Irreversible Electroporation Therapy in the Management of Locally Advanced Pancreatic Adenocarcinoma

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BACKGROUND: Locally advanced pancreatic cancer patients have limited options for disease control. Local ablation technologies based on thermal damage have been used but are associated with major complications in this region of the pancreas. Irreversible electroporation (IRE) is a nonthermal ablation technology that we have shown is safe near vital vascular and ductal structures. The aim of this study was to evaluate the safety and efficacy of IRE as a therapy in the treatment of locally advanced pancreatic cancer.

STUDY DESIGN: We performed a prospective multi-institutional pilot evaluation of patients undergoing IRE for locally advanced pancreatic cancer from December 2009 to March 2011. These patients were evaluated for 90-day morbidity, mortality, and local disease control.

RESULTS: Twenty-seven patients (13 women and 14 men) underwent IRE, with median age of 61 years (range 45 to 80 years). Eight patients underwent margin accentuation with IRE in combination with left-sided resection (n = 4) or pancreatic head resection (n = 4). Nineteen patients had in situ IRE. All patients underwent successful IRE, with intraoperative imaging confirming effective delivery of therapy. All 27 patients demonstrated nonclinically relevant elevation of their amylase and lipase, which peaked at 48 hours and returned to normal at 72 hour postprocedure. There has been one 90-day mortality. No patient has shown evidence of clinical pancreatitis or fistula formation. After all patients have completed 90-day follow-up, there has been 100% ablation success.

CONCLUSIONS: IRE ablation of locally advanced pancreatic cancer tumors is a safe and feasible primary local treatment in unresectable, locally advanced disease. Confirming these early results must occur in a planned phase II investigational device exemption (IDE) study to be initiated in 2012. (J Am Coll Surg 2012;215:361–369. © 2012 by the American College of Surgeons)

Pancreatic cancer is the second most common gastrointestinal malignancy and although it is the ninth most common cancer among all sites, it is the fourth leading cause of cancer deaths in the United States. In 2009, it is estimated that 42,470 people developed pancreatic cancer and 35,240 died from this challenging disease.[1] Pancreatic cancer carries a grave prognosis, with overall 1- and 5-year survival rates of 24% and 5%, respectively.[2] Moreover, only 7% of cases are diagnosed at an early stage and only 15% to 20% of patients have resectable disease at diagnosis. Larger proportions have locally advanced unresectable tumor (approximately 30% to 40%) or metastatic disease (40%) at diagnosis.[2,3] It can be estimated from recent a population-based study that approximately 20% to 30% of all pancreatic adenocarcinoma patients present with stage III — locally advanced cancer[4] that corresponds to the recent American Joint Committee on Cancer (AJCC) staging[5] guidelines. Advanced T-stage adenocarcinomas involve either the superior mesenteric artery or celiac axis or both. This extension seen on cross-sectional imaging is the only accepted definition of "unresectable" based on local invasion.[6,7] Median survival of locally advanced pancreatic cancer remains at 6 to 11 months in the majority of prospective clinical trials despite advances in chemotherapy, radiation therapy, and chemoradiation therapy in the last 2 decades.[8-13] Improvement in durable

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relief of pain and sustained quality of life remains a great problem. In the last 2 decades, a few noteworthy improvements in chemotherapy, radiation therapy, and a combination of chemo-radiation therapy have made only a very modest impact on the overall prognosis. Gemcitabine-based chemotherapy has improved response rate and survival.[14]

Irreversible electroporation (IRE) is a technique in which short, high-voltage pulses are applied to tissues[15-18] to permeabilize the cell membranes. The cell membrane can either be permeabilized reversibly and temporarily, as is commonly performed in basic science research for the loading of cell lines, or permeabilized irreversibly, in which case the cell will subsequently undergo cell death (IRE). The optimal mechanism through which electrical pulses permeabilize the cell membrane is not completely understood from a frequency or repetition standpoint, with outcomes depending on pulse amplitude, duration, and the number of pulses.[15] IRE uses a nonthermal-based method of action and can be used to treat vital structures such as the urethra, larger blood vessels, nerves, and by itself to produce tissue ablation in vivo.[16] It has been shown that IRE can be used to nonthermally ablate large volumes of tissue in a controlled manner with a sharp boundary between affected and unaffected tissues.[17,19,20] We have recently published our findings regarding safety of IRE in the pancreas.[21] In this chronic animal model we demonstrate that IRE of the pancreas performed at an optimal voltage is well tolerated, with rapid resolution of pancreatic inflammation and preservation of vascular structures.

So the aims of this study were to evaluate the safety and toxicity of IRE in locally advanced pancreatic cancer patients, to obtain local control of the disease, and to compare our results with the results of other prospective therapies in the palliation of locally advanced pancreatic cancer.

METHODS

We performed a prospective evaluation of patients undergoing irreversible electroporation for locally advanced pancreatic cancer from December 2009 to March 2011. Locally advanced pancreatic cancer was defined as per the 7th edition of the AJCC staging system for pancreatic cancer – described as arterial encasement of either the celiac axis or superior mesenteric artery or both.[6,7] IRE was not used on patients with borderline resectable lesions. The study protocol was approved by the Institutional Review Board (IRB), and all patients were provided with written, informed consent forms. Before IRE treatment, all patients were reviewed in a multidisciplinary tumor conference to ensure that all treating physicians—who represented the disciplines of medical oncology, radiation oncology, gastroenterology, interventional radiology, and surgery—agreed with treatment planning.

Table 1. Surgical and Electroporation Decision Making in Patients with Locally Advanced Pancreatic Cancer

Characteristic	Pancreatic head/uncinate	Pancreatic body/medial tail
Portal vein-SMV occlusion	IRE	IRE
Celiac axis encasement and <180° abutment of SMA	NA	Subtotal pancreatic resection with celiac axis resection and IRE
Celiac axis encasement and >180° abutment of SMA	IRE	IRE
SMA encasement without celiac axis involvement	Whipple with IRE	NA

IRE, irreversible electroporation; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

Surgical and electroporation technique

The surgical decision making of these patients was to offer either surgical resection with IRE for margin accentuation or IRE (in situ) alone. The decision to performed resection was based on location of disease in patients with pancreatic body tumors (Table 1). Ultimately the decision to perform pancreatic resection with IRE or IRE alone was at the surgeon's discretion based on intraoperative assessment, patient comorbidities, previous therapy, and patient desire. The surgical technique was carried out as described by Martin and colleagues[22] for pancreatic head lesions and by Makary and associates[23] for pancreatic body-medial tail lesions. Resection and IRE in these unique cases were performed to treat suspected positive margins and were not done when gross residual disease would be left behind. A jejunal feeding tube was used at the surgeon's discretion, but was placed in most cases secondary to a conservative approach and to avoid a prolongation of hospital stay related to delayed gastric emptying.

Comorbidities were defined as significant cardiac (past coronary infarction), pulmonary, renal, or pancreatic dysfunction. Additional organ resection excluded cholecystectomy, included adrenal resection, gastric (for distal pancreatectomy), liver, or any other solid organ in combination with pancreatic resection. Total preprocedure narcotic use was normalized to total fentanyl daily dosing for each patient and an established 10-point pain scale was used both preoperatively and at a 3-month postoperative visit.

Postoperative complications and the length of hospital stays were recorded prospectively at all institutions and graded by using our standard classification scale of compli-

cations, which has been reported previously.[22,24,25] For patients with more than 1 complication, comparison of in-hospital and 90-day postoperative complications were evaluated by assigning the complication with the highest severity for each patient. All postoperative complications were monitored and graded prospectively according to a previously published 5-point scale.[22] Briefly, grade 1 complications required only supportive care or oral medications; grade 2 complications required intravenous medication or parenteral nutrition; grade 3 complications required ICU admission or relatively noninvasive procedures; grade 4 complications involved chronic disability or required major reoperation (eg, decortication or enteral diversion). Major complications were defined as grade > 3. Grade 5, a postoperative death, was defined as any patient death that occurred within 90 days postoperatively.

The delivery of IRE was performed via the Nanoknife system (Angiodynamics, Lanthan), as described in our previous manuscript of IRE in the porcine pancreas.[21] High definition intraoperative ultrasound imaging was used in all cases, and is required to demonstrate nontraumatic precise needle placement and continuous ablation assessment during IRE delivery. In short, 2 monopolar probes with 2-cm spacing will deliver an electroporation defect of approximately axial 3.5 cm, anterior-posterior 2.5 cm, and cranial-caudal of 2.5 cm. This electroporation defect is achieved through a maximum of 1.5-cm exposure, 1,500 volts/cm, with 100 μsec wavelength. All patients were treated under general endotracheal anesthesia with deep paralysis, defined as zero twitches before IRE delivery as per a standard anesthesia twitch monitor. Preoperative narcotic management was normalized to fentanyl dosages because that was the predominant narcotic used, with additional wide ranges of other narcotics being used.

Follow-up imaging was performed at the time of discharge or with 2 weeks of IRE therapy for safety evaluation and then at 3-month intervals. Ablation recurrence was defined as persistent viable tumor as defined by dynamic imaging in comparison to pre-IRE scan, persistent hypermetabolic activity if there was hypermetabolic activity on pre-IRE scan, or tissue diagnosis. Ablation success was defined as the ability to deliver the planned therapy in the operative room and at 3 months to have no evidence of residual tumor, as described above. The method of evaluating local recurrence is the combination use of both cross-sectional imaging, either a CT scan or MRI, with or without PET scanning, based on the ability to obtain a preoperative PET scan and the fact that the primary lesion in question had PET activity. Those imaging modalities, CA 19-9 values, and clinical values were all used to determine local recurrence. All images were read by dedicated body imagers, none of whom were IRE proceduralists. The imaging of post-IRE to the pancreas is challenging given the acute inflammatory changes seen from postoperative day 1 through day 10, as well as the persistent soft tissue inflammation that occurs during the apoptotic process, as described by Bower and colleagues[21] that persists out to 6 to 8 weeks postablation. So involvement of a dedicated body imager is recommended when initiating a pancreatic IRE ablation program. A representative figure of a pre-, immediate post-, and then locally recurrent lesion is shown in Figure 1.

RESULTS

From December 2009 to March 2011, 27 patients underwent either IRE alone or IRE in combination with resection (Table 2) for locally advanced pancreatic adenocarcinoma; 12 were from Henry Ford Hospital and 14 from the University of Louisville. This included 14 men and 13 women, with a median age of 61 years (range 45 to 82 years). The patients had similar incidence of comorbidities, body mass index, and racial distribution, as in previous studies. There was an even distribution of pancreatic head ($n = 15$) and body/neck ($n = 12$) locations, with the median lesion size being 3 cm at its longest axis on the axial plane (Table 2). A majority (85%) had undergone multiple lines of previous chemotherapy and chemoradiation therapy (Table 2), with a median time to IRE from diagnosis of 6.6 months (Table 3). All patients (100%) had locally advanced pain related to celiac plexus invasion, with a median pain score of 5 (range 3 to 9) and were taking a median dose of 75 mcg fentanyl per day (range 50 mcg to 150 mcg).

Twenty-six of the patients underwent an open approach for IRE delivery, through a supine midline incision in most (80%) cases; 8 had IRE with resection (Table 3). One patient was treated percutaneously because of her multiple earlier surgical procedures unrelated to her disease; the treating physicians believed that an operative approach would be prohibitive, so they attempted this percutaneous approach for evaluation. Additional procedures were often performed at the time of IRE; the most common was gastrojejunostomy in order to prevent delayed gastric emptying in the in-situ patients. The median number of IRE probes used was 4, with an ability to deliver a minimum of 90 pulses successfully in all patients. A majority of patients did have to have 2 to 3 pull-back IREs because the longest probe exposure is 1.5 cm, in order to treat a 3-cm target lesion.

After all patients had completed 90-day follow-up, 9 (33%) sustained a total of 18 complications (Table 4). The complications were variable, but were most commonly associated with open surgical procedures, with possible IRE device-related complications occurring in 4 patients.

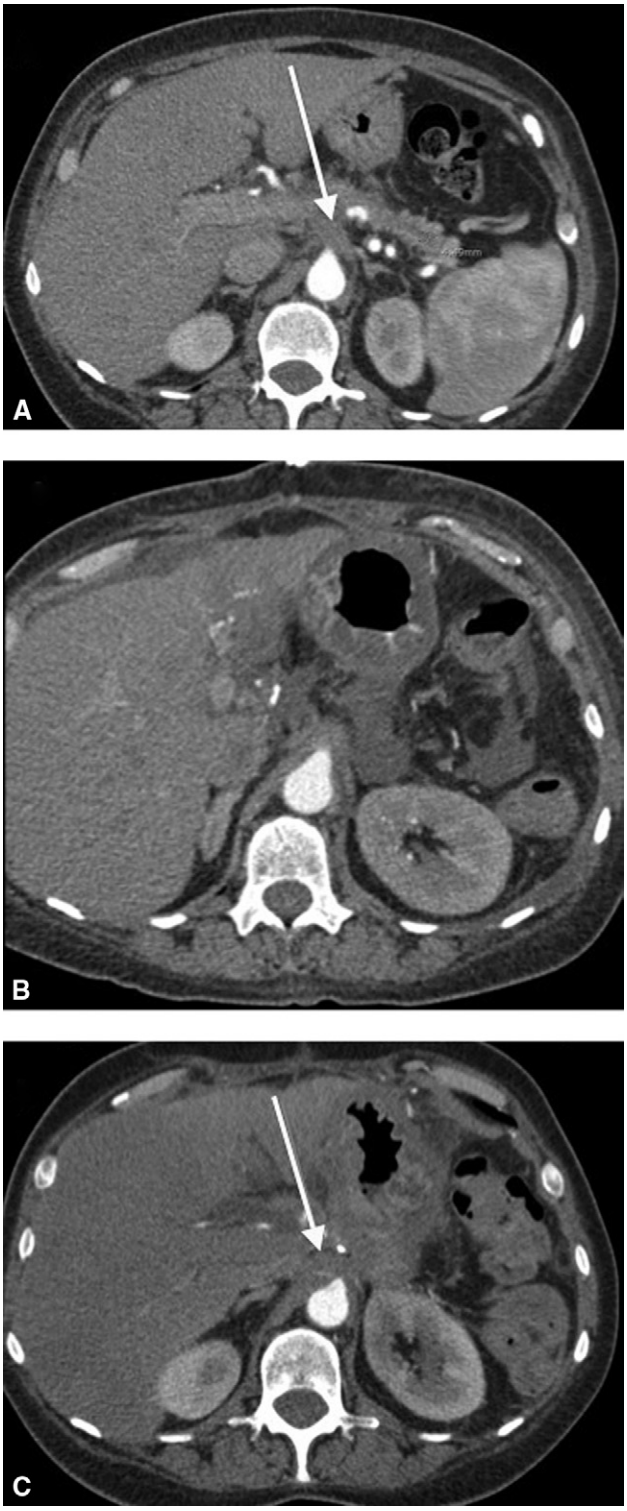

Figure 1. Representative CT image of patient with locally advanced pancreatic cancer; (A) immediate pre-IRE, arrow demonstrating locally advanced pancreatic neck tumor with celiac encasement; (B) 7 days post-IRE and subtotal pancreatectomy with celiac axis resection; (C) 3-month follow-up with local recurrence (arrow). IRE, irreversible electroporation.

Table 2. Characteristics of Locally Advanced Pancreatic Cancer Treated with Irreversible Electroporation

Characteristics (n = 27)	Data
Age, median, y (range)	61 (45–82)
Sex (male/female)	14/13
Race	
White	25
African American	1
Asian	1
Body mass index, median, kg/m^2 (range)	27.2 (23.0–42.4)
Past medical history, n	
Cardiac	5
Vascular	1
Pulmonary	0
Diabetes	5 (4 noninsulin)
Smoking	5
Hypertension	10
Other	14
Past surgical history, n	
Cholecystectomy	3
Abdominal hysterectomy	3
Location, n	
Head	15
Body/neck	12
Lesion size, median, cm (range)	
Axial	3 (1–5.5)
Anterior to posterior	2.8 (1–5.3)
Caudal to cranial	2.6 (1–4.1)
Performance status, n	
100%	24
90%	2
80%	1
Previous chemotherapy, n	
Gemzar	8
FOLFOX	3
FOLFIRI	1
Oxaliplatin	1
Avastin	1
Cisplatin	2
Taxol	1
FOLFIRINOX	4
Other	15
Previous radiation therapy	
5FU and radiation	3
Gemzar and radiation	6

FOLFIRI is a combination of folinic acid, fluorouracil, and irinotecan; FOLFIRINOX is a combination of oxaliplatin, irinotecan, fluorouracil, and leucovorin; FOLFOX is a combination of 5-FU, leucovorin, and oxaliplatin.

The first patient presented with a pancreatic head tumor with partial portal vein thrombus that had been stable for 4 months based on imaging and without anticoagulation,

Table 3. Operative and Ablative Characteristics of Patients with Locally Advanced Pancreatic Cancer Treated with Irreversible Electroporation

Characteristics	Data
Median time from diagnosis to electroporation, mo (range)	6.6 (1–28.5)
Approach, n	
Open – supine midline	26
Percutaneous	1
Pancreatic operations, n	
Whipple	4
Subtotal panc	4
Other operations, n	
Hepticojejunostomy	4
Gastrojejunostomy	9
Partial gastrectomy*	3
Other	17
No. of IRE probes used	
Bipolar	4 patients
Monopolar	23 patients
Probes, median, n (range)	4 (3–5)
Direction of IRE probes	
Anterior to posterior, n	7
Caudal to cranial, n	20
Success of IRE delivery, %	100
Total IRE delivery time, median, min (range)	10 (2–97)
Total procedure times, median, min (range)	160 (40–365)
Length of stay, median, d (range)	9 (1–58)
Complete ablation, n	26 of 27
Adverse events, n (%)	9 (33)
Follow-up recurrence, n	
6 wk	0
3 mo	1

*Considered additional organ when performed in conjunction with distal pancreatectomy.
IRE, irreversible electroporation.

underwent in-situ IRE treatment and on day 45, presented with worsening ascites, hepatic and renal failure and died on day 70, within our 90-day morbidity evaluation. The patient was treated with postoperative anticoagulation. In this case, we believe IRE was related to the progression of portal vein thrombus, most likely through edema after ablation, even though he had also had earlier radiation therapy, and we were not able to document a low flow state before portal vein thrombosis was identified. All of the needles were placed with continuous ultrasound imaging to ensure that needle damage was not an additional source of injury.

The second patient had undergone an obvious R2 resection at another institution and was treated with postoperative radiation therapy and chemotherapy for 5 months post Whipple. She was referred for obvious recurrent-residual disease and underwent an uncomplicated IRE in situ. Discharge CT scan on postoperative day 22 demonstrated a well-treated lesion with no evidence of portal vein thrombosis. However, on the day 90 CT scan, when she was back home and following up with the referring physician, she was found to have a complete portal vein thrombosis with ascites that required 1 paracentesis and subsequent oral aldactone. At 6 months post-IRE she remains stable with no evidence of recurrence and improved portal flow through collaterals.

The third patient was a locally advanced pancreatic cancer patient diagnosed for 6 months, who had a metal stent in place, which was taken out at the time of operation through a duodenotomy. The metal stent had to be removed because the conductivity of the metal stent has not been evaluated both in the degree of deflection of the electrical energy and to the safety of excessive energy delivery to the immediate surrounding structures around the stent. The patient then underwent successful IRE in situ, but on postoperative day 6 had a duodenotomy leak, which required percutaneous draining for 2 additional weeks. The fourth patient also underwent IRE, but with needles placed through a transduodenal approach, and on day 5 developed a duodenal leak that required percutaneous drainage. Both the third and fourth patients had undergone concomitant gastrojejunostomy and J-tube, so their postoperative lengths of stay were not prolonged.

At 90-day follow-up for all patients there has been 100% ablation success with no evidence of local recurrence. At 90-day follow-up the median narcotic use was 25 mcg fentanyl per day (range 0 mcg to 75 mcg; $p = 0.03$), with a median pain score of 3 (range 0 to 6; $p = 0.04$).

DISCUSSION

Locally advanced pancreatic cancer remains a challenging multidisciplinary management problem for optimal palli-

Table 4. Ninety-Day Adverse Events in Patients with Locally Advanced Pancreatic Cancer Treated with Irreversible Electroporation

Type of complication	Grade
Hematologic, n = 3	1,2,2
Ileus, n = 1	2
Bile leak, n = 2	3,4
Portal vein thrombosis, n = 2	5,2
Deep venous thrombosis, n = 2	2,2
Pulmonary, n = 2	3,3
Renal failure, n = 1	3
Ascites, n = 1	3
Wound infection, n = 3	2,2,2

Table 5. Reported Morbidity from Palliative Surgical Procedures in Unresectable Pancreatic Cancer

First author, y	n	Procedure	Morbidity, %	Mortality, %	Length of stay, d
Kneuertz, 2011[29]	553	Surgical bypass	141	2	11
Chandrasegaram, 2011[53]	19	Gastrojejunostomy	37	21	10
Allen, 2011[54]	20	Laparoscopic celiac block	No major	0	Outpatient

ation of symptoms. Patients with locally advanced pancreatic cancer can present with debilitating symptoms including gastric outlet obstruction, biliary tract obstruction, pruritus, and pain.[26,27] Palliation is, therefore, a key component of the therapeutic management of patients with pancreatic cancer. Although chemoradiation remains the optimal initial palliative,[28] surgery has traditionally played an important role in a potentially more durable palliation of symptoms (Tables 5,6). In the past, routine palliative bypass has been advocated for palliation of patients with adenocarcinoma in the head of the pancreas who were explored with curative intent but had inoperable disease discovered at the time of surgery. Surgical palliative procedures may include bypasses such as hepaticojejunostomy or gastrojejunostomy, as well as chemical celiac splanchnicectomy. However, with the advent of higher quality cross-sectional imaging and the development and refinement of endoscopically placed biliary and enteric stents, there have been significant advances in nonoperative palliation.[29,30] As such, the role, indication, and relative use of palliative surgical procedures for advanced pancreatic cancer are ill-defined.

In this report we present the first 27 patients who underwent IRE for palliation of their stage III pancreatic adenocarcinoma. We have demonstrated acceptable morbidity, one 90-day mortality, and currently durable palliation of pain with reduction of overall narcotic use. This therapy is, however, not without cost, both to the patient with an inpatient stay of a median of 9 days, and the expense of the device and the probes (approximately $2,000 per probe). Similarly, the complications that have been presented in this manuscript demonstrate the initial use of this therapy and therefore capture the learning curve of both institutions.

Locally advanced pancreatic cancer pain associated most commonly with superior mesenteric artery and/or celiac axis invasion from pancreatic cancer may be palliated with radiation therapy, with or without chemotherapy[31-33] or with chemical splanchnicectomy with 50% alcohol at the time of surgical exploration. However, the duration of pain relief can be limited, with reported pain palliation lasting 8 to 12 weeks, followed by a return of the debilitating symptoms. For the unique stage III pancreatic cancer patient who does not have metastatic disease, further palliation of pain and other concomitant symptoms of delayed gastric emptying or intermittent biliary obstruction still need to be relieved.[34]

Methods used for alleviating pain associated with pancreatic malignancy have included nonsteroidal anti-inflammatory agents, narcotic pain medications, epidural analgesics, and neurolytic celiac plexus block. Previously described techniques for celiac plexus block include percutaneous CT-guided alcohol injection, injection at time of laparotomy, thoracoscopic neurolysis, and endoscopic ultrasound-guided celiac injection.[35-37] Many of these approaches have been evaluated in randomized settings, and all have been reported as effective at decreasing pain in patients with pancreatic cancer.

Table 6. Reported Morbidity Palliative Radiation and/or Chemotherapy in Unresectable Pancreatic Cancer

Author, y	n	Therapy	Morbidity, %	90-d Mortality, %
Crane, 2011[41]	69	Gem-Ox-Cetux	70	5
Melnik, 2010[55]	40	Gem-Etoposide	80	9
Didolkar, 2010[40]	85	Sterotactic XRT – then Gem	22	9
Wyse, 2011[56]	48	EUS – celiac plexus block	48	2
Arnoletti, 2011[57]	16	Gem-Cetux with XRT	66	0
Milandri, 2011[58]	33	GEMOX – XRT	55	0
Shibuya, 2011[59]	19	Gem – XRT	67	0
Oberic, 2011[60]	18	5FU – DCT – CDDP – XRT	75	4
Mamon, 2011[61]	81	Gem-XRT	41	5
Maluta, 2011[62]	66	XRT – Hyperthermia – Gem – Ox	35	4
Brunner, 2011[63]	93	5FU – Gem – Mito – XRT	45	5
Loehrer, 2011[64]	69	Gem vs Gem-XRT	79	6

Gem, gemcitabine; Ox, oxaliplatin; Cetux, cetuximab; XRT, radiation therapy; EUS, endoscopic ultrasound; CDDP, cisplatin; DCT, docetaxel; Mito, mitomycin.

In the last 7 years, further improvement in the precise delivery of high-dose radiation therapy to the tumor has been achieved with the advent of real-time image-guided stereotactic radiosurgery. This technique has allowed for a larger dose of radiation to be delivered in 1 to 3 fractions as opposed to 30 to 40 fractions, as has historically been used in conventional methods of delivery.[38,39] The largest study to date by Didolkar and colleagues[40] reported on 85 patients with locally advanced or recurrent unresectable pancreatic cancer by stereotactic radiosurgery and Gemzar-based chemotherapy after stereotactic radiosurgery (Table 6).

Similarly, palliative systemic and regionally delivered chemotherapy has also been reported in treatment for locally advanced pancreatic cancers. The most recent report from Crane and coworkers[41] reported on a triple regimen for locally advanced pancreatic cancer demonstrating modest response rates and acceptable toxicity. Regional chemotherapy has also been reported in the treatment of locally advanced pancreatic cancer with reasonable response rates, but with a wide range of therapies and a lack of standardization of delivery.

IRE was originally conceived from theoretical considerations with the capability of using cellular selectivity to treat biologic tissues.[17] Rather than using drug-induced chemical selectivity through reversible electroporation, IRE is based on fundamental biophysical principles. The cell ablation technique used in this study is based on the both bioelectric and biothermal phenomena. The bioelectric phenomenon is characterized by the permeabilization of the cell membrane's lipid bilayer through the application of very brief (nanosecond to millisecond), high field (in the range of MV/m) electric pulses across the cell.[42] This biophysical phenomenon has been observed and studied intensively since the mid 1900s. Several different names have been used in literature to describe this phenomenon; electropermeabilization is used describe the physical effect of the pulses on the cell membrane,[43] and electroporation describes the hypothetical pores that form.[44] The effects of electroporation depend on the magnitude and duration of the pulsed electric field as well as on other factors such as cell size and shape and number of electrical pulses applied. The electric field magnitude triggers pore formation;[45,46] the pulse length influences the pore expansion process.[47] The family of electrical pulses that cause electroporation is divided into 2 types. In reversible electroporation, the cells survive the permeabilization process. In irreversible electroporation, cell death results due to the lipid bilayer destabilization and permeabilization.[42,48] Physical principles indicate that the energy dissipation of high electric fields such as those involved in electroporation can lead to an increase in tissue temperature due to Joule heating.[49] Indeed, these thermal effects have been used in minimally invasive surgery with such applications as radiofrequency, microwave, laser, high frequency ultrasound, and even conventional electric heating ablation.[17] We believe such elevated temperatures, however, ablate tissue by denaturation of all the molecules in the treated volume. This biothermal effect depends on the electrical parameters; it can elevate the tissue temperature to levels at which the cells become damaged, or it can result in only slight temperature increases that do not cause thermal damage.[50] We have found that within the family of electric fields that cause irreversible electroporation, there is a subset that minimizes Joule heating, resulting in temperature increases that stay below the threshold for thermal damage.[17]

Before this evaluation in patients, extensive preclinical testing has been performed in chronic porcine animal models, demonstrating the safety of IRE in and around the pancreas, arterial, venous, and biliary systems. Both reports from University of Louisville[21] and from Charpentier and colleagues[51,52] have demonstrated the safety of IRE when used appropriately. The use of IRE in patients with locally advanced pancreatic cancer should not be underestimated based on critical decision making for the appropriate patients, the demand for the highest quality of intraoperative imaging for needle placement, and a complete understanding of the mechanism of action for IRE. At a minimum, IRE of the pancreas should be undertaken only by physicians with extensive thermal ablation experience (minimum of 50 cases of radiofrequency, microwave, or cryoablation in the liver, lung, or kidney), as well as a minimum of 5 IRE cases on solid organs that have greater degrees of tolerance, eg, the liver and kidney. These recommendations are predicated on the established learning curve that occurs with IRE, and to ensure that not just safety is obtained with the use of this device, but just as importantly, that overall ablation success is achieved as well.

CONCLUSIONS

In conclusion, IRE ablation of locally advanced pancreatic adenocarcinoma is safe and feasible as a primary local treatment in unresectable locally advanced disease, in the appropriate patient and undertaken by the appropriate physician. Exceptional care must be taken if this therapy is to be used in locally advanced pancreatic cancer patients and still remains in the very early evaluation phase of its use and efficacy. Longer-term follow-up is needed to establish overall survival in patients treated with IRE in order to evaluate if additional quality of life time is achieved when compared with other established treatments. Confirming these early results must

occur in a planned phase II investigational device exemption study to be initiated in 2012. This trial must also capture long-term overall survival and disease-free survival before IRE can be confirmed as an acceptable treatment option in these patients.

Author Contributions

Study conception and design: Martin, McFarlin, Velanovich
Acquisition of data: Martin, Ellis, McFarlin, Velanovich
Analysis and interpretation of data: Martin, Ellis, McFarlin, Velanovich
Drafting of manuscript: Martin, McFarlin, Velanovich
Critical revision: Martin, Ellis, McFarlin, Velanovich

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