Systematic review of irreversible electroporation in the treatment of advanced pancreatic cancer

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Abstract

Background: Irreversible electroporation (IRE) is a novel procedure to combat pancreatic cancer, whereby high voltage pulses are delivered, resulting in cell death. This represents an ideal alternative to other thermal treatment modalities, as there is no overriding heat effect, therefore reducing the risk of injury to vessels and ducts.

Methods: Multiple databases were searched to January 2014. Primary outcome measures were survival and associated morbidity. 41 articles were initially identified; of these 4 studies met the inclusion criteria, yielding 74 patients in total.

Results: 94.5% of patients had locally advanced tumours, the remainder had metastatic disease. Treated tumour size ranged from 1 to 7 cm. IRE approach included open (70.3%), laparoscopic (2.7%) and percutaneous (27%; ultrasound-guided 30%, CT-guided 70%) Morbidity ranged from 0 to 33%; due to the high number of simultaneous procedures performed (resection/bypass) it was difficult to ascertain IRE-related complications. However no significant bleeding occurred when IRE-alone was performed. Survival statistics suggest a prognostic benefit. Reported survival included: 6 month survival of 40% \((n = 5)\) and 70% \((n = 14)\); PFS and OS 14 and 20 months respectively \((n = 54)\). Results of most interest showed a significant survival benefit in matched IRE vs non-IRE groups \((PFS 14 \text{ vs } 6 \text{ mths}; p = 0.01, \text{ OS } 20 \text{ vs } 11 \text{ mths}; p = 0.03)\).

Conclusion: Initial evidence suggests IRE incurs a prognostic benefit with minimal morbidity. More high quality research is required to determine the role IRE may play in the multi-modal management of pancreatic cancers.

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Keywords: Irreversible electroporation; Pancreatic cancer

Introduction

Pancreatic cancer remains one of the most challenging malignancies to treat due to its late presentation, aggressive nature and resistance to most currently available treatments. As a result prognosis is dismal, with 1 and 5 year survival rates being 18% and 3.5% respectively. It represents the fifth most common cause of cancer death in the UK, with approximately 8000 cases per year.\(^1\) The location of the pancreas means patients are often asymptomatic until the disease presents at an advanced stage, at which point curative resection is not possible due to either distant metastases or involvement of local vascular structures, such as the portal vein, coeliac trunk and superior mesenteric vessels.\(^2\) At presentation only 20% of patients are suitable for surgery.\(^3\)

In the palliative setting combination chemotherapy regimens have been developed to improve survival. This includes the FOLFIRINOX/gemcitabine combination which demonstrated marginally improved survival,\(^4\) and more recently the promising phase 3 study of Abraxane (nab-paclitaxel) plus gemcitabine demonstrating significantly improved OS, PFS and response rate.\(^5\) Patients can also receive adjuvant chemotherapy post-resection to combat the risk of recurrence. However despite many well-designed RCT’s describing aggressive chemotherapy (E-\(\text{PAC}\))\(^6\) and/or radiotherapy\(^7\) combined with surgical resection, survival rates have remained relatively unchanged with postoperative 5 year survival of 10−20%.

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Neoadjuvant chemotherapy for borderline resectable locally advanced tumours also has a role, with evidence suggesting this can offer the potential for cure by inducing resectability in 30–40%.

An alternative method of providing symptomatic relief, survival benefit, and potentially downsizing tumours to facilitate resection involves a number of ablative techniques. This includes radiofrequency ablation (RFA) and microwave ablation (MWA). These modalities demonstrate promising results, however due to the highly vascular nature of the pancreas, inadvertent thermal injury to adjacent vessels can result in significant bleeding. Furthermore thermal injury to the pancreatic and bile duct can result in fistulae or bile leaks respectively.

Irreversible electroporation (IRE) is a relatively novel procedure which represents a potentially ideal solution for the ablative treatment of pancreatic tumours as no thermal tissue damage occurs, thus avoiding vessel or duct injury. This technique involves the delivery of a high voltage current through electrodes placed into the tumour, either under radiological guidance, via laparoscopy or by an open surgical approach. This method results in the creation of pores in the phospholipid bilayer, and the cell membrane damage disrupts intra-cellular homeostasis, ultimately causing apoptotic cell death, whilst sparing surrounding structures such as vessels, ducts (biliary and pancreatic) and connective tissue.

This review concentrates on current evidence regarding the clinical applicability of IRE in the management of pancreatic tumours, examining efficacy, safety and survival.

Methods

Search strategy

Multiple databases were searched up to January 27th 2014, including Medline, Embase, Pubmed, Cochrane library and Google Scholar. Search terms based on MeSH key words included pancreatic cancer/carcinoma/neoplasm and irreversible electroproporation. The literature was searched and data extracted independently by the first author (JM), and any inconsistencies discussed with a second author (SW).

Criteria for inclusion/exclusion

Studies included were any retrospective or prospective case series or reports. The main aim of this review is to examine the safety and efficacy of IRE, therefore the types of outcome measurements concentrated on survival and associated morbidity. Studies were also included to observe details regarding patient selection and the IRE procedure itself. Given the above criteria a number of conference abstracts were excluded; however given the paucity of evidence on the subject, these will be discussed briefly in a later section of this review. Other reasons for exclusion included; animal or in vitro studies; studies not representing primary research (review article or letter to editor etc.); and any studies representing duplication of publications by the same institution.

Results

The search strategy initially yielded 33 citations. After review of titles and abstracts 27 studies were excluded with reasons as documented in Fig. 1. Two studies were excluded after full text review, leaving a total of 4 included studies.

Study characteristics

Table 1 demonstrates basic characteristics of the treatment groups. Of the 4 studies included, 3 were case series and 1 was a case report, amounting to a total of 74 patients who underwent IRE. Most studies treated patients with locally advanced disease (96%), however there were instances of IRE being performed in those with distant metastases (4%); it is notable that these patients all failed to respond to chemotherapy, therefore IRE was being used as a “salvage” therapy. Mansson et al. did not disclose tumour location; however of the remaining studies 60.9% were in the head of pancreas, and 39.1% in the body or tail. The sizes of tumours treated were similar, with median sizes of 3–4 cm diameter; the smallest and largest tumour treated was 1 cm and 7 cm respectively.

IRE procedure details

Table 2 details information regarding the timing and technique of the procedure. The time from diagnosis to IRE was significantly different when comparing the two larger studies ranging from 1 to 50 months. Martin et al. are the only authors to utilise IRE whilst simultaneously performing surgery. In another 19 patients, during initial exploratory surgery the degree of arterial encasement was much less severe than anticipated, so much so that resection...
was deemed appropriate. As a result IRE was initially performed for margin accentuation and extension, followed by either a Whipple’s procedure (9/54) or partial pancreatectomy (10/54). Of those having simultaneous treatment 29 patients underwent palliative bypass in the form of hepaticojejunostomy (10/54) or gastrojejunostomy (19/54) at the same time as the IRE procedure. As such it can be seen that the majority of procedures performed by Martin et al. were open procedures, in contrast to the remaining studies which rather utilise IRE in the non-surgical radiologically guided setting, using either ultrasound or computed tomography. Regarding the types of IRE probes, the majority that are used are monopolar; whilst Narayanan et al. did not specify exact numbers, they stated that monopolar was more commonly used.

**Morbidity and survival**

Table 3 details reported morbidity and survival data. Martin et al. were the only study to declare a specific morbidity follow up period of 90-days post-IRE, whilst the remaining studies simply specify complications potentially related to the procedure. Associated complications ranged from 0 to 33%. Martin et al. experienced the most morbidity, however this is most likely associated with the high number of open procedures and simultaneous procedures performed, and potentially a more prolonged follow up period. Adverse events encountered included wound infection (n = 7), bile leak (n = 2), pancreatic leak (n = 2), DVT (n = 2), portal vein thrombosis/graft failure (n = 4), pulmonary (n = 3), bleeding (n = 3), ascites (n = 3) and ileus (n = 2). One IRE specific complication occurred; needles had been placed by a transduodenal approach and the patient suffered from a duodenal leak from these puncture sites. In the remaining studies pancreatitis occurred in 2 cases; in both instances this resolved with conservative management.

When considering the associated prognostic benefit of IRE, one must consider any adjunctive treatment the patients may have already received or after the IRE treatment. In the 2 studies that specifically reported this, 63/68 (92.6%) had received chemotherapy and/or radiotherapy. Survival results of most interest are presented by Martin et al., who compare patients who underwent IRE and chemotherapy and/or radiotherapy (n = 54) with a chemotherapy and/or radiotherapy alone (n = 85). These patients, also with locally advanced tumours, were matched with each IRE patient based on a propensity score, centred on patient age, tumour size, performance status, cardiac co-morbidities and pulmonary co-morbidities. When cross-examining the two groups, tumour size, performance status and prior chemo/radiotherapy all revealed p values >0.05. Comparing the IRE group with the non-IRE group, there was an improved local progression free survival (14 vs 6 months, p = 0.01) and distant progression free survival (15 vs 9 months, p = 0.02) and overall survival (20.2 vs 11 months, p = 0.03). However Kaplan Meier survival curves were found to converge at 20 months due to rapid progression of distant disease in the IRE group. Patients who underwent resection with simultaneous IRE did not have significantly improved survival compared to IRE alone (23.1 months vs IRE alone 17.2 months, p = 0.1), most likely due to the development of metastatic disease being the most common cause of death in both groups.

Narayanan et al. reported limited follow up data as the median OS was not reached. However 6 month OS was 70% (95%CI 35–93). Median event free survival was 6.7 months (95%CI 0.7–12.7). Localised disease was found
to result in significantly prolonged OS compared with the metastatic disease group \((p = 0.02)\). However there was no difference in OS comparing those who went on to resection.

Masson et al. had limited follow up duration, however 40% were still alive at 6 months, and there was no mortality within 30 days. The patient in the Bagla case report was found to have a liver metastasis at 3 months follow up imaging; this was treated with RFA and subsequent imaging at 6 months post-IRE revealed no progressive or recurrent disease.

**Results from selected abstracts**

Despite the limited amount of data that can be extracted from abstracts we deemed it worthwhile to present any salient findings from conference abstracts, particularly given the small amount of evidence regarding the use of IRE in pancreatic cancer. Of the 15 abstracts excluded in the initial data extraction stage, 3 yielded relevant results. The remaining abstracts were excluded for the following reasons; included duplication of research already discussed, there were no pancreas specific outcomes stated in the abstracts, the studies were not relevant to the pancreas or were animal studies.

Watkins et al. presented a retrospective case series of 16 patients with pancreatic cancer, with 13 having in situ ablation and 3 undergoing margin treatment prior to distal resection. Patients were selected due to the proximity/involvement of the tumours to the adjacent vasculature, biliary tree and viscera. One patient died peri-operatively due to bleeding and one patient experienced pancreatic fistula post-distal pancreatectomy. No other significant complications specific to IRE were experienced. Bagla et al. reported a series of 4 patients; one procedure was complicated by partial splenic infarction, and one patient suffered from intra-operative transient hypertension which settled in the postoperative period. No mortality was reported within 30 days. Brauacci et al. report a case of a patient with a T4N1Mo unresectable tumour who underwent US-guided IRE following 6 months of chemotherapy. Subsequent CT scans up to 6 months post-IRE revealed a reduction in size of tumour from \(40 \times 22\) mm to \(60 \times 30\) mm, with an associated decrease in ca19-9.\(^{18}\)

**Discussion**

Pancreatic cancer remains one of the most difficult malignancies to manage and survival remains poor due to late presentation with either locally advanced or metastatic disease. Typical management currently consists of chemotherapy, with or without radiotherapy, in an attempt to reduce tumour growth and dissemination, and control symptoms such as pain from neural invasion.

A multi-modal approach to treatment offers the greatest promise for improved outcomes, and the use of localised targeted minimally invasive therapies represent a useful adjunct by inducing tumour regression. This has typically included RFA, MWA and cryosurgery. RFA is a localised thermal treatment used to treat a variety of solid organ malignancies (lung, kidney, prostate, brain and breast) and has been particularly successful in treating small liver tumours.\(^{19}\) However its use remains controversial due to high complication rates, with a systematic review indicating expected morbidity of 28%\(^{20}\); this can be attributed to the fact the pancreas is highly vascular and in close proximity to ductal structures, therefore inadvertent thermal injury to adjacent vessels and ducts poses a potential risk of bleeding (22%), pancreatic fistulae (14%) or bile leaks (14%). Pancreatitis (2.9%) can also occur and can be particularly severe.\(^{20,21}\) The use of RFA in combination regimes has demonstrated potential, whereby chemo-radiotherapy has been observed to induce peri-tumoural fibrosis, therefore reducing thermal conduction in the surrounding normal parenchyma, and thus facilitating a successful RFA procedure with a reduced risk of associated pancreatitis or fistulae formation.\(^{22}\) Microwave ablation has shown promising results with only minor morbidity, even in the treatment of tumours with major vascular involvement.\(^{23}\)

The electromagnetic mechanism of this technique means

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**Table 3**

Morbidity and survival statistics; CT = chemotherapy, RT = radiotherapy, PFS = progression free survival, OS = overall survival, EFS = event free survival.

<table>
<thead>
<tr>
<th>Author</th>
<th>Complications</th>
<th>Pre-IRE Tx</th>
<th>Post-IRE Tx</th>
<th>Recurrence/survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin ((n = 54))</td>
<td>9 (33%) (\frac{1}{4}) duodenal leak from IRE needle puncture</td>
<td>CT (+) RT 49 (90%)</td>
<td>47 (37 CT, 10 CT + RT)</td>
<td>Comparing IRE + CT vs CT alone: local PFS (= \frac{1}{4}) vs 6 mths ((p = 0.01)), Distant PFS 15 vs 9 ((p = 0.02)), OS 20 vs 11 ((p = 0.03))</td>
</tr>
<tr>
<td>Narayanan (n = 14)</td>
<td>2 (14%) — pancreatitis, pneumothorax</td>
<td>CT in 4, CT + RT in 10, previous whipples in 1</td>
<td>2 — resection</td>
<td>Median EFS 6.7 mths (0.7—12.7), 6 mths-OS 70% ((95%CI 35—93%)) — significantly longer OS in localised vs metastatic group ((p = 0.02))</td>
</tr>
<tr>
<td>Mansson (n = 5)</td>
<td>1 (20%) — subclinical pancreatitis</td>
<td>All patients unresectable after CT/RT, or deemed unfit for surgery or CT</td>
<td>1 — whipples</td>
<td>6 mths survival — 40%, 30 day mortality — 0</td>
</tr>
<tr>
<td>Bagla (n = 1)</td>
<td>0</td>
<td>Nil</td>
<td>Chemo and RFA to liver met</td>
<td>Liver metastasis at 3 mths, Post-Tx MRI at 6 mths revealed no progression/recurrence</td>
</tr>
</tbody>
</table>

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there is no tissue impedance as experienced in RFA whereby water vapour and charring act as electrical insulators; as a result higher intra-tumoural temperatures can be achieved with larger ablation volumes in a shorter time. Nonetheless the theoretical risk of thermal injury to vessels and ducts still exists. More recently cryoablation has also been utilised in the palliative setting, with a retrospective study of patients who underwent cryoablation combined with palliative bypass demonstrating tumour shrinkage and a reduction in tumour markers. Regarding morbidity, a recent study of 73 patients with unresectable PDAC showed patients commonly experienced transient abdominal pain (76%), fever (49%) and hyperamylasaemia (57%), whilst 3.4% experienced intra-abdominal bleeding which necessitated drainage, demonstrating damage to vessels is still a relative concern, albeit less so than in the thermal procedures.

Treating the pancreas with a thermal procedure carries an inherent risk of damage to the host of vascular structures, as well as stromal damage resulting in inflammation, therefore the risk profile remains a concern. Furthermore heat sink remains a major limitation. This process refers to heat loss in the tissues due to a cooling effect by blood in adjacent vessels, resulting in incomplete ablation and resultant increased risk of local recurrence. Therefore tumours in proximity to major vessels such as the hepatic veins, the portal vein and inferior vena cava are at greatest risk of this effect.

Irreversible electroporation (IRE) is a novel non-thermal technique which has been used for tumours of the liver, lung, prostate, kidney and pancreas. The procedure is performed under general anaesthesia, as it is necessary to administer a neuromuscular blocking agent to prevent uncontrolled severe muscle contractions. This technique involves the delivery of high frequency energy (pulses of standard default voltage of 1500 V/cm DC) between electrodes placed into the tumour. Unipolar electrodes are now considered the gold standard, as opposed to the use of a single bipolar electrode. Multiple short pulses are delivered which cause permeabilisation and destabilisation of the cell membrane lipid bilayer, and in turn triggers cell death. At low intensity this technique causes reversible damage to the cell membranes and is often used in vitro to allow the passage of large macromolecules such as drugs or proteins. However by altering the duration, magnitude and number of transmitted electrical pulses the effect becomes irreversible.

One of the most significant benefits of IRE is the fact it does not induce a significant thermal effect, and therefore there is no heat sink effect. In vitro studies have demonstrated that the structure of bile and pancreatic ducts, and connective tissue remain intact, whilst ablation occurs to the margin of blood vessels without affecting their functionality, though the exact reason for this sparing has not yet been ascertained. Animal studies have thus far demonstrated its efficacy and safety when directed at the pancreas, with resolution of inflammation and histological evaluation at 2 weeks post-treatment again revealing preservation of both the vascular structures and pancreatic duct. Given the proximity of the pancreas to vascular and biliary structures, as well as the associated morbidity of thermal ablative techniques, IRE represents an ideal technology in the treatment of pancreatic tumours.

This review presents a limited amount of clinical evidence that is currently available regarding the use of IRE in the treatment of pancreatic cancers; however it highlights some of the pertinent points regarding efficacy and safety which helps in guiding patient selection. Clearly there is a range of approaches undertaken, varying between percutaneous, laparoscopic and open procedures. Ultimately IRE needs to be considered in the context of unresectable locally advanced disease. With this in mind, palliative bypass in the form of hepaticojejunostomy or gastrojejunostomy has an important role in palliative treatment by relieving gastric outlet obstruction and pain. Martin et al. describe the simultaneous use of IRE at the time of resection/bypass and demonstrate promising results. However the data is limited by the fact it is not specified as to whether there was any difference in response and subsequent survival in the differing groups (IRE + chemo/radiotherapy vs chemo/radiotherapy alone). Furthermore comparative analysis is not performed with relation to resection margin status. They utilised IRE for “margin accentuation and extension”, and it would have been interesting to know if this had an effect on R0/R1 margins. Nonetheless, this simultaneous approach appears to be an ideal method of concurrently and directly treating the tumour with the aim of inducing necrosis and slowing progression.

A percutaneous method was utilised in the 3 other studies in this review (n = 20), with either ultrasound or CT guidance in 30% and 70% respectively. With this radiological approach it is essential that patients are screened to ensure a “safe window” is available for electrode placement. This is particularly pertinent with respect to pancreatic cancer, with portal or splenic vein thrombosis resulting in varices which should be ruled out on pre-procedural imaging. However a significant limitation of the percutaneous approach exists, whereby one is unable to rule out radiologically-occult metastatic disease which would be detected by a laparoscopic/open surgical approach.

Current evidence suggests IRE has a role in both the palliative management, as well as potentially facilitating surgical resection. IRE seems to incur a survival benefit, and this is most usefully demonstrated by Martin et al. in comparing the IRE group to chemotherapy alone, with a significant improvement in local and distant PFS and OS. A notable limitation was the fact the duration and type of chemotherapy before IRE was not standardised and thus highly variable, however the degree of variability between the two groups was not significant. Narayanan et al. observed improved OS in the localised group when compared to the metastatic group which would be expected. The impact on survival shows some promise,
however further controlled studies are required to elucidate the true benefit IRE may entail.

As well as survival, one must also consider symptomatic improvement that IRE may incur. Pancreatic cancer typically causes pain due to vascular invasion of the SMA/coeliac axis. Management of pain is challenging; a variety of simple and stronger opioid analgesics are used, as well as epidurals and coeliac plexus blocks in severe instances. Chemoradiation improves pain to a degree; however the duration of effect is typically only 8–12 weeks. In an earlier publication by Martin et al. involving preliminary data of the final study, it was shown that IRE significantly reduced the median fentanyl dose of 75 mcg/day pre-IRE to 25 mcg/day at 90 days post-IRE ($p = 0.03$). This correlated with a reduction in median pain scores from 5/10 to 3/10 ($p = 0.04$).

Evidence also suggests IRE may also be used to facilitate surgical resection, either in a simultaneous or anticipatory approach. In cases of pancreatic head tumours with SMA encasement without coeliac involvement, Martin et al. advocate the use of IRE to accentuate margins prior to a Whipple’s procedure. The same approach was used to facilitate subtotal pancreactectomy if there was a pancreatic body/medial tail tumour with coeliac encasement and <180° abutment of the SMA. Alternatively, IRE may be used to control tumours with a view to future resection; Narayanan went on to perform a Whipple’s procedure with RO margins on 2 (14%) patients, however it is noteworthy to mention follow up imaging revealed stable disease. Nonetheless they hypothesise that IRE prevented further progression, and allowed patients time to subsequently undergo exploratory surgery.

Recent scientific studies have demonstrated the key role that the tumour stroma plays in cancer progression. Stroma is defined as the interstitial tissue surrounding a malignant tumour, consisting of a wide variety of inflammatory, vascular and neural components which interact with tumours resulting in a desmoplastic reaction which encourages tumour invasion, dissemination, and chemoresistance. Stromal activity is most linked with epithelial tumours (breast, prostate, ovarian, colorectal), with pancreatic cancer perhaps demonstrating the most prominent ‘stromal’ reaction. Therefore one can postulate that IRE may disrupt the cancer–stroma relationship, therefore not only improving the delivery of chemotherapeutics but also slowing tumour progression.

In considering associated morbidity, again it is difficult to elucidate which were directly related to IRE when considering the study by Martin et al. The duodenal injury highlights the need for precise electrode placement by a fully trained clinician who is fully aware of the device mechanism of action. Martin et al. propose that IRE should only be performed by a physician who has done a minimum of 50 RFA/microwave/cryoablation procedures on the liver, lung or kidney, as well as 5 IRE’s on more tolerant organs such as liver or kidney. Pancreatitis that occurs is only mild and settles with conservative measures, in contrast to potentially fatal necrotising inflammation that can occur following RFA. A porcine study had observed a transient increase in amylase and lipase levels which settled by day 3 post-IRE; this may be attributed to the small degree of thermal effect and resultant mild inflammation. Comparative studies comparing IRE with thermal ablative therapies may help distinguish which has the better side effect profile, however on the theory that thermal treatments are un-wise on the highly vascular and easily inflamed pancreas, IRE certainly seems a safer option.

With more studies in this field one may be able to gauge which patients are most likely to have a successful response to IRE. With optimal patient selection in mind, suggested indications and contraindications have been published by one of the authors of the included studies (Martin) regarding the use of open IRE in the treatment of locally advanced stage 3 PDAC. The paper suggests 3–4 months of induction chemotherapy (+/- radiotherapy), during which time if the local tumour diameter increases by >30% then the patient is declined IRE. Furthermore tumour size is considered an important indicator of response, whereby the maximum axial and AP tumour dimensions must be ≤3.5 cm to proceed to IRE, with >5 cm being an absolute contraindication. As expected the presence of metastatic disease is an absolute contraindication, and is ruled out by laparoscopy prior to the open procedure. Furthermore the patient should be deemed fit for anaesthesia with an adequate performance status.

**Conclusion**

Initial evidence suggests IRE has a role in the management of locally advanced pancreatic cancer, with studies thus far suggesting a potential survival benefit, symptomatic improvement with limited morbidity, and a potential role as a bridge to surgery. Further studies are still required to determine if any significant survival benefit is achieved and to further define its place in the armamentarium of treatments against pancreatic cancer. Various questions are still to be answered, such as which approach is most appropriate, at what disease stage is IRE most useful and successful, and whether it is a feasible conversion therapy to induce resectability. Nonetheless, regarding morbidity alone, IRE represents an ideal non-thermal modality as compared to procedures such as RFA and MWA. Limitations of studies thus far include the lack of a controlled patient population, for example there are significant variances in chemoradiation regimens. A randomised controlled trial of either percutaneous or laparoscopic IRE, initially in the palliative setting, would be of great interest to more accurately determine efficacy. This may then be progressed towards comparing IRE with thermal techniques (RFA/MWA). Given the increasingly multi-directional attack taken towards tumours in the 21st century, in combining systemic regimes with minimally invasive procedures, we envisage non-thermal treatments such as IRE as having a key future role in the treatment of this devastating disease.
Conflict of interest statement

All authors confirm there is no financial or personal conflict of interest with regards to this article.

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