Horizon Scanning in Surgery: Application to Surgical Education and Practice

Irreversible electroporation for tumor ablation

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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 that is based on a search of studies published in the peer-reviewed literature. This report 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.

This report is a preliminary summary of the safety, efficacy and cost-effectiveness of irreversible electroporation (IRE) for tumor ablation.

Introduction

Indication

Cancer arises from the accumulation of somatic mutations in normal cells, which result in evasion of tumor suppression, inhibition of cell death, uncontrolled proliferation, and creation of a vascularized microenvironment (angiogenesis). Collectively, these mutations confer a growth advantage that contributes to the invasive and metastatic potential of cancer (Blanpain 2013). Cancer begins to harm the body when these damaged cells divide uncontrollably, resulting in tumors which can interfere with the functioning of the digestive, renal, nervous and circulatory systems.

The International Classification of Diseases for Oncology, Third edition (ICD-O-3), categorizes cancer based on the anatomical location in which the cancer first occurred (e.g. breast cancer, colon cancer) and the cell type and biological activity of the cancer (e.g. sarcoma, myeloma) (World Health Organization 2000). Cancer is further classified according to the disease stage. Staging describes the extent or severity of the cancer and is important in planning treatment and providing patients with a prognosis. There are various systems for classifying the stage of cancer; however, the TNM classification is the most widely used (National Cancer Institute 2013). Exceptions include cancers of the brain and spinal cord as well as cancers of the blood and bone marrow, which are classified differently. The stage of a person's cancer, using the TNM classification, is determined by:

- the size or extent of the tumor (T)
- the level of regional lymph node involvement (N)
- the number of tumors and metastases (M) (National Cancer Institute 2013).

Cancer is then classified according to stages I, II, III, and IV. Generally, the higher the stage the more extensive the disease, with stage IV indicating spread to distant tissues and organs. Classification and staging are determined by physical examination, imaging studies, laboratory tests, and pathology and surgical reports, and ultimately assist in determining the appropriate treatment pathway.

Burden of disease

In 2008, the America's region (North, South and Central America) had the second highest incidence of cancer worldwide, with the United States of America (USA) accounting for 60 per cent of recorded cases *(Globocan 2008a; Globocan 2008b; World Health Organization 2008)*. Within the USA, approximately 13 million people have a history of cancer (National Cancer Institute 2013) with an additional 1.7 million anticipated to be diagnosed in 2013 (American Cancer Society 2013). Despite this, the incidence rate of cancer has decreased over the past ten years (from 1999 to 2010), with the age-standardized incidence rate now at 463 per 100,000 people. It should be noted that the age-standardized incidence rate is highest among African Americans, men, and the elderly (National Cancer Institute 2013). The American Cancer Society suggests, however, that the incidence rate of cancer can be reduced if modifiable risk factors, such as obesity, physical inactivity, and poor nutrition, are addressed. It is estimated that more than one in four cancers are related to one or more of these modifiable risk factors. In addition, ensuring appropriate skin protection could prevent some of the two million skin cancers diagnosed each year (American Cancer Society 2013).

Cancer is a leading cause of mortality in the USA, accounting for approximately one in every four deaths. In 2013, an estimated 580,350 Americans will die from cancer (excluding in situ carcinoma), corresponding to approximately 1600 deaths per day (American Cancer Society 2013). Improvements in diagnostic and treatment methods have meant that the rate of cancer-related death has decreased by 1.5 per cent between 2001 and 2010. Also, the relative five-year survival rate of people with cancer has increased from 49 to 68 per cent between 1977 and 2008. However, survival rates vary greatly depending on the type and stage of cancer. Similar to the incidence rate of cancer, mortality rates are highest among African Americans, men, and the elderly (National Cancer Institute 2013).

Of particular importance to the studies included in this report are cancers of the digestive tract, specifically the foregut—the esophagus, stomach, duodenum, liver, gallbladder, pancreas and spleen. In 2013, cancer of the foregut will account for 7 and 15 per cent of all cancer diagnoses and deaths in the USA, respectively (American Cancer Society 2013). However, the main importance of these cancers is their extremely low survival rate. For example, pancreatic, esophageal, and liver cancers exhibit an average five-year survival of less than 40 per cent. In particular, pancreatic cancer has a five-year survival rate of approximately 6 per cent. The poor life expectancy associated with these types of cancers is thought to be related to the presentation of symptoms late in disease progression, which limits treatment options (American Cancer Society 2013).

Cancer of the foregut is typically diagnosed in the elderly, with a median age of both diagnosis and death occurring late in the sixth decade of life. The risk factors for foregut cancers include poor diet, high alcohol intake, obesity, family members who have had cancer, tobacco smoking, and medical conditions such as inflammatory bowel disease, hepatitis, and hypertension (American Cancer Society 2013).

Technology

Irreversible electroporation is a novel, minimally invasive, ablative treatment for cancer. Patients undergoing IRE can receive single or multiple treatments. In contrast to current ablative technologies, which rely on thermal energy to induce cell death, IRE utilizes non-thermal (electrical) energy to destroy tissue. The device consists of a generator/workstation, a foot pedal and 15 cm to 25 cm single-use bipolar or unipolar electrodes. The IRE procedure is performed under general anesthesia and a neuromuscular blocking agent is used to prevent muscle contractions caused by the electric current. The electrodes are introduced percutaneously, under computed tomography (CT) or ultrasound guidance (US) or during surgery (open or laparoscopic), and placed within and adjacent to the tumor. The number and type of electrodes will depend on the size, shape, and location of the tumor. In general, bipolar electrodes are used for tumors in difficult locations. A test pulse is delivered to measure tissue conductivity. If conductivity is inadequate, the electrode position is adjusted. A series of 90 electrical pulses is delivered in approximately two minutes, ablating the tumor. The electrodes can then be repositioned to ablate another area. Postoperative CT or magnetic resonance imaging (MRI) scans are used to confirm the extent of ablation. It is important to synchronize the electrical pulses to the refractory period of the patient's cardiac cycle to avoid arrhythmias.

The precise mechanism by which IRE achieves cell death remains to be determined. It has been suggested that the electric pulses delivered during IRE disrupt the electrochemical membrane potential of the cell, leading to membrane instability and the formation of nanopores. The nanopores allow an influx of extracellular ions that disrupt cellular homeostasis and initiate apoptosis (cell self-destruction) (Yu et al. 2012). It is important to note that cell death is apoptotic rather than necrotic, as seen in current ablative technologies. Apoptotic cell death is associated with less inflammation and generates clearer treatment boundaries than necrotic cell death. An additional advantage of IRE over current ablative techniques is the ability to ablate pathological tissue whilst leaving the extracellular environment (blood vessels, major ducts, and the extracellular matrix) intact. This allows treatment of tumors previously deemed unresectable owing to their location near critical structures. However, it is currently unclear why IRE selectively ablates only pathological tissue (Charpentier 2012; Kingham et al. 2012).

Intended population

Patients who may be eligible for IRE are likely to have undergone prior therapies, such as chemotherapy, or radiotherapy. However, most patients undergoing IRE are not eligible for surgery or have chosen not to undergo surgery. IRE is used to ablate liver, kidney, lung, prostate, and pancreatic cancers (Narayanan 2011). Often patients may receive combination therapy in addition to or prior to treatment with IRE. Treatments which may be considered comparators to IRE include ablative therapies and embolization procedures.

Stage of development

At present, the only marketed IRE device is the NanoKnife® by AngioDynamics (Latham, NY, USA). In the USA, the diffusion of IRE is difficult to determine. At present, eight clinical trials evaluating the NanoKnife in centers across the United States have been published. In 2012, Ochsner Health System reported that approximately a dozen (NanoKnife) devices are in use across the USA (Ochsner Health System 2013).

Regulatory approval

The NanoKnife received Food and Drug Administration (FDA) 510(k) clearance in 2008 for surgical ablation of soft tissue (Food and Drug Administration 2008). However, in 2011 AngioDynamics received a letter from the FDA alleging that the NanoKnife had been promoted for use beyond the currently cleared indications (Bloomburg 2013). In June 2013, the FDA granted investigational device exemption approval to conduct a clinical trial of the NanoKnife system for the ablation of prostate cancer (MedGadget 2013).

Internationally, the NanoKnife has received CE mark approval in Europe. However, the National Institute for Health and Care Excellence (NICE) recommends IRE be used only in the context of research.

Current clinical trials

The WHO, ANZ trial registry and Clinicaltrials.gov were searched for clinical trials evaluating IRE for tumor ablation. Ten clinical trials were identified (Table 1), eight of which are assessing the NanoKnife. The other two studies did not list the type of IRE device used. The trials consisted of one randomized controlled trial, one non-randomized comparative study, and eight case series studies, evaluating the safety and efficacy of IRE in patients with colorectal, prostate, liver, pancreatic, renal, and lung cancer. The main outcomes measured are the number of adverse events, patient quality of life, technical success, and tumor response.

Seven trials have surpassed or do not report their completion date; of these, three trials reported ongoing recruitment and four trials were not recruiting.

Table 1 Current clinical trials evaluating IRE for tumor ablation

Trial Identifier Country	Study design	Population	Interventions	N	Trial status	Estimated completion date
NCT01835977 Netherlands	Multicenter, single-blind (patients) randomized controlled trial	T1-T2 prostate cancer	Hemi-ablation with NanoKnife Total ablation with Nanoknife	32 54	Not yet recruiting	January 2018
NCT01563679 United States of America	Multicenter Case series	Cancer patients	Percutaneous ablation using locoregional therapies (RFA, IRE, MWA, cryoablation, chemical ablation)	500	Recruiting	August 2013
NCT01078415 France, Italy, Germany, Spain	Multicenter Case series	Hepatocellular carcinoma	IRE using the NanoKnife	25	Active, not recruiting	October 2011
NCT01726894 United Kingdom	Single center Case series	Prostate cancer	IRE using the NanoKnife	20	Not yet recruiting	September 2014
DRKS00004266 Germany	Single center Case series	Renal cell carcinoma	IRE	20	Not yet recruiting	NR
NCT01790451 Netherlands	Single center Case series	T1-T2 prostate cancer	IRE using the NanoKnife	16	Not yet recruiting	March 2014
NCT01369420 Italy	Single center Case series	Pancreatic adenocarcinoma	IRE using the NanoKnife	10	Active, not recruiting	December 2011
NCT01799044 Netherlands	Single center Case series	Colorectal cancer	IRE using the NanoKnife followed by immediate tumor resection	10	Recruiting	March 2013
NCT01442324 Italy	Single center Case series	Liver cancer or cholangiocarcinoma	IRE using the NanoKnife	5	Recruiting	September 2012
ACTRN12612000523808 Australia	NR	T1-T2 prostate cancer	IRE	5	Recruiting	NR

NR=not reported

Current treatment and alternatives

Current treatment pathways include surgical resection, ablative therapies, radiotherapy, chemotherapy, and watchful waiting. However, patient survival is dependent on the extent of resection, which may be limited by underlying comorbidities or the location of tumors next to critical areas such as blood vessels or major ducts (Lacroix et al. 2001). A patient's cancer treatment options will be guided by the comorbidities and preferences of the patient, as well as their cancer stage. Many treatments for cancer may be used in combination to provide better local control or palliation of symptoms.

Surgical resection is the preferred treatment for most tumors and is associated with an increased survival compared to other treatments (Li et al. 2012). Resection is aimed at removing pathologic tissue and achieving safe margins. This may also involve resection of the surrounding tissues, vessels and lymph nodes. Depending on the site and stage of cancer, surgical resection may be curative. Surgical resection may be undertaken using open or laparoscopic methods and is often performed in combination with chemotherapy and/or radiotherapy as adjuvant or neoadjuvant therapies. Surgical resection is not a direct comparator to irreversible electroporation, although patients receiving irreversible electroporation may have undergone prior resection.

Chemotherapy is a systemic therapy consisting of cytotoxic drugs which target rapidly dividing cells. Chemotherapy, while not curative, is commonly used as an adjuvant or neoadjuvant therapy to shrink tumors prior to surgery or radiation therapy, or to reduce the chance of cancer recurrence. Chemotherapy can also be used as a palliative therapy to improve symptoms and prolong life (Cancer Council 2012a).

Radiotherapy uses x-rays, gamma rays, electron beams, or protons to damage cancerous cells and inhibit cell division. Radiotherapy can be external or internal (brachytherapy) and is generally used in combination with other treatments such as surgery and chemotherapy. Radiotherapy can be used as a curative therapy, for local tumor control, and for palliation (The Cancer Council 2012b).

Treatments that may be used at specific sites and in more advanced disease include thermal ablative technologies and embolization techniques. Ablative and embolization procedures are not considered first-line therapies in patients with cancer, although they are used as adjunct treatments or as alternatives to resection in patients who are not able or choose not to undergo surgery (Kunzli, Abitabile & Maurer 2011).

Thermal ablative techniques include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation and laser ablation. Radiofrequency, microwave, and laser ablation use radio waves, microwaves, and laser light, respectively, to generate heat within the tumor and thereby coagulate and destroy cancer cells (Narayanan 2011; Bala Malgorzata et al. 2012; Konopke et al. 2012). In contrast, cryoablation utilizes liquid nitrogen or argon to freeze the lesion, causing ablation by disruption of cell membranes, coagulation, and induction of apoptosis (Erinjeri and Clark 2010). Chemical ablation includes percutaneous ethanol or acetic acid injection into the lesion, which causes cytotoxic cell death through dehydration. (Evans 2007).

Embolization techniques include trans-arterial embolization and trans-arterial chemo-embolization. These techniques involve injecting small particles into the blood vessels supplying a tumor, thereby blocking them and causing ischemic necrosis of the tumor (Riemsma Robert et al. 2013).

While ablative technologies may offer the benefit of tumor resection in patients deemed unsuitable for open surgery, these technologies, like surgery, have limited application. For example, ablative treatments are best suited for small, localized tumors (smaller than 3 cm) and are not recommended for tumors close to blood vessels and major ducts (Mulier et al 2005; Rhim et al 2008). In addition, ablative techniques are still being tested and the appropriate indications for these therapies are not yet well established.

Literature review

Search criteria

Keyword/MeSH terms utilized:

In Pubmed

#1 Electroporation[Mesh]

#2 Electroporation

#3 Irreversible electroporation

#4 IRE

#5 Electropermeabili$ation

#6 Non-thermal irreversible electroporation

#7 N-TIRE

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 Neoplasm[Mesh]

#10 Neoplasm*

#11 Cancer*

#12 Tumo*

#13 Metastas*

#14 lesion*

#15 #9 OR #10 OR #11 OR# 12 OR #13 OR #14

#16 #15 AND #8

Limits

Year 2008 – July 2013 (first clinical trial utilizing IRE published in 2010)

Databases utilized:

PubMed, EMBASE, the Cochrane Database of Systematic Reviews, York CRD databases, guideline.gov, NICE.org, WHO databases, Australia and New Zealand clinical trials registry

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	Meta-analysis, systematic reviews, randomized controlled trials, non-randomized comparative studies and case series ≥20 patients
Patient	Patients with primary or secondary cancer
Intervention	Irreversible electroporation
Comparator	Ablative technologies, chemotherapy, embolization technologies
Outcome	Mortality, adverse events, technical success, tumor recurrence (local, distal and overall), quality of life, length of hospitalization
Language	English only

Included studies

A total of 568 studies were retrieved using the search strategy outlined. No meta-analyses, systematic reviews or randomized controlled trials were identified. One non-randomized controlled study and three case series were selected for inclusion in this report. Table 3 outlines the level of evidence and characteristics of the included studies. Each of the studies was designated a level of evidence according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence (Appendix A). Further study details are provided in Appendix B, with excluded studies and reasons for exclusion provided in Appendix C.

Table 3 Characteristics of included studies

Study/location	Study type/Evidence level	Intervention	No. of patients	Cancer type	Duration of follow-up	Losses to follow-up
Martin et al. 2012 United States of America	Non-randomized comparative study with mixed current and historical controls Level III-2/III-3	IRE Standard therapy	n=54 n=85	Local advanced pancreatic cancer (stage III)	15 months	None
Cannon et al. 2013 United States of America	Prospective case series Level IV	IRE	n=44	Primary and secondary liver tumors	12 months	None
Thomson et al. 2011 Australia	Prospective case series Level IV	IRE	n=38	Primary and secondary tumors (liver, lung, kidney)	3 months	1
Kingham et al. 2012 United States of America	Retrospective case series Level IV	IRE	n=28	Primary and secondary liver tumors	12 months	None

The evidence available for inclusion was limited to one non-randomized comparative study (level III-2/3 evidence), and two prospective and one retrospective case series (level IV evidence). The sample size of the case series was small, ranging from 28 to 44 participants. The non-randomized control study reported the largest number of patients undergoing IRE, which was matched on a 1:1.5 ratio to patients receiving standard therapy (chemotherapy and/or

chemoradiation therapy). Inclusion and exclusion was reported in one study (Kingham et al. 2012). Patients were included if their tumors were not appropriate for resection due to pathological subtype, disease state, tumor location, or disease extent, or if tumors were sub-optimally located for RFA or MWA. Patients were excluded if they had a history of myocardial infarction or arrhythmia or the tumor was within the vicinity of a defibrillator or pacemaker. The remaining three studies did not mention an inclusion or exclusion criteria.

Patient characteristics were reported in three studies (Cannon et al. 2013; Kingham et al. 2012; Martin et al. 2012). However, the description was limited to age, gender and Karnofsky performance status (KPS). Martin et al. (2012) and Cannon et al. (2013) reported approximately equal numbers of males and females, with a median age of 60. Additionally, the median preoperative KPS score, which measures patients' general well-being and activities of daily living (range 0 [death] –100 [perfect health]), was 90 in Cannon et al. (2013) and 100 in Martin et al. (2012). Three studies reported previous cancer direct therapies, with most patients undergoing chemotherapy (range of 60% to 83% of all patients). Additional therapies included radiotherapy, surgical resection and RFA.

The size, number, type and stage of the tumors differed between the studies. The non-randomized study included patients with locally advanced (stage III) pancreatic cancer (Martin et al. 2012). The case series included patients with primary and secondary cancers within the liver, kidney, lung, breast, renal bed or lymph node (Table 4). The most featured cancer was metastatic liver cancer.

Table 4 Cancers included in each study

Thomson et al 2011	Kingham et al 2012	Cannon et al 2013	Martin et al 2012
Liver *Primary* HCC, n=11 (27%) HEHE, n=1 (2.7%) *Secondary* Metastasis from: Leiomyosarcoma, n=1 (2.7%) Neuroendocrine tumor, n=1 (2.7%) Breast cancer, n=2 (5.4%) Colorectal carcinoma, n=6 (16.2%) Ovarian cancer, n=1 (2.7%) Renal cell carcinoma, n=1 (2.7%) Kidney *Primary* RCC, n=4 (10.8%) *Secondary* Metastasis from: Colorectal carcinoma, n=2	Liver *Primary* HCC, n=2 (7.1%) *Secondary* Metastasis from: Colorectal, n=21 (75%) Pancreatic neuroendocrine tumor, n=2 (7.1%) Ampullary carcinoma, n=1 (3.6%) Hemangiopericytoma, n=1 (3.6%) Leiomyosarcoma, n=1 (3.6%)	Liver *Primary* HCC, n=14 (29%) *Secondary* Metastasis from: Colorectal n=24 (50%) Breast cancer, n=2 (4.2%) Non-small cell lung cancer, n=2 (4.2%) Carcinoid/neuroendocrine tumors, n=3 (6.3%) Melanoma, n=1 (2.1%) Renal cell carcinoma, n=1 (2.1%) Soft tissue tumor, n=1 (2.1%)	Pancreatic All patients Local advanced pancreatic cancer (stage III) (7th edition of the AJCC staging system)

(5.4%) Transitional cell carcinoma, n=1 (2.7%) Renal Bed Renal angiosarcoma recurrence, n=1 (2.7%) Lung *Primary* Non-small cell lung carcinoma, n=1 (2.7%) *Secondary* Metastasis from: Colorectal carcinoma, n=2 (5.4%) Breast cancer, n=1 (2.7%) Lymph nodes Palliative abdominal lymph node, n=1 (2.7%) Palliative thoracic lymph node, n=1 (2.7%)			

HCC=hepatocellular carcinoma; HEHE=hepatic hemangioendothelioma; RCC=renal cell carcinoma; AJCC =American Joint Committee on Cancer

The non-randomized controlled trial reported a median tumor size of 3.2 cm for patients undergoing IRE and 3.1 cm for those undergoing standard therapy. By contrast, the overall median tumor size observed in the case series was small (less than 3 cm). The largest size (2.7 cm) and range (1.1–11 cm) of tumors was reported by Cannon et al. (2013). The smallest tumor size (1 cm) was reported by Kingham et al. (2012). The diverse group of cancers included in Thomson et al. (2011) ranged from 1 to 8.8 cm.

The IRE procedure was performed similarly across all four studies with each study using the NanoKnife. However, both Martin et al. (2012) and Kingham et al. (2012) preferred to introduce the electrodes during open surgery. By contrast, Cannon et al. (2013) and Thomson et al. (2011) preferred to introduce electrodes percutaneously (under image guidance). In addition, the median number of electrodes varied between the studies, ranging from two to four. Thomson et al. (2011) did not report the median number of electrodes used; however, they noted it ranged from one to five.

Postoperative complications were assessed using a five point scale (range 0 [no complication] – 5 [death]) (Martin et al. 2002) by Martin et al. (2012) and Kingham et al. (2012). Chemotherapeutic adverse events were recorded and graded by Martin et al. (2012) and Cannon et al. (2012) as per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (grade 1, mild adverse event, to grade 5, death).

One patient was lost to follow-up in Thomson et al. (2011). The remaining studies did not report any losses to follow-up

Critical appraisal

Cannon et al. (2013) provided a brief exclusion criterion (an inability to tolerate surgery); however, the authors note that there was no standardized protocol dictating patients' selection criteria, which was left to the discretion of the treating physician. Both Martin et al. (2012) and Thomson et al. (2011) did not mention inclusion or exclusion criteria. However, three patients were rejected by both Martin et al. (2012) and Thomson et al. (2011) due to metastatic disease and underlying comorbidities respectively.

The main limitation of the included studies was the heterogeneous population of tumors.

Three studies administered adjuvant therapies during or immediately after IRE (Cannon et al. 2013; Kingham et al. 2012; Martin et al. 2012). Chemotherapy was the most frequently used adjuvant therapy (range of 4%–89% of all IRE patients), with a minority of patients receiving surgical resection, abdominal procedures, antibody therapy and radiotherapy. The potential confounding effects of heterogeneous adjuvant therapies makes the efficacy of IRE difficult to determine.

All studies were supported by research grants from AngioDynamics. In addition, the first author of the non-randomized controlled trial is a paid consultant for AngioDynamics.

Only one study (Thomson et al 2011) reported losses to follow-up.

It is unclear how patient selection was made in the non-randomized control trial (Martin et al. 2012).

Patients were consecutively recruited in Kingham et al. (2012). However, it is unclear whether patients were consecutively recruited in Martin et al. (2012), Cannon et al. (2013) and Thomson et al. (2011).

The non-randomized control trial compares a palliative treatment (chemotherapy) to an ablative treatment (IRE) (Martin et al. 2012).

Safety and efficacy

Safety

Mortality

One patient died before the 90-day follow-up in the non-randomized control trial. The case series did not report any deaths following IRE.

Adverse events

The non-randomized control study reported 56 and 200 adverse events in patients who received IRE and standard therapy respectively (Table 5). Dehydration or failure to thrive, hematologic and "other" were common complications observed in both treatment arms. However, patients undergoing standard therapy were more likely to exhibit diarrhea and liver insufficiency. Conversely, patients undergoing IRE were more likely to experience bile, pancreatic and duodenal leaks (Martin et al. 2012).

Within the case series, the number of adverse events ranged from 3 to 41 in 28 and 38 patients respectively (Table 6). Due to the diverse location of tumors treated, there was no general trend in the types of adverse events. The most significant adverse events, two cases of cardiac arrhythmia (Thomson et al, 2011), resulted in a change to the IRE procedure. Subsequent patients and clinical trials required the IRE pulses to be synchronized to the patient's cardiac cycle. However, despite synchronization, atrial fibrillation, ventricular tachycardia and an arrhythmia were still observed in two studies.

Table 5 Adverse events from the non-randomized control trial

Martin et al. (2012)	Complication	IRE cohort n (%)	grade	Standard therapy n (%)	grade
32 adverse events in 54 patients (IRE)	Hematologic	4 (7.1%)	-	20 (10%)	-
	Ileus	2 (3.6%)	2	-	-
	Bile leak	2 (3.6%)	-	-	-
200 adverse events in 85 patients (standard therapy)	Portal vein thrombosis/graft failure	4 (7.1%)	2, 5	8 (4%)	3-4
	Deep vein thrombosis	2 (3.6%)	2	9 (4.5%)	1-2
	Pulmonary	3 (5.3%)		9 (4.5%)	2, 3
	Renal failure	-	-	8 (4%)	1-3
	Ascites	3 (3.6%)	1, 3, 4	8 (4%)	1-3
	Wound infection	7 (12.5%)	1-2	6 (3%)	1, 2
	Dehydration/failure to thrive/nausea	8 (14.2%)		45 (22.5%)	1-4
	Bleeding	3 (3.6%)	2, 4	8 (4%)	1-3
	Diarrhea	3 (3.6%)	1	25 (12.5%)	1-4
	Duodenal leak	2 (3.6%)	4	-	-
	Liver insufficiency	1 (1.8%)	2	19 (9.5%)	2, 3
	Pancreatic leak	2 (3.6%)	3	-	
	Other	10 (17.8%)	1 -3	35 (17.5%)	1-5

Grade 0=no complication; Grade 1=oral antibiotics, bowel rest, basic monitoring, supportive care; grade 2=intravenous antibiotics, total parenteral nutrition, drainage not required, prolonged tube feedings, transfusions, arrhythmia, treated with intravenous medication, chest tube insertion; grade 3=interventional radiology drainage, operative drainage, intensive care unit admission, intubation, pacemaker placement, bronchoscopy; grade 4=chronic disability, organ resection, enteral (esophagostomy diversion); grade 5=death due to complication (Martin et al 2002).

Table 6 Adverse events from the case series

Study	Adverse Events
Thomson et al. (2011) 41 Adverse events in 38 patients	*Cardiac* Cardiac arrhythmias (transient), n=2 Ventricular tachycardia (no cardioversion required), n=4 Bigeminy (occurred after tachycardia), n=1 Transient supraventricular tachycardia, n=1 Atrial fibrillation (required cardioversion), n=1 *Pulmonary* Collapse of the right upper lobe (lung), n=1 Pneumothorax, n=3 *Urinary* Ureteric obstruction, n=1 Transient hematuria, n=2 Urinary tract infection, n=1 *Pain* Upper limb neurapraxia, n=2 Severe pain in the right upper abdomen and shoulder, n=1 *Other* Postural hypotension, n=1 Flushing allergic reaction, n=1 Advance carcinoid syndrome, n=1 *Biochemical* Increased alanine aminotransferase level at 3 months, n=1 Transient increase in bilirubin, n=9 Deterioration in renal function (up to 6 months), n=2 Transient increase in serum creatinine level (up to 1 month), n=6
Kingham et al. (2012) 3 adverse events in 28 patients	major vessel occlusion, n=1 arrhythmia, n=1 thrombus (grade 1 complication), n=1
Canon et al. (2013) 9 adverse events in 44 patients	Leukocytosis, n=1 Urinary tract infection, n=1 Dehydration, n=1 Biliary stent occlusion, n=1 Cholangitis due to biliary stent occlusion, n=1 Acute renal failure, n=1 Neurogenic bladder, n=1 Abdominal pain, n=1 Flank pain, n=1

Efficacy

Procedural time

The median procedural time in the non-randomized control trial was 180 minutes (range, 40–500) (Martin et al. 2012).

The range of operating times was reported by Thomson et al. (2011). The overall procedural time took between 2.5 and 4.5 hours, with the IRE procedure itself taking between 1.5 and 2 hours.

Length of stay

Three studies reported length of stay. Thomson et al. (2011) and Canon et al. (2013) discharged patients one day after undergoing IRE. In contrast, the median length of stay recorded in Martin et al. (2012) was seven days.

Technical success

Ablation success was defined by the ability to deliver all planned pulses (n=90) with no evidence of residual tumor recurrence at eight weeks (Cannon et al. 2013) or three months (Martin et al. 2012).

Technical success was reported in three studies (Table 7) and was defined as the ability to deliver at least 90 pulses at the appropriate voltage to the ablation area (Cannon et al. 2013; Martin et al. 2012; Kingham et al. 2011). The non-randomized control trial (Martin et al. 2012) reported a high technical success rate, as did the case series by Cannon et al. (2013). In contrast, in the Kingham et al. (2011) study, IRE was aborted on 19 separate occasions and 60 per cent of patients required repeated treatment due to uncertainty about the size of tumor ablation as predicted by the computer software. The main reason for aborting the procedure was due to a high IRE current.

Table 7 Technical success of IRE

	Martin et al. 2012	Thomson et al. 2011	Cannon et al. 2013	Kingham et al. 2012
Technical success, n (%)	n=53/54 (98%)	Not reported	n=45/46 (98%) By cancer type: Colorectal metastasis n=21/22 (95%) Hepatocellular carcinoma n=14/14 (100%) Other n=10/10 (100%)	n=21/53 (40%) Repeated treatment n=32/53 (60%) Reasons for aborting High current n=9/50 (18%) Reposition probes n=6/50 (12%) Unknown n=3/50 (6%) Arrhythmia n=1/50 (2%)

*Patients had more than one tumor

Complete ablation

Complete ablation was reported in 51 of the 54 patients enrolled in the non-randomized control trial (Martin et al. 2012). Complete ablation was reported in two case series and ranged from 48 per cent (n=39/81 in Thomson et al. 2011) to 100 per cent (n=48/48 in Cannon et al. 2013).

Further analysis revealed considerable variability in rates of complete ablation between the different types of tumors in Thomson et al. (2011). For example, primary liver tumors achieved the highest rate, with renal bed, lymph node and lung cancers reporting the lowest rates of complete ablation (Table 8). Within the lung, IRE was observed to produce “ground-glass opacity” which interfered with tumor margin visibility on CT scans. A subsequent biopsy of one patient revealed viable tumor cells at the margin of the treated lesion.

Table 8 Complete ablation by tumor type in Thomson et al. 2011

Cancer type	Complete ablation, n (%)
Liver (primary)	18/22 (82%)
Liver (secondary)	16/40 (40%)
Kidney	5/10 (50%)
Renal bed	0/1 (0%)
Lung	0/6 (0%)
Lymph node	0/2 (0%)

IRE vs. chemotherapy

IRE demonstrated an increase in local and distal progression-free survival when compared with standard therapy (14 versus 6 months, p=0.01; 15 versus 9 months, p=0.02, respectively). Overall survival time was also increased in patients who underwent IRE compared with standard therapy (20.2 versus 11 months, p=0.03). However, the survival graph demonstrated overlap at approximately 20 months due to the rapid progression of pancreatic cancer at this time point (Martin et al 2012).

Tumor response

Ablation recurrence was defined by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria in Martin et al. (2012), Cannon et al. (2013) and Thomson et al. (2011). However, the method of reporting recurrence differed. Martin et al. (2012) and Cannon et al. (2013) reported recurrence as either yes or no; Thomson et al. (2011) reported recurrence as a complete response (disappearance of all target lesions), progressive disease (at least a 20 per cent increase in the sum of lesion diameter) or stable disease (neither sufficient shrinkage to qualify for partial response nor sufficient gain to qualify for progressive disease).

All studies reported tumor recurrence. The longest follow-up was reported by Martin et al. (2012) and Cannon et al. (2013) who reported tumor recurrence at 12 and 15 months respectively. Conversely, Kingham et al. (2012) and Thomson et al. (2011) reported short follow-ups at six and three months respectively. Both Thomson et al. (2011) and Cannon et al. (2013) reported that tumors greater than 4 cm generally did not respond to IRE.

Three months

Immediate local tumor recurrence was fairly low in two studies (Table 9). The non-randomized control trial reported a local tumor-free survival of 89 per cent (Martin et al. 2012). Similarly, the case series by Cannon et al. (2013) reported a local tumor-free survival of 97 per cent. Conversely, the complete response rate was fairly low in Thomson et al. (2011) study. Only 47 per cent of tumors exhibited a complete response, with 40 and 14 per cent of tumors exhibiting either progressive or stable disease states, respectively. Thomson et al. (2011) noted that completely ablated tumors were more likely to demonstrate complete response at three months.

Primary liver tumors reported the highest complete response rate (63%), with the lowest being reported in cancers of the lung, lymph nodes, and renal bed (0%).

Distal recurrence was observed in two patients (Martin et al. 2012).

Table 9 Tumor recurrence and response at three months following IRE

Martin et al. 2012	Cannon et al. 2013	Kingham et al. 2012	Thomson et al. 2011
Overall recurrence n=8/54 (15%) Local recurrence n=6/54 (11%) Distal recurrence n=2/54 (4%)	Overall recurrence 2.6% Colorectal metastasis 0% Hepatocellular carcinoma 10% Other 0%	Not reported	Complete response n=38 (47%) Progressive disease n=32 (40%) Stable disease n=11 (13%) Primary liver CR, n=14 (63.6%) PD, n=3 (13.6%) SD, n=5 (22.7%) Secondary liver CR, n=19 (47.5%) PD, n=15 (37.5%) SD, n=6 (15%) Kidney CR, n=5 (50%) PD, n=5 (50%) Renal bed PD, n=1 (100%) Lung PD, n=6 (100%) Lymph nodes PD, n=2 (100%)

CR=complete response; PD=progressive disease; SD=stable disease

Six months

Three studies reported local tumor-free survival at six months (Table 10). The non-randomized control trial demonstrated a high local tumor-free survival at 76 per cent (Martin et al. 2012). However, both case-series reported an even higher local tumor-free survival at 95 and 94 per cent respectively (Cannon et al. 2013; Kingham et al. 2012).

Distal recurrence was observed in an additional two patients enrolled in Martin et al. (2012). Persistent disease was observed in one patient in Kingham et al. (2012).

Table 10 Tumor recurrence at six months following IRE

Martin et al. 2012	Cannon et al. 2013	Kingham et al. 2012	Thomson et al. 2011
Overall recurrence n=13/54 (24%) Local recurrence n=9/54 (17%) Distal recurrence n=4/54 (7%)	Overall recurrence (5%) Colorectal metastasis (6%) Hepatocellular carcinoma (10%) Other (0%)	Local tumor recurrence n=3 (6%) Persistent disease n=1 (2%)	Not reported

12 months

By 12 months, local tumor free-survival had dropped to 52 per cent for patients enrolled in Martin et al. (2012) and 60 per cent for Cannon et al. (2013) (Table 11).

Distal disease progression was observed in an additional seven (20%) patients enrolled in Martin et al. (2012).

Table 11 Tumor recurrence at 12 months following IRE

Martin et al. 2012	Cannon et al. 2013	Kingham et al. 2012	Thomson et al. 2011
Overall recurrence n=26/54 (48%) Local recurrence n=15/54 (28%) Distal recurrence n=11/54 (20%)	Overall recurrence (40%) Colorectal metastasis (50%) Hepatocellular carcinoma (50%) Other (0%)	Not reported	Not reported

15 months

Of the 54 patients who underwent IRE in Martin et al. (2012), 15 (28%) and 12 (22%) exhibited local or distal disease at 15 months.

Percutaneous versus surgical IRE

Cannon et al. (2013) compared patients who underwent percutaneous IRE to surgical (open or laparoscopic) IRE. Local tumor-free survival was similar between the two groups at 3 (100% for surgical versus 96.4% for percutaneous), 6 (100% versus 92.7%), and 12 months (80% versus 50.7%) (p=0.344). However, it is worth noting that the local tumor-free recurrence rate was lower at 12 months after percutaneous IRE (50.7% for percutaneous versus 80% for surgical).

Cost impact

No cost-effectiveness studies were identified in the published literature. The single-use IRE electrodes are reported to cost approximately $2,000 each (USD) (Martin et al. 2012). However, the precise capital outlay for the IRE unit and additional electrodes is unknown. Existing hospital CT and US guidance technology can be utilized.

Clinical practice guidelines and consensus statements

There were no guidelines identified in the literature.

NICE Interventional Procedure Guidance (IPG441-5)

The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has provided guidance on irreversible electroporation for the treatment of:

- renal cancer (NICE 2013a)
- liver metastases (NICE 2013b)
- pancreatic cancer (NICE 2013c)
- primary liver cancer (NICE 2013d)
- primary and metastatic lung cancer (NICE 2013e).

At present, NICE concludes that the safety and efficacy evidence of irreversible electroporation is inadequate in terms of quantity and quality. It is, therefore, recommended that IRE be used in the context of research only. NICE further recommends that studies should report on the effect of the procedure on both local tumor control and patient survival.

NICE acknowledged that IRE may result in less damage to surrounding structures, such as blood vessels, than other forms of ablative treatments. However, further evidence is required to support this claim.

Training and education impact

No training or education impact studies were identified in the published literature. However, Cannon et al. (2013) noted that for the open approach, at least five cases are required for the operating surgeon to have a basic competency in both the technique and patient selection. A further five cases would be required for the laparoscopic approach which is more difficult. They further suggest that five to seven patients would be required to gain basic competency in the percutaneous approach.

Summary

The evidence used in this report to assess the safety and efficacy of IRE was limited to a non-randomized controlled trial and three small case series.

The safety of IRE was difficult to determine with the rate and grade of adverse events varying considerably between the studies (range 3 to 41). However, all adverse events appeared to be managed effectively. Similarly, the rate of technical success and complete ablation also varied between the included studies, with two studies reporting high rates of technical success and complete ablation (98% and 100% respectively). In contrast, however, 60 per cent of all patients required retreatment in the study by Kingham et al. (2012). Local tumor-free survival was fairly high at three and six months follow-up (97% and 95% respectively). However, by 12 months follow-up, local disease-free survival had decreased to approximately 60 per cent. When compared with standard therapy, IRE demonstrated a significant increase in local (14 versus 6 months), distal (15 versus 9 months) and overall survival (20.2 versus 11 months).

It is worth noting, however, that the tumors treated in the included studies were generally small (less than 3 cm) and patients often received concurrent adjuvant therapies such as chemotherapy and surgical resection with margin extension, which makes it unclear whether the results observed were obtained as a result of IRE, the adjuvant therapy, or both. Therefore, additional studies should determine which adjuvant or neoadjuvant therapy works best in combination with IRE. Further limitations include the heterogeneous population of cancers and differences in the criteria used to assess adverse events and complete ablation, as well as differences in the methods used to perform IRE and the limited duration of follow-up. As such, the limited evidence cannot be used to make an informed decision regarding the safety and efficacy of IRE.

Recommendation

At present, there is limited information regarding the safety and efficacy of IRE. The included studies varied considerably in terms of safety (number of reported adverse events) and efficacy (technical success, complete ablation and local recurrence). In addition, while IRE has the potential to treat many cancer types, information regarding its use in cancers other than those of the liver and pancreas is limited. Furthermore, the precise mechanism of cell death and the ability of IRE to selectively ablate pathological tissue is yet to be determined. It is also unclear which tumor type responds best to IRE.

Despite this, the evidence base is expanding. Nine ongoing clinical trials were identified, of which one was a large (n=200) randomized controlled trial with long-term follow-up. Additional high-quality comparative studies of IRE versus other ablative techniques with long-term follow up and a focus on patient quality of life are required before an informed decision regarding the use of IRE can be made.

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Appendix A

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

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [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 'Aetiology' 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 or 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 is 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 and 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, for example, level II intervention evidence, level IV diagnostic evidence or 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 trials

Study	Martin et al. (2012)	Thomson et al. (2011)	Cannon et al. (2013)	Kingham et al. (2012)
Study type	III-2	IV (prospective)	IV (prospective)	IV (retrospective)
Location	USA, Multi-center	Australia, Single Center	USA, Multi-center	USA, Single center
Study period	*IRE*: December 2009 – March 2012 *Standard therapy*: December 2008 – March 2012	November 2008 – November 2009	2009–2011	January 2011 – November 2011
Number of included patients (n)	IRE: n=54 Standard therapy: n=85	n=38	n=44	n=28
Inclusion/exclusion criteria	Not reported Three patients were rejected due to metastatic disease.	Not reported Three patients were rejected due to medical comorbidities: cardiac failure, recent liver embolization, and imminent liver failure.	There was no standardized protocol dictating patient selection, which was left to the discretion of the treating physician. Exclusion criteria: unfit to undergo general anesthesia, extensive extra-hepatic disease, and multifocal hepatic disease, not amenable to complete ablation.	Inclusion criteria: Tumors which were not appropriate for resection due to pathologic subtype, disease state, tumor location, disease extent, and that were sub-optimally located for RFA or MWA. Exclusion criteria: Location of lesions in the vicinity of defibrillators or pacemakers, history of cardiac arrhythmia or recent myocardial infarction.
Indication for IRE	The decision to perform pancreatic resection with IRE or IRE alone was at the surgeon's discretion, based on intraoperative assessment, patient comorbidities, previous therapy, and patient desire.	Not reported	The majority of patients (72%) had received and failed at least one other form of therapy prior to being referred for IRE.	Tumors that were not appropriate for resection because of pathologic subtype, disease stage, tumor location, or disease extent, and that were suboptimally located for RFA or MWA as determined by the treating physician.
Patient details, n (%)	KPS scale: *IRE* 100%, n= 34/54 (64%) 90%, n= 10/54 (18%) 80%, n= 10/54 (18%)	Not reported	Median age: 60 years. Sex: Males, n=23 (52%) Females, n=21(48%) Mean BMI: 24.9 kg/m^2	Median Age: 61 years (range 32–81) Sex: men, n=17 (61%); women, n=11 (39%)

Study	Martin et al. (2012)	Thomson et al. (2011)	Cannon et al. (2013)	Kingham et al. (2012)
	Standard therapy 100%, n= 60/85 (70%) 90%, n= 18/85 (16%) 80%, n= 17/85 (14%) Median time from diagnosis to IRE: 5.1 months (range 1 - 32).		Median KPS scale: 90 (range 80–100, 14 versus 6 months, p=0.01; 0) Medical comorbidities: Cardiac/peripheral vascular, n=4 (10%) Pulmonary, n=4 (10%) Diabetes mellitus, n=4 (10%) Hypertension, n=22 (50%) Chronic hepatitis, n=8 (20%) Cirrhosis, n=6 (15%)	
Tumors	Not reported	Primary and secondary tumors	Primary and secondary tumors	Primary and secondary tumors
Tumor size	Average tumor size: *IRE* Axial, 3.2 cm (range 1–5.5) Anterior-posterior, 2.6 cm (range 1–4.7) Caudal-cranial, 2.9 cm (range 1–4.9) *Standard therapy* Axial, 3.1 cm (range 1.9–5) Anterior-posterior, 2.6 cm (range 1.1–5.1) Caudal-cranial, 2.8 cm (range 1.5–5)	Tumor size: 1–8.8 cm Average volume of tumors treated: 46 cm^3 (range 9–476)	Median tumor size: Colorectal metastasis, 2.7 cm (range 1.2–11) Hepatocellular carcinoma, 2.1 cm (range 1.3–4.5) Other, 2.5 cm (range 1.1–5.0)	Median tumor diameter: 1 cm (range 0.5–5) <1cm, n=36 (60%) 1– 2cm, n=11 (18%) 2.1 – 3cm, n=12 (20%) >3cm, n=1 (2%)
Comparison population	Patients who underwent standard therapy (chemotherapy and/or chemoradiation therapy) alone. Matching was performed after 4 months of induction therapy by propensity scoring, with scores based on patient age, size of tumor, performance status, cardiac comorbidities and pulmonary comorbidities.	N/A	N/A	N/A
Neoadjuvant therapy, n (%)	*IRE*: Prior rounds of chemotherapy: 83 Prior radiation therapy: 24 *Standard therapy*: Prior rounds of chemotherapy: 147	Not reported	Systematic chemotherapy, n=26 (60%) Any liver directed therapy, n=22 (55%) Hepatic resection, n=10 (23%) RFA, n=5 (12%) Hepatic arterial therapy, n=10 (23%) 3D conformal radiation, n=6 (15%)	Preoperative chemotherapy, n= 24 (86%)

Study	Martin et al. (2012)	Thomson et al. (2011)	Cannon et al. (2013)	Kingham et al. (2012)
	Prior radiation therapy: 5FU + radiation, n=42 (50%) Gemzar + radiation, n=15 (18%)			
Adjuvant therapy, n (%)	*IRE*: Chemotherapy (during study period), n=47 (87%) Radiation therapy, n=10 (19%) *IRE + Standard therapy* Pancreatic operations Whipple, n=9 (6.5%) Subtotal, n=10 (7.1%) Other operations Hepaticojejunostomy, n= 10 (7.1%) Gastrojejunostomy, n= 19 (13.7%) Partial gastrectomy, n= 6 (4.3%) Celiac plexus block, n= 9 (6.5%) Other, n= 29 (20.9%)	Not reported	Chemotherapy concomitant with IRE, n=2 (4.5%) Avastin and Erlotinib at the time of IRE, n=1 (2.3%) Concurrent abdominal procedure, n=7 (15.9%)	IRE was performed alone or in combination with liver resection, thermal ablation or implantation of a hepatic artery infusion pump. Postoperative chemotherapy, n=20 (71%) Perioperative pump chemotherapy, n=2 (7%)
Total number of IRE procedures in each study	Not mentioned	n=69	n=48	n=31
Surgery or percutaneous IRE, n (%)	Laparoscopic, n=2 Open, n=52	Percutaneous	Percutaneous, n=28 (64%) Laparoscopic, n=2 (5%) Laparotomy, n=14 (32%)	Percutaneous, n=6 (19%) Laparotomy, n=25 (81%)
Number of electrodes used	Median, n=4 (range 3–6)	Range: 1–5	Colorectal metastasis Median, n=3 (range 2–5) Hepatocellular carcinoma Median, n=3 (range 2–4) Other Median, n=4 (range 3–5)	Two, n= 36 (64%) Three, n= 11 (20%) Four, n= 6 (11%) Five, n= 3 (5%)
Number of tumors treated	Not reported	n=59	Not reported	n=65
IRE technique	Local-progression-free survival 14 vs. 11 months (p=0.01) Distal-progression-free survival	Not reported	Local-recurrence-free survival 3 months Surgical=100%	Not reported

Study	Martin et al. (2012)	Thomson et al. (2011)	Cannon et al. (2013)	Kingham et al. (2012)
	15 vs. 9 months (p=0.02) Overall survival 20.2 vs. 11 months (p=0.03)		Percutaneous=96.4% 6 months Surgical=100% Percutaneous=92.7% 12 months Surgical=80% Percutaneous=50.7%	
Length of stay, n	Not reported	Patients discharged within 24 hours, n=34 (89%)	Median=1 day	Not reported
Statistical analysis		Not reported	Continuous variables were summarized by median and interquartile range and compared using the Wilcoxon-Mann-Whitney test. Categorical variables were summarized as count (percentage) and analyzed using Chi-squared or Fischer's exact test. Survival estimates were determined according to the Kaplan and Meier method, with survival curves compared by the log rank test.	Not reported

BMI = body mass index; KPS = Karnofsky performance status scale; MWA = Microwave ablation; RFA = Radiofrequency Ablation

Appendix C

Additional papers not included in this assessment

Article reference	N	Conclusions	Reason for exclusion
Pech, M, Janitzky, A, Wendler, JJ, Strang, C, Blaschke, S, Dudeck, O, Ricke, J & Liehr, UB 2011, 'Irreversible electroporation of renal cell carcinoma: a first-in-man phase I clinical study', *Cardiovasc Intervent Radiol,* vol. 34, no. 1, pp. 132–8.	6 Renal tumors	No mortality, 1 complication was reported (supraventricular extrasystole)	Safety only, small number of patients (<20)
Bagla, S & Papadouris, D 2012, 'Percutaneous irreversible electroporation of surgically unresectable pancreatic cancer: a case report', *J Vasc Interv Radiol*, vol. 23, no. 1, pp. 142–5.	1 Pancreatic cancer	No mortality or complications. Liver metastasis developed 3 months after treatment, successfully treated with RFA. No residual disease at 6 months	Small number of patients (<20)
Kasivisvanathan, V, Thapar, A, Oskrochi, Y, Picard, J & Leen, EL 2012, 'Irreversible electroporation for focal ablation at the porta hepatis', *Cardiovasc Intervent Radiol*, vol. 35, no. 6, pp. 1531–4.	1 Liver cancer	No mortality or complications. At 3 months, tumor size had decreased by 39%	Small number of patients (<20)
Martin, RC, 2nd, McFarland, K, Ellis, S & Velanovich, V 2012, 'Irreversible electroporation therapy in the management of locally advanced pancreatic adenocarcinoma', *J Am Coll Surg,* vol. 215, no. 3, pp. 361–9.	27 Pancreatic cancers	One patient died within the 90 day follow-up. 18 complications occurred, 4 of which were possibly device-related. At the 90 day follow-up, there was 100% ablation success with no local recurrence.	Small number of patients (<20), time period overlaps with the larger non-randomized control trial by Martin et al. (2012) – could be the same patients.
Usman, M, Moore, W, Talati, R, Watkins, K & Bilfinger, TV 2012, 'Irreversible electroporation of lung neoplasm: a case series', *Med Sci Monit,* vol. 18, no. 6, pp. CS43–7.	2 Lung cancers	Patient 1: At six months, tumor size increased. Patient 2: At 2 months, increase in tumor mass. At 9 months, tumor appeared to invade nearby tissue.	Small number of patients (<20)
Cheung, W, Kavnoudias, H, Roberts, S, Szkandera, B, Kemp, W & Thomson, KR 2013, 'Irreversible electroporation for unresectable hepatocellular carcinoma: initial experience and review of safety and outcomes', *Technol Cancer Res Treat,* vol. 12, pp. 233–41.	11 Liver cancers	No major complications. Four patients developed urinary retention (transient) and seven developed local post-procedural pain (transient). 73% of tumors were completely ablated, with 93% success for lesions ≤3cm. Six patients required repeated treatment for recurrent or residual disease. Local recurrence-free period was 18±4 months, distal recurrence was 14±6 months.	Small number of patients (<20)

Studies excluded from this assessment

Article reference	Reason for exclusion
Mannelli, L, Padia, SA, Yeung, RS & Green, DE 2013, 'Irreversible electroporation of a liver metastasis', *Liver Int,* vol. 33, no.1, p. 104.	No reporting of safety or efficacy data