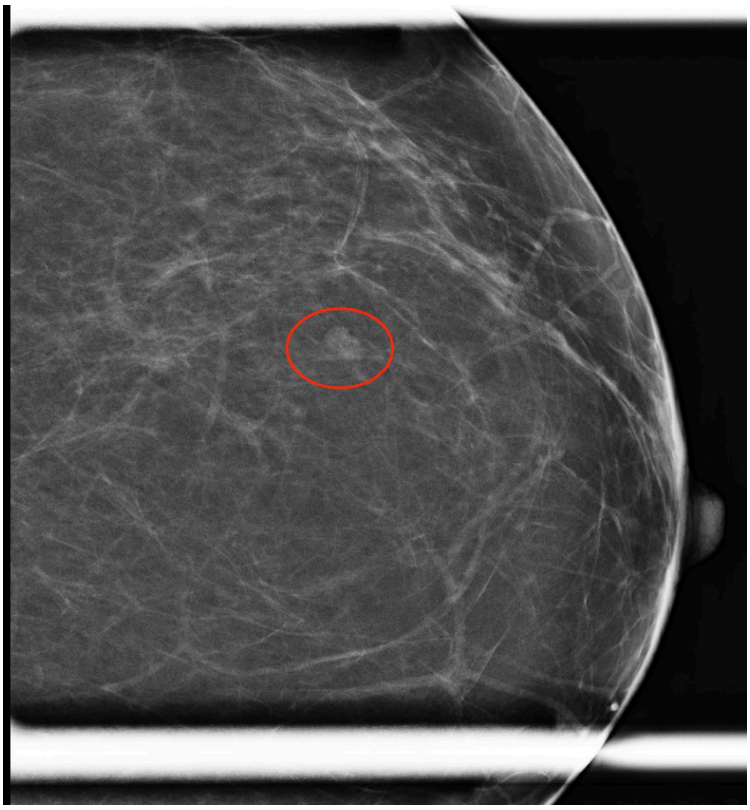

Figure 8: Spot compression left breast CC view demonstrates an isodense oval circumscribed mass. This was seen on a baseline mammogram and had no sonographic correlate. This was assessed as BI-RADS 3:Probably benign.

2. Solitary group of punctate calcifications on a baseline exam with no suspicious features on additional mammographic (magnification) imaging.

Ultrasound [3]:

a. A complicated cyst

b. An oval, circumscribed, parallel, hypoechoic mass with features of a fibroadenoma (Figure 9)

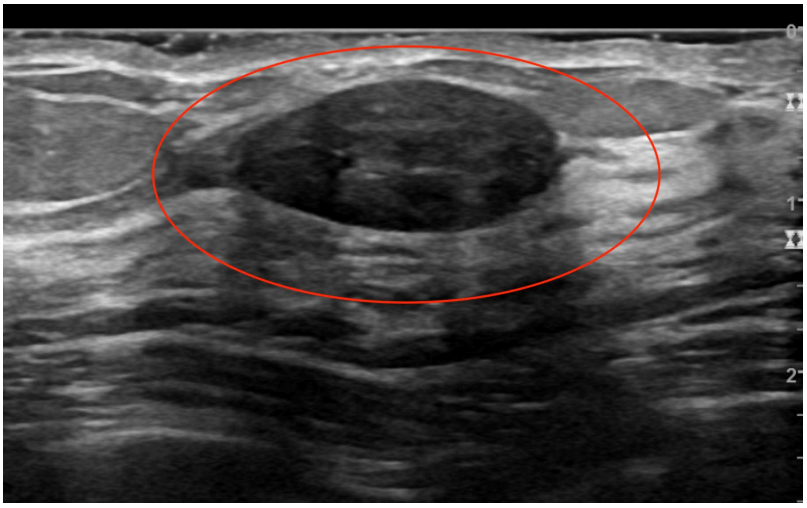

Figure 9: Targeted gray-scale B-mode ultrasound of the left breast at 12 o'clock 3 cm from nipple demonstrates an oval circumscribed parallel hypoechoic mass with posterior enhancement. The finding is most consistent with a fibroadenoma. This was seen in a 38-year-old female and was assessed as BI-RADS 3: Probably benign.

c. Clustered microcysts

d. Edge shadowing

e. Architectural distortion thought to represent post-surgical change

f. A hyperechoic mass thought to represent fat necrosis

MRI [4]:

a. New focus, similar in appearance to background parenchymal enhancement, but separate from the background breast tissue and showing benign features

b. Oval, circumscribed mass with benign features

e. BI-RADS 4: This assessment indicates that the finding is suspicious. In general, a suspicious assessment warrants tissue diagnosis, often with imaging-guided core-needle biopsy. When

no imaging-guidance is available for biopsy, close attention is needed to correlate the imaged finding of interest with the biopsied lesion. Category 4 is further subdivided to provide more specific guidance regarding the possibility of malignancy. In general, a category 4 involves lesions that have anywhere from >2% to <95% likelihood of malignancy. Since this range is broad, the subdivisions were created to provide management in cases where a patient may not benefit from tissue diagnosis. Reasons may include medical comorbidities, personal conflicts, or other circumstances [1].

i. BI-RADS 4a: The risk of malignancies in this subcategory ranges from >2% to ≤10%. This subcategory is called 'low suspicion' and examples may include solid masses with partially circumscribed margins, complicated cysts, or abscesses that may be atypical in appearance. Figure 10 demonstrates an oval hypoechoic mass that had somewhat heterogeneous internal echotexture, prompting biopsy. This was thought to likely represent a fibroadenoma, which was confirmed on pathologic exam.

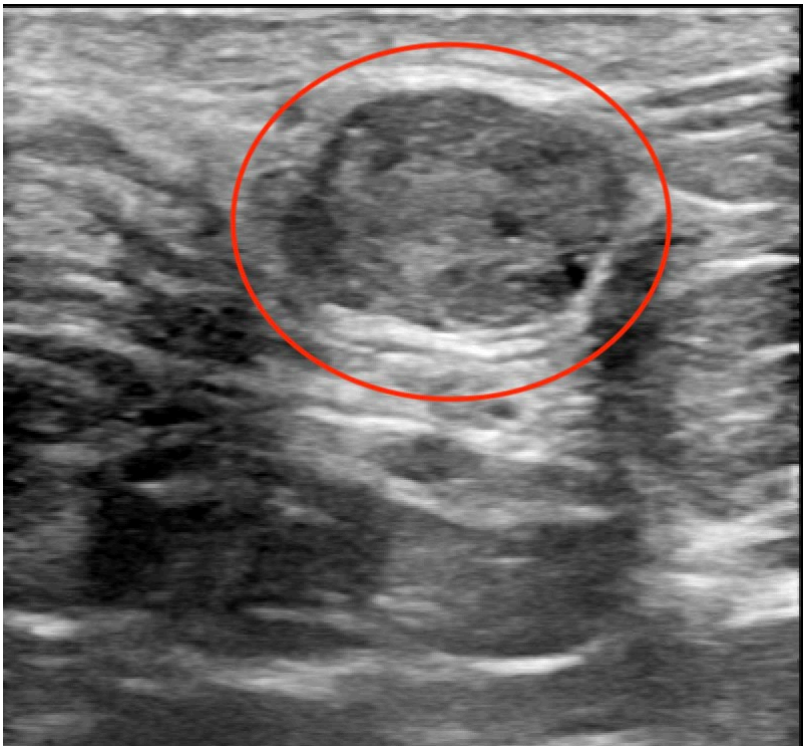

Figure 10: In the left breast at 3 o'clock 2 cm from the nipple, targeted gray-scale B-mode ultrasound shows an oval isoechoic parallel mass with circumscribed margins. This was newly palpable in a 47-year-old female. Although the imaging appearance was most suggestive of fibroadenoma, biopsy was performed for confirmation, yielding a fibroadenoma. The overall assessment was a BI-RADS 4a: Suspicious, low suspicion.

ii. BI-RADS 4b: The risk of malignancies in this subcategory, referred to as moderate suspicion, ranges from > 10% to ≤ 50%. Examples include solid masses with indistinct margins, grouped amorphous calcifications, or grouped fine pleomorphic calcifications. Amorphous calcifications outlined in red in Figure 11 were recommended for biopsy due to both morphology and distribution. Pathology reported low-grade ductal carcinoma in situ (DCIS).

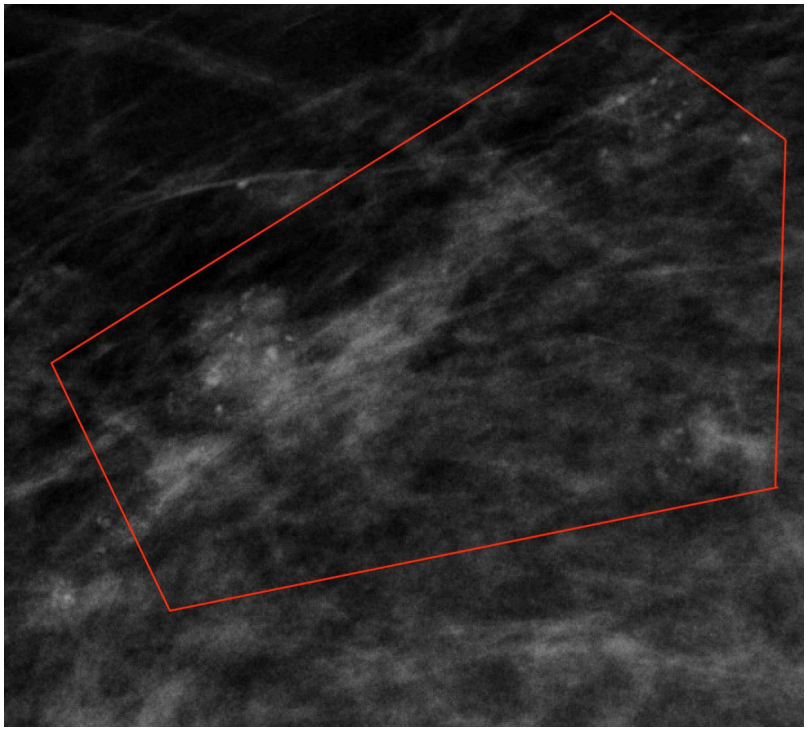

Figure 11: Magnification CC view of right breast in the upper outer quadrant middle depth demonstrates grouped amorphous microcalcifications. These were biopsied demonstrating DCIS. They were assessed as a BI-RADS category 4b: Suspicious, moderate suspicion.

iii. BI-RADS 4c: The risk of malignancies in this subcategory, termed high suspicion, ranges from >50% to <95%. Examples include irregular masses with non-circumscribed margins, fine pleomorphic calcifications in a segmental distribution, or fine linear branching calcifications. Figure 12 demonstrates magnification mammography depicting high-grade DCIS, manifesting as extensive fine linear branching and coarse heterogeneous microcalcifications.

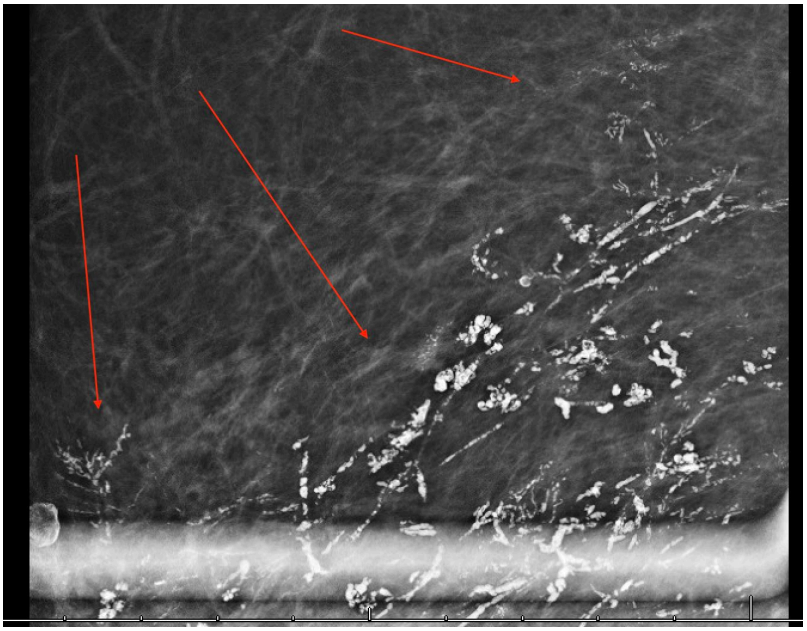

Figure 12: Magnification ML view of the right breast in the upper outer quadrant posterior depth demonstrates fine linear and coarse heterogeneous microcalcifications in a segmental distribution. Biopsy demonstrated high-grade DCIS. These were assessed as a BI-RADS category 4c: Suspicious, high suspicion.

f. BI-RADS 5: This particular BI-RADS assessment is only used in cases where malignancy is expected with ≥ 95% certainty. Since this assessment carries such a high likelihood of malignancy, typically there are multiple suspicious imaging characteristics needed to assign a category 5. In addition, because of the level of suspicion, any biopsy yielding a benign pathologic diagnosis is considered discordant and excision should ultimately be performed in most cases [1]. Figures 13 and 14 show a high-grade invasive ductal carcinoma that demonstrated worrisome features both on mammography (Figure 13) and sonography (Figure 14). Multiple suspicious characteristics of this mass combined to render an assessment of BI-RADS 5.

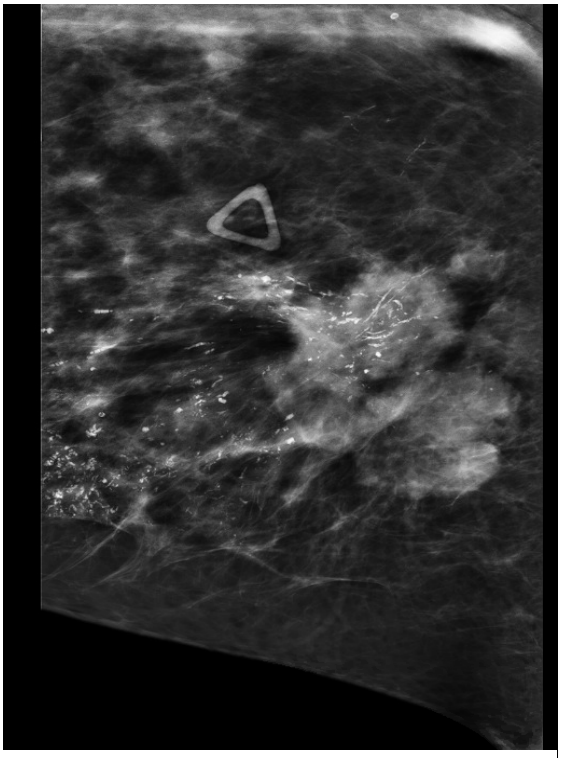

Figure 13: Right breast magnification view in the ML projection in the inferior breast at posterior depth demonstrates a high-density irregular mass with fine pleomorphic segmental microcalcifications. This mass was also palpable. This was assessed in conjunction with ultrasound as BI-RADS 5: Highly suggestive of malignancy. Pathology yielded high-grade invasive ductal carcinoma.

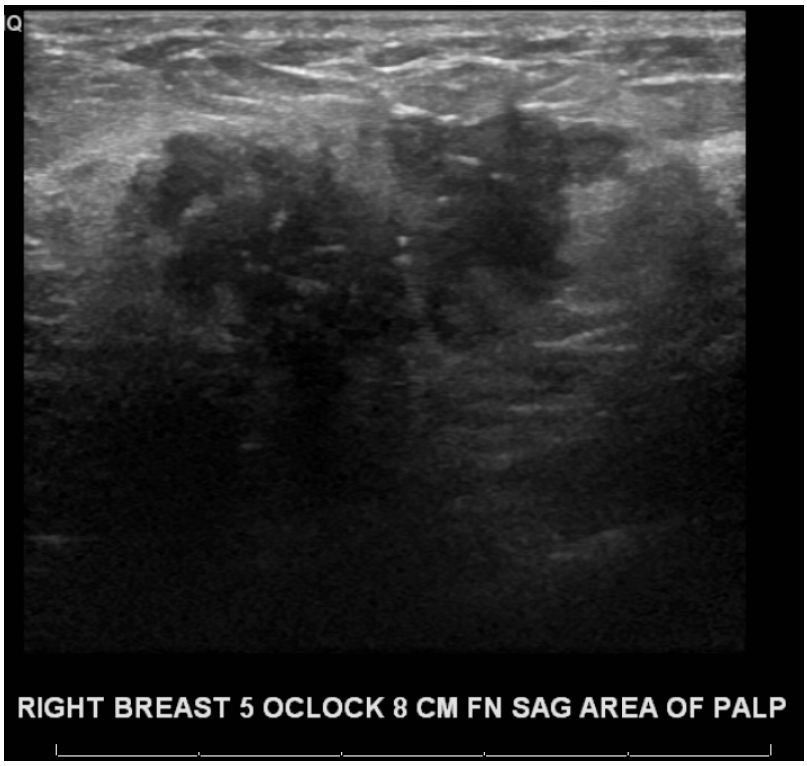

Figure 14: Right breast targeted B-mode grayscale ultrasound image of the 5 o'clock 8 cm from location in the area of palpable abnormality shows an irregular hypoechoic, not parallel mass with calcifications within the mass. Margins are microlobulated. There is posterior acoustic shadowing. This was seen in conjunction with the mammographic high-density irregular mass with fine pleomorphic segmental microcalcifications. This was assessed as BI-RADS 5: Highly suggestive of malignancy. Pathology yielded high-grade invasive ductal carcinoma.

g. BI-RADS 6: A category 6 assessment is reserved for cases in which a malignant diagnosis has already been rendered by tissue sampling. This category is also used in the setting of positive margins after excision; however, it is suggested that a '6' should indicate that there is an imaging finding to correlate with the malignant pathology. For example, a mammogram performed after excision of a malignant mass will show architectural distortion at the site of surgery, and microscopic positive margins are indistinguishable from normal surgical change. In such a situation, the overall assessment would be a BI-RADS 2 with a

recommendation for surgical excision due to positive margins. Alternatively, if a surgical excision is performed for microcalcifications, pathologically diagnosed as DCIS, and the post-excision mammogram demonstrates architectural distortion with residual microcalcifications, these would be appropriately reported as BI-RADS 6. The same method of evaluation is used for both ultrasound and MRI. If the imaging appearance is indeterminate, possibly residual disease, then the standard BI-RADS categories 4 and 5 should be utilized. The right CC view mammogram in Figure 15, which demonstrates two sites of previously biopsied malignancy (arrows indicating sites of biopsy clips), was assessed as BI-RADS 6.

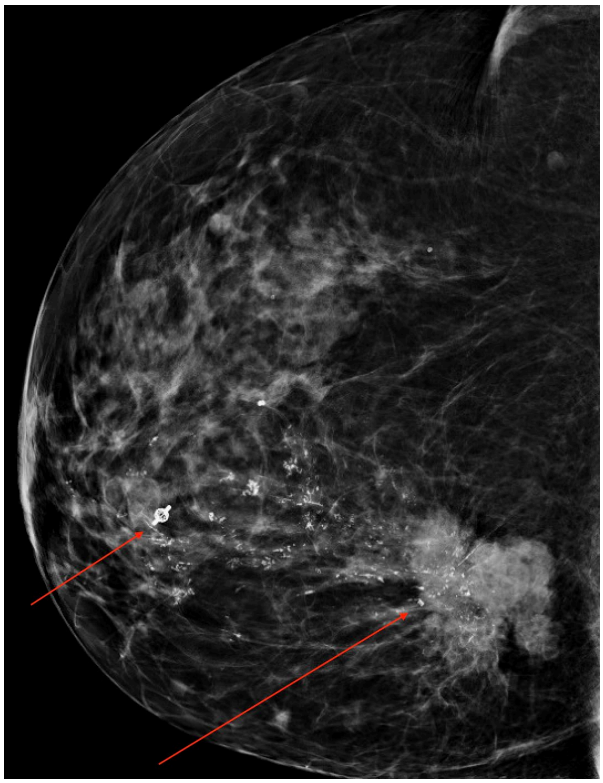

Figure 15: Right breast CC view of a patient with known multifocal breast cancer seen in follow-up after neoadjuvant chemotherapy. Clips can be seen both at posterior and anterior depth. This exam was assessed as BI-RADS 6: Biopsy-proven malignancy.

For a complete description of terms, one should refer to the BI-RADS atlas in its entirety [1]. This section will provide an overview of some of the more commonly used BI-RADS descriptors in mammography, ultrasound, and MRI.

Mammography

Breast tissue: There are four categories of breast composition, ranging from fatty to very dense. As density increases, not only does cancer detection become more difficult, but the risk of developing breast cancer also increases. The category divisions are as follows: breasts are almost entirely fatty (Figure 16), there are scattered areas of fibroglandular density (Figure 17), breasts are heterogeneously dense (Figure 18), and breasts are extremely dense (Figure 19) [2].

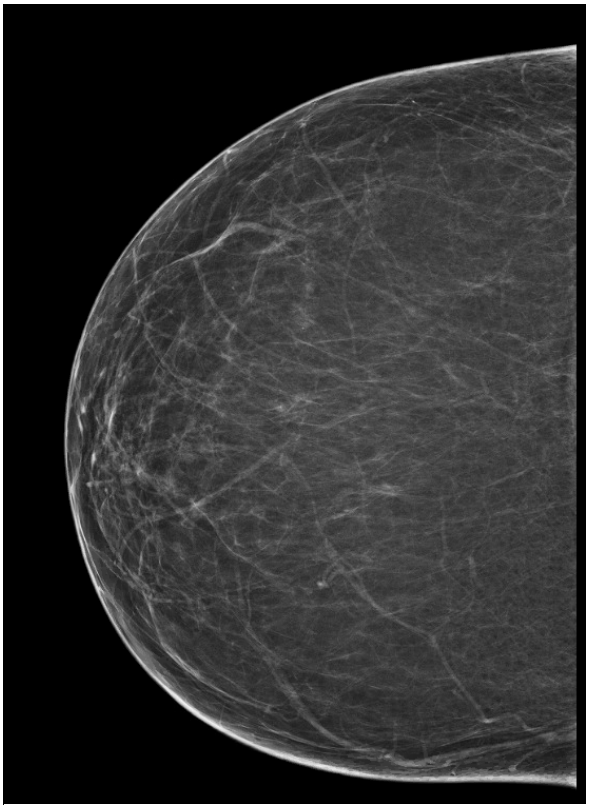

Figure 16: Right breast full-field CC view mammogram demonstrating breasts that are almost entirely fatty.

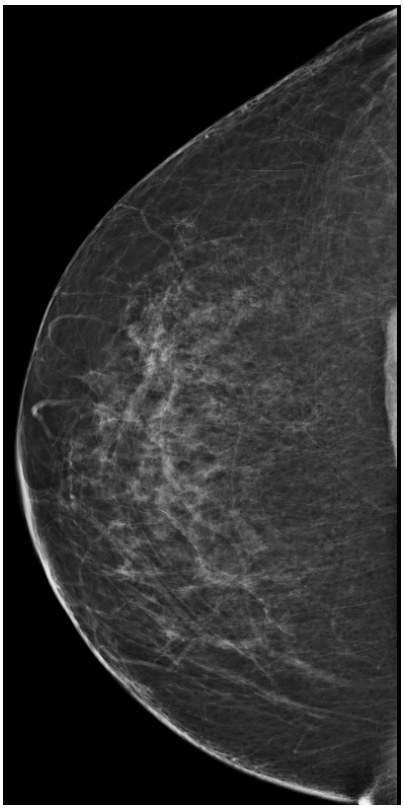

Figure 17: Right breast full-field CC view mammogram demonstrating breasts with scattered areas of fibroglandular density.

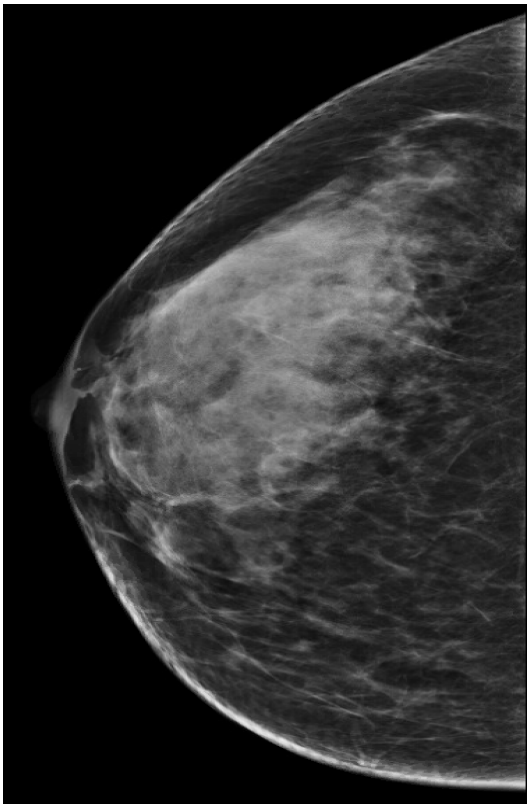

Figure 18: Right breast full-field CC view mammogram demonstrating breasts that are heterogeneously dense.

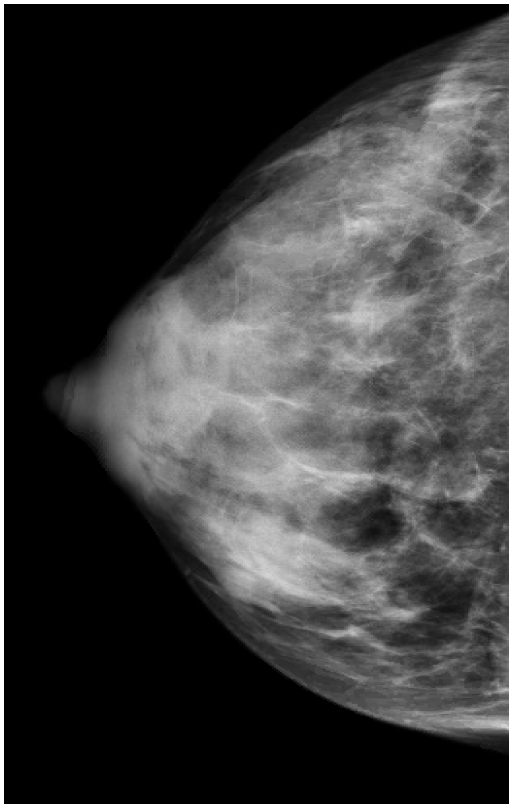

Figure 19: Right breast full-field CC view mammogram demonstrating breasts that are extremely dense.

Findings: Masses are 3-dimensional objects and should be seen in at least two mammographic views. They have convex-outward borders. They are described in terms of shape (oval, round, irregular), margin (circumscribed, obscured, microlobulated, indistinct, spiculated), and density (high, equal, low, fat-containing). Figure 20 depicts the LM view of an irregular high-density mass.

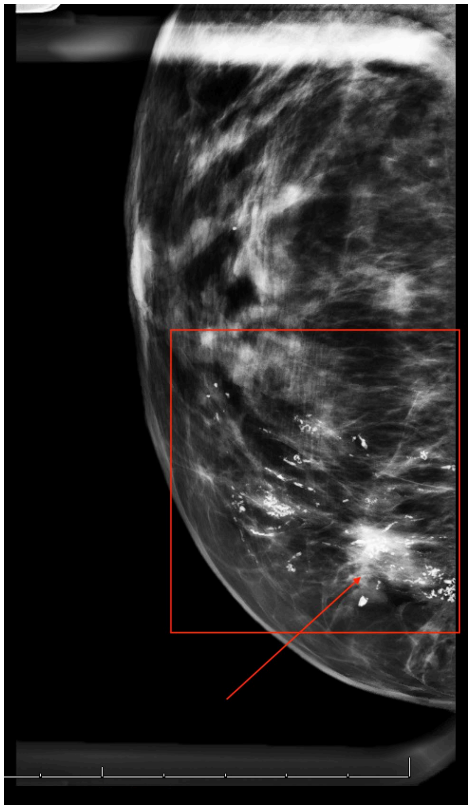

Figure 20: Spot magnification view of the right anterior breast in the LM projection demonstrates coarse heterogeneous segmental microcalcifications extending toward the nipple(rectangle). An irregular mass can be seen posteriorly (arrow). Pathology demonstrated high-grade DCIS.

Asymmetries are differences in an area of tissue in one breast compared to the other. They are classified in terms of the amount of the breast involved and views in which the finding is seen. An asymmetry is a one-view finding and a focal asymmetry is a two-view finding. A global asymmetry is a difference in overall appearance of one breast from the other (typically considered a benign variant if found at baseline but possibly malignant if new), and a developing asymmetry is a focal asymmetry that is detrimentally changing or new from previous exams (Figures 21, 22, and 23).

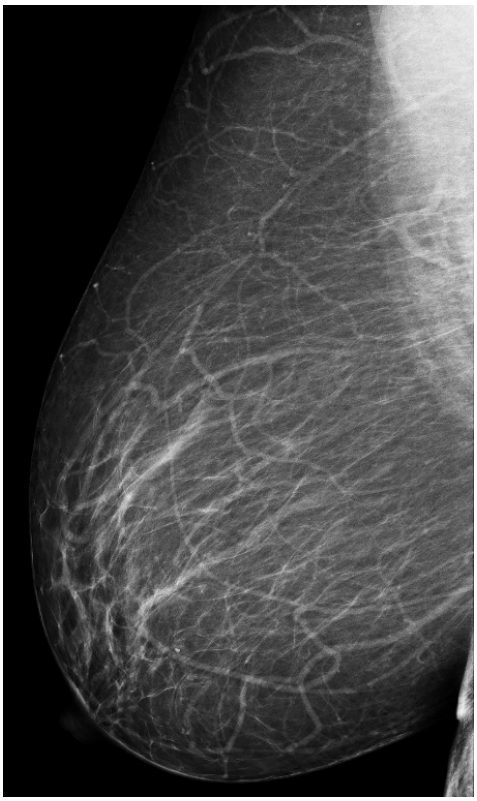

Figure 21: Right full-field MLO view screening mammogram (2 years prior) demonstrates no suspicious mass, microcalcification, distortion, or asymmetry. The retromammary fat is normal.

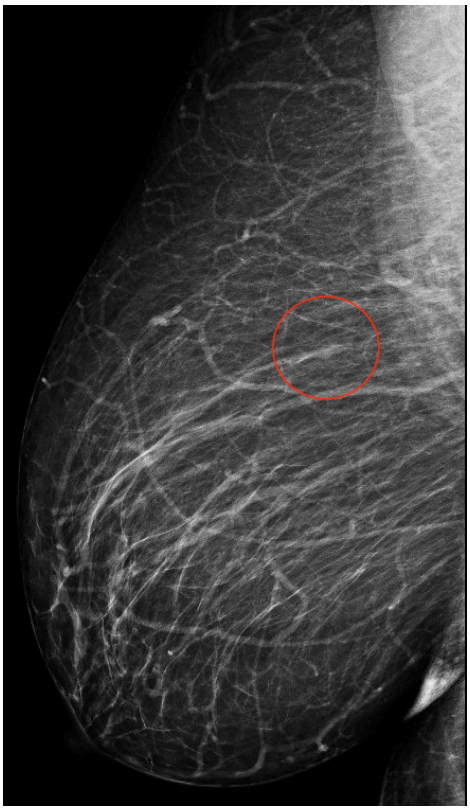

Figure 22: Right full-field MLO view screening mammogram (1 year prior)demonstrates a very subtle focal asymmetry (CC view not shown)in the upper outer quadrant of the right breast at posterior depth in the retromammary fat.

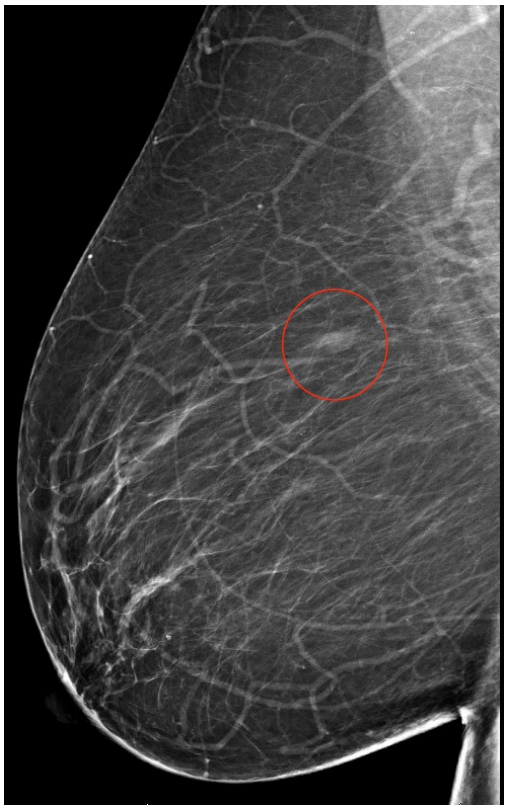

Figure 23: Right full-field MLO view screening mammogram (current)demonstrates a now more conspicuous focal asymmetry (CC view not shown) in the upper outer quadrant of the right breast at posterior depth in the retromammary fat. This lesion can be described as a 'developing asymmetry.'

Calcifications are described in terms of benign-appearing and suspicious-appearing. Benign calcium includes the following: skin, vascular, "popcorn" or coarse, large rod-like, round, rim, dystrophic, milk of calcium, and sutural. Suspicious calcium includes the following four descriptors: amorphous, coarse heterogeneous, fine pleomorphic, and fine linear or fine-linear branching. The distribution of calcifications is described (from lowest to highest likelihood of malignancy) as diffuse, regional, grouped, linear, and segmental. Associated features are also included as mammographic descriptors. These include skin or nipple retraction, skin or

trabecular thickening, axillary adenopathy, and architectural distortion. Figures 20-44 are mammographic examples of the more common BI-RADS descriptors for this section [2].

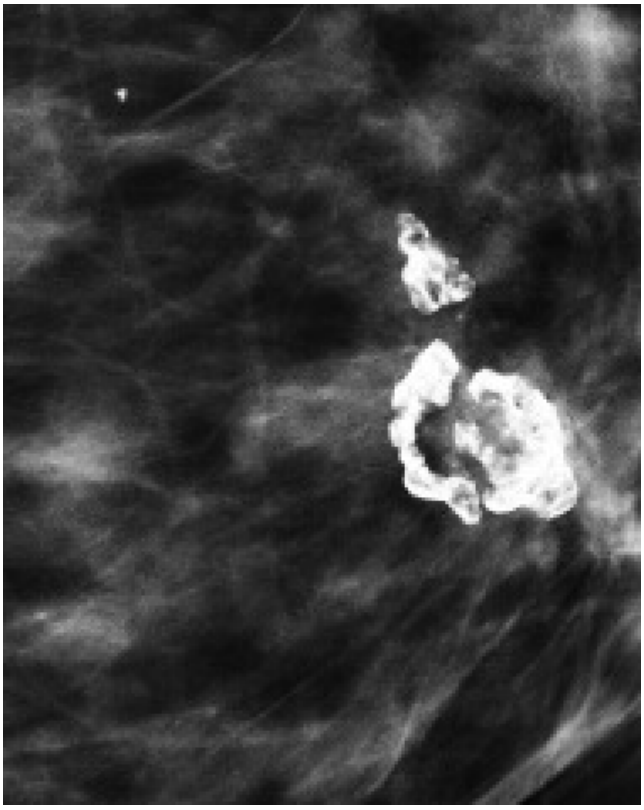

Figure 24: Spot magnification CC view of the right breast demonstrates typical dystrophic calcifications in a grouped distribution. These are larger than 1 mm in size and are often the result of surgery or trauma. They may exhibit a central lucency.

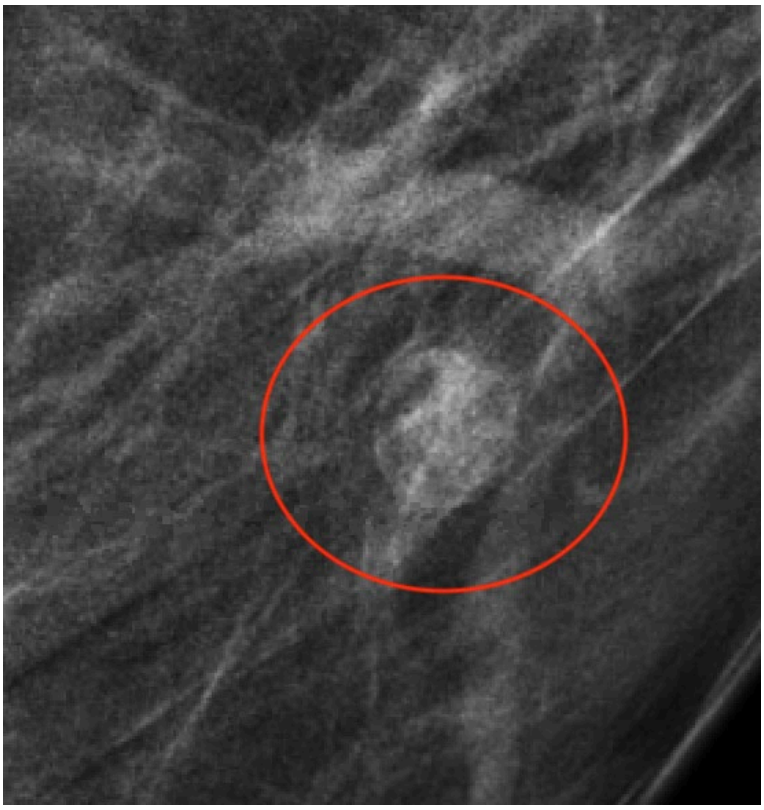

Figure 25: Spot magnification CC view of the right breast demonstrates typical rim calcification. These are smaller than 1 mm in size and are also referred to as oil cysts.

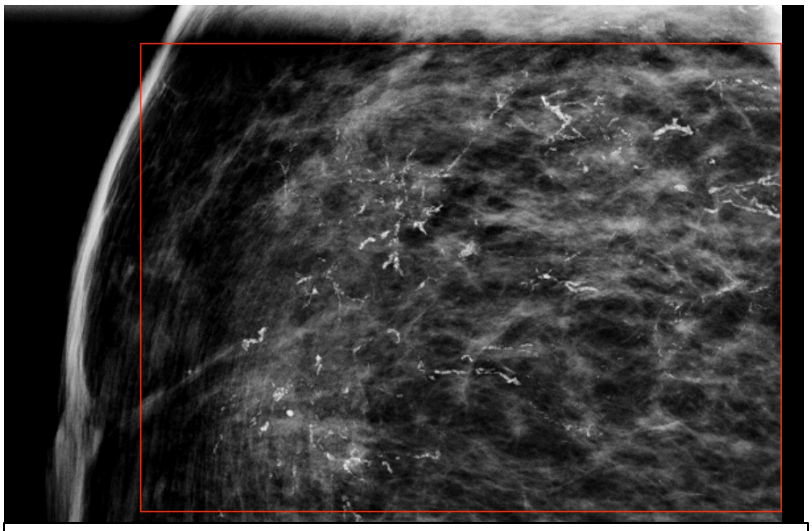

Figure 26: Spot magnification CC view of the right breast demonstrates fine linear and fine linear branching microcalcifications in a sentimental distribution. These are suspicious and have the highest positive predictive value of all microcalcifications. They are less than 0.5 mm in size. Pathology demonstrated high-grade DCIS.

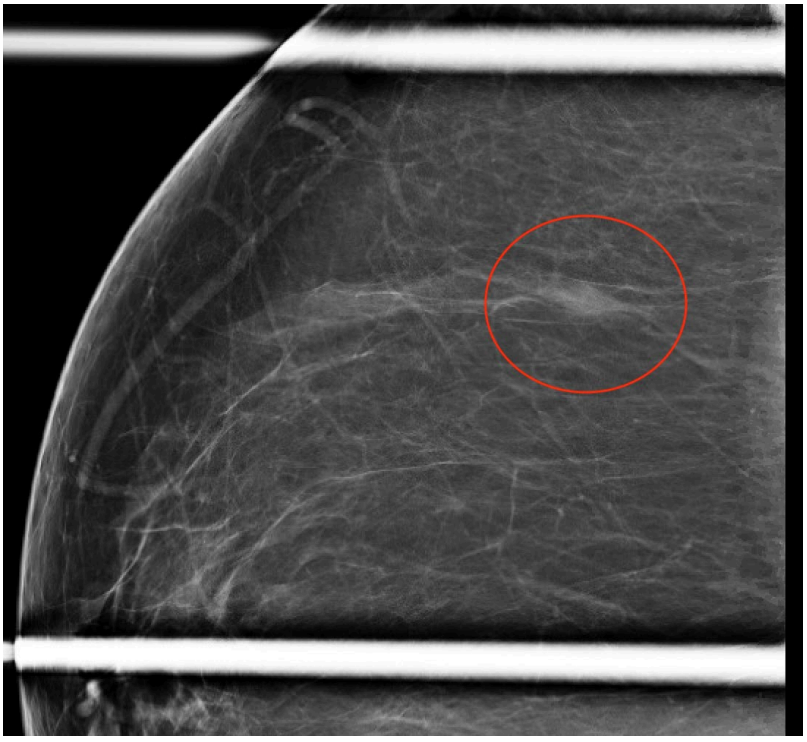

Figure 27: Spot view of the right breast in the CC projection demonstrates a focal symmetry (MLO view is not provided) that persists with spot compression. This proved to be a low-grade invasive ductal carcinoma.

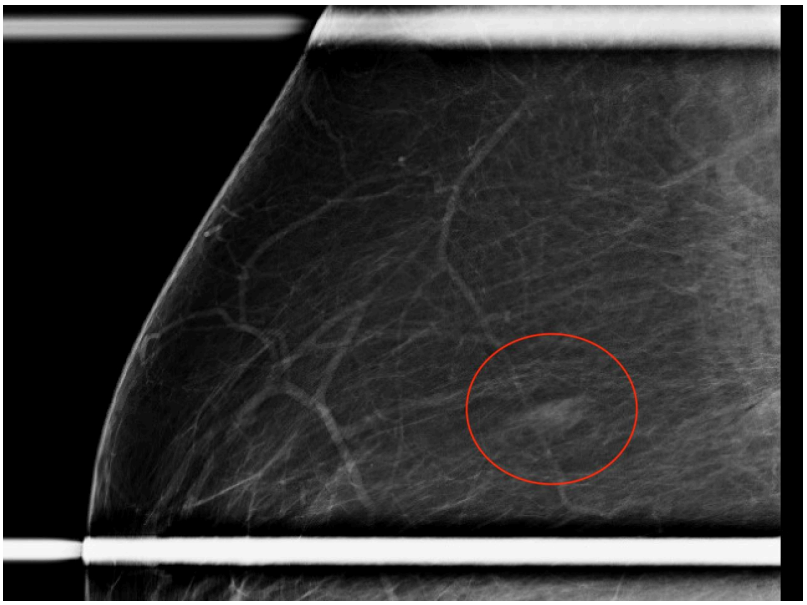

Figure 28: Spot view of the right breast in the MLO projection demonstrates a focal symmetry (CC view is not provided) that persists with spot compression. This proved to be a low-grade invasive ductal carcinoma.

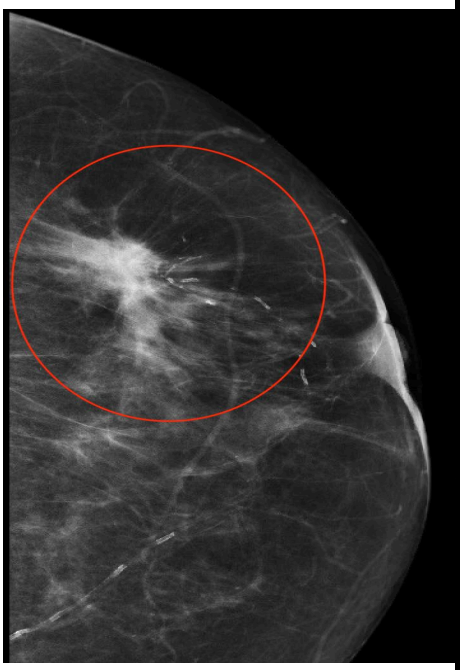

Figure 29: Left breast CC view mammogram demonstrates a high-density irregular mass with spiculated margins in the upper outer quadrant (MLO view not provided) at middle depth. Pathology demonstrated invasive ductal carcinoma grade 2.

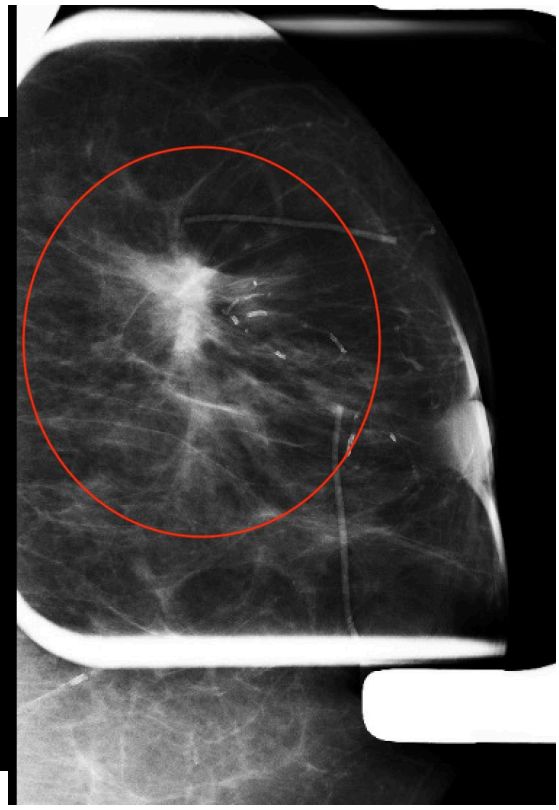

Figure 30: Left breast spot CC view mammogram demonstrates a high-density irregular mass with spiculated margins in the upper outer quadrant (MLO view not provided) at middle depth. Pathology demonstrated invasive ductal carcinoma grade 2.

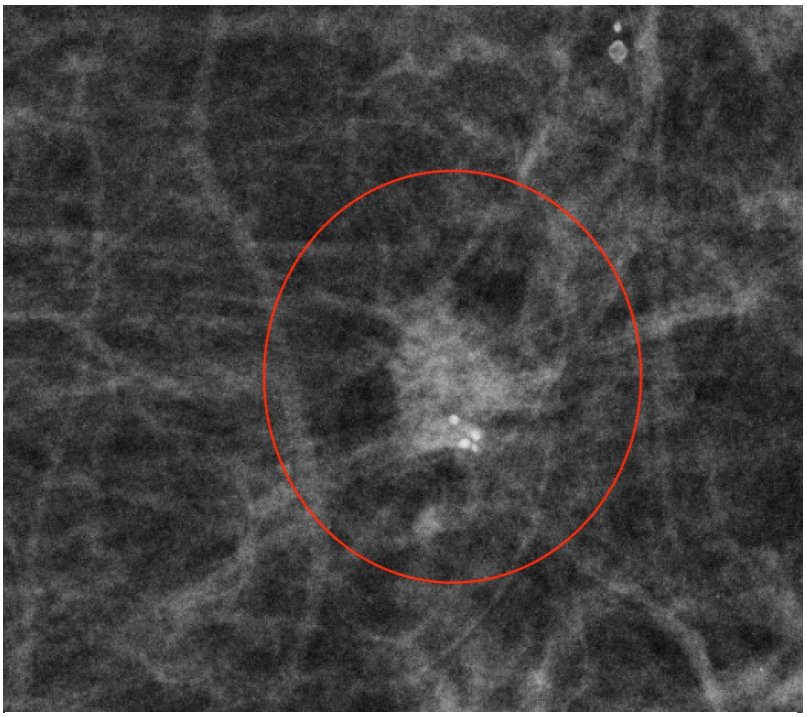

Figure 31: Spot compression view of the left breast in the CC projection demonstrates an isodense mass with indistinct margins. This was ultimately biopsied demonstrating grade 1 invasive ductal carcinoma.

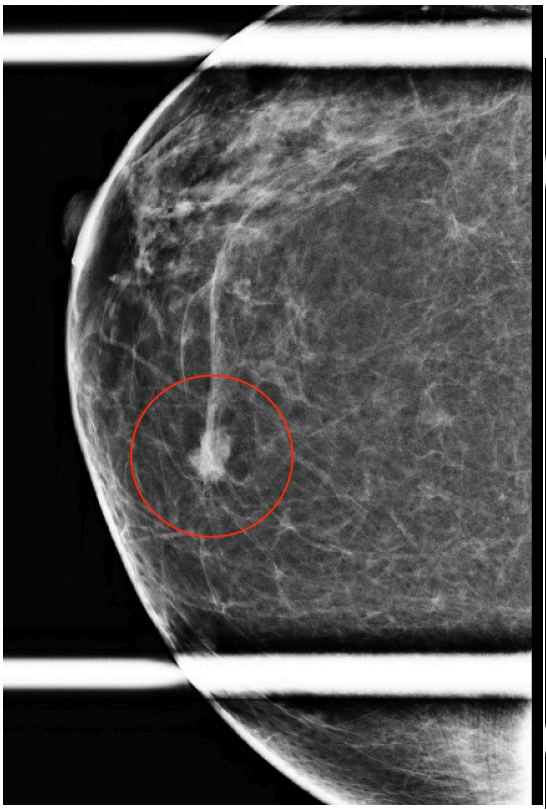

Figure 32: Spot compression CC view of the right breast demonstrates a high-density mass with microlobulated margins. This was noted in the upper inner quadrant middle depth. Pathology showed intermediate grade invasive ductal carcinoma.

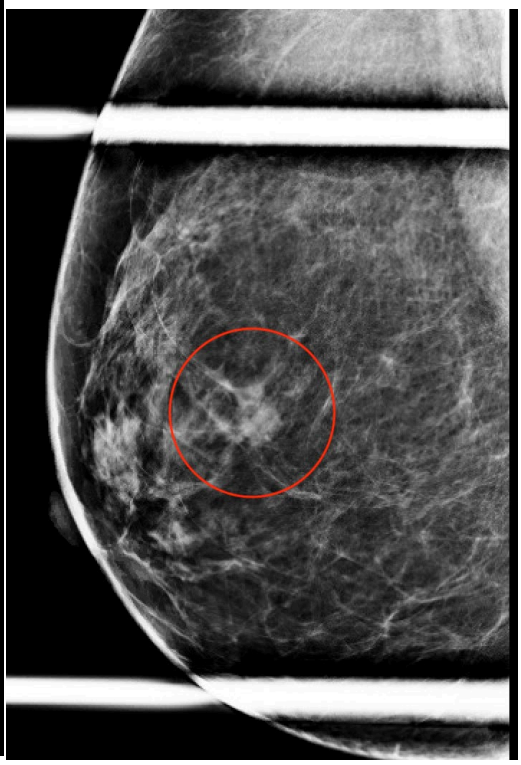

Figure 33: Spot compression MLO view of the right breast demonstrates a high-density mass with microlobulated margins. This was noted in the upper inner quadrant middle depth. Pathology showed intermediate grade invasive ductal carcinoma.

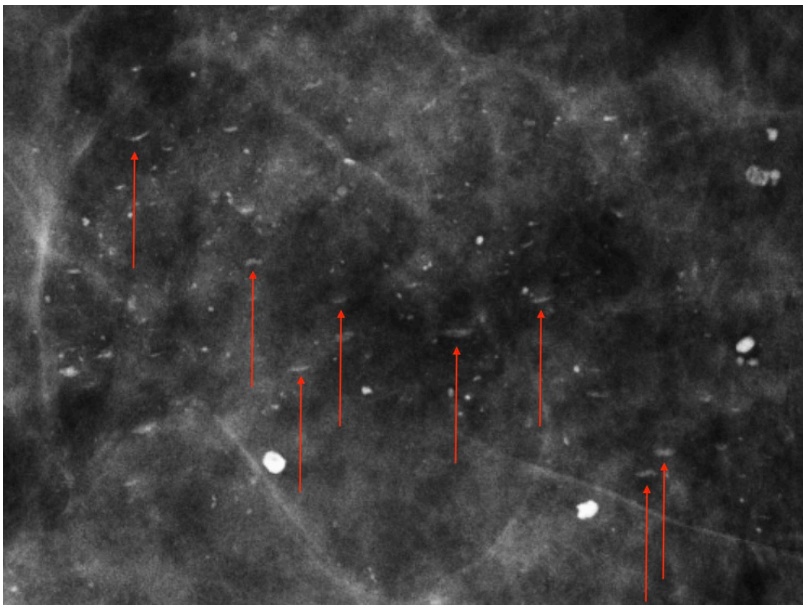

Figure 34: Magnification ML view of the right breast demonstrates the typical “layering” appearance of microcalcifications consistent with milk of calcium. These show a crescentic appearance.

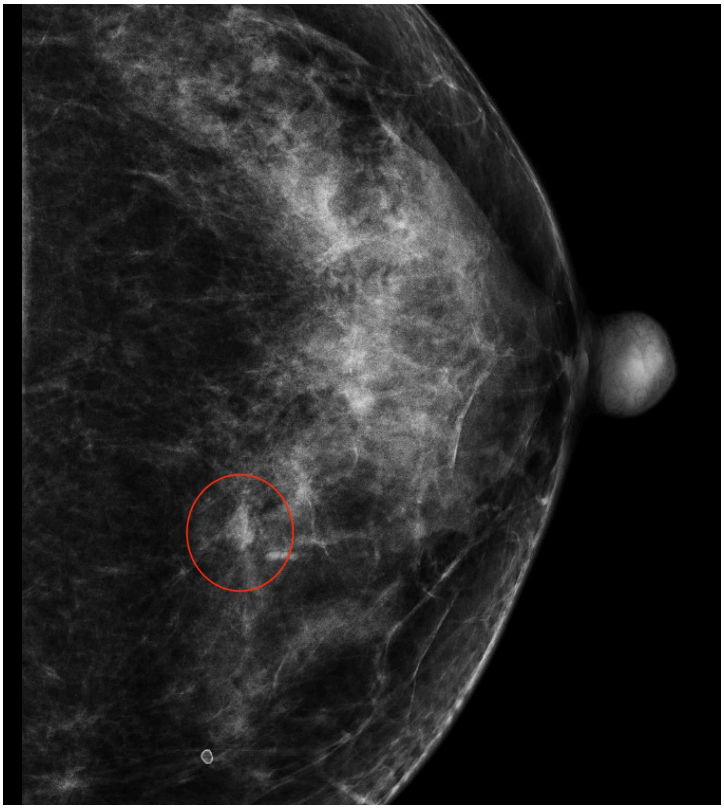

Figure 35: Left CC mammogram shows an irregular mass in the medial breast (in the lower inner quadrant with ML view not provided). Margins are obscured. This was a tubular carcinoma.

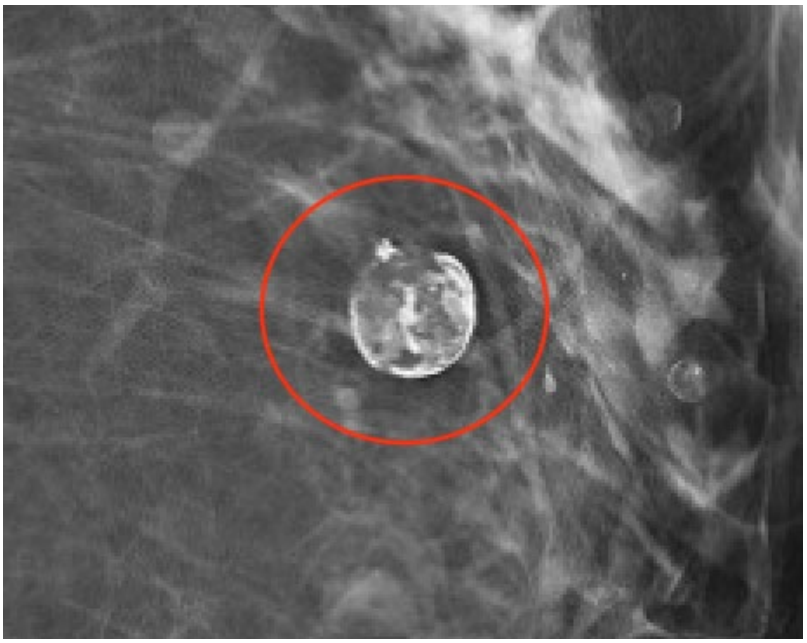

Figure 36: ML magnification view in the left breast demonstrates a rim calcification. This is consistent with a benign oil cyst.

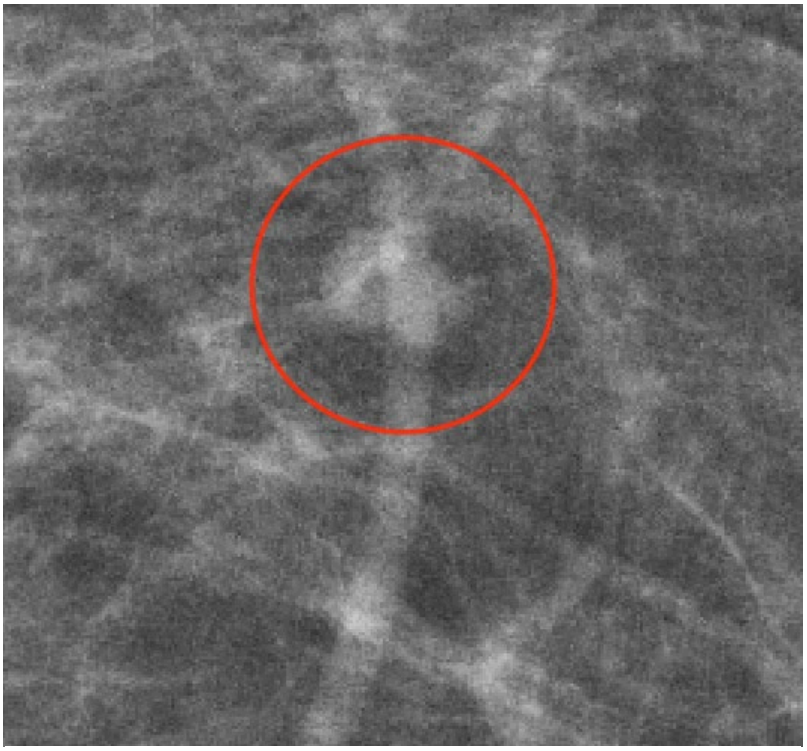

Figure 37: CC spot compression view left breast demonstrates an equal density oval mass with central fat. Margins are circumscribed. This is an intramammary lymph node.

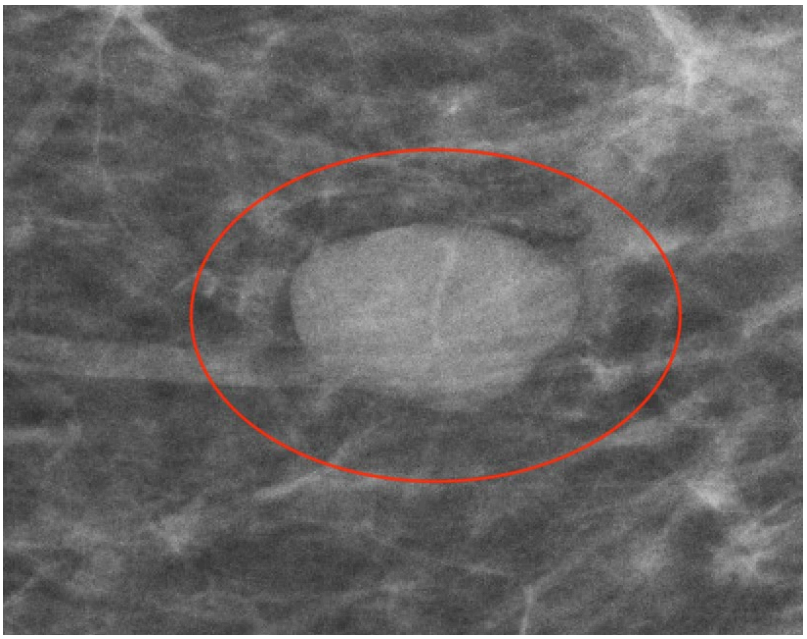

Figure 38: CC spot compression view left breast demonstrates an equal density oval mass. Margins are circumscribed. This is a benign simple cyst.

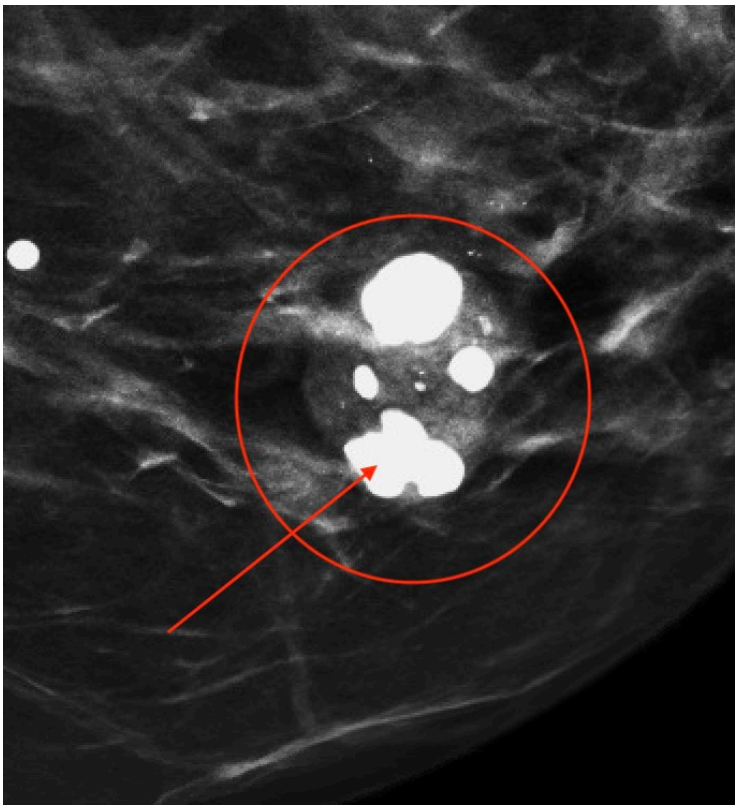

Figure 39: ML view of the left breast demonstrates popcorn-like calcifications. These are greater than 2-3mm in size. These are typical of fibroadenomas, characteristically benign.

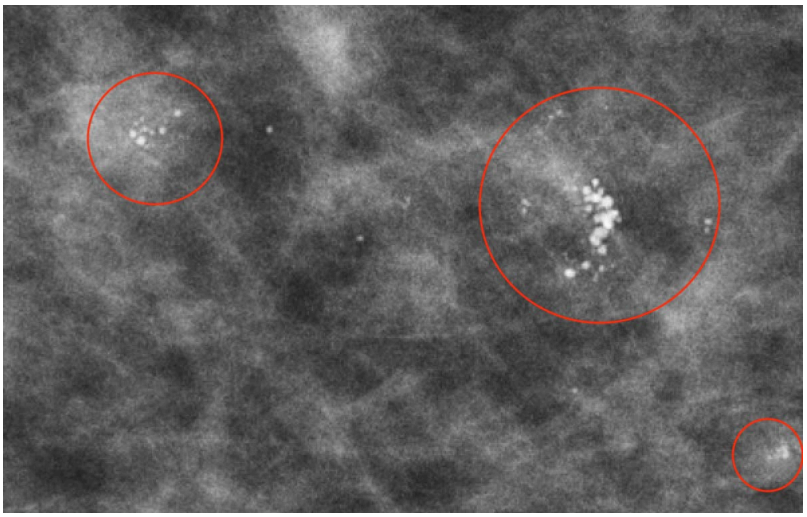

Figure 40: Magnification ML view of the right breast demonstrates grouped round and punctate microcalcifications. These are less than 1 mm in size when described as round; however, they are called punctate when smaller than 0.5 mm in size. These were stable and benign.

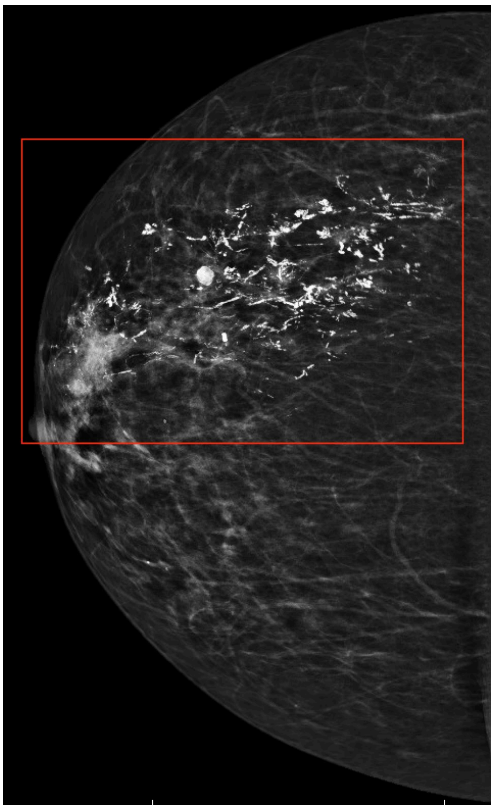

Figure 41: Right breast CC full-field mammogram demonstrates coarse heterogeneous, fine pleomorphic, and fine linear branching microcalcifications throughout the right breast. These are in a segmental distribution. Pathology showed DCIS, intermediate grade with comedonecrosis.

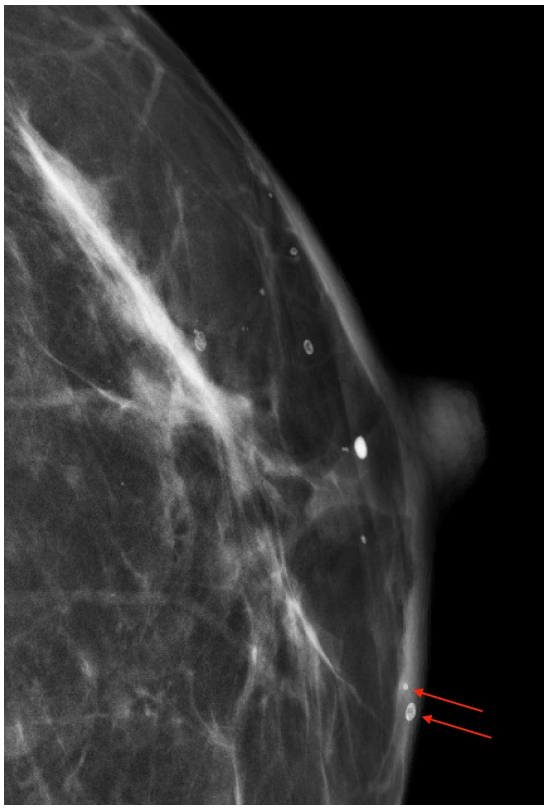

Figure 42: Left breast magnification, CC view demonstrates skin calcifications regionally distributed throughout the anterior breast along the areola. These often have lucent centers and are less than 5mm in size. These are benign.

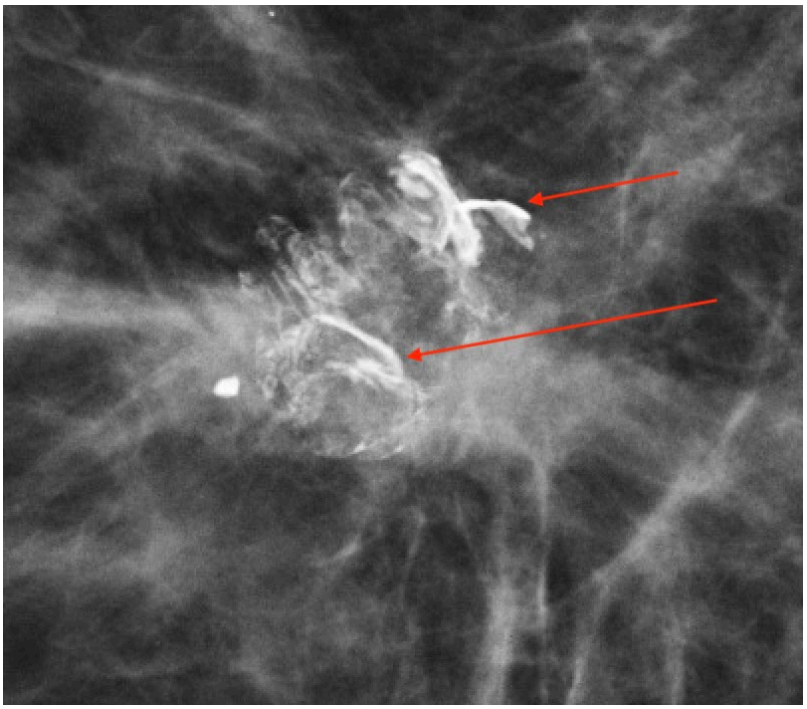

Figure 43: Spot magnification view of the right breast in the ML projection demonstrates dystrophic microcalcifications at the site of a lumpectomy bed. Sutural calcification involves a portion of this (arrows).

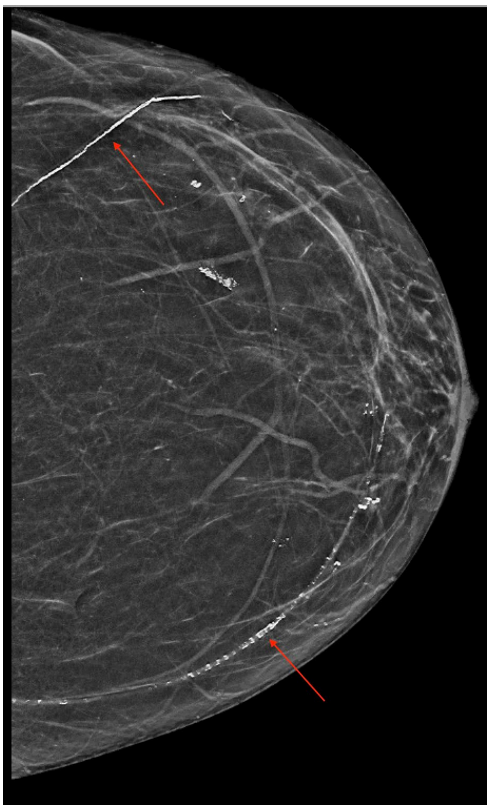

Figure 44: Left breast 2-D synthesized view (from a tomosynthesis exam) demonstrates the typical vascular calcifications

Ultrasound

Breast tissue: Composition of breast tissue on ultrasound is divided into the following three categories: homogeneous background echotexture of fat, homogeneous background echotexture of fibroglandular tissue, and heterogeneous background echotexture [3].

Findings: Masses on ultrasound, just as in mammography, occupy a volume of space and are seen in multiple planes whether with 2-dimensional or 3-dimensional ultrasound. Masses are described in terms of shape (oval, round, irregular), orientation (parallel or not parallel), margin (circumscribed vs. not circumscribed, which includes indistinct, angular, microlobulated, or

spiculated margins), echo pattern (anechoic, hyperechoic, complex cystic solid, hypoechoic, isoechoic, and heterogeneous), and posterior features (none, enhancement, shadowing, combined). Calcifications are less conspicuous on ultrasound than on mammography; however, when visualized, the descriptions include the following: calcifications in or outside of a mass and intraductal calcifications. The associated features seen on sonography include architectural distortion, duct changes, skin changes, edema, and vascularity. There are special cases in ultrasound that, when seen in the typical imaging appearance, are pathognomonic. These cases include simple cysts, clustered microcysts, complicated cysts, masses in/on skin, foreign bodies, intramammary or axillary lymph nodes, vascular abnormalities, post-surgical fluid collections, and fat necrosis. Figures 45-54 provide illustrations of various commonly seen sonographic breast findings [3].

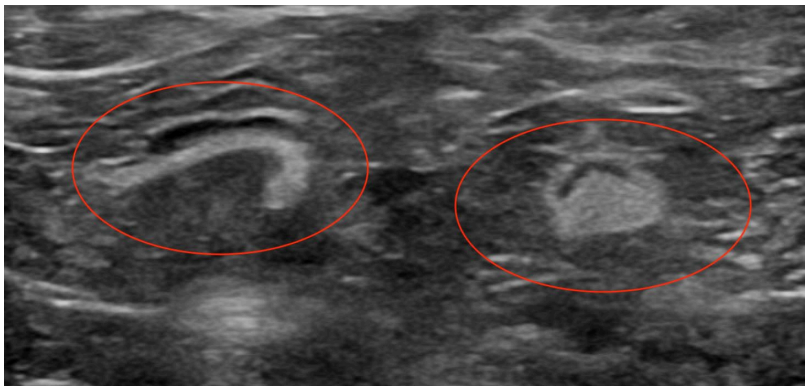

Figure 45: B-mode grayscale targeted ultrasound of the left axilla in the transverse plane demonstrates 2 morphologically normal lymph nodes with associated normal fatty hila.

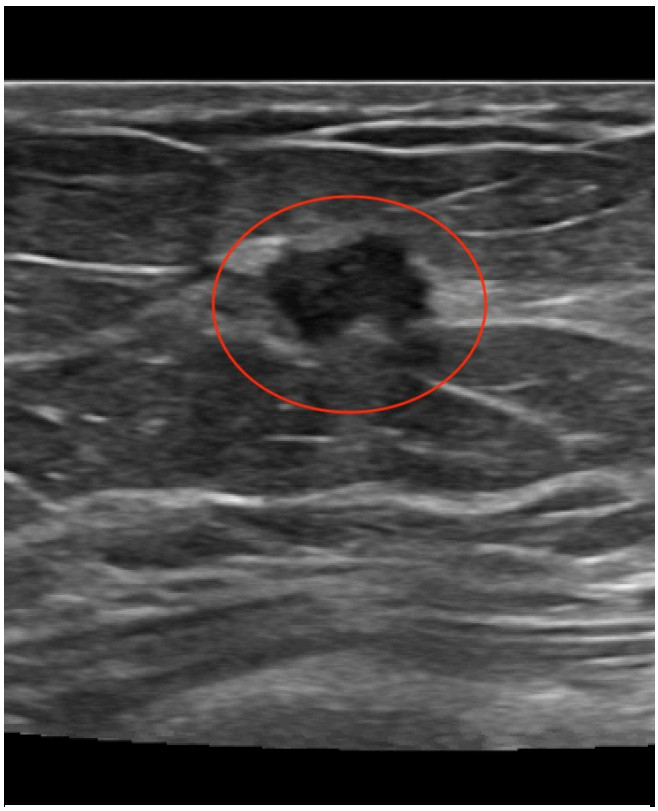

Figure 46: B-mode grayscale targeted ultrasound of the left breast in the transverse plane demonstrates an irregular parallel hypoechoic mass with angular margins. Pathology showed low-grade invasive ductal carcinoma.

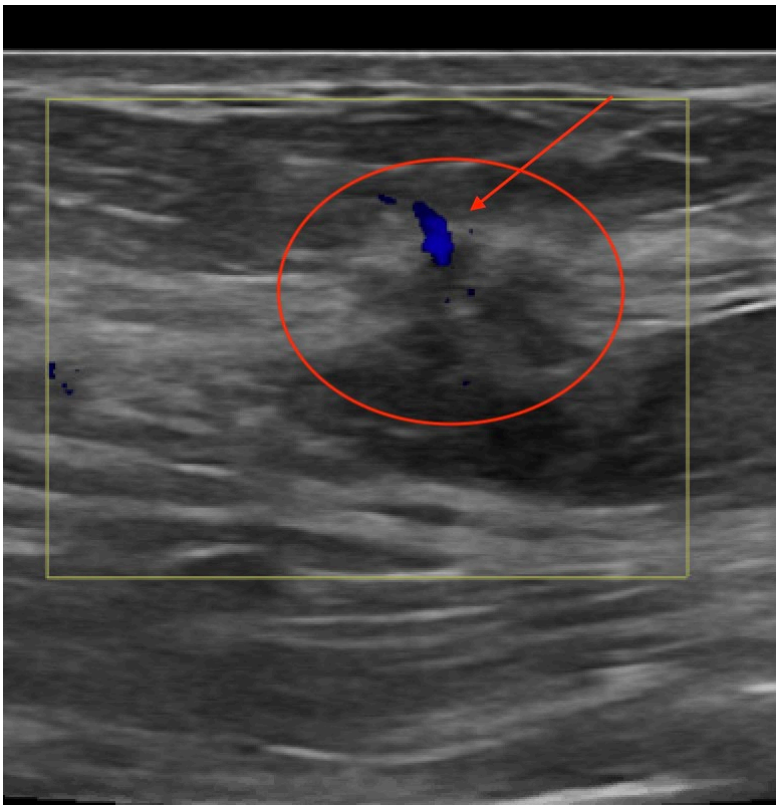

Figure 47: B-mode grayscale targeted ultrasound of the left breast in the transverse plane demonstrates an irregular mass with indistinct margins, hypoechoic. Color Doppler is evidenced by the yellow rectangle, indicating there is internal vascularity (arrow). Pathology showed low grade invasive ductal carcinoma.

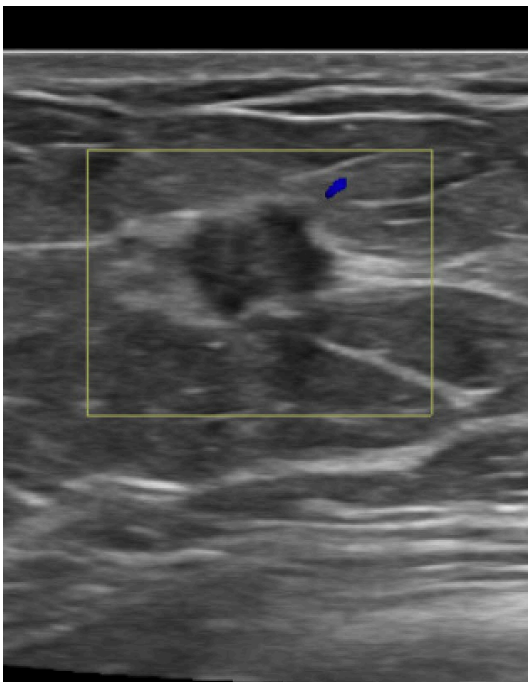

Figure 48: B-mode grayscale targeted ultrasound of the right breast in the sagittal plane demonstrates an irregular mass with indistinct margins, hypoechoic. Color Doppler is evidenced by the yellow rectangle, and there is no internal vascularity. Duct changes are noted. Pathology showed low-grade invasive ductal carcinoma.

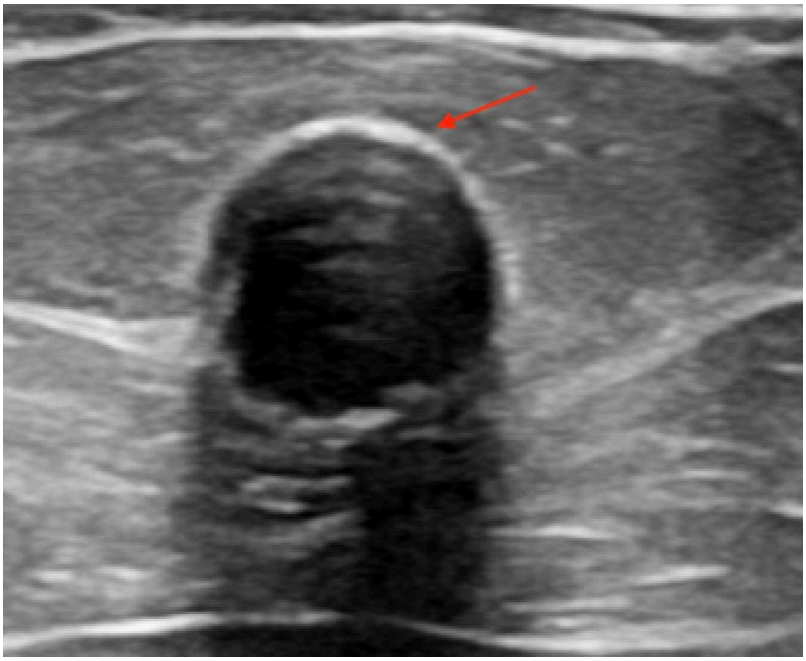

Figure 49: B-mode grayscale targeted ultrasound of the left breast in the transverse plane demonstrates a noval parallel circumscribed simple cyst with an echogenic superficial rim(arrow). Corresponding mammography demonstrated a rim calcification from an oil cyst. This is benign.

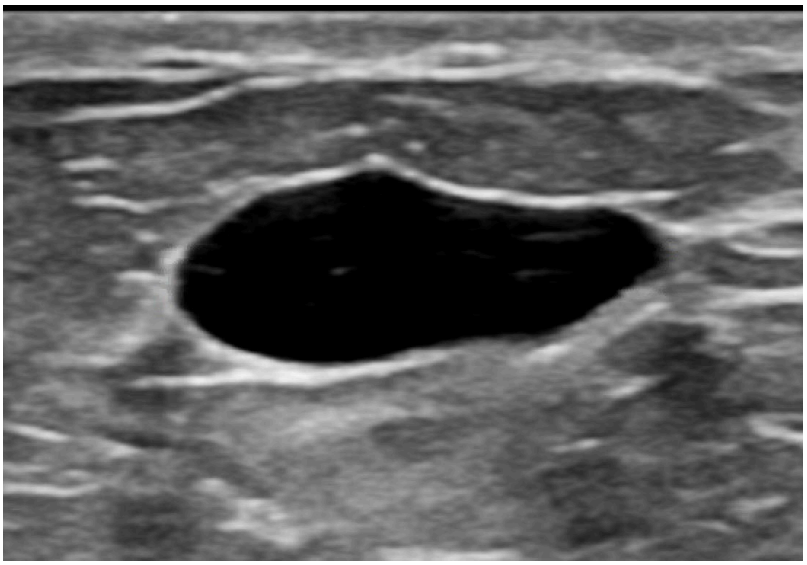

Figure 50: B-mode grayscale targeted ultrasound of the right breast in the transverse plane demonstrates a noval parallel circumscribed anechoic simple cyst. This is benign.

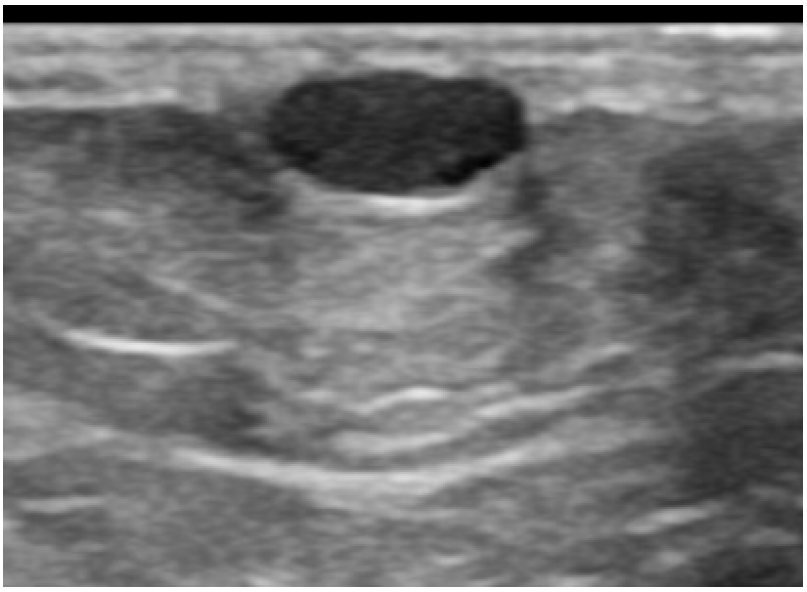

Figure 51: B-mode grayscale targeted ultrasound of the left breast in the transverse plane demonstrates an oval simple skin cyst. This is typical of a sebaceous or an epidermal inclusion cyst.

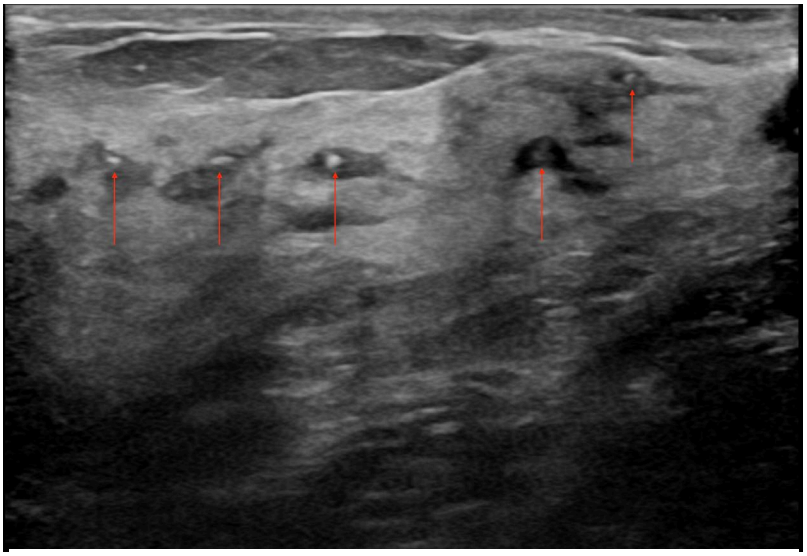

Figure 52: B-mode grayscale targeted ultrasound of the right breast in the sagittal plane demonstrates microcalcifications within ducts(arrows). These intraductal microcalcifications corresponded with segmental coarse heterogeneous microcalcifications on mammography. Pathology demonstrated intermediate-grade DCIS.

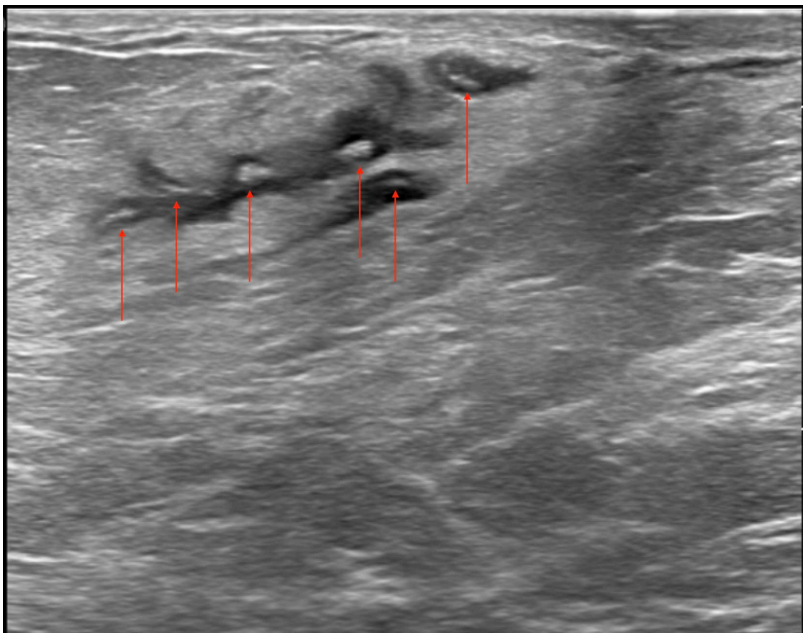

Figure 53: B-mode grayscale targeted ultrasound of the right breast in the sagittal plane demonstrates microcalcifications within ducts(arrows). These intraductal microcalcifications corresponded with segmental coarse heterogeneous microcalcifications on mammography. Pathology demonstrated intermediate-grade DCIS.

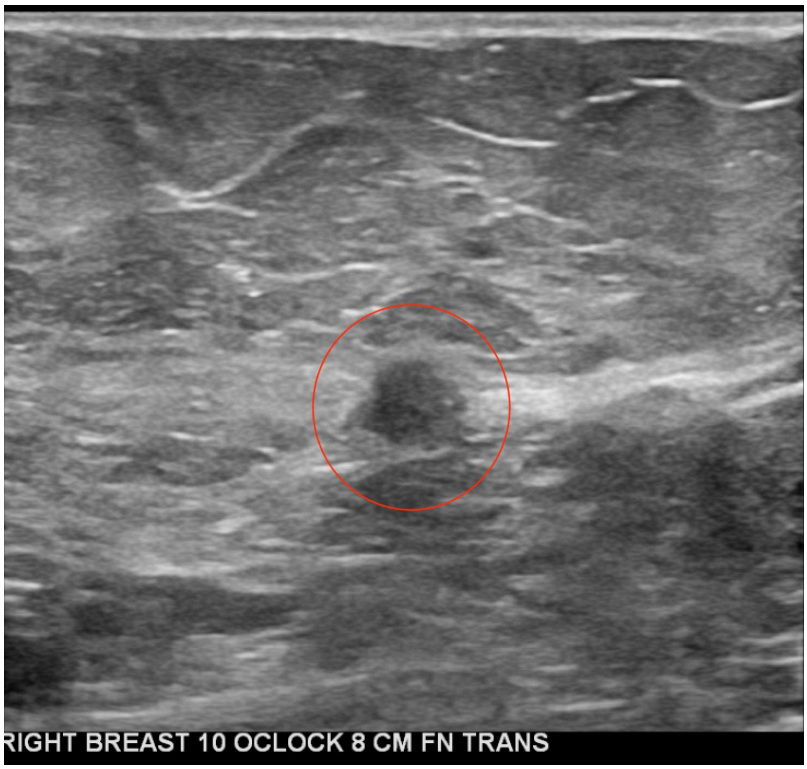

Figure 54: B-mode grayscale targeted ultrasound of the left breast in the transverse plane demonstrates an irregular not parallel hypoechoic mass with indistinct margins. There are no posterior acoustic features. Pathology demonstrated a tubular (grade 1) carcinoma.

MRI

Breast tissue: The following four categories are used to describe the amount of glandular tissue on MRI: almost entirely fat, scattered fibroglandular tissue, heterogeneous fibroglandular tissue, extreme fibroglandular tissue. The level of background parenchymal enhancement is also described in the following terms: minimal, mild, moderate, and marked. The background enhancement is also described as symmetric or asymmetric [4].

Findings: On MRI, the three descriptors used for distinct types of lesions include foci, masses, and non-mass enhancement. These are typical benign lesions and associated features listed in the BI-RADS atlas. MRI also includes the evaluation of lesion vascularity using a kinetic curve assessment. This is determined by the inflow and outflow pattern of blood supply to each lesion. Breast implants can also be assessed with specific MRI sequences [4]. Figures 55-61 illustrate some of the more common imaging appearances of benign and malignant lesions on MRI.

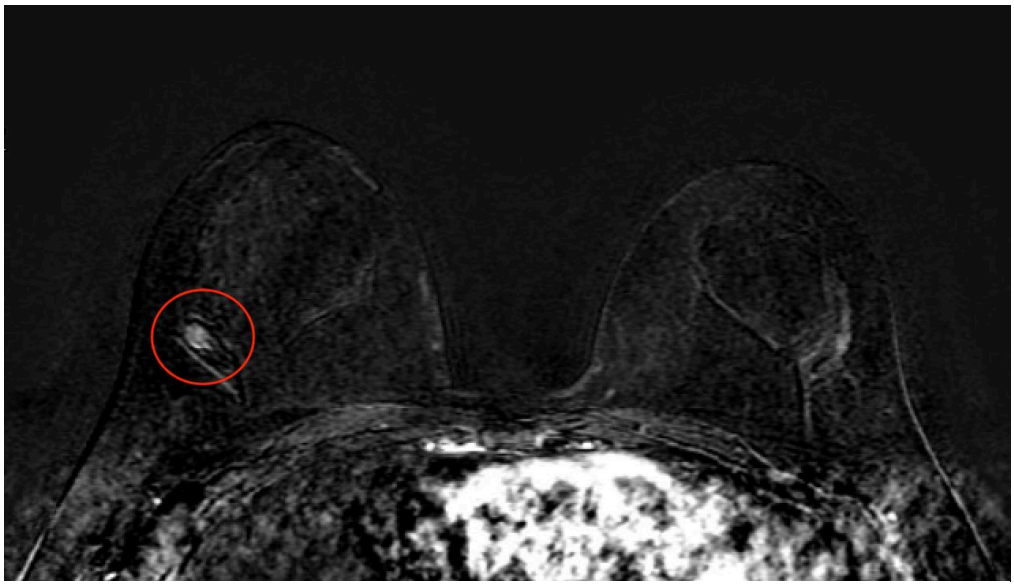

Figure 55: Axial T1-weighted post-contrast subtraction bilateral breast MRI demonstrates an oval circumscribed enhancing mass in the right breast lower outer quadrant posterior depth. This was considered consistent with a fibroadenoma.

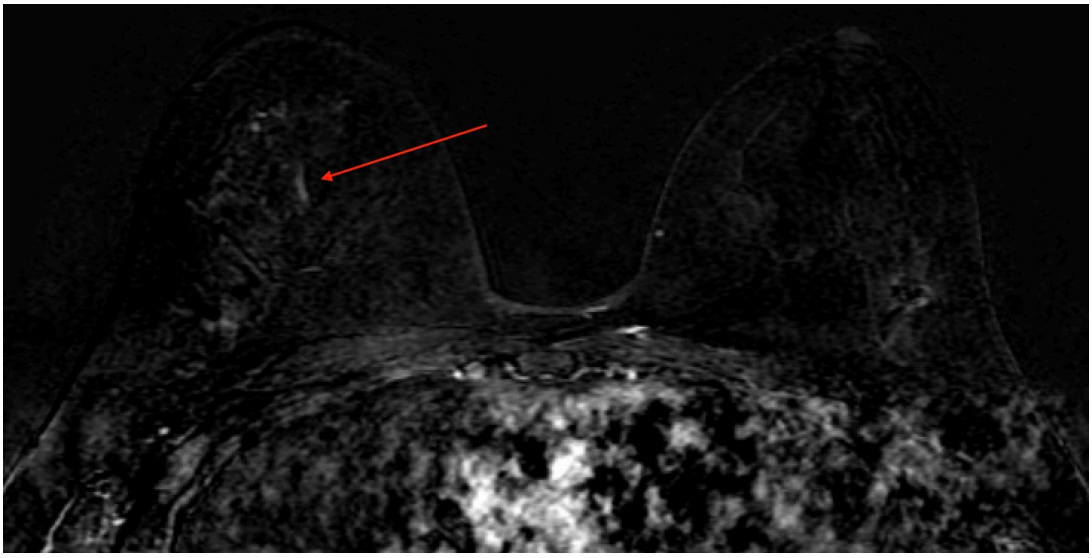

Figure 56: Axial T1-weighted post-contrast subtraction bilateral breast MRI demonstrates linear non mass enhancement in the right breast 12 o'clock middle depth. MRI-guided biopsy demonstrated intermediate grade DCIS.

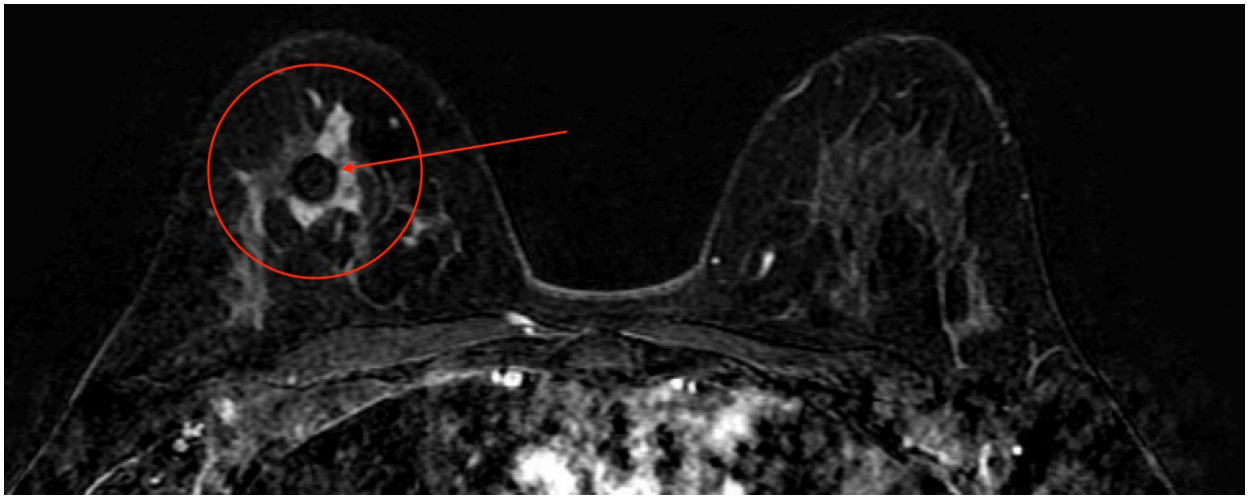

Figure 57: Axial T1-weighted post-contrast subtraction bilateral breast MRI demonstrates an irregular mass in the right breast at 12 o'clock middle depth. Susceptibility artifact can be seen within the mass that represents the biopsy clip(arrow). Pathology demonstrated high-grade invasive ductal carcinoma.

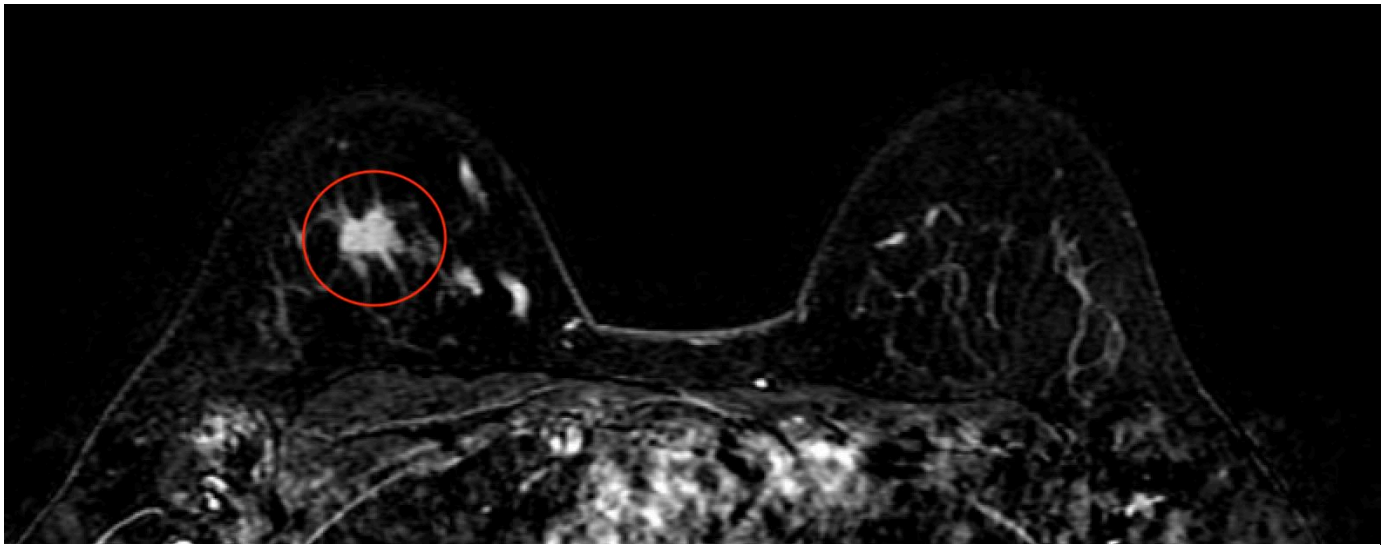

Figure 58: Axial T1-weighted post-contrast subtraction bilateral breast MRI demonstrates an irregular mass in the right breast upper outer quadrant posterior depth. Pathology demonstrated high-grade invasive ductal carcinoma.

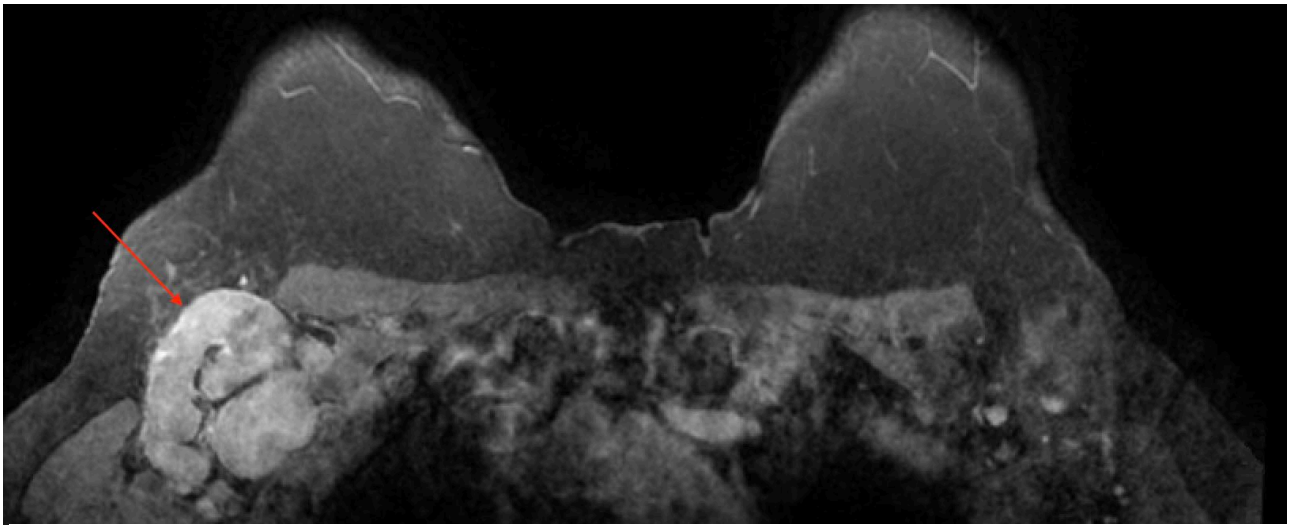

Figure 59: Axial T1-weighted post-contrast bilateral breast MRI demonstrates right axillary lymphadenopathy. Nodes were determined metastatic from biopsy.

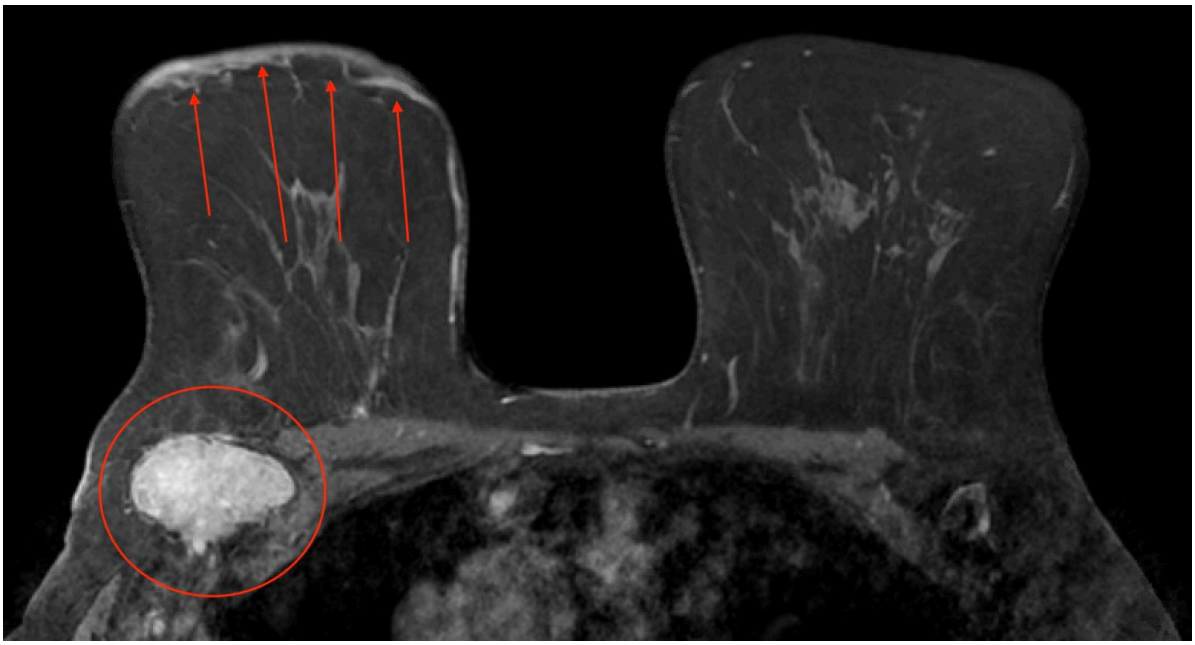

Figure 60: Axial T1-weighted post-contrast bilateral breast MRI demonstrates right axillary lymphadenopathy(circle)as well as ipsilateral skin thickening with enhancement (arrows). Nodes were determined metastatic from biopsy. Skin enhancement represented inflammatory breast cancer.

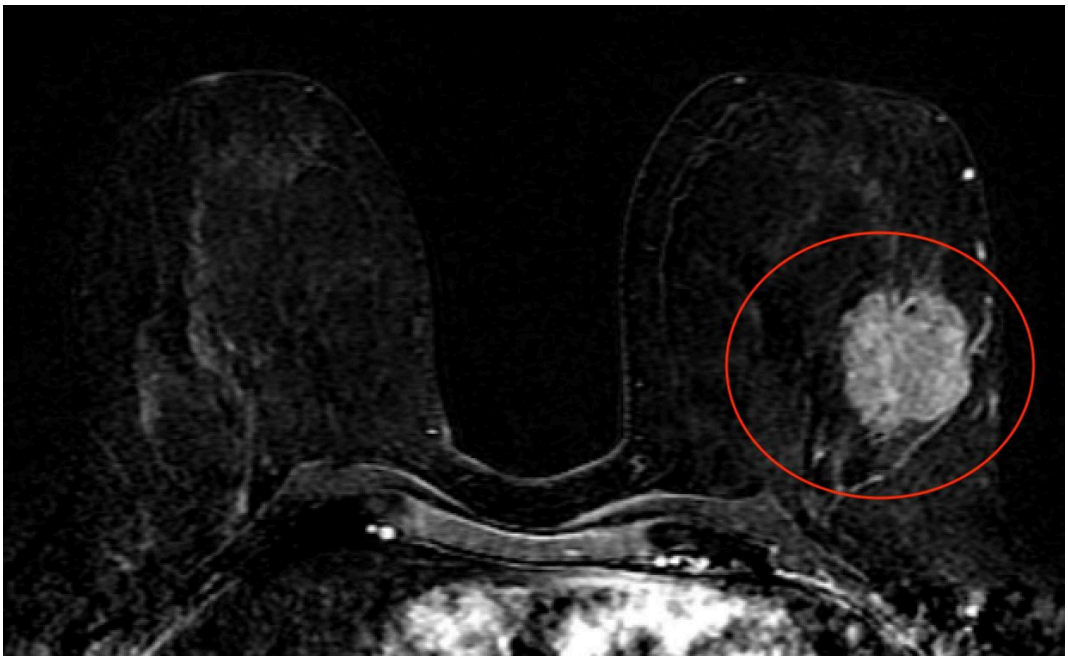

Figure 61: Axial T1-weighted post-contrast subtraction bilateral breast MRI demonstrates an irregular mass in the left breast upper outer quadrant posterior depth. Pathology demonstrated high-grade invasive ductal carcinoma.

Quality and Monitoring Outcomes

Thorough evaluation and monitoring involve not only the management of active problems (i.e. new cancers, symptoms, or imaging findings) but also quality assurance (QA) of the imaging facility. An internal audit should be maintained at each facility, which may or may not be regulated at a local, regional, or national level. Facility audits depend on whether screening examinations are performed throughout the geographic region, if there are screening regimens, and how each facility monitors its outcomes. For an audit to be meaningful, it is suggested that data collection include the following information: the modality of imaging, total number of exams performed, separated data regarding screening and diagnostic evaluation (if applicable), number of cases called back from screening, number of cases reported as BI-RADS 3, 4, and 5, tissue diagnosis from biopsies, cancer staging, and cases of cancers developing within screening intervals. Some of these measurables are irrelevant if screening is not prevalent throughout the region; nonetheless, diagnostic audits remain important for quality assurance. In the diagnostic setting, important data calculations include true positives (TP, tissue diagnosis of cancer in one year of BI-RADS assessment of '4' or '5'), true negatives (TN, benign concordant tissue diagnosis OR no cancer diagnosis within one year of a BI-RADS assessment of '1', '2', or '3'), false positives (FP, benign tissue diagnosis OR no cancer diagnosis within one year of a BI-RADS assessment of '4' or '5'), and false negatives (FN, tissue diagnosis of cancer in one year of BI-RADS assessment of '1', '2', or '3'). The formulas for sensitivity, specificity, and positive predictive value (PPV) are calculated as follows: Sensitivity = TP/(TP + FN), Specificity = TN/(FP + TN), PPV = TP/(FP + TP). PPV is divided into three subcategories, PPV1, PPV2, PPV3; however, PPV1 is exclusive to screening and may not be applicable in countries without routine screening programs. PPV1 is the positive predictive value of cases called BI-RADS 0, 3,

4, or 5 at screening. PPV2 is the based on BI-RADS categories 4 and 5, determined by recommendations for tissue diagnosis. PPV3 includes only those cases in which biopsy was performed. Regardless of the number of quality metrics utilized by each facility, a standardized QA program should be followed to ensure optimal patient care [5].

Salient Points

- Mammography, ultrasound, and MRI are three of the most widely used imaging modalities for breast evaluation, and BI-RADS offers a standardized lexicon for lesion description, assessment, and management.
- The BI-RADS assessments should be used to provide clinical guidance and direct management in patients with findings on breast imaging exams.
- Terms in the BI-RADS atlas have discrete definitions created with specific implications for both benign and malignant descriptors.

Suggested Reading

1. Rao A, Feneis J, Lalonde C, Ojeda-Fournier H. A Pictorial Review of Changes in the BI-RADS Fifth Edition. Radiographics 2016;36(3): 623-639.

2. Entire ACR BI-RADS Atlas. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

References

1. Entire ACR BI-RADS Atlas. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

2. Mammography section. Sickles, EA, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS® Mammography. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

3. Ultrasound section. Mendelson EB, Böhm-Vélez M, Berg WA, et al. ACR BI-RADS® Ultrasound. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

4. MRI section. Morris EA, Comstock CE, Lee CH, et al. ACR BI-RADS® Magnetic Resonance Imaging. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

5. Outcome monitoring section. Sickles, EA, D'Orsi CJ. ACR BI-RADS® Follow-up and Outcome Monitoring. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

6. Rao A, Feneis J, Lalonde C, Ojeda-Fournier H. A Pictorial Review of Changes in the BI-RADS Fifth Edition. Radiographics 2016;36(3): 623-639.

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