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Irreversible Electroporation of Malignant Lesions: An Institution Experience

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ORIGINAL ARTICLE

Irreversible electroporation of malignant lesions: An institution experience

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Abstract

Background: Irreversible electroporation (IRE) is a tumor ablation technique where short, high-voltage pulses are applied to tumors to permeabilize the cell membranes. Since no thermal energy is created, it can be used near vital structures. We report our experience in a wide array of anatomic locations and on diverse oncologic processes.

Methods: We performed a retrospective review of all IRE cases performed at our institution from September 2010 to September 2013. Patients were evaluated for peri-operative morbidity, mortality, and oncologic outcome.

Results: Twenty-seven patients underwent IRE during 16 laparotomies and 12 CT guided percutaneous procedures. Anatomic locations: 9 liver, 7 pancreas, 7 pelvis, 2 retroperitoneal, 1 lung, 1 chest wall, and 1 mesentery. Lesion types: 14 metastases, 8 primary tumors, 5 recurrences, and 1 lesion not confirmed malignant. Three cases involved margin accentuation prior to resection. One treated the IVC margin of a radiofrequency ablation site. Twenty-four procedures attempted complete ablation. Lesions ranged from 1.0 cm to 6.0 cm. Median hospital stay: 1 day (percutaneous treatment) and 9 days (laparotomy). 30-day mortality was 0%. Complications included muscle weakness, gastric outlet obstruction, intragastric hematoma, pancreatic fistula, small bowel obstruction, and urinary retention. Another patient experienced obstructive jaundice and portal vein thrombosis. Eight patients developed recurrence. The median length of follow-up is 12.5 months.

Conclusion: Our experience suggests that IRE is safe and feasible in a variety of situations. Several pitfalls were identified to prevent unnecessary morbidity. Our data suggests a local control benefit, but randomized studies are needed.

Key words

Irreversible electroporation, Non-thermal ablation, Pancreatic adenocarcinoma, Liver metastasis, Cancer ablation, Ablation safety, Pelvic ablation, Percutaneous ablation

1 Introduction

Irreversible Electroporation (IRE) is a method of inducing cell death first described in 1961 for sterilization in the food industry [1], but since 2007 this procedure has been increasingly described in the context of tumor ablation. IRE utilizes short, pulsed, high-voltage electric fields to disrupt cell homeostasis by inducing irreversible pores in the cell membrane leading to cell death predominantly by apoptosis [2]. This concept came logically out of the lower voltage reversible electroporation technique used in research labs to move macromolecules across cell membranes [3].

The apoptotic mechanism of IRE maintains the tissue structure, cell remnants are removed by phagocytosis, and the cells are then replaced by innate cellular regeneration [4]. Consequently, IRE has been demonstrated to have two major benefits over other ablation methods. First, it has been demonstrated in animal models to be safe for treatment around sensitive organs including bowel, ductal structures, and critical vascular supply because of preservation of the extracellular matrix [4, 5]. Recent human studies have been corroborating these findings [6]. In contrast, other forms of ablation which induce coagulation necrosis result in denaturing of the tissue protein matrix and are followed by fibrosis making them riddled with complications around such sensitive structures [4]. Secondly, animal studies have shown IRE is effective around high flow vascular structures where thermal sink and chemical ablation wash-out result in treatment failures when using other ablation methods [3].

IRE has been tested in a myriad of anatomic locations in the preclinical setting however safety and efficacy data in the clinical setting is still limited [3]. A recent systematic review found safety data in the literature for 129 liver and 42 pancreas cases with complication rates of 16% and 19% respectively [6]. Additional literature reviews and case series have suggested an IRE related complication rate between 0% and 33% when used in the pancreas [8-10]. Several authors have indicated great variation between studies demonstrating the need for additional cases to be reported allowing for more robust statistical analysis. These reviews have found safety data in other organs so limited that location specific conclusions cannot be made [7].

We present our institutions experience with this novel technique in a wide array of anatomic locations and on a diversity of oncologic processes. We intend to contribute cases to the growing safety data in the literature, discuss feasibility of the procedure in a wide array of anatomic locations, and discuss any observed oncologic benefit.

2 Methods

A retrospective chart review was performed at our institution of all the patients who underwent an IRE procedure from September 2010 to September 2013. All of the patients were required to meet all of the following selection criteria. The patient had to have primary, recurrent, or metastatic oncologic disease in a localized region with limited disease burden. Each patient was evaluated by an interdisciplinary oncology team for optimized therapy. The patient's disease had to be considered unresectable or the patient was unwilling to undergo resection. Lastly, all patients were not candidates for any typical thermal ablation method.

Charts were analyzed for patient demographic and comorbidity information including: age, gender, body mass index, ASA score, past medical history, and past surgical history. Disease information was collected including diagnosis, disease history, tumor size, past and present treatments, and tumor markers if applicable. Procedure details were defined including procedure date, probe number, and probe configuration. Lastly, outcome data was collected including length of stay, complications, serial imaging studies, date of recurrence or progression, and time of patient follow-up.

3 Results

The patient age ranged from 29 to 82, the median BMI was 31 (range 29-40), and the mean ASA score was three. The data set included 16 males and 11 females. Several patients had additional comorbidities outside of cancer; however no direct correlation was seen relative to specific comorbid conditions.

The indication for IRE over thermal ablation was related to the proximity of either high flow vasculature or a thermally sensitive organ (see Table 1). The approach of open versus percutaneous was decided by applicability of percutaneous access. The pancreas always required an open laparotomy. The liver and pelvis were often able to be approached in a percutaneous fashion based on imaging evaluation by a single radiologist (SK). In addition, the median number of intraoperative probe placement sites was four with a range from one to nine. The number of separate depths needed for multiple ablations ranged from one to three. Twenty-four of the procedures had a goal of complete ablation of the target lesion. Three ablations were used for margin accentuation of the tumor prior to resection. This included one case of a pancreatic body cancer where the proximal margin was accentuated prior to distal pancreatectomy. The other two margin accentuation ablations were performed along the pelvic sidewall prior to pelvic mass resection to allow for probe placement. One procedure was performed to accentuate a radiofrequency ablation site along the IVC margin in order to mitigate the heat sink effect.

Table 1. Procedure Data and Indications

Location	Procedure Number	Laparotomy Approach [16]	CT-guided Approach [12]	Indication Over Thermal Ablation Method
Liver	9	5 (56%)	4 (44%)	Proximity to IVC, aorta, bowel, and/or porta hepatis
Pancreas	7	7 (100%)	0	Proximity to SMA, SMV, duodenum and/or common bile duct
Pelvis	7	4 (57%)	3 (43%)	Proximity to ureter, bowel, iliac artery, bladder, and/or iliac bone
Retroperitoneum	2	0	2	Proximity to aorta and/or IVC
Lung	1	0	1	Proximity to brachiocephalic vein
Chest Wall	1	0	1	Proximity to bowel
Mesentery	1	0	1	Proximity to mesenteric vessels and bowel

The location, size, and type of different oncologic processes were found to be very diverse. The lesions where complete ablation was attempted ranged in size from 1.0 cm to 6.0 cm. The nine liver lesions included two hilar cholangiocarcinomas, five colorectal metastases, one thyroid metastasis, and one renal cell metastasis. The seven pancreas lesions included six primary pancreatic cancers and one recurrent pancreatic cancer. The seven pelvic lesions included one primary sarcoma, one recurrent sarcoma, one recurrent bladder cancer, one recurrent rectal cancer, two rectal cancer metastases, and one endometrial cancer metastasis. The retroperitoneal lesions included a recurrent sarcoma and metastatic carcinoid tumor. The remaining lesions included a colorectal metastasis to the lung, a chest wall recurrence of mesothelioma, and a carcinoid metastasis to the mesentery.

The outcome data demonstrated the median length of stay following percutaneous ablation was one day while the laparotomy patients had a median length of stay of nine days. The 30-day mortality was 0%. Eight complications were seen including gastric outlet obstruction, temporary muscle weakness, obstructive jaundice, portal vein thrombosis, urinary retention following pelvic ablation, gastric wall hematoma, pancreatic fistula, and small bowel obstruction. The median follow-up interval was 12.5 months with a range from 1.5 to 35 months. A local recurrence was found in eight of the twenty eight procedures at a median time interval of seven months.

Two example imaging series of patients without local recurrence are included to demonstrate how serial imaging was used to monitor local disease status. Figure 1 demonstrates serial imaging following IRE ablation of a pancreatic adenocarcinoma recurrence. The patient had undergone a margin negative pancreaticoduodenectomy one year prior to this ablation and experienced an isolated local recurrence with no evidence of systemic disease. The imaging series demonstrates post ablation changes and two year repeat imaging. Figure 2 demonstrates serial imaging following IRE ablation of an isolated retroperitoneal recurrence of liposarcoma. The imaging series includes the ablation itself and follow-up imaging at 35 months.

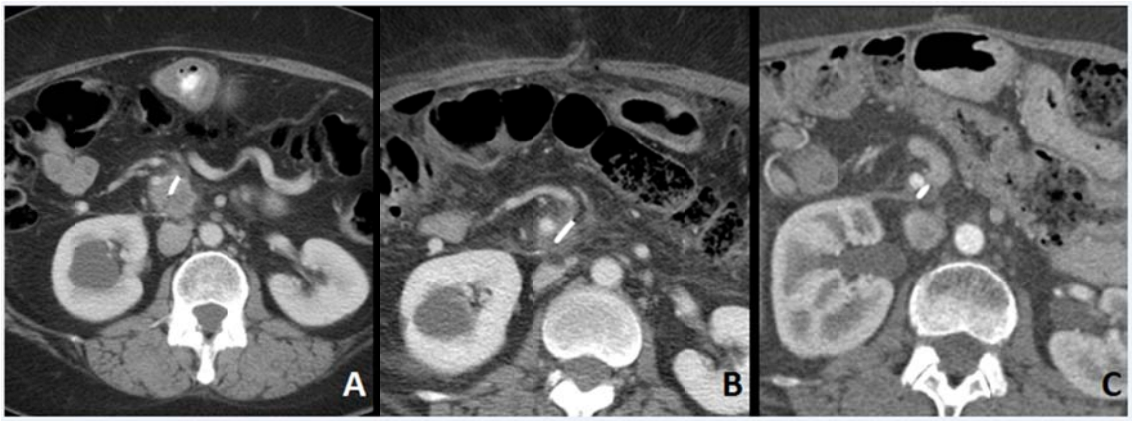

Figure 1. A. Retroperitoneal Recurrence post-whipple surrounding the surgical clip and involving the SMV and root of the mesentery; B. Post-ablation day #1 demonstrating hypodensity/non-enhancement of the mass; C. 24 month follow-up imaging demonstrating minimal residual non-enhancing tissue/scar.

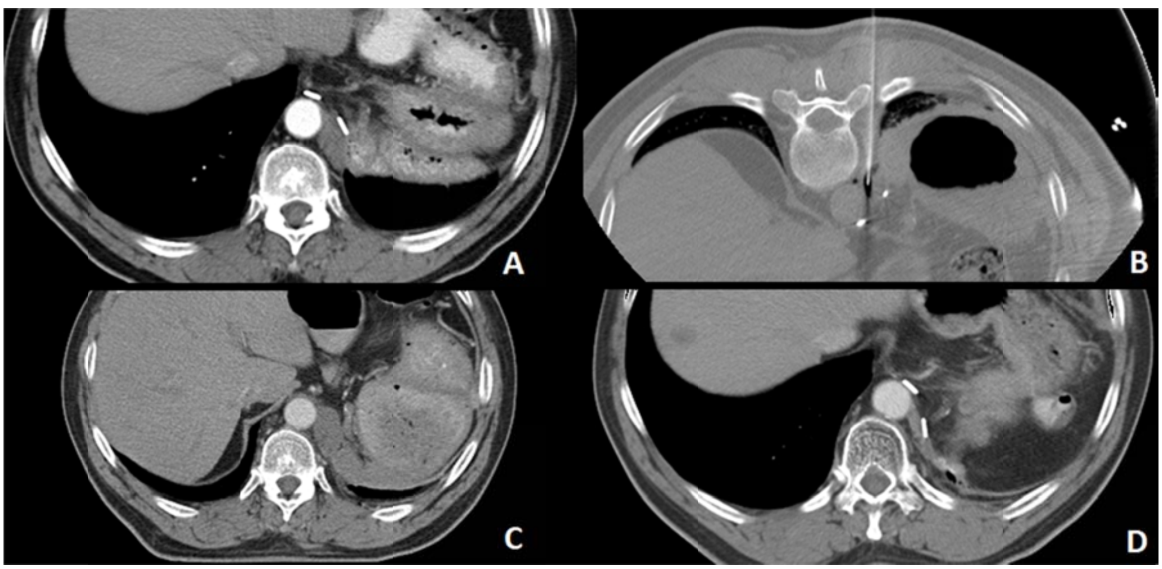

Figure 2. A. Retroperitoneal recurrence of liposarcoma following multiple excisions and located between the posterior surgical clip and aorta; B. Percutaneous IRE ablation of recurrence; C. Post-ablation day #1; D. 35 month post-ablation imaging demonstrating minimal residual scar tissue.

4 Discussion

IRE can be considered a safe ablation method in a wide array of anatomic locations due to minimal morbidity and mortality. A 30 day mortality rate of zero percent suggests that no patient deaths were the direct result of IRE ablation. In terms of morbidity, several complications were likely the result of the surgical approach itself including gastric wall hematoma, pancreatic fistula, and small bowel obstruction as opposed to resulting from the IRE ablation. Urinary retention occurred in a patient who underwent both pelvic surgery and pelvic ablation and could have been the result of either. In either case, temporary urinary retention seems to be an acceptable morbidity in comparison to the underlying disease. Lastly, a case of post-operative gastric outlet obstruction likely occurred from local edema post-IRE which exacerbated an underlying partial obstruction from the pancreatic head mass. To address this issue, a prophylactic G-J tube or gastro-jejunostomy bypass is now placed intra-operatively following ablation of all tumors >2 cm. With this intervention, no additional issues were observed. These minimal morbidities suggest IRE is safe in proximity to the aorta, IVC, SMA, SMV, iliac artery, brachiocephalic vein, common bile duct, bowel, ureter, bladder, and iliac bone.

The complication of muscle weakness requires additional consideration. Two patients experienced mild quadriceps muscle weakness following IRE ablation in proximity to the femoral nerve. Both patients regained full function within two days. In human studies only one other case has been reported near a major nerve and a similar self-resolving weakness occurred [11]. Animal studies have demonstrated that IRE can result in wallerian degeneration of the axon with preservation of the endoneurium and extracellular matrix resulting in the potential for nerve regeneration [12-14]. The very limited studies and potential for long term deficits warrant further studies.

Additional safety consideration is also needed for hilar cholangiocarcinoma ablation. One of our two cases was complicated by post ablation obstructive jaundice and portal vein thrombosis which likely resulted in worsening liver function. No additional IRE ablations of hilar cholangiocarcinoma have been reported in the literature to date. A case series of 11 patients undergoing 22 IRE ablations for metastatic disease in the liver located within 1 cm of the common, left, or right hepatic duct demonstrated no complications related to the IRE ablation [15]. Consequently, IRE may be safe near the liver hilum where significant narrowing is not already present, but additional studies are needed to better understand the safety of IRE ablation in hilar cholangiocarcinoma. We have found pre-IRE stenting beneficial in the common bile duct for pancreatic head ablations, and the same concept may be explored in future studies with the use of hepatic duct stenting prior to ablation.

Our experience demonstrates the feasibility of IRE use in a wide array of locations. In addition to the already described application in primary pancreatic tumors and liver metastasis, we have demonstrated that this technology can easily be applied to pelvic lesions adjacent to the bowel, bladder, ureter, and major vasculature. It can be used for margin accentuation prior to resection of large lesions abutting vasculature in the pancreas or abutting the pelvic bones. Margin accentuation prior to resection allows patients with expected positive margins to potentially still benefit from resection [16]. It can be applied to lesions abutting vasculature in the retroperitoneum, lungs, or mesentery. And lastly, to lesions located in the mesentery or chest wall with margins in close proximity to vital structures. Consequently, we believe IRE should be considered in a wider population than previously described. This population should include all patients with unresectable local oncologic disease, minimal disease burden, and who are not candidates for thermal ablation methods. If these criteria are followed additional locations will inevitably be identified where this versatile procedure can be applied.

Our experience with percutaneous ablation compared to open surgery demonstrated a shorter length of hospital stay, a likely decrease in the corresponding cost, and an avoidance of laparotomy related complications. Our data suggests that laparotomy is generally needed for all pancreas ablations, hilar cholangiocarcinoma ablations, and margin accentuation procedures due to the related resection. However with the development of newer posterior approach techniques there may be an increasing ability to access specific pancreatic lesions in a percutaneous fashion [17]. More superficial lesions in the mesentery, retroperitoneum, lung, and chest wall can generally be ablated through percutaneous means with much difficulty. Lesions lying in the liver and pelvis varied in accessibility and these patients would likely benefit from a multispecialty evaluation which includes surgical and interventional oncology to determine the best ablation approach.

The survival data has limitation in application due to the wide array of disease types and relatively few cases in each category; however there appears to be a local control benefit. This is exemplified in the 20 ablations where no recurrence of the local disease has been found on imaging at a median follow-up of 12.5 months. Additionally, a median seven month delay in the local progression was seen in the eight cases with recurrence. Lastly, the potential for cure of purely localized disease is even suggested in Figure 1 and Figure 2 where these patients are disease free at 2 years and almost 3 years respectively.

Future studies are needed to analyze technical aspects that may lead to recurrences. While some evidence has already suggested a direct relationship between recurrence rate and lesion size [18, 19], our smaller sample size did not show any clear relationship. The recurrences did appear to occur in cases where less aggressive overlap margins were attempted. The above evidence demonstrating minimal morbidity near sensitive organs may allow for future studies to examine larger overlap with normal tissue and the effect on recurrence. Similarly, the safety profile may allow for the study of stronger electric fields in order to overcome the electric field sink phenomenon recently described in heterogeneous tissues near large and clustered vessels [20].

5 Conclusion

IRE appears safe near many sensitive structures where thermal ablation methods would result in unacceptable complications. IRE is feasible in a wide array of anatomic locations through open-surgical and percutaneous means. IRE can be combined with other oncologic treatment modalities for optimal disease control. Lastly, IRE appears to have a local control benefit. Further studies are needed to assess disease specific survival benefit.

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