Original Article

A Single-institution Experience with Open Irreversible Electroporation for Locally Advanced Pancreatic Carcinoma

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Abstract

Background: Locally advanced pancreatic carcinoma (LAPC) is characterized by poor prognosis despite recommended concurrent chemoradiotherapy. Irreversible electroporation (IRE) has emerged as a potential option for the management of unresectable pancreatic cancer. This study was conducted to evaluate the safety and short-term efficacy of open IRE for the treatment of LAPC.

Methods: Retrospective data of 25 consecutive patients receiving IRE for T3 lesions from July 2015 to June 2016 at a single center were analyzed. The perioperative and long-term IRE-related complications were reviewed to evaluate the safety of the procedure. The tumor reduction and biological response were analyzed through computed tomography/magnetic resonance imaging; the serum level of CA19-9 was measured as a secondary endpoint to evaluate the short-term efficacy of IRE.

Results: All patients were successfully treated; the median tumor size was 4.2 cm and the median IRE time was 36 min. Four intraoperative procedure-related complications were observed (16%): two transient hypertensive episodes, one hypotension case, and one transient supraventricular tachycardia case. Nine postoperative complications were described, including three Grade A pancreatic fistulas, three delayed gastric emptying, one acute pancreatitis, one upper gastrointestinal hemorrhage, and one portal vein thrombosis. The overall rate of stable disease was 28%, 36% achieved partial response, and lower serum CA19-9 levels were recorded in all patients at discharge.

Conclusions: IRE is feasible for the treatment of LAPC and is a reasonable intervention strategy owing to its combined attributes of safety and efficacy.

Key words: CA19-9; Irreversible Electroporation; Locally Advanced Pancreatic Carcinoma

Introduction

Pancreatic cancer is characterized by extremely poor prognosis, with overall 1- and 5-year survival rates of 24% and 7%, respectively.[1,2] More than 80% of patients are unable to undergo curative treatment because of delayed diagnosis, resulting in late-stage complications such as distant metastases or locally advanced disease.[3] Conventional treatment options such as chemotherapy, chemoradiotherapy, and palliative surgery can improve prognosis. However, such treatments often have unsatisfactory efficacy as well as a high rate of systemic side effects.[4] Hence, novel and effective locoregional approaches for treating unresectable pancreatic tumors are needed.

Irreversible electroporation (IRE) is an emerging nonthermal technique that delivers short high-voltage electrical fields to puncture cell membranes and induce apoptosis.[5,6] In contrast to thermal ablation techniques, IRE has an improved safety profile and has been preliminarily demonstrated to be efficacious against solid tumors, especially locally advanced pancreatic carcinoma (LAPC), in terms of local progression-free, distant progression-free, and overall survival.[7-9]

Herein, we evaluated our first 25 consecutive IRE patients with unresectable pancreatic carcinoma without metastatic disease.

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Methods

Study design

This was a retrospective, single-center clinical study of patients diagnosed with unresectable LAPC using imaging and cytohistological analysis. LAPC was defined as an unresectable tumor that encased one or more important large arterial vessels surrounding the pancreas (i.e., the celiac axis and/or superior mesenteric artery) or infiltrated the venous vessel wall (i.e., the portal vein [PV], and/or superior mesenteric vein [SMV]), but with no evidence of distant metastasis.[10,11] All LAPC patients at our institution underwent IRE only after consensus was reached by a multidisciplinary medical team. Treatment plans were developed with written informed consent where patients agreed to the off-label use of this technology.

The primary endpoint of this study was the perioperative safety of IRE for pancreatic cancer; secondary objectives included the evaluation of the short-term efficacy of this modality through imaging, laboratory tumor data, and clinical assessment. Data were collected on baseline characteristics for all patients, and events potentially related to IRE (adverse or otherwise) were recorded and graded according to the Clavien-Dindo classification. Procedure-related adverse events included intra- and post-operative complications such as hypertension, arrhythmia, gastrointestinal bleeding, pancreatic fistula, acute pancreatitis, PV thrombosis, gastroplegia, and duodenal injury.

Inclusion and exclusion criteria are listed in Table 1. Patients who were deemed eligible for IRE treatment underwent preoperative evaluation including routine blood tests, liver and renal function tests, serum CA19-9 value, three phase contrast-enhanced abdominal computed tomography (CT)/magnetic resonance imaging (MRI) scans, positron emission tomography-CT, and cardiopulmonary function evaluation. All patients underwent follow-up every week for 90 days post-IRE. Radiological imaging was performed at days 7, 30, and 90, and serum CA19-9 levels were tested on days 1, 7, 30, and 90 following the procedure, according to our protocol. Meanwhile, the visual analog scale (VAS) and the Karnofsky performance score (KPS) were used to evaluate patients' pain levels and performance statuses, respectively.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
18–80 years old
Locally advanced unresectable pancreatic carcinoma
Maximum tumor size <5 cm (longest axis)
Willing to sign an informed consent form
Exclusion criteria
Known history of epilepsy
Known history of severe cardiovascular diseases such as atrial or ventricular cardiac arrhythmia, myocardial infarction, and uncontrolled hypertension
Have implanted cardiac pacemakers or defibrillators
Have implanted metallic stent or electronic devices adjacent to the target lesion
Intolerant to treatment with muscle relaxant and anticoagulant

Operative technique

All patients underwent open IRE treatment *in situ* with or without bypass surgery; the NanoKnife IRE System (AngioDynamics, Queensbury, New York, USA) was used. The device was set up to produce high-voltage direct current electrical pulses; delivery was at least 1500 V/cm at 90 μs, typically for a total of 100 pulses in ten sets of ten pulses between each paired probes. The electrode length was 1.0–1.5 cm, and the voltage setting was determined by the distance between each pair of electrodes. Before the IRE procedure, three-dimensional (3D) reconstruction was performed using CT/MRI images to reconfirm the relationship between the tumor and the vessels it invaded; the placement of the electrodes was guided using this virtual tumor model. An intraoperative fine-needle biopsy was obtained to verify LAPC diagnosis histologically. General anesthesia involving neuromuscular blocking was necessary to prevent muscle contraction before the application of high-voltage electrical pulses. The electrodes were then placed within or around the tumor under biplane ultrasonic guidance, which helped monitor the ablation procedure in real time. In practice, electrode pairs were placed into the tumor perpendicular to the major axis of the pancreas in a caudal-to-cranial or an anterior-to-posterior direction; the appropriate distance between the electrodes was 2 cm to maximize the ablation zone. The pullback was performed if the target ablation zone was >2 cm so that the overlapping ablation allowed for complete coverage of the entire target. All IRE procedures were performed by a board-certified surgeon trained to operate the IRE device.

Statistical analysis

Data were collected retrospectively. Continuous variables were described as *n* and medians (range or interquartile range); categorical variables were reported as proportions and percentages. All statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From July 2015 to June 2016, 25 LAPC patients underwent IRE treatment at our institution, 22 of whom as a primary treatment. Of the other three patients, two had received radiation therapy and one received three cycles of chemotherapy; all were unresponsive to these treatments before the application of IRE. Table 2 shows the baseline pretreatment characteristics of the patients; their median age was 58 years, and 76% were men. Only a small percentage of patients had a history of cardiovascular disease (12%). The median baseline lesion diameter was 4.2 cm at the longest axis (range: 2.8–4.9 cm); the celiac axis was the most commonly invaded vessel (56%) while approximately 28% (7/25) of lesions infiltrated more than one large vessel.

Surgical details

The median duration of anesthesia was 225 min (range: 100–420 min) and the median IRE time was 36 minutes (range: 23–101 min) [Table 2]. All treatments were successfully completed with a delivery of 100 pulses per pair of probes for each electroporation. Nine patients underwent IRE *in situ* while the remainder received IRE during double bypass surgery (gastric and biliary). Among these 16 patients, half without preoperative jaundice and gastrointestinal obstruction underwent precautionary double bypass surgery to prevent gastrointestinal tract obstruction due to disease progression after the IRE treatment. In practice, a median of four probes was used (range: 2–6 probes), which were placed in a caudal-to-cranial direction in 16 patients and an anterior-to-posterior direction in nine [Figure 1]. The pullback was performed twice in nine patients to verify ablation zone coverage of the lesion. IRE was well tolerated intraoperatively; only four intraoperative procedure-related adverse events were observed, including two transient hypertensive episodes, one case of hypotension, and one case of transient supraventricular tachycardia; these all resolved spontaneously.

Complications

Apart from the intraoperative IRE-related adverse events, postoperative procedure-related complications were recorded and graded according to the Clavien-Dindo classification [Table 3]. The overall morbidity was 36% (9/25). Most hospitalized patients experienced minor abdominal complications (Grade 1 or 2) at 30 days after the procedure, including three cases of pancreatic fistula (Grade A), one of acute pancreatitis, and one of delayed gastric emptying. In the meantime, one patient experienced a gastrointestinal hemorrhage (6 days after IRE; Grade 3) and presented with tarry stool; this was managed medically with short-term administration of hemostasis drugs and was likely related to the IRE procedure since the ablation zone covered the duodenal wall. At 30–60 days, Grade 2 and 3 complications had developed in two and one patient, respectively, one of whom experienced PV thrombosis requiring systemic anticoagulation, while the remaining two experienced gastrointestinal obstructions requiring total parenteral nutrition.

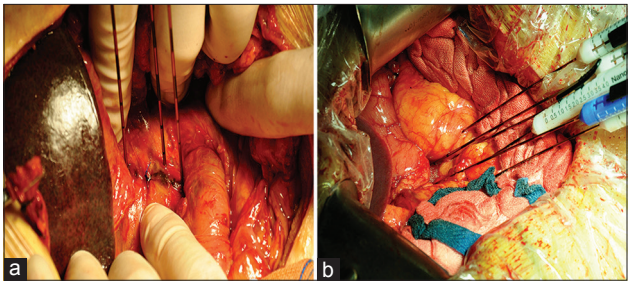

Figure 1: Intraoperative images of *in situ* irreversible electroporation being performed in two patients with locally advanced pancreatic carcinoma through an anterior-to-posterior approach (a) and a caudal-to-cranial approach (b), respectively.

No deaths were directly attributed to IRE. Five patients died during the course of follow-up at 8, 12, 24, 37, and

Table 2: Clinicopathologic characteristics of 25 patients with locally advanced pancreatic carcinoma treated with IRE

Characteristics	Values
Age (years), median (range)	58 (49–80)
Sex, *n* (male/female)	19/6
Tumor location, *n* (%)	
Head	15 (60)
Body/neck	10 (40)
Tumor size (cm), median (range)	4.2 (2.8–4.9)
Vessel invasion at diagnosis, *n* (%)	
Celiac only	12 (48)
SMA only	6 (24)
Celiac and SMA	2 (8)
PV/SMV occlusion	3 (12)
Celiac/SMA and PV/SMV occlusion	2 (8)
Surgery, *n* (%)	
Open IRE *in situ*	9 (36)
Open IRE and double bypass surgery	16 (64)
Approach of IRE probes, *n* (%)	
Anterior-to-posterior	9 (36)
Caudal-to-cranial	16 (64)
IRE time (min), median (range)	36 (23–101)
Surgery time (min), median (range)	225 (100–420)
Probes (*n*), median (range)	4 (2–6)
Pullbacks (*n*), median (range)	2 (1–3)
Probe exposure (cm), median (range)	1.0 (1.0–1.5)
Time from diagnosis to treatment (months), median (range)	2.5 (0.5–4.0)
Serum CA19-9 (U/ml), median (IQR)	
At admission	217 (901)
Day 1 after IRE	383 (1249)
Day 7 after IRE	106 (766)
Day 30 after IRE	90 (863)
Day 90 after IRE	444 (1968)
Overall hospital stay (days), median (range)	17 (12–24)
Postoperative hospital stay (days), median (range)	9 (8–15)

IRE: Irreversible electroporation; IQR: Interquartile range; SMA: Superior mesenteric artery; PV: Portal vein; SMV: Superior mesenteric vein.

Table 3: Complications experienced by 25 patients within 90 days after IRE

Type	*n*	Clavien-Dindo classification
Intraoperative complications		
Transient hypertension	2	–
Transient hypotension	1	–
Transient supraventricular tachycardia	1	–
Postoperative complications		
Pancreatic fistula (Grade A)	3	Grade 1
Acute pancreatitis	1	Grade 2
Upper gastrointestinal hemorrhage	1	Grade 3
Delayed gastric emptying	3	Grade 2
PV thrombosis	1	Grade 3

–: Not applicable; IRE: Irreversible electroporation; PV: Portal vein.

42 weeks after the procedure, respectively. The patient who died in the 8th week was 80 years old and received IRE *in situ* without precautionary double bypass surgery; however, this patient did not achieve a complete response to the treatment as the tumor at the head of the pancreas progressed and compressed the bile duct and duodenum. Thus, the patient was jaundiced and had gastrointestinal obstruction and eventually died of cachexia. Another four patients died of progressive metastatic disease. No deaths were attributed to the IRE procedure.

Efficacy

Postprocedural radiological imaging and serum CA19-9 testing were performed to evaluate the efficacy of IRE. A review of CT/MRI scans 1 week post-IRE revealed expected hypoattenuation in the treated zone, with a peripheral edema around the target area indicating inactivated tumor cells and a regional inflammatory response [Figure 2a and 2b]. The hypoattenuation zone progressively decreased on days 30 and 90 after IRE, and the edema disappeared [Figure 2c and 2d]. Furthermore, all available postprocedural imaging, including 3D reconstruction, did not reveal any vessel injury within or near the ablation zone. Serum CA19-9 levels of most patients (92%) rose temporarily, peaking on the 1st day after IRE and then decreasing at varying rates; levels in 8/25 patients (32%) had fallen back to normal at discharge.

Nine cases of partial response according to the RECIST criteria version 1.1[12] (36%) were recorded at the last evaluation as were nine cases of progressive disease (36%) and seven of stable disease (28%). Among the nine patients with disease progression, one developed multiple liver metastases 5 months post-IRE, and another had bone metastasis 8 months after the procedure.

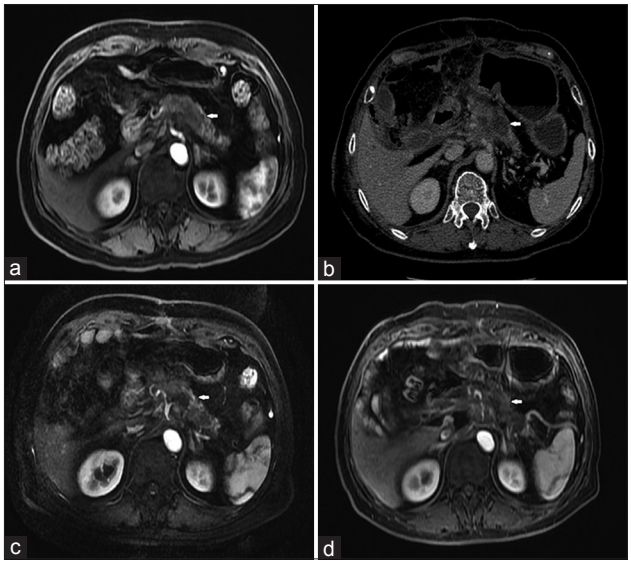

Figure 2: Computed tomography and magnetic resonance images of an 80-year-old woman with locally advanced pancreatic cancer, including celiac artery encasement. Images acquired at diagnosis (a), 1 week (b), 30 days (c), and 90 days (d) after irreversible electroporation. Arrows indicate celiac artery encasement.

The median preoperative VAS was 4; the scores at 1, 7, 30, and 90 days of follow-up were 6, 4, 3, and 1, respectively. The median baseline KPS was 90, the scores at 7, 30, and 90 days were 58, 86, and 75, respectively. Only seven patients received radio- or chemotherapy after IRE.

Discussion

As an emerging technique, IRE is more favored than other ablation methods such as microwave, radio-frequency ablation (RFA), and cryoablation for treating unresectable tumors, especially LAPCs; protocols such as chemotherapy and radiotherapy frequently lead to disappointing results. The safety and efficacy of IRE have been verified in several western studies although its application in China is still in the initial stages. Therefore, the present study was designed to assess the safety and feasibility of IRE for treating LAPC at our institution in China.

Our data suggest that devising a standard set of inclusion and exclusion criteria for IRE candidates is important. Interestingly, and in contrast to other ablation techniques, IRE protects surrounding vital structures such as vessels or nerves, resulting in less damage and/or complications.[13,14] However, because of its electrophysiological nature, IRE may cause arrhythmia and can also negatively affect blood pressure, thus leading to a cardiovascular accident during surgery. Furthermore, high-intensity IRE currents may sometimes produce coagulative necrosis, similar to that produced by thermal ablation techniques such as RFA; IRE-induced cellular damage may also be partially thermal.[15] This notion was explored by Dunki-Jacobs *et al*.,[16] who concluded that IRE did not produce significant thermal damage when the usual equipment settings were applied. On the other hand, they also reported that the metallic stent could increase the risk of producing thermal damage when IRE was applied in tumors located at the head of the pancreas due to its conductivity.[17] Hence, it is critical that careful attention is paid to appropriate patient selection. In our protocol, IRE is absolutely contraindicated in patients with severe cardiac arrhythmias or pacemakers, or with implanted biliary metallic stents; this was in accordance with the previous clinical studies at other centers.[9,18] Intolerance to muscle relaxants and anticoagulants is also considered an absolute contraindication because these agents are indispensable during the perioperative period. Furthermore, the tumor diameter is a crucial parameter when evaluating IRE applicability; it was previously recommended that tumor sizes be limited to <4 cm for better efficacy.[19] Nevertheless, we expanded the upper tumor size limit to 5 cm in our inclusion criteria because we found that the baseline tumor diameter of most patients was >4 cm at diagnosis. Moreover, when considering the limited numbers of electrical probes (<6), tumor size should be limited to <5 cm so that the ablation zone can cover the lesion completely.

Another important lesson from this study is that safety remains a primary concern during the application of IRE for pancreatic cancer. As shown in Table 3, four intraoperative

and nine postoperative adverse events were reported, with an overall rate of 52% IRE-related complications in the entire study. The morbidity was consistent with several recent overlapping multi-institutional studies investigating IRE management of LAPC, in which the 90-day complication rates ranged from 33% to 59%.[9,18,20] Although our total complication rate was relatively high, all intraoperative complications were transient, and the postoperative complication rate was only 36%. Moreover, the Clavien-Dindo grades tended to be less severe; only 8% of patients had Grade 3 complications in a manner that involved upper gastrointestinal hemorrhaging. Although this was not caused by direct damage owing to the insertion of IRE electrodes or biopsy needles, we estimate that hemorrhaging was caused by secondary damage from stress ulceration of the duodenal wall that was invaded by the tumor in the ablation zone. While we did not demonstrate a relationship between bleeding and adjustable IRE parameters, selection of IRE for LAPC that has invaded the duodenum should be performed with caution.

Only one patient experienced PV thrombosis at 30–60 days post-IRE. This complication was reported in 4–7% of patients in the previous series.[9,20] Narayanan *et al*.[21] also reported a 4.4% thrombosis rate even though vascular patency was still intact after IRE. Kluger *et al*.[22] attributed the occurrence of portal or SMV thrombosis to the combination of hypercoagulability associated with pancreatic cancer, a low flow state from prior stenosis, as well as theoretical damage to the venous endothelium secondary to IRE. While the exact process and mechanism of thrombogenesis after IRE is still unknown, therapeutic post-IRE anticoagulation is nevertheless routinely recommended in the current protocols.

In the current study, most patients underwent IRE *in situ* with bypass surgery; in clear contrast to the previous IRE series, half of our patients underwent precautionary double bypass surgery despite no sign of jaundice or gastrointestinal obstruction before IRE. It is possible that such procedures lower the risk of readmission due to the bile duct or gastrointestinal tract obstruction resulting from disease progression. This notion is supported by the fact that one patient who only underwent IRE *in situ* in the early phase of this series experienced jaundice and gastrointestinal tract obstruction caused by tumor progression and eventually died of cachexia. We consider it necessary for patients with tumors located in the pancreatic head or body to undergo precautionary bypass surgery so that they can achieve a better quality of life. Moreover, bypass surgery is generally performed after IRE; therefore, probe placement is not a concern.

CA19-9 is a valuable indicator of the efficacy of IRE in conjunction with CT or MRI and can be used to monitor disease progression after the procedure. As shown in Table 2, there was an obvious fluctuation of patients' serum CA19-9 levels pre- and post-IRE. We attributed this phenomenon to a transient release of intracellular proteins following damage to the neoplastic cell membranes as has previously been shown to occur. Even though these neoplastic cells are subsequently driven to apoptosis after IRE, it is possible that some are not ablated and thus become more aggressive.[23]

Because electroporation can enhance the delivery of molecules into tissues,[24,25] it potentially holds significant value for the treatment of LAPC. We posit that IRE efficacy would be dramatically reinforced if combined with gemcitabine-based regional intra-arterial infusion chemotherapy (RIAC), where chemotherapeutics would be delivered to the target area through a selective interventional indwelling catheter. Although it was demonstrated that IRE could enhance the delivery of gemcitabine to pancreatic tumors in nude mice,[26] the application of this novel combined therapy in LAPC requires further clinical validation.

CT/MRI is considered the major modality with which to evaluate the efficacy and possible complications of IRE.[19] Only 28% of our patients achieved stable disease and 36% achieved a partial response according to CT/MRI evaluation post-IRE. Given that most patients in our study received IRE treatment as their first medical intervention, and that our cohort size was too small for adequate analysis, we attribute these response rates to our learning curve as well as relatively inaccurate postoperative measurements. A contrast-enhanced CT/MRI scan after IRE could exhibit different results compared to RFA because of the former's nonthermal noncoagulative action and the consequent preservation of vital vessels. In addition, several researchers recommended that the postcontrast vein phase of the contrast-enhanced CT is the best for the evaluation of efficacy due to the congestion of blood in the tumor vessels.[5,6] However, Martin *et al*.[9] stated that an early post-IRE scan should be performed to rule out possible complications, rather than to assess ablation efficacy. In either case, CT/MRI scanning combined with testing of serum CA19-9 post-IRE was indispensable, not only for evaluating the procedure's efficacy but also for assessing the short-term local control of the disease.

The limitations of this study include the absence of an appropriate control group for analysis of the complications. In addition, the study's retrospective nature and its small cohort size inevitably produce a bias during survival analysis, which is also limited by the short follow-up period. The heterogeneity of patients with respect to having undergone previous therapies also had a negative impact on the evaluation of efficacy. Moreover, too few patients agreed to receive RIAC after IRE; therefore, we could not compare the efficacy of this novel combined therapy to that of IRE alone or of other traditional therapies.

In conclusion, IRE is a relatively safe and feasible treatment option for a majority of patients with LAPC and can be combined with regional chemotherapy. Other palliative surgical procedures such as double bypass surgery can be performed as a precautionary measure to facilitate patients' rehabilitation with a better quality of life. Although we could not ascertain the efficacy of IRE when combined with RIAC,

this novel combination therapy appears feasible. Therefore, further studies investigating the safety and utility of IRE combined with RIAC for the treatment of LAPC with a larger patient sample are warranted.

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Conflicts of interest

There are no conflicts of interest.

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