Horizon Scanning in Surgery: Application to Surgical Education and Practice

Microwave ablation for hepatic metastases

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment based on a search of studies published in peer-reviewed literature. It is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Acronyms

CEA	Carcinoembryonic antigen
CEUS	Contrast enhanced ultrasound
CT	Computed tomography
FA	l-folinic acid
FDA	Food and Drug Administration
5-FU	5-fluorouracil
MWA	Microwave ablation
PET	Positron emission tomography
PS	Prediction Score
PVE	Portal vein embolization
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
SIRT	Selective radioembolization

Introduction

Background

Microwave ablation is proposed for the treatment of some hepatic metastases.

Surgical resection remains the gold standard treatment in the curative treatment of hepatic metastases. However, some patients are not eligible for surgical resection due to a number of factors including comorbidities, inability to achieve complete resection, sufficient volume of the liver remaining after resection, the feasibility of preserving two contiguous hepatic segments with adequate vascular inflow and outflow as well as biliary drainage, tumor biological aspects and the surgeon's experience (Grundmann et al 2008).

Alternative options for patients with non-resectable liver metastases include minimally invasive options such as ablation and embolization. Ablation modalities include radiofrequency ablation (RFA), laser ablation, cryoablation and microwave ablation (MWA). Of the ablative techniques, RFA is the most widely used in clinical practice (Veltri et al 2012). However, MWA potentially offers larger volumes of ablation, higher temperatures, shorter ablative duration and the ability to utilize multiple antennae compared with other ablative techniques (Ong et al 2009).

The main objective of tumor ablation therapy is to eradicate all viable malignant cells in the target (with a safety margin to ensure complete eradication), while minimizing the damage to surrounding tissue (Vogl et al 2011).

Burden of disease

Colon or rectal primary tumors

The American Cancer Society estimates that approximately 143,460 Americans are diagnosed with colon or rectal cancer annually, and 51,690 will die from this disease (Siegel et al 2012). Colorectal carcinoma is the leading cause of malignancy in western countries, and the primary cause of hepatic metastases (Sheth and Clary 2005). During the course of colorectal cancer about 50 percent of patients will develop hepatic metastases (Tsoulfas and Pramateftakis 2012) and 20 to 25 percent will present with metastases at the time of diagnosis. Patients with untreated hepatic metastases of colorectal origin have a poor prognosis with a median survival of six to 12 months (Bengtsson et al 1981). At present, surgical resection offers the best chance of long-term survival with reported five-year survival of 31 to 58 percent (Flanders and Gervais 2010).

Other primary tumors

Almost 10 percent of all hepatic metastases are neuroendocrine in origin (Lee et al 2012). Similar to patients with primary colorectal tumors, hepatic metastases occur in more than half of patients with primary neuroendocrine tumors (Chamberlain et al 2000). In contrast to patients with hepatic metastases of colorectal origin, patients with untreated hepatic metastases of neuroendocrine origin have reported survival rates ranging from 13 to 54 percent over five years (Modlin et al 2003; Thompson et al 1988).

Approximately 50 percent of all women diagnosed with breast cancer develop metastatic disease and for these patients the average survival time is 18 to 30 months (Li et al 2005). Up to one in five of those patients who die from breast cancer die from liver failure as a result of the hepatic metastasis (Gunabushanam et al 2007).

Technology

MWA of hepatic metastases involves the destruction of tumor cells by thermal energy. The MWA application causes the rotation of water molecules which follow the alternating electric field component of the microwaves. The resultant friction generates heat locally, leading to cell death through coagulation necrosis. The extent of necrosis is dependent on the conductivity of the tissue, the type of equipment used and the time-temperature profile of the treatment (Ong et al 2009).

The equipment required for the procedure includes a microwave generator and needle electrodes. The needle electrode is advanced into each targeted hepatic metastasis under image guidance (Ong et al 2009). Real-time ultrasound guidance is currently the most precise modality used to aid in the insertion of probes and antennae (Sindram et al 2010). Computed tomography (CT) systems exist and are currently confined for use during percutaneous ablations (Sindram et al 2010). Average ablation times range from 60 to 300 seconds. Lower frequency microwave radiation requires a longer ablative duration. Ablation is designed to achieve the focal destruction of the tumor and to create a margin of destruction around the tumor to prevent recurrence (Solomon and Sofocleous 2012). The ablations are carried out at intervals until ablation of the entire tumor is achieved. Larger tumors may require a higher volume of treatment sessions. Multiple needle electrodes can also be used to treat larger tumors.

The MWA procedure can be performed either via percutaneous access or during open or laparoscopic surgery (NICE 2011c). Operative ablation of hepatic metastases of colorectal origin is often done in combination with both minimally invasive hepatic resection and open hepatic resection, whereas percutaneous ablation is appropriate in cases in which no resection is planned (Gueorguiev et al 2011). The percutaneous approach is frequently carried out under local anesthesia and sedation whereas laparoscopic and open surgical procedures require general anesthesia (Ong et al 2009).

Stage of development

Clinical trials for microwave ablation for the treatment of liver cancer are under way or have been completed in Belgium, the United States and China.

Regulatory approval

The MWA devices used in the eligible studies included in this report are listed below and have received marketing approval (510k) by the United States Food and Drug Administration (FDA):

- Evident™ system by ValleyLab/Covidien (Boulder, Colorado) (K072687)
- Microtherm X-100™ from BSD Medical (Salt Lake City, UT) (K081042)
- MedWaves AveCure™ system (San Diego, CA) (K070356)
- Certus 140™ from Neuwave Medical (K100744)
- Vivawave™ from ValleyLab (Boulder, Colorado) (K053535) (Lubner et al 2010).

Current clinical trials

Three current clinical trials were identified in a search of the ClinicalTrials.gov database that are investigating the clinical effectiveness of MWA in the treatment of hepatic tumors (Table 1).

Table 1: Current clinical trials involving microwave ablation for primary or secondary hepatic tumors

Study	Location	Study population, design, study purpose	Status and primary endpoint	End date
Microwave Ablation of Resectable Liver Tumors NCT00892255	Orange, USA	Purpose: To pathologically evaluate the destruction by MWA of primary and metastatic liver tumors with the MedWaves Microwave Ablation/ Coagulation Ablation System. Population: Diagnosis of primary or metastatic liver cancer for which surgery is planned. Design: Observational.	Recruiting. Measure of the tissue destruction with the MedWaves Microwave Ablation/ Coagulation Ablation System.	April 2015
Analysis of Percutaneous Ablations for Cancer Treatment NCT01563679	Atlanta, USA	Purpose: To study patients' clinical, radiological and pathological findings, survival, treatment responses and complications after locoregional therapy. Population: Patients who undergo ablative therapy procedures as part of a clinical treatment for cancer. Design: Observational.	Recruiting. Effect of percutaneous and transarterial treatment for cancer on quality of life.	December 2015
MWA versus RFA for hepatocellular carcinoma NCT01340105	Hong Kong, China	Purpose: To see whether MWA gives an improved ablation compared to RFA Population: Unresectable hepatocellular carcinoma and tumor amendable for local ablation Design: Randomized controlled trial	Recruiting. Complete ablation rate at 1 month	April 2016

MWA: microwave ablation, RFA: radiofrequency ablation.
Source: Clinical Trials Database (US) accessed December 2012.

Current treatment and alternatives

The gold standard curative treatment for hepatic metastases is resection (Flanders and Gervais 2010).

With respect to patients with non-resectable hepatic metastases, a range of alternative treatment modalities have been used over the past 5–10 years, including:

- chemotherapy
- radiotherapy
- laser ablation
- radiofrequency ablation
- cryoablation
- chemical ablation
- transarterial embolization (TAE)
- transarterial chemoembolization (TACE)

In addition to being an alternative treatment for patients unable to have a resection, ablation has also been used as an adjunct to resection, with patients having the majority of the tumor burden resected with remaining disease eradicated via ablation (Pathak et al 2011).

Literature review

Search criteria

Keyword/MeSH terms utilized:

Search strategy for PubMed

#1 microwave.tw
#2 micro-wave.tw
#3 microwaves/therapeutic use.MeSH
#4 #1 or #2 or #3
#5 exp Liver Neoplasms/
#6 liver tumo*.tw
#7 liver neoplasm*.tw
#8 liver malign*.tw
#9 liver carcinoma*.tw
#10 liver metastas*.tw
#11 liver and lesions.tw
#12 metastatic liver cancer.tw
#13 hepatic metastas*.tw
#14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 #4 and #14

Search strategy for Ovid EMBASE

#1 microwave.tw
#2 micro-wave.tw
#3 exp microwave therapy/
#4 #1 or #2 or #3
#5 exp Liver Metastasis/
#6 exp Liver Tumor/
#7 exp Liver Cancer/
#8 exp Liver Carcinoma/
#9 liver tumo*.tw
#10 liver neoplasm*.tw
#11 liver malign*.tw
#12 liver carcinoma*.tw
#13 liver metastas*.tw
#14 liver and lesions.tw
#15 metastatic liver cancer.tw
#16 hepatic metastas*.tw
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #4 and #17

Databases utilized:

PubMed, OVID EMBASE, Cochrane, York CRD

Inclusion criteria

Inclusion criteria used to determine study eligibility are listed in Table 2

Table 2: Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials, non-randomized comparative studies and case series. Case series studies with ≤ 20 patients with metastases were excluded
Patients	Patient with hepatic metastases from any primary source. Studies including patients with primary and secondary hepatic cancers in which the safety or efficacy (or both) were not reported separately were excluded
Intervention	Microwave ablation
Comparator	Resection or any ablative technique
Outcome	Safety: adverse events Efficacy: tumor response, tumor recurrence, patient survival rate, down-staging of the disease, quality of life Studies not including both safety and efficacy data were excluded
Language	English only

Included studies

A total of 1,635 studies were retrieved using the search strategy outlined. Closer examination of these studies with the application of the inclusion criteria revealed a total of six studies for inclusion. Of these one was a randomized controlled trial (Shibata et al 2000), two non-randomized comparative studies (Hompes et al 2010; Tanaka et al 2006) and three case series (Liang et al 2003; Lorentzen et al 2011; Martin et al 2010). Table 3 presents the level of evidence and the characteristics of the six included studies. Further details of the included studies are provided in Appendix B. Excluded studies, along with the reasons for the exclusion are presented in Appendix C.

Table 3: Included studies

Study/Location	Level of evidence[a]	Number of patients
Shibata et al (2000) Japan	Level II	30 (14 microwave ablation, 16 resection)
Hompes et al (2010)[b] Belgium	Level III-2	19 (6 microwave ablation, 13 radiofrequency ablation)
Tanaka et al (2006) Japan	Level III-2	53 (16 microwave ablation plus resection, 37 resection alone)
Liang et al (2003) China	Level IV	74 (all with metastases)
Lorentzen et al (2011) Denmark	Level IV	39 (all with metastases)
Martin et al (2010) United States	Level IV	100 (83 with metastases)

[a] See Appendix A for NHMRC Evidence Hierarchy
[b] It is not clear from the methodology whether microwave ablation and radiofrequency ablation treatments occurred during the same time periods. Therefore, this study may potentially be a Level III-3.

Study profiles

Profiles of the included studies are summarized in Appendix B and described in greater detail below.

Randomized controlled trial evidence

Shibata et al (2000) compared patient outcomes in 30 patients from a single site following liver resection or MWA. Patients with multiple hepatic metastases of colorectal origin and that were potentially amenable to resection between December 1990 and August 1997 were eligible for inclusion. Computer randomization was used to assign the patients to a treatment group; there were 14 in the MWA group and 16 in the resection group. The patients in both groups had similar characteristics at baseline. MWA was performed after laparotomy using a frequency of 2,450 MHz and a single antenna, under ultrasonic guidance. The antenna was inserted into each metastasis several times for a 10–30 second ablation period followed by a 10 second ablation-free period, for a net period of 2–20 minutes. For metastases located at superficial sites in the liver, a 2 cm long antenna and a power output of 100W was used. For metastases located more deeply, a 20 cm long antenna and a power output of 60W was used. Hepatic resection was performed according to a standard method; lobectomy, segmentectomy, subsegmentectomy and/or wedge resection were performed depending on the number, location, and size of tumors. Safety outcomes included intraoperative or postoperative deaths, complications and surgical invasiveness. Effectiveness outcomes included survival rates, disease-free time and tumor marker levels. After treatment, there were monthly follow-up visits during which routine biochemical analyses of blood were performed, with imaging performed every three months.

Non-randomized comparative evidence

Tanaka et al (2006) compared 53 patients with five or more bilobar liver metastases, at a single site between 1992 and 2004, treated with either resection plus MWA (total n= 16;1-step resection+MWA n=10; 2-step resection+MWA n=6) or treated using resection only (total n=37; 1-step resection n=23, 2-step resection n=14). MWA was only used in combination with resection on those patients whom the investigators assessed to be unable to complete treatment by resection alone while preserving sufficient vascularized hepatic parenchyma to support post-resection hepatic function. The characteristics of the two groups were evenly matched on clinical characteristics at baseline; however, those in the resection/MWA group had significantly more metastases (13.6 ± 9.5 versus 8.1 ± 4.4), were more likely to have had neoadjuvant chemotherapy but less likely to have had a major resection. All procedures were undertaken via laparotomy. MWA was performed using a frequency of 2,450 MHz and a single antenna under ultrasonic guidance. The antenna was inserted into each metastasis four to five times at a power of 70W for a 45 second ablation period followed by a 15 second ablation-free period, for a net period of 4–5 minutes. Follow-up occurred monthly. Safety outcomes recorded included operative deaths and postoperative complications. Effectiveness outcomes included hepatic recurrence-free survival, overall survival and disease-free survival. The median follow-up time for all 53 patients was 21 months (range 1–91 months).

Hompes et al (2010) compared 19 patients with hepatic metastases smaller than 3 cm, throughout 2008 treated with either MWA (n=6) or from a historical control group who had received radiofrequency ablation (RFA) (n=13). Patients were considered for MWA but not resection due to a high clinical risk score, had no or minimal response to systemic chemotherapy

and suffered from severe systemic disease. The two groups were matched for metastases size and localization but additional baseline information was not reported. MWA was performed laparoscopically (n=5) and percutaneously (n=1). MWA was performed using a frequency of 915 MHz and a single antenna under ultrasonic guidance. The antenna was inserted into each metastasis at a power of 40W for a 10 minute ablation. No mention was made of the number of cycles used or the ablation free period between cycles. RFA was performed via laparoscopy (n=7), laparotomy (n=4) and percutaneously (n=2). Safety outcomes reported included perioperative mortality and complications. Efficacy outcomes included local recurrence, defined as cancer recurrence at the site of ablated hepatic metastasis, and tumor response, as measured by change in tumor diameter. Postoperative measurements were performed within one week and at three months after surgery. The median follow-up time after MWA was 6.3 months (range 4.9–7.8).

Case series evidence

Liang et al (2003) reported on 74 patients, from a single site between July 1995 and March 2002, in a case series of MWA of hepatic metastases. The primary sources of the metastases were colorectal adenocarcinoma (n=28), gastric or cardiac adenocarcinoma (n=12), lung cancer (n=12), breast (n=11) or other (n=11). The majority of the patients (n=58, 78%) were unable to undergo resection for various reasons, whilst the remaining 16 patients (22%) were able to have resection but chose not to. All procedures were performed percutaneously. MWA was performed using a frequency of 2,450 MHz, using a single antenna and a power output range of 10–80W under ultrasonic guidance. For metastases less than 14 mm in diameter a single-puncture simultaneous emission technique was used and for those metastases 14 mm or larger, a multiple-puncture simultaneous-emission technique was employed. An average of 2.6 punctures and 4.6 emissions per metastasis were used. Safety outcomes reported included complications. Efficacy outcomes reported included survival, local recurrence and calculation of predictive factors' effect on survival rate using multivariate analysis (Cox proportional hazards model). The mean follow-up period (mean ± SD) was 25.1 ± 11.4 months (range, 5–83 months).

Martin et al (2010) reported on 100 patients, from a single site between January 2004 and January 2009, treated with MWA for either primary hepatic cancer (n=17) or hepatic metastases (n=83). The primary sources of the metastases were colorectal (n=50), carcinoid cancer (n=11) and other types (including cholangiocarinoma, breast cancer, renal cell carcinoma, bladder, carcinoid, melanoma and sarcoma) (n=22). Patients amenable to resection alone were excluded. MWA was performed using an open (n=60) or laparoscopic (n=22) technique. MWA was performed using a frequency of 915 MHz under ultrasonic guidance. The antenna was inserted into each metastasis median ablation time was 13 minutes but the power was not reported. Smaller metastases (< 1.5 cm) were treated using a single antenna, whereas most metastases were treated with multiple antennae (maximum of 3). In all cases with multiple metastases, multiple ablations were performed simultaneously. All ablations were conducted under ultrasonic guidance. No details were provided regarding the number of cycles used or the ablation-free period between cycles. Safety outcomes reported included mortality and perioperative and delayed complications. Efficacy outcomes included the rate of complete ablation of hepatic metastases. The median follow-up time after MWA was 36 months (range 2–60).

Lorentzen et al (2011) reported on 39 patients, from a single site between July 2008 and December 2009, in a retrospective case series on MWA of hepatic metastases. The primary sources of the metastases were colorectal (n=31), breast (n=6), carcinoid (n=1) and

gastrointestinal stromal (GIST) (n=1). Patient selection criteria for MWA were not explicit. The authors state that prior to MW ablation oncological downstaging had been performed on 26 patients (67%) with a significant tumor load in the liver that had made primary surgery and/or ablation impossible. Two patients had already undergone liver resection. The MWA was performed either percutaneously (n = 30), during laparotomy (n = 3) or during laparotomy combined with hepatic resection (n = 12). MWA was performed using a frequency of 915 MHz and a power output of up to 45W for 10 minutes, under ultrasonic guidance. The majority (85%) of the metastases were small (< 2 cm) and were treated using a single antenna, whereas the large metastases (> 2 cm) were treated with multiple antennae (maximum of 3). Safety outcomes included major and minor complications and deaths. Efficacy outcomes included 1) technical success, defined as correct placement of the antenna in the metastasis as seen in ultrasound or contrast-enhanced ultrasound, 2) clinical effectiveness, defined as complete ablation of the metastasis as seen in immediate post-procedure contrast-enhanced ultrasound and 3) local recurrence, defined as a recurrence located at the site of the original metastasis. Patients were followed-up for at least four months with a median duration of 11 months (range 4–20 months).

Other systematic reviews and health technology reports

Previously conducted systematic reviews and health technology assessments are summarized in Table 4. One systematic review (Pathak et al 2011) of relevance was identified and two health technology reports (BCBSKC 2012; NICE 2011c). In their systematic review, (Pathak et al 2011) considered ablative therapies for colorectal metastases, including MWA. Shibata et al (2000), Tanaka et al (2006) and Liang et al (2003) included in this systematic review. One of the health technology assessments was on microwave tumor ablation (BCBSKC 2012). A section of the report was on hepatic metastases from primary cancers from other sites. Shibata et al (2000), Martin et al (2010) and Lorentzen (2011) were included in this assessment report. The other health technology assessment (NICE 2011c) focused on MWA for haptic metastases. Shibata et al (2000), Tanaka et al (2006), Hompes et al (2010), Liang et al (2003), Martin et al (2010) were also included in this assessment report.

Table 4: Summary of previous systematic reviews and health technology reports on microwave ablation for hepatic metastases

Study	Number of included studies	Comparisons (number of studies)
Pathak et al (2011)[b]	13	The review did not provide details of the level of evidence of the included studies. Only four where discussed in detail. Of these: RCT – comparator resection (1) Non RCT - comparator resection vs. (MWA plus resection) (1) Case series (2)
BlueCross BlueShield Association of Kansas City (2012)[a]	6	Systematic reviews (3) RCT – comparator resection (1) Case series (2)
NICE Interventional Procedural Overview (2011c) Guidance (2011b)	8	RCT – comparator resection (1) Non RCT Comparators: resection vs. (resection plus MWA) (1) radiofrequency ablation (2) Case series (5)

MWA, microwave ablation; RCT, randomized control trial

[a] The policy document by BlueCross Blueshield of Kansas City is on microwave tumor ablation. One section of the document is on hepatic metastases from primary cancer from other sites.

[b] Systematic review was on ablative therapies (cryotherapy, radiofrequency ablation and microwave ablation) for colorectal metastases only. The study included 75 studies, 13 of which were on microwave ablation.

Critical appraisal

All studies

The sample sizes of all six studies were small, ranging from 19 to 83 patients. In the largest study, which was a case series, the data on the 83 patients were extracted from an original group of 100 patients who had both primary and secondary hepatic cancers.

Patient inclusion and exclusion criteria were applied in two of the studies (Martin et al 2010; Shibata et al 2000). One of the studies had inclusion criteria but no exclusion criteria (Tanaka et al 2006) and two others had limited inclusion but no exclusion criteria (Hompes et al 2010; Liang et al 2003). One study mentioned the use of inclusion criteria but did not provide them, only mentioning the reason for the exclusion of 11 patients (Lorentzen et al 2011).

With respect to inclusion criteria, the patients differed between the studies with respect to their amenability or potential to undergo resection. In the majority of studies MWA was undertaken in patients who were not amenable for surgical resection, although there was variability between the studies in the exact definition of the patient population (Tanaka et al 2006, Martin et al 2010, Lorentzen et al 2011, Hompes et al 2010). In addition to this population, one study also included some patients (22%) that chose not to receive surgical resection (Liang et al 2003). In the randomized comparative study, patients were selected if they were potentially amenable to hepatic resection (Shibata et al 2000).

Patient characteristics such as type (source of primary cancer), size and number of tumors varied between all studies. In two studies, the metastases were all colorectal in origin (Shibata et al 2000; Tanaka et al 2006), whilst in the other four studies (Hompes et al 2010; Liang et al 2003; Lorentzen et al 2011; Martin et al 2010) the primary cancers were from mixed origins, although primarily from colorectal cancer. With respect to metastasis size, in two studies the metastases that were treated were all less than 3 cm in dimension (Hompes et al 2010; Tanaka et al 2006), whilst in another two studies the mean size of the metastases ranged from 2.7 to 2.9 cm (Martin et al 2010; Shibata et al 2000). In the remaining two studies one only provided a median value for metastasis size of 1.5 cm (range 0.6–4.0) (Lorentzen et al 2011) and the other reported that the largest metastasis in each patient ranged from 0.7 to 6.8 cm (mean, 3.12 cm; median 3 cm). In two of the studies the number of metastases was a criterion for patient inclusion. One study only included patients with less than 10 metastases (Shibata et al 2000) whilst the other stated that it included patients with five or more metastases in a bi-lobar distribution (Tanaka et al 2006).

In addition to tumor-related variables, patients also differed between and within studies with respect to prior and concomitant treatment received. Two studies did not mention the use of any neoadjuvent therapy. In the other four studies chemotherapy was used in some patients. Similarly, adjuvant therapy was not mentioned in two studies (Hompes et al 2010; Shibata et al 2000). One study reported that all patients were given chemotherapy (Tanaka et al 2006), another pointed out that the majority of patients had either concomitant resection and/or concomitant extrahepatic tumor resection (Martin et al 2010), another reported that the majority of patients also received chemotherapy and/or hepatic resection with MWA (Lorentzen et al 2011). The remaining study reported that 77 percent of the patients had systemic chemotherapy before and after MWA (Liang et al 2003).

MWA methodology and surgical approach varied between studies. Ablation times ranged from 10–35 seconds at 60–100 W with 10–15 second breaks (Shibata et al 2000; Tanaka et al 2006) to 10 minutes at 40–45 W (Hompes et al 2010; Lorentzen et al 2011). One study did not provide details of the power discharged from the MWA device, but reported median ablation times of 10 minutes for metastases of colorectal origin to 20.5 minutes for metastases that were carcinoid in origin (Martin et al 2010). Two studies reported using single and multiple antennae (Lorentzen et al 2011; Martin et al 2010) whilst the other studies stated that only a single antenna was used (Shibata et al 2000; Tanaka et al 2006; Hompes et al 2010; Liang et al 2003). With respect to surgical approach, ablations were conducted by laparotomy (Shibata et al 2000; Tanaka et al 2006), percutaneously (Liang et al 2003), laparoscopically or percutaneously (Hompes et al 2010), by laparotomy or laparoscopy (Martin et al 2010) and either percutaneously, by laparotomy or during hepatic resection (Lorentzen et al 2011).

Follow-up differed between the studies both with respect to duration and number of patients who completed treatment. Median duration ranged from 6.3 months (Hompes et al 2010) to 36 months (Martin et al 2010). The randomized controlled trial failed to mention the duration of any follow-up (Shibata et al 2000). Three of the studies reported no losses to follow-up. The randomized controlled trial lost 25 percent of patients during the surgery phase (Shibata et al 2000). One of the case series stated that 10 percent of the patients had died by the end of the follow-up period (Lorentzen et al 2011), whilst another reported that 45 percent had died by the end of the follow-up period (Liang et al 2003).

Comparative evidence

With respect to the three comparative studies, only the randomized controlled trial reported that there were no statistically significant differences between treatment groups with respect to baseline data such as age, number of hepatic metastases and greatest dimension of the largest metastases. One of the non-randomized comparative studies merely stated that patients were matched for size and location without providing any further details or statistical verification (Hompes et al 2010). The other non-randomized comparative study reported significant differences between the two patient groups (Tanaka et al 2006) whereby the MWA plus resection group had significantly more metastases and a significantly higher number of patients who had undergone pre-resection chemotherapy than in the resection only group. However, it should be noted that only the randomized controlled trial attempted to match both MWA and resection groups to patients amenable to resection. In the other comparative studies, MWA was only considered for patients who were not amenable to resection (Tanaka et al 2006, Hompes et al 2010).

In the non-randomized study by Tanaka et al (2006), the number of patients who had major resections (those exceeding 2 resections) was significantly greater in the resection only treatment group. Evaluation of this study is complicated by the fact that in the two treatment groups (MWA in combination with resection and resection only), 38 percent of the patients in each group underwent a second planned resection.

Evaluation of the non-randomized comparative study by Hompes et al (2010) is complicated due to the fact that a range of surgical approaches (laparoscopy, laparotomy and percutaneous approach) were used in both treatment groups (RFA and MWA groups). In one patient with hepatic metastases of colorectal origin, laparoscopic MWA was combined with segmental resection.

In summary, specific methodological issues that were identified in the three comparative studies included lack of reporting of details regarding duration of follow-up and large losses to follow-up (Shibata et al 2000), and no comparison of treatment groups at baseline (Hompes et al 2010). The significant differences between patient treatment groups at baseline in Tanaka et al (2006) is a consequence of the clinical decision that patients undergoing ablation should be ineligible for surgical resection. These variables such as patients' potential to undergo resection, tumor characteristics, prior and concomitant treatments, and surgical approaches impedes detailed comparison between studies. In addition, it is not known whether any of the studies were designed to provide statistically meaningful results.

Safety and efficacy

Safety

All six studies reported safety outcomes ranging from death to perioperative complications such as wound infections, hepatic abscesses, bleeding and biliary leakage.

Mortality

None of the six studies reviewed reported deaths following MWA.

Complications

All the studies reported complications (Table 5). Shibata et al (2000) reported that two patients from the MWA group and three from the resection group experienced one complication each. In the MWA group these included one patient with a biliary leakage and another with a hepatic abscess. In the resection group one patient had an intestinal obstruction, another had a wound infection and the third had biliary leakage. There were no significant difference observed between the treatment groups. Perioperative blood loss was also reported. The number of patients requiring blood transfusions (n=6) and the amount of blood transfused was significantly greater in the resection group with no patients requiring transfusion in the MWA group. No significant differences were found between the two groups with respect to operation time and period of hospitalization.

Tanaka et al (2006) reported four complications in the case of three patients in the resection plus MWA and six complications occurred in six patients in the resection only treatment group. The complications reported included infection and biliary leakage (both groups), bleeding (only MWA plus resection group), hyper-bilirubinemia and intestinal obstruction (resection-only group). A small number of patients (n=6) underwent a two-step resection plus MWA. Three of these patients experienced complications; biliary leakage, transient hepatic failure and a liver stump abscess. In two patients these complications responded to medical or interventional treatment. The third patient required more extensive treatment (laparotomy for hemostasis). The authors reported that the difference in the number of complications between treatment groups was significant ($p < 0.05$). Perioperative blood loss was also reported. All patients, other than three in the resection-only group, received blood transfusions.

Hompes et al (2010) reported that one patient in the MWA group developed hemobilia that was resolved with conservative management. No complications were reported in the RFA group.

Liang et al (2003) reported a total of 79 non-severe complications in 74 patients. The list included local pain (n=67, 91%), minor to medium pleural effusion (n=7, 9%), slight subcapsular bleeding not requiring transfusion (n=2, 3%) and skin burns (n=3, 4%).

Martin et al (2010) reported that for patients with metastases (n=82), in the subgroup presenting with primary colorectal cancer (n=50), 15 patients (30%) had 20 complications with the highest grade complication score of 3. Of the subgroup presenting with primary hepatocellular cancer (n=17), 3 patients (18%) had five complications with the median highest grade score of 1 and the subgroup presenting with primary metastatic carcinoid (n=11), 3 patients (27%) had

3 complications with a with the highest grade complication score of 1. Of all other primary cancers (n=22), 7 patients (32%) had eight complications with the highest grade complication score of 2. It was reported that no patients experienced bleeding complications. Complication grade was based on a 5 point scale; however no further details were reported.

Lorentzen et al (2011) reported one major complication and four minor complications in 37 patients. The major complication was a hepatic abscess that resolved after percutaneous drainage. The four minor complications were experienced by three patients who had pain at the puncture site, requiring them to stay one or two days extra in hospital and one patient who developed minor ascites that resolved without any treatment.

Table 5: Complications reported in the six studies

Study	Treatment group (N)	Complication (n, %)
Comparative studies		
Shibata et al (2000)	MWA (14)	Biliary leakage (n=1, 7%) Hepatic abscess (n=1, 7%)
	Resection (16)	Internal obstruction (n=1, 6%) Biliary leakage (n=1, 6%) Wound infection (n=1, 6%)
Tanaka et al (2006)	1-Step resection (23) and first resection from 2-step resection (14) (total 37)	Intestinal obstruction (n=3, 8%) Infection (n=1, 3%) Biliary leakage (n=1, 3%) Hyperbilirubinemia (n=1, 3%)
	2-Step resection (14) after second resection	No complication after second resection.
	1-Step resection + MWA (10) and first resection from 2-step resection MWA (6) (total 16)	Infection (n=2, 20%) Biliary leakage (n=1, 10%) Postoperative bleeding (n=1, 10%)
	2-Step Resection + MWA (6) after second resection	Biliary leakage (n=1, 17%) Transient liver failure (n=1, 17%) Liver stump abscess (n=1, 17%)
Hompes et al (2010)	MWA (6)	Hemobilia (n=1, 17%)
	RFA (13)	None reported
Case series		
Liang et al (2003)	MWA (74)	Local pain (n=67, 91%) Minor to moderate pleural effusion (n=7, 9%) Skin burns (n=3, 4%) Slight subcapsular bleeding (n=2, 3%)
Martin et al (2010)	MWA (83)	Only total number of complications reported
	Primary colorectal (50)	20 Complications (n=15, 30%)
	Primary hepatocellular (17)	5 Complications (n=3, 18%)
	Primary metastatic carcinoid (11)	3 Complications (n=3, 27%)
	All other primary cancers (22)	8 Complications (n=7, 32%)
Lorentzen et al (2011)	MWA (37)	Hepatic abscess (n=1, 3%) Pain at puncture site (n=3, 8%) Minor ascites (n=1, 3%)

MWA, microwave ablation; RFA, radiofrequency ablation; N and n, number of patients

Efficacy

Common efficacy outcomes reported included treatment success, tumor recurrence and patient survival. Other efficacy outcomes reported but not discussed here include pre- and post-treatment tumor ablation diameters (Hompes et al 2010) and change in serum concentrations of biochemical tumor markers (Shibata et al 2000).

Treatment success

Only three of the six studies reported treatment success including one comparative study and two case series (Hompes et al 2010; Lorentzen et al 2011; Martin et al 2010). In the comparative study reported by Hompes et al (2010) a CT scan conducted within one week after MWA showed that metastasis ablation was complete. The authors did not report metastasis ablation success after RFA. Lorentzen et al (2011) also reported complete ablation of all metastases as confirmed by immediate post-ablation contrast enhanced ultrasound (CEUS). Martin et al (2010) reported that complete ablation occurred in 98% of colorectal primary tumors, 90% of carcinoid primary tumors and 100% of the group defined as 'other' primary tumors (included breast, renal cell carcinoma, bladder, carcinoid, melanoma and sarcoma) as confirmed by CT within two weeks of MWA.

Tumor recurrence

All studies reported on tumor recurrence. With respect to the comparative studies, Shibata et al (2000) reported that recurrence of the ablated metastases were not found for at least three months in all patients whose tumors were judged to be completely ablated. The tumor recurrence-free time for the resection group was not reported. Tanaka et al (2006) reported that 14 of the 37 patients (38%) in the resection only group and 11 of the 16 patients (67%) in the MWA plus resection group developed hepatic metastases recurrence. However, in a subsequent section of their study on liver recurrence patterns they report that 19 patients in the resection only and nine patients in the MWA plus resection treatment groups experienced recurrence. The reason for the discrepancy in their reporting could not be determined. Hompes et al (2010) reported that no local tumor recurrences (defined as recurrence at the site of the ablated liver metastasis) occurred in the RFA treatment group whereas one out of the six patients in the MWA group had a local recurrence during follow-up (median time of 6.3 months). This patient had been treated for a solitary hepatic metastasis of colorectal origin.

In the case series study by Liang et al (2003), 48 patients (65%) developed local recurrence or new metastasis after MWA. Ten of these patients (14%) had a local regrowth of a MWA metastasis whilst the other 38 (51%) had new metastases in the liver but removed from the original tumor site. Five of the 83 patients (6%) with metastatic cancers in the study by Martin et al (2010) experienced recurrences at the ablated site. Three of these patients had colorectal cancer as the primary cancer source and two were from the group defined as 'other' (these included breast, renal cell, carcinoid melanoma and sarcoma as the primary cancer sites). No patients who had carcinoid as the primary cancer experienced a recurrence. Lorentzen et al (2011) reported local recurrence in 12 of the 125 treated metastases in 10 of the 39 patients (26%). Nine of the patients with local recurrence had colorectal cancer as the primary cancer and the other had breast cancer. No recurrence was observed in the single patient with carcinoid cancer as the primary tumor. The median time span from ablation to recurrence was five months (range 2–12 months).

Patient survival

Five of the six studies reported on overall patient survival after MWA (Shibata et al 2000; Tanaka et al 2006; Martin et al 2010; Liang et al 2003; Lorentzen et al 2010) with four of these reporting on disease-free survival (Liang et al 2003; Martin et al 2010; Shibata et al 2000; Tanaka et al 2006).

Disease-free survival

With respect to disease-free survival Shibata et al (2000) reported mean times of 11.3 months in the MWA group and 13.3 months in the resection group. The authors reported that the difference was not statistically significant ($p > 0.05$). Tanaka et al (2006) reported on Kaplan-Meier estimates of disease-free survival rates. In patients who had resection only the one and three year disease-free survival rates were 26 and 11 percent respectively. In patients who had MWA plus resection they were 33 and 17 percent respectively. Tanaka et al (2006) also reported the differences were not statistically significant ($p > 0.05$). Martin et al (2010) reported the highest median disease-free survival was 12 months. This was observed in the group who had colorectal cancer as the primary cancer. In comparison, Liang et al (2003) reported that disease-free survival was one or more years for 21 patients, two or more years for 13 patients, three or more years for seven patients, four or more years for five patients and more than five years for two patients. Disease-free survival for the entire follow-up period of 25.1±11.4 months (mean ±SD) was seen in 26 patients (35%).

Overall survival

Shibata et al (2000) reported that nine of the 14 patients treated with MWA ablation and 12 of the 16 who had resection died during follow-up. In six patients in the MWA group and seven in the resection group the deaths were due to hepatic failure. The remaining patients in each treatment died without hepatic failure. Mean survival times of 27 months for the MWA group and 25 months for the resection group were reported. Shibata et al (2000) reported Kaplan-Meier estimated cumulative survival. Estimated 1-year, 2-year and 3-year survival rates were 71%, 57% and 14% respectively in the microwave group and 69%, 56% and 23% respectively in the resection group. The differences between the MWA group and the resection group in estimated cumulative survival rates did not differ significantly ($p > 0.05$). The authors reported that the statistical power calculated for the 3-year survival rates with a one-sided significance level of 0.05 was 0.65. Tanaka et al (2006) reported median (± SD) survival times of 39 ± 5 months for resection only and 28 ± 4 months for MWA plus resection. Tanaka et al (2006) also reported Kaplan-Meier estimated cumulative survival. Concomitant extrahepatic metastases precluded curative resection in three patients in the resection only, and one patient in the MWA plus resection treatment. Among the 49 patients with potentially curative resections, the cumulative survival rates at 1, 3 and 5 years in the resection only treatment were 87%, 49% and 44%, respectively. In patients who had MWA plus resection the cumulative survival rates at 1, 3 and 4 years were 80%, 51% and 15%, respectively. The authors reported no significant difference between treatments in cumulative survival rates ($p > 0.05$).

All three case series reported on overall survival. Liang et al (2003) reported that 33 patients (45%) died during follow-up. Survival times ranged from 5 to 65 months (mean, 22.1±13.8 months; median, 20.5 months). In the study by Martin et al (2010) the highest median overall survival was 36 months, in the group who had colorectal cancer as the primary source. Lorentzen et al (2011) simply reported that at the end of the follow-up period 35 patients (90%) were still alive.

Cost impact

No studies were identified that specifically assessed the cost-effectiveness of MWA for the treatment of hepatic metastases. Martin et al (2010) compared the variable direct and fixed direct charges of MWA and RFA in a matched pair evaluation of patients who were treated for hepatic tumors (Table 6). Patients were matched for sex, age, histology, number of tumors, size of tumors, operative exposure, and the lack of the need to perform additional concomitant hepatectomy or extrahepatic organ resection. The study reported significantly shorter ablation and operating times in the MWA group. This related to the ability to do simultaneous ablations with multiple probes. The reduced ablation and operating room times led to significant improvements in operating room charges, operating room variable direct charges and operating room fixed direct charges for MWA (p = 0.02).

Table 6: Matched ablation efficiency, success, recurrence and operative charges in microwave and radiofrequency ablated patients treated for hepatic tumors (Martin et al 2010)

	MWA (40 patients)	**RFA (40 patients)**
Number of tumors	1–2	1–2
Operating time[a]	56.9 (23.8–125.6)	125.8 (21.2–243.6)
Operating charges[b] Median (range)	$13,389 ($8,059–18,136)	$25,687 ($19,410–40,235)
Operating room variable direct charges[b] Median (range)	$909 ($562–1,420)	$2,903 ($2,052–4,503)
Operating room fixed direct charges[b] Median (range)	$514 ($337–628)	$787 ($565–1,305)

MWA, microwave ablation; RFA, radiofrequency ablation
[a]Unit of time not provided
[b]Costs are in US dollars

Clinical practice guidelines and consensus statements

NICE guidance: microwave ablation for the treatment of liver metastases 2011

The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has provided guidelines on MWA for the treatment of liver metastases (NICE 2011b).These guidelines provide the observation that the current evidence on MWA does not raise any major safety concerns. However, NICE (2011b) conclude that owing to the inadequate evidence on its efficacy the procedure should only be used with appropriate arrangements for clinical governance, consent, audit or research.

Key recommendations in the NICE guidelines are outlined below (NICE 2011b).

- Clinicians wishing to undertake MWA for the treatment of liver metastases should:
    - inform relevant clinical governance
    - ensure that patients and their carers understand the procedure's efficacy and should be provided with clearly written instructions
    - audit and review clinical outcomes of all patients having MWA for the treatment of liver metastases.
- Patient selection should be carried out by a hepatobiliary cancer multidisciplinary team.
- NICE encourages further research into MWA for the treatment of liver metastases, suggesting that research should clearly define patient selection criteria and report tumor recurrence and patient survival. They also note that comparison with other ablative techniques would be useful.

BlueCross BlueShield of Kansas City (BCBSKC): policy on microwave tumor ablation

The BCBSK policy on microwave tumor ablation contains a summary of the National Comprehensive Cancer Network (NCCN) guidelines on neuroendocrine tumors. The guidelines list MWA as a treatment option for liver metastases as hepatic regional therapy in carcinoid tumors and pancreatic endocrine tumors when there is non-resectable disease and/or distant metastases. The guidelines note that data on ablative techniques for liver metastases are emerging but that there are limited prospective data and no randomized controlled clinical trials (BCBSKC 2012).

Training and education impact

No literature was identified addressing the training and educational requirements to undertake MWA in the treatment of liver metastases. The technique appears to be similar to RFA in terms of training and educational requirements. In its clinical guidance document on MWA for the treatment of liver metastases, NICE (2011b) recommend additional training specifically on operating the microwave generator.

Summary

Although the supporting literature is limited, microwave ablation may prove to be a safe and effective treatment for hepatic metastases. In particular, it may offer patients who are unable or unwilling to undergo surgical resection an alternative to radiofrequency ablation. Treatment success following MWA was high in the three studies that reported treatment success and tumor recurrence at the site of ablation was very low. Common complications include pain, biliary leakage, hepatic abscess and infection, although in the majority of cases they were mild or easily resolved.

Whilst this report contained three comparative studies, one of which was a randomized controlled trial, only two had the same comparator (resection). Of the two studies that had the same comparator (resection), one combined MWA with resection, whilst the other investigated MWA treatment alone. In addition, several potential sources of bias and complicating factors were noted in the studies, including variability in patient selection, procedural approach and concurrent interventions. As such, there is insufficient evidence at this time to reach sound conclusions regarding the safety and efficacy of MWA in comparison with other procedures for the treatment of hepatic metastases. However, preliminary data suggest that the safety and effectiveness profile is similar to both resection and radiofrequency ablation.

Recommendation

The evidence base for microwave ablation for the treatment of hepatic metastases is limited. There are very few studies and these are small and may be typically characterized as ‘phase II clinical trials’ designed to evaluate the short-term therapeutic effect of microwave ablation in patients who suffer from the target disease; they confirm the safety outcomes established in smaller pilot studies. Much larger randomized clinical trials need to be conducted to determine whether an MWA is, in terms of safety and effectiveness, either equivalent to or superior to other treatment modalities. It is only after larger trials are run and assessed that it will be possible to determine whether MWA has a place in the treatment of patients with hepatic metastases and which types would benefit most.

References

BCBSKC. 2012. Microwave tumor ablation. *policy number: 7.01.133* [Online]. Available: http://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/microwave_tumor_ablation.pdf [Accessed September 2012].

Bengtsson G, Carlsson G, Hafstrom L & Jonsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981; 141(5): 586-589.

Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y & Blumgart LH. Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg* 2000; 190(4): 432-445.

Flanders VL & Gervais DA. Ablation of liver metastases: current status. *J Vasc Interv Radiol* 2010; 21(8 Suppl): S214-222.

Grundmann RT, Hermanek P, Merkel S, Germer CT, Hauss J, Henne-Bruns D, Herfarth K, Hopt UT, Junginger T, Klar E, Klempnauer J, Knapp WH, Kraus M, Lang H, Link KH, Lohe F, Oldhafer KJ, Raab HR, Rau HG, Reinacher-Schick A, Ricke J, Roder J, Schafer AO, Schlitt HJ, Schon MR, Stippel D, Tannapfel A, Tatsch K & Vogl TJ. [Diagnosis and treatment of colorectal liver metastases - workflow]. *Zentralbl Chir* 2008; 133(3): 267-284.

Gueorguiev AL, Mackey R, Kowdley GC, Esquivel J & Cunningham SC. Minimally invasive evaluation and treatment of colorectal liver metastases. *Int J Surg Oncol* 2011; 2011686030.

Gunabushanam G, Sharma S, Thulkar S, Srivastava DN, Rath GK, Julka PK & Bhatnagar S. Radiofrequency ablation of liver metastases from breast cancer: results in 14 patients. *J Vasc Interv Radiol* 2007; 18(1 Pt 1): 67-72.

Hompes R, Fieuws S, Aerts R, Thijs M, Penninckx F & Topal B. Results of single-probe microwave ablation of metastatic liver cancer. *Eur J Surg Oncol* 2010; 36(8): 725-730.

Lee SY, Cheow PC, Teo JY & Ooi LL. Surgical treatment of neuroendocrine liver metastases. *Int J Hepatol* 2012; 2012146590.

Li XP, Meng ZQ, Guo WJ & Li J. Treatment for liver metastases from breast cancer: results and prognostic factors. *World J Gastroenterol* 2005; 11(24): 3782-3787.

Liang P, Dong B, Yu X, Yang Y, Yu D, Su L, Xiao Q & Sheng L. Prognostic factors for percutaneous microwave coagulation therapy of hepatic metastases. *AJR Am J Roentgenol* 2003; 181(5): 1319-1325.

Lorentzen T, Skjoldbye BO & Nolsoe CP. Microwave ablation of liver metastases guided by contrast-enhanced ultrasound: experience with 125 metastases in 39 patients. *Ultraschall Med* 2011; 32(5): 492-496.

Lubner MG, Brace CL, Hinshaw JL & Lee FT, Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol* 2010; 21(8 Suppl): S192-203.

Martin RC, Scoggins CR & McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. *Ann Surg Oncol* 2010; 17(1): 171-178.

Modlin IM, Lye KD & Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; 97(4): 934-959.

NICE. 2011b. National Institute for Health and Clinical Excellence. IPG406 Microwave ablation for the treatment of liver metastases: guidance Available: http://guidance.nice.org.uk/IPG406/Guidance/pdf/English [Accessed 7th August 2012].

NICE. 2011c. National Institute for Health and Clinical Excellence. Interventional procedure overview of microwave ablation for the treatment of liver metastases. Available: http://www.nice.org.uk/nicemedia/live/11333/55908/55908.pdf [Accessed 7th August 2012].

Ong SL, Gravante G, Metcalfe MS, Strickland AD, Dennison AR & Lloyd DM. Efficacy and safety of microwave ablation for primary and secondary liver malignancies: a systematic review. *Eur J Gastroenterol Hepatol* 2009; 21(6): 599-605.

Pathak S, Jones R, Tang JM, Parmar C, Fenwick S, Malik H & Poston G. Ablative therapies for colorectal liver metastases: a systematic review. *Colorectal Dis* 2011; 13(9): e252-265.

Sheth KR & Clary BM. Management of Hepatic Metastases from Colorectal Cancer. *Clin Colon Rectal Surg* 2005; 18(3): 215-223.

Shibata T, Niinobu T, Ogata N & Takami M. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. *Cancer* 2000; 89(2): 276-284.

Siegel R, Naishadham D & Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62(1): 10-29.

Sindram D, Lau KN, Martinie JB & Iannitti DA. Hepatic tumor ablation. *Surg Clin North Am* 2010; 90(4): 863-876.

Solomon SB & Sofocleous CT. *The interventional radiologist role in treating liver metastases for colorectal cancer,* 2012. http://www.asco.org/ASCOv2/Home/Education%20&%20Training/Educational%20Book/PDF%20Files/2012/zds00112000202.PDF [Accessed].

Tanaka K, Shimada H, Nagano Y, Endo I, Sekido H & Togo S. Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver. *Surgery* 2006; 139(2): 263-273.

Thompson GB, van Heerden JA, Grant CS, Carney JA & Ilstrup DM. Islet cell carcinomas of the pancreas: a twenty-year experience. *Surgery* 1988; 104(6): 1011-1017.

Tsoulfas G & Pramateftakis MG. Management of rectal cancer and liver metastatic disease: which comes first? *Int J Surg Oncol* 2012; 2012196908.

Veltri A, Gazzera C, Rotondella C, Camerano F, Busso M & Gandini G. Image-guided microwave ablation of hepatic tumours: preliminary experience. *Radiol Med* 2012; 117(3): 378-392.

Vogl TJ, Naguib NN, Lehnert T & Nour-Eldin NE. Radiofrequency, microwave and laser ablation of pulmonary neoplasms: clinical studies and technical considerations--review article. *Eur J Radiol* 2011; 77(2): 346-357.

Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD, 3rd, Dorfman GS, Eng C, Fong Y, Giusti AF, Lu D, Marsland TA, Michelson R, Poston GJ, Schrag D, Seidenfeld J & Benson AB, 3rd. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 2010; 28(3): 493-508.

Appendix A

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Etiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Etiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Appendix B

Profiles of the included studies

Study	Shibata et al (2000)	Tanaka et al (2006)[b]	Hompes et al (2010)[d]	Liang et al (2003)	Martin et al (2010)[e]	Lorentzen et al (2011)
Number of patients	30 (14 MWA, 16 resection)	53 (16 MWA + resection, 37 resection only)	19 (6 MWA, 13 RFA)	74 (all with metastases)	100 (83 with metastases)	39 (all with metastases)
Inclusion/exclusion criteria	Yes	Inclusion criteria but no exclusion criteria	Limited inclusion criteria, no exclusion criteria	Limited inclusion criteria and no exclusion criteria	Yes	Use of inclusion criteria mentioned but not provided. Reason for exclusion of 11 patients provided
Patient details	Patients with multiple colorectal tumors (< 10) potentially amenable to resection	Patients with five or more hepatic tumors in a bilobar distribution	Patients with liver metastases < 3 cm without underlying liver disease	All patients had metastases confirmed histologically and had undergone resection of the primary tumor 5–74 months prior to MWA	Patients with liver metastases or primary disease that was amenable to complete ablation or a combination of resection and ablation. Those amenable to resection alone and those with any metastasis > 5 cm were excluded	No details provided other than patients had liver metastases
Size of tumors	Mean ± (SD) = 27 ± (11) mm (MWA group) and 34 ± (17) mm (hepatectomy group)[a]	Mean ± (SD) = 7.9 ± (5.3) mm (range 1 to 20 mm)	All < 3 cm; no further details provided	Largest metastases in each patient ranged from 0.7 to 6.8 cm (mean = 3.12 cm, SD = 1.81 cm)	Metastatic cancers had mean ± (SE) size of 2.4 (0.3), 2.9 (0.2) & 2.4 (0.2) cm for colorectal, carcinoid and other types	Median = 1.5 cm (range 0.6–4 cm)

Study	Shibata et al (2000)	Tanaka et al (2006)[b]	Hompes et al (2010)[d]	Liang et al (2003)	Martin et al (2010)[e]	Lorentzen et al (2011)
Primary cancer source	All colorectal	All colorectal	Colorectal (16 patients), lung, cervix and ampulla Vateri (1 patient each)	Colorectal (28 patients), gastric/cardiac (12 patients), lung (11 patients), breast (11 patients), pancreatic adenocarcinoma (1 patients), gallbladder adenocarcinoma (2 patients), renal cell carcinoma (5 patients), ocular melanoma (1 patient), leiomyosarcoma of the small bowel (2 patients)	Colorectal (50 patients), carcinoid (11 patients), other (22 patients)	Colorectal cancer (31 patients), breast cancer (6 patients), carcinoid tumor (1 patient), gastrointestinal stromal tumor (1 patient)
Comparative treatment	Resection	Resection	RFA	NA	NA	NA
Comparison of patient populations	No significant differences in mean age, mean number of tumors in the liver or mean dimension or largest tumor	Patient groups differed significantly in number of metastases (more in resection + MWA group), pre-resection chemotherapy (had by more patients in resection + MWA group) and major resections (exceeding two sections) which were performed more frequently in patients in resection only group. No significant differences in age and gender patients or size of tumors	Tumors matched for size and location. No other details provided.	NA	NA	NA
Randomization	Yes – computer generated sequence	NA	NA	NA	NA	NA

Study	Shibata et al (2000)	Tanaka et al (2006)[b]	Hompes et al (2010)[d]	Liang et al (2003)	Martin et al (2010)[e]	Lorentzen et al (2011)
Neoadjuvant therapy	None mentioned	Chemotherapy given to 30 patients irrespective of initial ability to successfully resect.	Patients with liver metastases from colorectal cancer had prior systemic chemotherapy.	All patients had undergone resection of the primary tumor	None mentioned	Six patients had been treated with intrahepatic chemotherapy and 20 patients had received intravenous chemotherapy. Two patients had undergone liver resection.
Adjuvant therapy	None mentioned	Chemotherapy given to all patients	None mentioned	77% of patients had concomitant systemic chemotherapy before and after MWA	Concomitant hepatectomy and concomitant extrahepatic tumor resection was performed in 58% and 28% of patients with metastatic cancers respectively.	Twelve patients had MWA with resection. Mentioned in discussion that the majority of patients also received chemotherapy and/or liver resection together with MWA.
Microwave ablation details	HSD-20M (Azwell, Osaka Japan). Ablation time of 10-30 seconds at 60–100 W followed by 10 second break. Net ablation time of 2–20 mins. Single antenna. Surgical approach: laparotomy.	Microtaze AZM-520 system (Azwell, Osaka, Japan). A time of 45 seconds at 70 W followed by 15 second break. Single antenna. Surgical approach: open laparotomy.	915 MHz Valleylab MWA generator (VTSYS3; Covidien Europe). Ablation time of 10 minutes at 40 W. Single antenna. Surgical approach: laparoscopic (5 patients), percutaneous (1 patient)	Ultrasound Guided Microwave Coagulator I (General Hospital and Institute 207 of the Aerospace Industry Company, Beijing, China). Power range of 10–80 W. An average of 2.6 punctures and 4.6 emissions per tumor were used. Single antenna. Surgical approach: percutaneous using 14-gauge guiding needing	Evident Microwave Ablation System (Covidien, Boulder, Colorado). Two types of probes used: open surgical antenna and laparoscopic antenna. Single and multiple probes used based on surgeon's discretion. Median ablation time 13 min. Power not stated. Surgical approach: laparoscopic (22 patients), open (60 patients).	Evident Microwave Ablation System (Covidien, Boulder, Colorado). Single antenna used to treat smaller tumors (< 2 cm) with generator capable of producing. In patients with multiple small tumors two or three antennas used simultaneously. Tumors larger than 2 cm were treated with two or three parallel antennas simultaneously. Ablation time of 10 minutes at 45 W. Surgical approach: percutaneous (30 patients), during laparotomy (3 patients) or during laparotomy combined with liver resection (12 patients).

Study	Shibata et al (2000)	Tanaka et al (2006)[b]	Hompes et al (2010)[d]	Liang et al (2003)	Martin et al (2010)[e]	Lorentzen et al (2011)
Comparator technique	Hepatic resection: lobectomy, segmentectomy, subsegmentectomy and/or wedge resection.	Hepatic resection. Patients with a prediction score[c] of 50 or more underwent either a 2-stage resection or pre-resection portal vein embolization.	RFA: 15 min per tumor using a monopolar 200 W RF generator (Covidien, Radionics Europe NV) Surgical approach: laparoscopy (7 patients), laparotomy (4 patients), percutaneously (2 patients).	NA	NA	NA
Statistical analysis	Cumulative survival rate calculated using the Kaplan–Meier method. Differences between treatments compared using a log-rank test. Other differences compared by using two-tailed, non-paired Student t test or a chi-square test. Difference considered significant when $p < 0.05$.	Survival rates calculated by the Kaplan–Meier method. Differences between treatments compared using a log-rank test. Difference considered significant when $p < 0.05$.	Mann–Whitney U tests were used to compare measured tumor diameters. A linear model was used to compare the changes between pre-operative diameters and postoperative ablation zones. Likelihood-ratio tests were used to assess differences in variability of post-treatment measurements. Difference considered significant when $p \leq 0.05$.	Cumulative survival rates were calculated using the Kaplan Meier method. Statistical comparison of the effect of each of the potential predictive factors on survival rates was conducted using log-rank tests. A multivariate Cox proportional hazard model was used to determine the covariate and their risk. Differences considered significant when $p < 0.05$	Differences considered significant when $p < 0.05$	Not mentioned
Follow-up	25% (10/40) of patients dropped out during the surgery phase. No details provided of duration of follow-up.	No losses to follow-up. Duration of follow-up was 20 months (median).	No losses to follow-up in MWA group. No mention of follow-up in RFA group. Duration of follow up in MWA group was 6.3 months (median) (range, 4.9-7.8 months).	Percentage follow-up: 1 or more years (81%) 2 or more years (58%) 3 or more years (39%) 4 or more years (24%) > 5 years (11%) 45% of patients died Mean follow-up duration of 25 months	No losses to follow-up. Median follow-up duration of 36 (range, 2–60) months.	90% (35/39) of patients still alive at the end of the follow-up period. Median duration of follow-up was 11 months (range, 4-20 months).
Conflict of interest	None reported	None reported	None reported	None reported	None reported	None reported

Study	Shibata et al (2000)	Tanaka et al (2006)[b]	Hompes et al (2010)[d]	Liang et al (2003)	Martin et al (2010)[e]	Lorentzen et al (2011)
Limitations	Duration of follow-up not provided	Non-randomized, retrospective design and significant differences between patient populations with respect to number of tumors and number of major hepatectomies. MWA received in combination with resection. Neoadjuvant therapy in some patients and not others. There is discrepancy in the text in regard to hepatic recurrence	Short follow-up, non-randomized, no comparison of patient characteristics at baseline, MWA combined with resection in one patient.	A proportion of the patients (77%) underwent systemic chemotherapy before and after MWA and 23% did not undergo any chemotherapy before or after MWA	Metastatic and primary cancer results not reported separately for all outcomes, particularly details of safety. Authors mentioned a limitation to their study is its single institutional review which brings surgical bias to use ablation as an adjunct to resection and not to replace resection as the optimal technique. Discrepancy in table regarding incision techniques for metastatic patients (numbers don't add up to 83).	Retrospective design. Majority of patients reported to have MWA with resection and/or chemotherapy but exact numbers not provided.

NA, not applicable; MWA, Microwave ablation; RFA, radiofrequency ablation; SD, standard deviation

[a] Means ± SD are of the first largest tumor of each patient in the respective groups.

[b] Patients had microwave ablation plus resection versus resection only

[c] Yamanaka et al (1994)

[d] MWA combined with resection in one patient

[e] Study included 100 patients of whom 83 had metastases

Appendix C

Additional papers (case series) not included in this assessment

Article reference	Number of patients	Conclusions	Reason for exclusion
Abe et al. Open-configuration MR-guided microwave thermocoagulation therapy for metastatic liver tumors from breast cancer. *Breast Cancer* 2005; 12(1): 26–31.	8	No mortality or complications; 5 patients with new metastatic foci	Small patient number
Iannitti et al. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2007; 9(2):120–124.	87 (64 with metastases)	For metastases patients: no procedure-related deaths, 27 patients with no evidence of disease and 17 alive with disease at 19 months follow-up for metastases group	Complications not reported separately
Jagad et al. Laparoscopic microwave ablation of liver tumors: our experience. *Hepatogastroenterology* 2008; 55(81): 27–32.	57 (46 with metastases)	NA	Results not reported separately
Jiao et al. Microwave ablation treatment of liver cancer with a 2,450-MHz cooled-shaft antenna: pilot study on safety and efficacy. *Asian Pacific Journal of Cancer Prevention* 2010; 13(2): 737–742.	60 (20 with metastases)	For metastases patients: complete ablation in the small (≤3 cm), medium (3.1-5 cm) and large (5.1-8.0 cm) cancers were 95%, 92% and 67% respectively	Not all results reported separately
Li et al. Percutaneous microwave ablation for liver cancer adjacent to the diaphragm. *International Journal of Hyperthermia* 2012; 28(3): 218–226.	189 (61 with metastases)	For metastases patients: complete ablation achieved in 93.3% of tumors. Local tumor progression was 31.1%.	No all results reported separately
Liang et al. Malignant liver tumors: treatment with percutaneous microwave ablation-complications among cohort of 1136 patients. *Radiology* 2009; 251(3):933–940.	1136 (257 with metastases)	For metastases patients major complications included skin burn requiring resection (<1%), pleural effusion (1.6%), liver abscess (<1%), biloma (1.6%)	No efficacy outcomes reported
Liu et al. Is percutaneous microwave ablation of liver tumor safe for patients with renal dysfunction. *European Journal of Radiology* 2011; 79(2):e103–e107.	23 (4 with metastases)	No severe complications reported	Small patient number and results not reported separately
Livraghi et al. Complications of microwave ablation for liver tumors: results of a multicentre study. *Cardiovascular and Interventional Radiology* 2012; 35(4):868–874.	736 (187 with metastases)	For metastases patients: six had major complications. These included hemothorax, biliary stenosis, peritoneal haemorrhage, hepatic abscess, pneumothorax and tumoral seeding	No efficacy results reported and complications not reported separately

Article reference	Number of patients	Conclusions	Reason for exclusion
Lloyd et al. International multicentre prospective study on microwave ablation of liver tumors: preliminary results. *HPB: the official journal of the International Hepato Pancreato Biliary Association 2011;13(8):579–585.*	140 (56 known to have metastases—11 patients etiology not provided)	NA	Results not reported separately
Martin et al. Microwave hepatic ablation: initial experience of safety and efficacy. *Journal of Surgical Oncology* 2007; 96(6):481–486.	20 (15 with metastases)	For metastases patients: 100% ablation success at discharge, no perioperative deaths, one ablation recurrence, six new liver recurrences at follow-up	Safety results (complications) not reported separately
Matsukawa et al. Percutaneous microwave coagulation therapy in liver tumors. A 3-year experience. *Acta Radiologica* 1997; 38(3):410–415.	24 (number of patients with metastases not stated)	For metastases patients: treatment was effective in 57% of cases	Small patient number and safety results not reported separately
Mitsuzaki et al. CT appearance of hepatic tumors after microwave coagulation therapy. *American Journal of Roentgenology* 1998; 171(5): 1397–-403.	63 (9 with metastases)	NA	Small patient number and results not reported separately
Morikawa et al. MR-guided microwave thermocoagulation therapy of liver tumors: initial clinical experiences using a 0.5 T open MR system. *Journal of Magnetic Resonance Imaging* 2002; 16(5):576–583.	30 (22 with metastases)	In seven patients with metastatic tumors no recurrence was observed in the treated area during the observation period of 13-21 months. Six patients with metastatic tumors subsequently died	Small patient number and limited results: the primary focus of the study was to assess MR imaging not microwave ablation.
Ogata et al. Intraoperative thermal ablation therapy for small colorectal metastases to the liver. *Hepato-Gastroenterology* 2008; 55: 550–556.	105 (18 patients had microwave ablation)	For MWA patients:11 patients had repeat or re-repeat treatment, liver abscess developed in two patients (all successfully treated conservatively) and tumor recurrence developed in 4/59 tumors (6.8%)	Not all results reported separately
Seki et al. Percutaneous microwave coagulation therapy for solitary metastatic liver tumors from colorectal cancer: A pilot clinical study. *American Journal of Gastroenterology* 1999; 94(2):322–327.	15	No serious side effects or complications encountered during or after the procedure. Ten patients survived. No recurrence has been detected in the treated area except two foci where treatment was insufficient	Small patient number
Shen P et al. Pathologic correlation study of microwave coagulation therapy for hepatic malignancies using a three-ring probe. *Journal of Gastrointestinal Surgery* 2007; 11(5):603–611.	9	No outcomes of interest reported	Small patient number and no outcomes of interest reported (pathology study)

Article reference	Number of patients	Conclusions	Reason for exclusion
Shibata et al. Percutanteous microwave coagulation therapy for patients with primary and metastatic hepatic tumors during interruption of hepatic blood flow. *Cancer* 2000; 88(2): 302–11.	25 (16 with metastases)	NA	Small patient number and some had temporary interruption of hepatic blood flow while others did not
Shibata et al. Cholangitis and liver abscess after percutaneous ablation therapy for liver tumors: incidence and risk factors. *Journal of Vascular and Interventional Radiology* 2003; 14(12): 1535–1542.	70	NA	Results not reported separately
Shimada et al. Complications and management of microwave coagulation therapy for primary and metastatic liver tumors. *Surgery Today* 1998; 28(11):1130–1137.	71 (29 with metastases)	For metastases patients: complications developed in 6 (20.6%) patients including bleeding, biliary leakage and abscesses	No efficacy results reported
Veltri et al. Image-guided microwave ablation of hepatic tumours: preliminary experience. Radiology Medicine 2012; 117(3): 478-392. *La Radiologia medica* 2012; 117(3):378–392.	15 (9 with metastases)	For metastases patients: two patients developed complications. In one the tumor recurred with biloma. The second patient developed a high fever treated successfully with antibiotics. Partial ablation occurred in two patients. Treatment failure was 33%.	Small patient number and not all results reported separately: main focus of study was to assess image guidance, not microwave ablation
Zhang et al. Microwave ablation with cooled-tip electrode for liver cancer: an analysis of 160 cases. *Minimally Invasive Therapy and Allied Technologies* 2008;17(5): 303–307.	160 (63 with metastases)	For metastases patients:1-year survival was 82.1%.	Safety results not reported separately
Zhou et al. Percutaneous microwave ablation of liver cancer adjacent to the gastrointestinal tract. Journal of Gastrointestinal Surgery 2009; 13(2): 318–324.	152 (28 with metastases)	NA	Result not reported separately

NA: not applicable as results not reported separately for primary and metastatic cancer groups

Studies excluded from this assessment

Ajisaka H & Miwa K. Acute respiratory distress syndrome is a serious complication of microwave coagulation therapy for liver tumors. *Am J Surg* 2005;189(6): 730-733.

Amer A, Strickland A & White S. A simple stabilising technique for laparoscopic microwave ablation of liver tumours. *Ann R Coll Surg Engl* 2012; 94(2): 134.

Bhardwaj N, Strickland AD, Ahmad F, El Abassy M, Morgan B, Robertson GSM & Lloyd DM. Microwave ablation for unresectable hepatic tumours: Clinical results using a novel microwave probe and generator. *European Journal of Surgical Oncology* 2010; 36(3): 264–268.

Khalifa F. Treatment options for primary and metastatic liver cancer: Role of locoregional therapy. *Emirates Medical Journal* 2005; 23(2): 105–108.

Kierans AS, Elazzazi M, Braga L, Leonardou P, Gerber DA, Burke C, Qureshi W, Kanematsu M & Semelka RC. Thermoablative treatments for malignant liver lesions: 10-year experience of MRI appearances of treatment response. *AJR Am J Roentgenol* 2010; 194(2): 523-529.

Kuang M, Lu MD, Xie XY, Xu HX, Mo LQ, Liu GJ, Xu ZF, Zheng YL & Liang JY. Liver cancer: increased microwave delivery to ablation zone with cooled-shaft antenna--experimental and clinical studies. *Radiology* 2007; 242(3): 914-924.

Li M, Yu XL, Liang P, Liu F, Dong B & Zhou P. Percutaneous microwave ablation for liver cancer adjacent to the diaphragm. *Int J Hyperthermia* 2012; 28(3): 218-226.

Littlejohns P, Tamber S, Ranson P & Campbell B. Treatment for liver metastases from colorectal cancer. *Lancet Oncology* 2005; 6(2): 73.

Liu C, Wang Y, Yu X, Dong B, Zhou P, Ren H & Liang P. Is percutaneous microwave ablation of liver tumor safe for patients with renal dysfunction. *Eur J Radiol* 2011; 79(2): e103-e107.

Meloni MF, Andreano A, Franza E, Passamonti M & Lazzaroni S. Contrast enhanced ultrasound: Should it play a role in immediate evaluation of liver tumors following thermal ablation? *Eur J Radiol* 2012; 81(8): e897-e902.

Murakami T, Shibata T, Ishida T, Niinobu T, Satoh T, Takamura M, Shibata N, Takami M & Nakamura H. Percutaneous microwave hepatic tumor coagulation with segmental hepatic blood flow occlusion in seven patients. *AJR Am J Roentgenol* 1999; 172(3): 637-640.

Ohmoto K & Yamamoto S. Percutaneous microwave coagulation therapy using artificial ascites. *American Journal of Roentgenology* 2001; 176(3): 817–818.

Petrovich Z, Langholz B, Astrahan M & Emami B. Deep microwave hyperthermia for metastatic tumors of the liver. *Recent Results Cancer Res* 1988; 107: 244-248.

Shiomi H, Naka S, Sato K, Demura K, Murakami K, Shimizu T, Morikawa S, Kurumi Y & Tani T. Thoracoscopy-assisted magnetic resonance guided microwave coagulation therapy for hepatic tumors. *Am J Surg* 2008;195(6): 854-860.

Yokoyama T, Egami K, Miyamoto M, Watanabe H, Hasegawa H, Iida S, Suzuki S, Nakamura Y, Okawa K, Hagiwara N, Takashima Y, Yoshioka M, Tajiri T & Onda M. Percutaneous and laparoscopic approaches of radiofrequency ablation treatment for liver cancer. *J Hepatobiliary Pancreat Surg 2003;* 10(6): 425-427.

Yu J, Liang P, Yu XL, Cheng ZG, Han ZY & Dong BW. Needle track seeding after percutaneous microwave ablation of malignant liver tumors under ultrasound guidance: Analysis of 14-year experience with 1462 patients at a single center. *Eur J Radiol* 2011; 81(1): 2495–2499.

Yu M-A, Liang P, Yu X-L, Cheng Z-G, Han Z-Y, Liu F-Y & Yu J. Liver abscess as a complication of microwave ablation for liver metastatic cholangiocarcinoma after bilioenteric anastomosis. *International Journal of Hyperthermia* 2011; 27(5): 503–509.