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Irreversible electroporation of the pancreas – A decade on

Daniel Yuxuan Ong, Guo Yuan How, Uei Pua *

Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore

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ABSTRACT

Irreversible electroporation (IRE) employs the use of an electric field to cause irreversible permeability of the cell membrane, inducing apoptosis. The use of IRE for locally advanced pancreatic cancer (LAPC) was first described in 2012. The crucial advantage of IRE compared with other devices employing thermal ablation is the safety around vital structures such as vessels and ducts. This makes it an attractive option for use in the pancreas due to the close proximity of multiple major vascular structures, biliary ducts, and adjacent gastrointestinal organs. Over the past decade, IRE has established itself as a useful treatment adjunct and may soon become the standard of care, particularly for LAPC. This article will explore the current evidence and provide a concise summary of pertinent issues, including patient selection, preoperative management, clinical outcomes, radiological response and future prospects of IRE in pancreatic cancer.

1. Background

Pancreatic adenocarcinoma is a leading cause of cancer death and is expected to become the second leading cause of cancer-related deaths by 2030.[1,2] To date, the 5-year overall survival for patients with pancreatic adenocarcinoma is approximately 8%.[3] Surgical resection with adjuvant chemotherapy is considered the best treatment option for long-term survival. However, fewer than 20% of patients present with resectable disease.[4] Majority of patients present with unresectable disease with concomitantly reduced survival rates.[5] A significant proportion of up to 30–40% has locally advanced pancreatic cancer (LAPC), defined as greater than 180° circumference tumour encasement of the superior mesenteric or celiac artery, or non-reconstructable venous involvement.[4,6]

For patients with LAPC, treatment options include stereotactic body radiotherapy, chemotherapy, chemoradiation, and so forth. By far, chemotherapy has been the preferred mode of treatment and is often regarded as the standard of care. Conroy et al. demonstrated that 5-FluoroUracil, Leucovorin, Irinotecan, and Oxaliplatin (FOLFIRINOX) treatment had a survival advantage over gemcitabine therapy, albeit with a higher toxicity profile (median OS in the FOLFIRINOX group was 11.1 months compared to 6.8 months in the Gemcitabine group, $p < 0.001$).[7] As such, in many countries, FOLFIRINOX is the first line chemotherapeutic regime. Overall, systemic chemotherapy still delivers poor median overall survival.[8–10] Moreover, the SCALOP I trial demonstrated that 44.5% of patients with pancreatic cancer treated with initial systemic chemotherapy developed distant metastases and 33.3% developed local disease progression.[11] Therefore, there is a need to explore local ablative therapies as treatment adjuncts. Table 1 provides a summary of the background of pancreatic cancer.

1.1. IRE in pancreatic cancer

The main objective of IRE in the treatment of LAPC would be to extend survival. In addition, IRE can bring about local control of tumour progression, symptom relief, and improved quality of life.[12]

IRE exerts its cytotoxic effect without relying on thermal injury.[13] IRE employs the use of high-voltage electrical pulses, which are applied between needle electrodes inserted within and around the tumour. The pulses irreversibly damage the cellular membrane by creating nanopores, inducing programmed cell death.[14] Additionally, there is mounting evidence of tumour necrosis occurring and contributing to IRE's tumoricidal effects.[15] Regardless of mechanisms, IRE is advantageous over thermal-based ablations due to its safety around vital structures such as blood vessels, bile ducts and intestinal structures.[13,16] Furthermore, IRE is not susceptible to the "heat sink" effect, where blood vessels adjacent to a cancer prevent the area of ablation from reaching effective temperatures for cellular damage, ultimately leaving viable tumour cells.[17]

Pancreas IRE therapy has no established protocol, with most studies to date using 90 pulses per treatment cycle, with each pulse length lasting 70–90 μs and between 1400 and 2000 V/cm being delivered.[18,19]

* Corresponding author. Department of Diagnostic Radiology, Tan Tock Seng Hospital 11 Jalan Tan Tock Seng, 308433, Singapore.
E-mail address: druei@yahoo.com (U. Pua).

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Table 1
Background of pancreatic cancer.

Background
Pancreatic adenocarcinoma is a leading cause of cancer death.
Significant proportion of patients has LAPC.
Chemotherapy has been standard of care for LAPC.
IRE is a useful local ablative modality.

Abbreviations: LAPC: locally advanced pancreatic cancer; IRE: irreversible electroporation.

Table 2
Patient selection and preoperative management of patients undergoing irreversible electroporation of the pancreas.

Irreversible Electroporation of the Pancreas	
Patient Selection	Preoperative To Do
Review by multidisciplinary tumour board	Anaesthesia review and clearance
ECOG status 0 to 1	Pre-operative serological testing
Stage 3 LAPC or low volume stage 4	Pre-operative imaging
Lack of surgical contraindications	Bowel preparation
60 years and below	Nasogastric tube
Without more than 2 comorbidities	
Without diabetes	
Lesser degree of vascular involvement	

Abbreviations: ECOG: Eastern Cooperative Oncology Group; LAPC: locally advanced pancreatic cancer.

1.2. Open, laparoscopic versus percutaneous IRE

IRE was initially performed mainly in open and laparoscopic approaches. The introduction of the percutaneous technique has provided a minimally invasive option for selected patients. Proponents of surgical approaches argued that more precise needle placement could be made under direct visualisation.[20] An open approach also allows for the assessment of distant disease, which may not be detected on preoperative imaging.[11,21] However, surgical IRE has been associated with higher morbidity rates and more severe complications.[22]

1.3. Patient selection & preoperative management

Patient selection for IRE is essential.[23–25] Narayanan proposed that patients should be reviewed in a multidisciplinary tumour board to determine if they are suitable candidates for IRE.[23] Some proposed criteria include having an Eastern Cooperative Oncology Group (ECOG) status of 0–1, with Stage 3 LAPC or low volume Stage 4 metastatic disease that has been stable over time.[23]

These patients should also be reviewed by the anaesthesia service to obtain clearance for general anaesthesia. Anaesthetic management during IRE differs from standard general anaesthesia, in that there is an increased risk of cardiac arrhythmias, and severe muscular contractions.[5]

Absolute contraindications for IRE include having a history of cardiac arrhythmias, having implanted cardiac stimulation device, uncontrollable hypertension, epilepsy and congestive heart failure, amongst others.[23,25] Relative contraindications include bleeding disorders, uncontrolled infections, etc.[25]

Matthew et al. found that there were several clinicopathologic characteristics that predict survival following open in-situ IRE for LAPC. The authors found that younger patients (60 years and below), patients without more than two comorbidities, and patients without diabetes display superior post-IRE outcomes.[24] On top of these, anatomic tumour characteristics need to be considered, with smaller tumours generally having prolonged survival outcomes. Vascular involvement of $\leq 180^{\circ}$ of their affected structure is also more likely to have significantly longer overall survival. These factors are useful to guide the selection of candidates for the IRE procedure.[24]

Apart from the usual pre-operative serological testing (coagulation panel, blood count, CA 19–9, etc) and imaging (such as computed tomography scan), it is also suggested that these patients undergo bowel preparation to decrease the risk of infection, and to decrease the chance of colon obscuring the pancreatic bed.[23] Nasogastric tube placement may be considered to allow the administration of contrast to delineate the small bowel and permit insufflation of the stomach to push the colon caudally, if necessary.[23] Table 2 summarises the pertinent points on patient selection and preoperative management.

Table 3
Complications of irreversible electroporation of the pancreas.

Complications of IRE	
Major Complications	Minor Complications
Death	Gastrointestinal symptoms
Severe pancreatitis	Abscess formation
Biliary obstruction	Post-procedural pneumonia
Fistula formation	
Portal vein thrombosis	
Bile leak	
Gastrointestinal tract perforations	

Abbreviations: IRE: irreversible electroporation.

1.4. Outcome of IRE for LAPC

There have been no prospective randomised trials to date evaluating the harms and benefits of IRE therapy in LAPC. Most of the current literature on IRE is retrospective studies. The survival figures reported for IRE in LAPC are varied as presented by Zainab et al.[26] The published median overall survival range in patients undergoing IRE ranges from 10 to 30 months.[12,27] Following propensity score matched analysis, He et al. found that the overall survival (OS) and progression free survival (PFS) rates of LAPC patients following neoadjuvant chemotherapy and the use of subsequent IRE treatment were better than that of patients treated with chemotherapy alone.[28] The PANFIRE-2 trial delivered encouraging results, where percutaneous irreversible electroporation in patients with locally advanced and recurrent pancreatic cancer seems to prolong survival (median overall survival, 17 months) compared with standard of care.[29] Critically, the study demonstrated that IRE was the key determinant for improved survival, regardless of the chemotherapy that was received pre-treatment.[29] Despite this, Alette et al. still recommend at least four cycles of FOLFIRINOX before IRE. The ongoing LAP-PIE clinical trial aims to perform a randomised comparison of combination therapy involving FOLFIRINOX treatment and IRE, with FOLFIRINOX treatment alone.[30] This study, along with the ongoing PANFIRE-3 trial, will soon shed more light on the outcome of IRE with LAPC. The available data supports the use of IRE for LAPC as a solitary treatment arm or an adjunct to conventional treatment regimes.

1.5. Complications of IRE

Whilst the survival rates show promising results, the cost of IRE would be the associated complications. The percutaneous approach has generally shown lower complication rates as compared to open/laparoscopic approaches. A systematic review by Ansari et al. found that post-IRE complication rates were around 35%.[31] In the PANFIRE-2 study, there was an astonishing 58% complication rate for percutaneous IRE.[29] Even more alarming is that there were more major adverse events than minor ones, including 2 deaths within 90 days of the procedure. Common minor complications encountered were gastrointestinal symptoms, abscess formation, post-procedural pneumonia, for instance. Severe complications include severe pancreatitis, biliary obstruction, fistula formation, to name a few. Other known severe complications not encountered in the PANFIRE-2 study included portal vein thrombosis, bile leak, gastrointestinal tract perforations, etc.[26,29] More recent data from a meta-analysis that evaluated the safety and efficacy of IRE for

Table 4
Radiological response to irreversible electroporation.

Radiological Response to IRE	
Computed Tomography	Magnetic Resonance Imaging
Ablation zone is irregular and shapeless without clear margins.	Hyperintense rim surrounding the ablation zone immediately post-IRE may represent reactive hyperemia and edematous inflammation, or residual disease.
Blood vessels narrow immediately following IRE, and will resolve or remain stable subsequently.	
Increased enhancement of the ablation zone may be seen due to granulation tissue and fibrosis.	
Ablation zone will shrink after resolution of surrounding oedema.	
Increase in size of ablation zone or new encasement or narrowing of vessels or extension of soft tissue outside of ablation zone is concerning for recurrence.	

Abbreviations: IRE: irreversible electroporation.

treating LAPC showed that major complication rates were approximately 17%,[32] with the authors concluding that IRE is a relatively effective and safe treatment method. Nevertheless, because of the potential for complications, the selection of patients who will benefit from treatment with IRE is of utmost importance.[29] The complications of IRE are summarised in Table 3.

1.6. Radiological response to IRE

IRE-treatment response in clinical studies has been determined by radiological imaging, mainly computerised tomography (CT) and magnetic resonance imaging (MRI). Akinwande et al. reviewed 5 patients who underwent IRE for LAPC. They reported that the arterial phase is the best for postoperative imaging to distinguish the hypoattenuating ablation zone from adjacent vasculature. They found the ablation zone irregular and shapeless on imaging without clear margins.[33] Blood vessels within the area of ablation demonstrated narrowing immediately following IRE (expected CT finding within 1-month post-IRE), which resolved or remained stable in subsequent scans. Subsequent follow-up imaging demonstrated an increased enhancement of the ablation zone (typically from 3 months onwards), which the authors postulated may be due to the formation of granulation tissue and fibrosis.[33] After the resolution of surrounding oedema, longer post-procedure scans showed a smaller ablation zone when compared with the initial post-operative scans. Due to the lack of defined margins, the authors concluded that size is a secondary objective in CT evaluation. However, the increase in the size of the ablation zone or any new encasement or narrowing of vessels or extension of soft tissue outside the ablation zone is concerning for recurrence.

Vroomen et al. assessed imaging characteristics in 25 patients with LAPC following CT-guided percutaneous IRE.[34] All patients underwent pre-procedural contrast-enhanced CT (CECT). Subsequent contrast enhanced MRI (CEMRI) was performed on the first postoperative day, at two weeks and six weeks. An additional CECT was performed at 6 weeks. They discovered that median tumour volumes show an increase in tumour volume in the initial post-IRE period on both CECT and CEMRI, followed by a decrease. Additionally, they observed a hyperintense rim surrounding the ablation zone on the first day after IRE which may represent reactive hyperaemia and oedematous inflammation or residual disease. Table 4 summarises the pertinent points on radiological response to IRE.

Currently, there is no consensus on the optimum time post-treatment to measure ablation zone, which would be an area for further research.

Table 5
Areas for further research.

Areas for Further Research
Patient selection for IRE.
Post-treatment imaging protocol.
Novel IRE techniques.
Pancreatic cancer genomics and immunology.

Abbreviations: IRE: irreversible electroporation.

Martin et al. recommended an immediate triple-phased CT scan in the plain, arterial, and venous phases within 1 month to assess the patency of vital structures. This is followed by serial imaging for 2–6 months to detect recurrence.[18]

2. Future prospects

Further research on patient selection would be pivotal for the future of IRE, in light of the potential risks and benefits. Guidelines on post-treatment imaging are also an area for further study. There has been research into novel IRE techniques. For example, O'Brien et al. performed single-needle high-frequency IRE in an in vivo pancreatic swine model. Without pair electrode deployment, this technique provides the promise of eliminating the need for intraoperative paralytics and cardiac synchronization.[35]

Another area of interest is the effects of IRE on immunomodulation. Imran et al. described the impact of IRE on IFNγ expression, which was thought to modulate immune checkpoint molecules, leading to tumour recurrence. As such, the research team suggested the co-therapeutic use of immune checkpoint inhibitors with IRE in patients with pancreatic cancer.[36] Other proponents of the potential immunological effects of IRE exist, such as Zainab et al. who found emerging data suggesting that IRE can be augmented with synergistic therapies such as immunotherapy.[26] This was supported by Tian et al., where it was found that IRE could enhance antitumour immune responses and combination with immunotherapy may play an important role in further prolonging the survival of pancreatic cancer patients.[37]

Whilst there are several notable ongoing trials including the LAP-PIE trial and PANFIRE-3 study, as previously mentioned, there is a paucity of studies that have genomic stratifications. This is relevant as there is a role in further exploring the pancreatic cancer genomics and microenvironment and tailoring combination therapies to optimise patient outcomes, as demonstrated by a few recent studies.[38,39] Darya et al. suggested that direct targeting of the involved signalling molecules and the immune checkpoint molecules, along with conventional combination therapies, will bring about the most promising results in pancreatic cancer treatment.[39] There is therefore a need for clinical trials with a more individualised approach that looks specifically into cancer genomics and immunology. Table 5 summarises the areas for further research.

3. Conclusion

The past decade has seen IRE grow into an established adjunct in the management of pancreatic cancer, particularly for LAPC. Percutaneous IRE provides a minimally invasive treatment option but due to its frequent association with major complications, it should be regarded as a high-risk procedure. IRE is a promising tool in the treatment of LAPC and may confer benefits in a carefully selected patient population.

Author's contributions

Daniel Yuxuan Ong: Manuscript writing, first author. Guo Yuan How: Manuscript writing, second author. Uei Pua: Manuscript writing, manuscript vetting, corresponding author.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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