

## Irreversible electroporation and the pancreas: What we know and where we are going?

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### Abstract

Pancreatic adenocarcinoma continues to have a poor prognosis with 1 and 5 years survival rates of 27% and 6% respectively. The gold standard of treatment is resection, however, only approximately 10% of patients present with resectable disease. Approximately 40% of patients present with disease that is too locally advanced

to resect. There is great interest in improving outcomes in this patient population and ablation techniques have been investigated as a potential solution. Unfortunately early investigations into thermal ablation techniques, particularly radiofrequency ablation, resulted in unacceptably high morbidity rates. Irreversible electroporation (IRE) has been introduced and is promising as it does not rely on thermal energy and has shown an ability to leave structural cells such as blood vessels and bile ducts intact during animal studies. IRE also does not suffer from heat sink effect, a concern given the large number of blood vessels surrounding the pancreas. IRE showed significant promise during preclinical animal trials and as such has moved on to clinical testing. There are as of yet only a few studies which look at the applications of IRE within humans in the setting of pancreatic adenocarcinoma. This paper reviews the basic principles, techniques, and current clinical data available on IRE.

**Key words:** Irreversible pancreatic adenocarcinoma; electroporation; Apoptosis; Percutaneous; Laparotomy; Overall survival

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**Core tip:** Pancreatic adenocarcinoma continues to have a poor prognosis and as such there is considerable interest in pioneering new techniques. Ablation holds promise in this area, however, the earliest studies looked at thermal ablation techniques which resulted in high morbidity rates. Irreversible electroporation, a relatively new technique, produces apoptosis instead of liquefactive necrosis and preclinical data shows it does not destroy scaffolding cells such as bile ducts and blood vessels. These characteristics have made it of interest in the setting of pancreatic adenocarcinoma. The available clinical data as well as the basic principles of this new technique are reviewed here.

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## INTRODUCTION

Pancreatic cancer, despite extensive research, remains one of the most aggressive cancers, having a poor prognosis with 1 and 5 years survival rates of 27% and 6% respectively<sup>[1]</sup>. According to the American Cancer Society and World Health Organization 46420 patients were diagnosed with pancreatic cancer in the United States in 2014 and 338000 in the world in 2012<sup>[1,2]</sup>. In the United States 39590 of those patients died in 2014, making it the fourth leading cause of death in both women and men with the prevalence increasing by 1.3% per year as well<sup>[1]</sup>.

Only approximately 10% of these patients present with local disease, which is considered surgically resectable, however even in these patients the 5 year survival rate remains low at 24%<sup>[1]</sup>. Of the remaining 90% of patients approximately 50% present with metastatic disease, leaving about 40% presenting with localized disease, which is considered surgically unresectable, generally secondary to encasement of adjacent vessels such as the portal vein, celiac artery, and superior mesenteric artery<sup>[1]</sup>. Patients without metastatic disease, but deemed unresectable due to locally advanced disease are now classified as locally advanced pancreatic cancer (LAPC).

While surgical resection, when a viable option, remains the gold standard the majority of patients will receive chemotherapy and/or radiation therapy. The mainstay of chemotherapy in pancreatic adenocarcinoma for close to fifty years was 5-fluorouracil (5-FU) monotherapy, despite a mean survival of less than 6 mo<sup>[3]</sup>. In the late 1990s gemcitabine was introduced and demonstrated a survival benefit as compared 5-FU and thus replaced it as first line therapy<sup>[3,4]</sup>. As gemcitabine became firmly established as the first line chemotherapeutic agent multiple trials looked at combining gemcitabine with a variety of other chemotherapeutic agents, however, only a few demonstrated a survival benefit<sup>[3,5]</sup>. The combination of gemcitabine with capecitabine showed a trend toward improved survival with *post hoc* analysis of two randomized controlled trials showing statistically significant improvement in overall survival in patients with a good performance status<sup>[6-8]</sup>. In 2011 a new trial found that FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) demonstrated a significant overall survival benefit in chemotherapy naive patients as compared to gemcitabine alone<sup>[9]</sup>. Lastly, a study in 2013 revealed a survival benefit when nab-paclitaxel was combined with gemcitabine as compared to gemcitabine alone<sup>[10]</sup>. Improving chemotherapeutic

options for pancreatic adenocarcinoma remains an active area of research with multiple ongoing studies.

Radiation therapy has been used in the setting of pancreatic adenocarcinoma both in the neoadjuvant setting and in an attempt to reduce local recurrence rates after resection. Attempting to prevent local recurrence after resection seemed like a natural role for radiation therapy, however, to date studies have shown a mixed response<sup>[11-13]</sup>. This controversial area is the focus of the AFACT trial which will hopefully provide a clearer answer<sup>[14]</sup>. The role of radiation therapy in the neoadjuvant setting is also as of yet unclear with a few studies showing some promise<sup>[14,15]</sup>. This is also an area of active study, with the recent clear definition of borderline resectable disease assisting in making future studies comparable<sup>[14,15]</sup>.

After the introduction of ablation, interest surrounded it as a possible way of improving patient outcomes in this difficult disease process. Initial investigations into ablation as a possible therapy centered on thermal techniques, with radiofrequency ablation (RFA) being the most studied modality. The reported morbidity rates were regrettably unacceptably high in the majority of these published studies<sup>[16-19]</sup>. Anatomy at least partially accounts for this elevated morbidity as the pancreas is surrounded by multiple delicate structures such as the common bile and pancreatic ducts. Several vessels, including the celiac artery, superior mesenteric artery, portal vein, and splenic vein also surround the pancreas further complicating and restricting efficacy of thermal ablation techniques primarily as a result of heat sink effect<sup>[20,21]</sup>. When heat sink effect, defined as tissue cooling during ablation by adjacent blood vessels, occurs the temperature surrounding major vessels does not attain high enough levels to manifest cell death. Although microwave ablation (MWA) has been shown to be less susceptible to heat sink effect it remains vulnerable to the phenomenon<sup>[22]</sup>. The above difficulties associated with the pancreas anatomically also provide a significant obstacle to other thermal ablation techniques including cryoablation, high intensity focal ultrasonography, and MWA which to date have not been as well studied as RFA.

Irreversible electroporation (IRE) provides a unique alternative, allowing tissue ablation without being reliant on thermal effects. It also has the added ability of maintaining the scaffolding of surrounding tissues, making it of great interest in this anatomically complex area.

## IRE TECHNIQUE

Reversible electroporation has been used for many years in the basic science setting to implant foreign molecules into cells<sup>[23,24]</sup>. Reversible electroporation works by applying an electrical field across the membrane causing the membrane to become porous, through a yet incompletely understood process<sup>[23,25]</sup>. This lets the investigator introduce a desired molecule, such as RNA or DNA, into

the cell<sup>[25,26]</sup>. IRE uses this theory but applies a higher voltage leading to cell death by apoptosis. Although the exact mechanism by which IRE induces apoptosis is not clear, it appears to be *via* permanent nanopore formation and resultant ion disruption<sup>[27]</sup>.

As previously noted, thermally based techniques struggle with high morbidity when treating pancreatic adenocarcinoma due to the delicate structures in close proximity<sup>[28]</sup>. IRE on the other hand has been shown, in animal studies, to produce apoptosis of cancer cells while sparing the delicate surrounding scaffolding, including bile ducts and blood vessels<sup>[29-31]</sup>. This distinctive property makes IRE a desirable modality, particularly given the structurally rich pancreatic region. IRE also provides the benefit of yielding apoptosis, rather than liquefactive necrosis as in thermal techniques, pardoning it from the burdens of heat sink phenomenon<sup>[29]</sup>. While initially IRE was thought to not induce any thermal effects recent studies have shown that a small area of thermal effect is likely present immediately adjacent to the probe<sup>[32]</sup>.

The unique mechanism of IRE results in a few necessary precautions during its utilization. High voltages created are by IRE and produce significant muscular contractions<sup>[33]</sup>. It is for this reason the patient must be placed under general anesthesia with full neuromuscular blockade<sup>[33]</sup>. The blockade is tested with a twitch technique prior to starting. ECG monitoring is also required to monitor for arrhythmias, which are rare and typically transient. The concern of arrhythmia leads some authors to promote the placement and use of arterial lines.

Currently there is one commercially available IRE machine, the NanoKnife (Angio Dynamics, Queensbury, New York). This device supports either unipolar or bipolar probes. The more commonly used unipolar probes require placement in pairs, which is technically challenging as they must be placed in parallel orientation and spaced no further than 1.5-2.0 cm apart. The probes create a relatively small ablation field (approximately 2-3 cm)<sup>[34-36]</sup> and therefore it is common for multiple probe pairs to be placed, and/or the probes to be repositioned several times during the procedure. Probes can be placed percutaneously, laproscopically, or using an open surgical approach. When placed intraoperatively, intraoperative ultrasound is used<sup>[37-39]</sup>. When placed percutaneously both ultrasound and CT placement have been described<sup>[40,41]</sup>.

After probe placement the ablation device is set to produce high voltages, usually between 1500-3000 V in pulses of 70-100 microseconds. Typically 90 such pulses are delivered which only takes a few minutes, after which the ablation is complete. Once the intended ablations have been performed the patient will typically undergo imaging, either by intraoperative ultrasound, contrast enhanced ultrasound, or CT to ensure that the lesion has been satisfactorily covered.

After finishing the IRE procedure the patient is observed with the average length of admission varying

significantly in the available studies from a same day discharge to admission for two weeks or more<sup>[29,37,39-41]</sup>.

## AVAILABLE DATA

A search of the Pubmed database with the terms "IRE AND pancreatic cancer" yielded 34 results, of which 6 studies were found to be case reports, case series, or prospective trials related to IRE and pancreatic cancer without significant patient overlap. Those studies are reviewed here. The remainder represented review articles ( $n = 16$ ), animal studies ( $n = 5$ ), or prior publications on a patient set that was reused as discussed below ( $n = 4$ ). Two studies were excluded as they were case reports only discussing a complication, and therefore not felt to be relevant to this discussion. A single study was eliminated as it was a review of anesthetic requirements during IRE.

Martin and his group have published multiple studies on pancreatic cancer and IRE<sup>[37,38,42,43]</sup>, because of significant patient overlap only two of these studies are included and discussed here. Table 1 provides some of the most pertinent data for the 6 below described studies.

In 2013 Martin *et al*<sup>[38]</sup> compared a group of fifty-four prospectively gathered IRE patients with pancreatic cancer, retrospectively to a group of eighty-five patients who received only chemotherapy and/or radiation. All of the patients had LAPC disease with none being considered borderline resectable or having metastatic disease. The two groups were matched using propensity scores based on age, size of tumor, performance status, cardiac comorbidities, and pulmonary comorbidities. Of the fifty-four IRE patients fifty-two (96%) patients underwent open surgical ablation and two (4%) underwent laparoscopic ablation. Nineteen patients underwent IRE followed by en bloc resection, after surgical restaging. Forty seven of the fifty-four (87%) IRE patients underwent post procedural chemotherapy while ten (19%) of them underwent post procedural radiation therapy. In a ninety day follow up period thirty two of the fifty-four (59%) IRE patients had adverse events. The average time from diagnosis to treatment was 5.1 mo with a range of 1 to 32 mo. The average length of hospital stay was 7 d. When the IRE and chemoradiation only groups were compared the IRE group had a better overall survival (20.2 mo vs 11 mo,  $P = 0.03$ ), progression-free survival (14 mo vs 6 mo,  $P = 0.01$ ), and distant progression-free survival (15 mo vs 9 mo,  $P = 0.02$ ). However, the survival curves of the two groups appeared to converge back together at twenty months, which was postulated to be secondary to rapid progression of distant metastatic disease by the authors.

Martin *et al*<sup>[37]</sup> also recently published a series of forty eight patients who had borderline resectable or LAPC disease in which they used IRE in an attempt to obtain a margin free, or R0, resection. Twenty three (48%) of the patients had LAPC while twenty five (52%) had borderline resectable disease. Of note, nineteen of these

Table 1 Comparison of the studies

Ref.	IRE placement technique	No. of patients	Age in years	Sex in male/female	Time from diagnosis to treatment in months	Survival time in months	Complications	No. of patients with metastasis	No. of patients who received pre IRE chemo and or radiation	No. of patient who received post IRE chemo and or radiation
Martin <i>et al</i> <sup>[38]</sup>	Open 52 (96%) lap 2 (4%)	54	Median 61 range 45-80	23 male/21 female	Median 5.1 range 1-32	Local PFS 14, distant PFS 15, and OS 20	32 (59%)	0 (0%)	49 (90%)	40 (73%)
Martin <i>et al</i> <sup>[43]</sup>	Open 48 (100%)	48	Median 61 range 27-81	26 male/22 female	6 range 4-13	OS 22 and PFS 11	18 (38%)	0 (0%)	33 (69%)	31 (65%)
Paiella <i>et al</i> <sup>[39]</sup>	Open 10 (100%)	10	Median 66	5 male/5 female	Mean 9.2	OS 7.5	2 (20%)	0 (0%)	10 (100%)	3 (30%)
Narayanan <i>et al</i> <sup>[40]</sup>	Perc CT guided 14 (100%)	14	Median 57 range 51-72	7 male/7 female	Mean 16.6 range 2.4-49.5	70% OS at 6 mo	2 (14%)	3 (21%)	14 (100%)	NP
Månsson <i>et al</i> <sup>[41]</sup>	Perc US guided 5 (100%)	5	Median 65 range 46-89	3 male/2 female	NP	40% OS at 6 mo	0 (0%)	0 (0%)	5 (100%)	NP
Bagla <i>et al</i> <sup>[44]</sup>	Perc US with CT confirm	1	78	Male	CT	Alive at 6 mo	None	None	No	No

IRE: Irreversible electroporation; US: Ultrasound; CT: Computed tomography; NP: Nondeterministic polynomial.

patients seem to be included in the previously discussed study by Martin *et al*<sup>[38]</sup>. Thirty three of the forty eight (69%) had undergone preoperative chemotherapy and thirty one (65%) underwent preoperative radiation therapy<sup>[12]</sup>. Thirty one of the forty eight (65%) patients underwent R0 resections with the remaining undergoing R1 resections (35%). Adverse events were recorded for 90 d and developed in eighteen of the forty eight (38%) patients. At twenty four months twenty eight patients (58%) had developed recurrence, the majority of which involved the liver or peritoneum.

Paiella *et al*<sup>[39]</sup> published a prospective study of ten patients who underwent IRE for LAPC utilizing a laparoscopic approach with intraoperative ultrasound (US) guidance. All patients who underwent IRE had previously undergone chemotherapy or chemoradiation therapy. The average length of hospital stay was 9.5 d with 1 patient (10%) developing a postoperative abscess. One other patient (10%) died of septic shock, which was attributed to complications of ulcerative colitis rather than the procedure. The average time of diagnosis to treatment was 9.2 mo. The average overall survival was 7.5 mo following the procedure, with diagnosis to death time averaging 16.8 mo. Three of the ten (30%) patients received post procedural chemotherapy. After treatment, four (40%) patients showed partial response, three (30%) had stable disease burden, and three (30%) demonstrated progressive disease per RECIST criteria.

Narayanan *et al*<sup>[40]</sup> published a series of fourteen patients who underwent percutaneous IRE in 2012. Eleven (79%) of the patients had disease localized to the pancreas, one (7%) had a sub centimeter lung metastasis, one (7%) had a sub centimeter liver metastasis, and one (7%) had a solitary peritoneal

metastasis. All of the procedures were performed using CT guidance and patients were discharged either the same or next day. No grade three toxicities occurred per SIR reporting guidelines. One patient (7%) developed a pneumothorax, while two (14%) others had subclinical complications (small hematoma seen on follow up imaging and subclinical pancreatitis). Two of the fourteen (14%) patients were able to undergo subsequent resection. The median event free survival (EFS) was 6.7 mo, and at 6 mo 70% of the patient cohort remained alive. Additionally the projected overall survival was statistically longer for patients with localized disease as compared to those with metastatic disease ( $P = 0.02$ ). No difference was seen in the overall survival between the patients who did and did not undergo resection, possibly as a result of the few deaths in the resection group.

Månsson *et al*<sup>[41]</sup> published a case series of five patients treated with US guided percutaneous IRE ablation. The patients all presented with jaundice and were deemed non-surgical candidates, presumably from LAPC although this was not specified. The patients underwent contrast enhanced US to ensure complete ablation. No grade three or higher complications occurred within the first 30 d. One (20%) patient did develop subclinical pancreatitis. Limited follow up data was presented, but 60% of patients were alive at six months, with two (40%) demonstrating no evidence of recurrence.

In 2012 Bagla *et al*<sup>[44]</sup> published a case report of a single patient with LAPC who was treated with US guided IRE, followed by a CT to confirm probe placement. This patient underwent two separate ablations two weeks apart due to tumor size. The patient developed liver metastasis at the 3 mo follow up exam, which were subsequently treated with RFA. The patient had no evidence of recurrent disease at the 6 mo follow up

exam and no significant complications were noted.

## DISCUSSION

Pancreatic cancer is the fourth leading cause of cancer related death in the US<sup>[1]</sup>. Despite considerable and meaningful research into surgical techniques and chemoradiation therapy, survival rates remain poor at 27% and 6% at 1 and 5 years respectively<sup>[1]</sup>. The majority of patients with pancreatic cancer present with unresectable disease, either due to LAPC (approximately 40%) or metastases (approximately 50%)<sup>[1]</sup>. Only approximately 10% of patients are considered surgically resectable at presentation, and unfortunately even in this group survival at 5 years is only 24%<sup>[1]</sup>.

IRE appears to hold great promise for improving survival in nonresectable patients, most clearly in the LAPC group. Animal studies have shown IRE has the ability to destroy cancer cells while leaving crucial underlying anatomic scaffolding such as blood vessels and bile ducts intact<sup>[29]</sup>. This is of paramount importance given the location of the pancreas and resultant high morbidity seen when thermal ablation techniques have been employed<sup>[19]</sup>.

Human data is limited, with only 6 relatively small case series published to date. The most promising data comes from the largest series by Martin *et al*<sup>[38]</sup> which revealed improved overall survival, progression-free survival, and distant progression-free survival when comparing patients who underwent IRE with those who underwent chemotherapy and/or radiation therapy alone. In this study the overall survival showed significant improvement, rising from 11 to 20.2 mo. This improvement of 9 mo is particularly encouraging given the notably poor prognosis of pancreatic cancer and continued difficulty in attaining improved survival with various other novel treatment methodologies such as new chemotherapeutic agents.

With early data demonstrating the possibility of prolonging overall survival of longer than 6 mo it appears that adding IRE may be of great value for patients without hope for cure. In this particular setting quiescing morbidity is the primary objective however, as clearly demonstrated by several authors, on occasion IRE can be used to downstage patients giving them a chance at curative therapy. The use of IRE to provide definitive therapy has also been investigated by Martin *et al*<sup>[38]</sup> in their attempts to expand the population of patients able to undergo R0 resections. These advances are vastly promising in regards to the treatment of pancreatic adenocarcinoma, yet they also raise several poignant questions.

Currently IRE is being delivered in a range from maximally invasive (open surgical placement) to minimally invasive (percutaneous placement), with laparoscopic placement falling somewhere in between. It appears likely that both the open surgical placement and percutaneous placement techniques are of benefit. Open surgical placement has the best data to support its

use thus far and also allows the surgeon to surgically stage the patient and consider proceeding to resection. Percutaneous placement appears to reduce morbidity and potentially hospital stay, although this point would need further clarification given the long average hospital admission seen in the Mansson *et al*<sup>[43]</sup> paper of 14 d. Reducing morbidity and hospital stay could be of great importance in maintaining quality of life when the disease is likely to remain unresectable and the goal is palliation. Further investigation into patient selection criteria will be essential in order to differentiate those patients best treated by open, from those best treated with percutaneous, placement. In their paper Narayanan *et al*<sup>[39]</sup> discussed this in brief, pointing out that certain patients, such as those with large varices, would likely not be best treated *via* the percutaneous approach.

Recent studies have demonstrated that stroma plays a larger than previously recognized role in regards to cancer characteristics, indicating this may be a critical area of future investigation<sup>[45-48]</sup>. Epithelial cancers such as pancreatic cancer are believed to be maximally affected by stromal cells<sup>[49]</sup>. The stromal activity prevents drug concentration and may at least partially account for the relatively poor response to chemotherapy seen in pancreatic cancer<sup>[50,51]</sup>. Disruption of the stromal cells and the cancer cells may help improve outcomes, and to some extent explain the encouraging outcomes which have been seen in early IRE studies. This also raises the question as to whether or not IRE's potential to disrupt the stromal effect could produce better outcomes in patients presenting with limited metastatic disease as well. It also highlights the importance of investigating the possible synergistic effects IRE and chemotherapy could obtain.

More data evaluating outcomes in patients with LAPC is also needed in the form of large case cohorts, and more importantly in the form of randomized controlled trials comparing this technique to radiation and chemotherapy alone. During these investigations the delineation of patient selection will be paramount, as there is likely a group of patients that will confer a good survival benefit, while others will likely not benefit from this invasive procedure. The Martin *et al*<sup>[37]</sup> paper describing the use of IRE to obtain R0 resections is of marked interest, however, again more data is needed in this newly introduced novel realm.

In conclusion IRE remains a new, exciting area of research in pancreatic cancer with multiple promising possible applications that will require investigation in the future.

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