Treatment of 200 Locally Advanced (Stage III) Pancreatic Adenocarcinoma Patients With Irreversible Electroporation

Safety and Efficacy

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Objectives: Ablative therapies have been increasingly utilized in the treatment of locally advanced pancreatic cancer (LAPC). Irreversible electroporation (IRE) is an energy delivery system, effective in ablating tumors by inducing irreversible membrane destruction of cells. We aimed to demonstrate efficacy of treatment with IRE as part of multimodal treatment of LAPC.

Methods: From July 2010 to October 2014, patients with radiographic stage III LAPC were treated with IRE and monitored under a multicenter, prospective institutional review board–approved registry. Perioperative 90-day outcomes, local failure, and overall survival were recorded.

Results: A total of 200 patients with LAPC underwent IRE alone (n = 150) or pancreatic resection plus IRE for margin enhancement (n = 50). All patients underwent induction chemotherapy, and 52% received chemoradiation therapy as well for a median of 6 months (range, 5–13 months) before IRE. IRE was successfully performed in all patients. Thirty-seven percent of patients sustained complications, with a median grade of 2 (range, 1–5). Median length of stay was 6 days (range, 4–36 days). With a median follow-up of 29 months, 6 patients (3%) have experienced local recurrence. Median overall survival was 24.9 months (range: 4.9–85 months).

Conclusions: For patients with LAPC (stage III), the addition of IRE to conventional chemotherapy and radiation therapy results in substantially prolonged survival compared with historical controls. These results suggest that ablative control of the primary tumor may prolong survival.

Keywords: IRE, irreversible electroporation, locally advanced pancreatic cancer, overall survival, stage 3 pancreatic cancer

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Irreversible electroporation (IRE) was first utilized in 2009 for a locally advanced pancreatic cancer (LAPC) as a consolidative therapy because of its nonthermal injury method of action.[1] IRE treatment has been successfully performed intraoperatively,[1,2] laparoscopically,[3] or percutaneously.[4,5] IRE's method of action does not rely on a thermal-based coagulative necrosis but on a high-voltage (maximum 3000 volts) small microsecond pulse lengths (70–90μs) to induce permanent cell membrane porosity, which leads to permanent cell death without collagenous structure destruction. This unique method of action has allowed for IRE to be successfully utilized in the palliative treatment of LAPC safely, with surprisingly prolonged survival.[1,2,6,7]

Recent advances in multimodality therapy of stage 3 LAPC have included chemotherapy, surgery, and/or radiation therapy. Surgical resection of LAPC in combination with multimodality treatment remains the optimal treatment option based on the improved overall survival in reported cases.[8,9] However, the percentage of the approximately 17,0000 new LAPCs diagnosed each year that can be resected in the United States is small. Several factors contribute to this including (1) the degree of vascular involvement, (2) patient comorbidities, (3) oncology-community bias, and (4) insufficient surgical expertise in all regions. Thus, there still remains a need for durable palliative strategies to improve quality-of-life time in patients with LAPC. The current options for palliation for appropriately and precisely staged LAPC include systemic chemotherapy (gemcitabine-Abraxane or FOLFIRINOX[10]), radiation therapy (intensity modulated radiation therapy [IMRT], Cyberknife[11] and proton therapy[12]), and surgical therapy (celiac axis alcohol ablation, thoracoscopic thoracic splanchnicectomy,[13] biliary bypass, and gastric bypass). All of these current modalities have been utilized with various effectiveness in terms of palliation, with fairly well-established risks/benefits. Optimal quality-of-life parameters have been limited in some of these studies, with only the most recent studies demonstrating the stabilization of quality-of-life while undergoing systemic and/or local therapy.[14]

Thus, the goal of this study was to evaluate the effectiveness of IRE as a consolidative therapy in combination with chemotherapy and/or chemoradiation therapy in the management of LAPC.

METHODS

Clinical data on patients treated for LAPC from March 2010 to October 2014 were retrieved from an institutional review board–approved, prospectively maintained soft tissue ablation registry (http://www.ablationregistry.com).

The method of staging and patient inclusion for LAPC has previously been described.[7,15] This includes a minimum of a triple-phase computed tomographic (CT) scan with pancreatic protocol (<1.5-mm cuts) at the time of diagnosis. After initial assessment and review by a multidisciplinary pancreatic tumor group, these patients were confirmed to have LAPC and not borderline resectable tumors. Pre-IRE medical history, surgical history, Charleston comorbidity index, Groningen Frailty Indicator, and Short Nutritional Assessment Questionnaire were captured.[16,17]

LAPC disease was defined at the time of diagnosis to include greater than 180-degree encasement of either superior mesenteric artery (SMA) or celiac artery, or unreconstructable venous

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involvement (see Supplemental Digital Content Figures, available at: http://links.lww.com/SLA/A838) and without evidence of any lesions suspicious for metastatic disease (defined as lesions >1 cm in size).[18,19]

Initial treatment with chemotherapy, chemoradiation, or both was administered to all patients per each institutions protocol. Approximately 4 to 6 weeks after completion of therapy, patients underwent restaging evaluation with repeat triple-phase CT scan and serum tumor markers. Patients found on restaging to be free of metastatic disease and without significant primary tumor progression were potential candidates for IRE therapy.

The surgical decision-making process has previously been described.[1] Succinctly, the decision to perform pancreatic resection with IRE for margin accentuation was at the surgeon's discretion based on patient's comorbidities, previous therapy, and intraoperative preresection margin assessment via ultrasonography and palpation.[20] Standard histopathologic evaluation using hematoxylin and eosin was used for all margins with the knowledge that the use of IRE on one or more margins would not affect the hematoxylin and eosin staining because there needs to be a minimum of 4 hours of perfusion to see IRE histopathologic effects. The use of resection and IRE margin accentuation was performed only in cases in which suspected microscopically positive margins (R1 resection) could/would occur. IRE was not used when an R2 resection could occur, and those patients underwent an IRE alone without resection.

Delivery of intraoperative IRE with the Nanoknife system has also been previously described.[6,15,20] For the margin accentuation technique, it is imperative that the IRE energy is delivered before complete dissection/transection, because there must be soft tissue in place for the IRE needle(s) insertion. The operative surgeon determined the number of IRE probes necessary to achieve the necessary electroporation zone along the margin (usually the SMA/retroperitoneal margin or base of celiac-aortic margin) where microscopic disease might exist. Commonly, the needles (2–3 monopolar probes) were placed in a caudal to cranial fashion after appropriate dissection had been performed, usually after the pancreatic neck has been transected and the ligament of Treitz had been mobilized but before any superior mesenteric vein (SMV)/SMA/retroperitoneal tissue dissection. The IRE probes were placed under direct ultrasound guidance to achieve adequate margin augmentation. Probe position relative to the tumor and/or vessels was evaluated in real time and was adjusted to maximize treatment effect.[21] For IRE alone (in situ), the IRE probes were placed and adjusted to bracket the entire tumor and the involved vasculature. Because of system limitations of maximal deliverable currents, typically probe exposures are 1 cm maximum, which require a series of pullbacks (~1–3) with sequential electroporation performed. Delivery of IRE was considered successful based on the combination of intraoperative ultrasonography and real-time assessment of resistance change of the ablation zone.[21]

After completion of treatment follow-up, imaging to confirm ablation success was performed at the time 12 weeks after of IRE therapy and then at 3-month intervals. An early postoperative scanning can be performed to evaluate for early complications from this new technique such as venous thrombosis but not for treatment efficacy. Ablation recurrence was defined as persistent viable tumor as defined by dynamic imaging in comparison with pre-IRE scanning 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 on cross-sectional imaging of treating-team's choice such as computed tomography and/or magnetic resonance imaging and/or positron emission tomography (if the patient had a preoperative avid tumor on positron emission tomography). Dedicated body imaging radiologists at each center, who were not blinded to treatment, made the radiologic interpretation of recurrence as defined by the RECIST (Response Evaluation Criteria in Solid Tumors) criteria. Thereafter, patients were evaluated every 3 to 4 months by physical examination and radiographic imaging. Development of new low-density lesions in the region of the IRE (with 1 cm) was considered evidence of local recurrence, even in the absence of symptoms. Similarly, suspicious low-density lesions in the liver or lungs were considered evidence of distant metastasis. Peritoneal recurrence was defined by suspicious nodules in the peritoneum or the omentum, or the presence of newly identified ascites. If findings were equivocal for recurrence, then imaging and CA19-9 were repeated at 2 months for confirmation of recurrence or disease free.

IRE-associated variables were also recorded, including operative time, total blood loss, length of hospital stay, resection margins, lymph node status, morbidity occurring within 90 days, and mortality. All postoperative complications out to 90 days were followed and scored prospectively according to a previously published 5-point scale. Overall survival was calculated from the date of diagnosis and the date of IRE treatment for both the resection with IRE and IRE in situ.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), and *P* values less than 0.05 were considered significant.

RESULTS

The clinical demographics of the 200 patients included in this prospective evaluation demonstrated a median age of 62 years (range: 27–88 years), and 86% of patients were white (Table 1). Only a small percentage of patients had any cardiac (10%) or pulmonary (2%) disease history (Table 1). The degree of comorbidities was also demonstrated by a low Charleston comorbidity index (median of 4), a low frailty index (median of 2), and a low short nutrition assessment score (median of 2) (Table 1).

The distribution of the target lesions was different in the resection + IRE group compared with the IRE alone (in situ) group. The

TABLE 1. Clinical Demographics of the 200 Patients With Stage 3 Locally Advanced Pancreatic Adenocarcinoma Treated With IRE

Characteristics (n = 200)	
Age, yr	62 (range: 27–88)
Sex (male/female)	101/99
Race/ethnicity	
White	172 (86%)
African American	18 (9%)
Asian/Hispanic/Other	5 (5%)
Body mass index	24.0 (range: 17.5–43.3)
Medical history	
Cardiac	20 (10%)
Vascular	5 (3%)
Pulmonary	5
Diabetes	40 (20%)
Smoking	58 (29%) pack year (50, 8–180)
Hypertension	100 (50%)
Surgical history	
Prior cholecystectomy	40 (20%)
Other	28 (14%)
Charleston Comorbidity Index (median, IQR)	4 (1)
Groningen Frailty Indicator (Median, IQR)	2 (2)
Short Nutritional Assessment Questionnaire (Median, IQR)	2 (1)

IQR indicates interquartile range.

in situ group presented with pancreatic head tumors (63%), whereas resection with IRE was more commonly used in patients with pancreatic body/neck tumors (75%). This is further demonstrated by the type of vascular invasion in both groups, with in situ IRE being associated more with venous involvement (Table 2). Both groups had similar lesion size, with a median of 2.8 cm in the longest axis and similar diameters across all 3 axes.

Patients who had celiac axis abutment or invasion only were more likely to undergo resection with IRE (60%) than patients who presented with long segment venous invasion/occlusion, who were more likely to undergo IRE in situ (27%). The patterns of LAPC vessel invasion at the time of diagnosis were significantly different in the group that was able to undergo resection with IRE versus in situ IRE. The most common reason for pancreatic resection was isolated celiac axis abutment or SMA abutment, with the use of IRE for margin accentuation. Both groups utilized similar induction systemic chemotherapy, which was either a gemcitabine-based or FOLFIRINOX-based chemotherapy.

For specific technical considerations, IRE involved a median of 4 probes for IRE in situ use and 2 probes for IRE with margin accentuation use (Table 3). The most common approach for the IRE needles was via a caudal-to-cranial fashion most commonly through the transverse mesocolon to obtain an adequate inferior margin. Because of the increase in number of probes in the IRE in situ group, the median needle placement time was 20 minutes versus 5 minutes in the resection group. To achieve adequate IRE (ie, change in resistance), the IRE delivery time was a median of 21 minutes, with a maximal delivery time of 125 minutes for in situ IRE and 58 minutes for margin accentuation (Table 3). A total of 54 patients who underwent IRE in situ had 100 complications, whereas 20 patients who underwent IRE for margin accentuation had 49 complications.

The specific complications and grades are outlined in Table 4, with the most common adverse event being some form of gastrointestinal complaint as described in Table 4. There were 3- to 90-day mortalities (2%) in the in situ group only. There were no 90-day mortalities in the resection with IRE group. The 3 deaths included 1 patient who developed a duodenal ulcer 55 days post-IRE and presented with upper gastrointestinal bleed; the bleeding was found

TABLE 2. LAPC Tumor Location and Induction Therapy Before IRE

Characteristics	LAPC Resection and IRE (Margin) (N = 50)	LAPC With IRE (In Situ) (N = 150)
Location		
Head	13 (25%)	95 (63%)
Body/neck	37 (75%)	55 (37%)
Lesion size		
Axial	2.5 (1.8 × 5.5)	3 (1.0–6 cm)
Anterior-posterior	2.7 (1.4 × 6.7)	2.7 (1.6–7)
Caudal to cranial	2.6 (1.6 × 5)	2.9 (1.5–5.5)
Vessel invasion at diagnosis		
Celiac only	60%	7%
SMA only	30%	33%
Celiac and SMA	5%	15%
PV-SMV occlusion only	0%	27%
Celiac/SMA w/vein occlusion	5%	18%
Prior chemotherapy	100%	100%
Gemzar-based	43%	60%
FOLFIRINOX	38%	29%
Prior radiation therapy	52%	47%
Type pancreatic resection		
Subtotal left panc with en bloc celiac resection	25	Not applicable
Subtotal left panc with portal vein resection and celiac	12	
Whipple with portal vein	13	
Post-IRE adjuvant chemotherapy	60%	69%
Post-IRE adjuvant XRT	11%	13%

PV-SMV indicates portal vein-superior mesenteric vein; SMA, superior mesenteric artery; XRT, radiation therapy.

TABLE 3. Operative and Ablative Characteristics of Patients With Locally Advanced Pancreatic Cancer Treated With IRE

Characteristics	LAPC Resection and IRE (Margin) (N = 50)	LAPC With IRE (In Situ) (N = 150)
Median time from diagnosis to electroporation	5.2 mo (range: 3–18 mo)	6.2 mo (range: 5–32 mo)
Approach		
Open-–supine midline incision	50	150
Other operations		
Hepaticojejunostomy	13	29
Gastrojejunostomy	13	30
Celiac plexus block	1	16
Cholecystectomy	10	12
No. IRE probes used		
Monopolar	50 patients	150 patients
No. probes	2 (2–4 probes)	4 (2–6 probes)
Probe exposure (median, range)	1.5 cm (1–2.5)	1.5 cm (1–2)
Direction of IRE probes		
Anterior to posterior	4	
Caudal to cranial	46	150 patients
Needle placement time (median, range)	5 (2–25) min	20 (5–40) min
No. pulses delivered	90 (40–200)	90 (70–200)
No. pullbacks	2 (1–4)	3 (1–5)
Success of IRE delivery	100%	100%
Total IRE delivery time	17 min (2–58 min)	35 min (10–125 min)
Total procedure times	240 min (152–740 min)	195 min (84–420 min)
Length of stay	7 (4–26 d)	6 (2–36) d
Complete ablation	50 of 50	148 of 150
Adverse events	20 patients had 49 complications	54 patients had 100 complications

TABLE 4. Adverse Events in Patients With Locally Advanced Pancreatic Cancer Treated With Resection and IRE or IRE Alone

	LAPC Resection and IRE (Margin) (N = 20 Patients With 49 Complications)		LAPC With IRE (In Situ) (N = 54 Patients With 100 Complications)	
Type of Complications	**No. Patients**	**Grade**	**No. Patients**	**Grade**
Cardiovascular	2	1,1	0	
GI	8	Grade 1 = 3 Grade 2 = 3 Grade 3 = 2	38	Grade 1 = 18 Grade 2 = 13 Grade 3 = 2 Grade 4 = 5
Hematologic	1	Grade 3 = 1	1	Grade 2 = 1
Infection	3	Grade 1 = 1 Grade 2 = 1 Grade 3 = 1	15	Grade 1 = 2 Grade 2 = 5 Grade 3 = 6 Grade 4 = 2
Liver	7	Grade 1 = 2 Grade 2 = 1 Grade 3 = 4	13	Grade 1 = 3 Grade 2 = 2 Grade 3 = 6 Grade 4 = 1 Grade 5 = 1
Neuro	3	Grade 1 = 2 Grade 2 = 1	1	Grade 3 = 1
Pancreatic	2	Grade 1 = 1 Grade 2 = 1	0	
Pulmonary	6	Grade 1 = 1 Grade 2 = 1 Grade 3 = 3 Grade 4 = 1	1	Grade 2 = 1
Renal	0		1	Grade 3 = 1
Urinary	3	Grade 2 = 3	4	Grade 1 = 2 Grade 3 = 2
Vascular	4	Grade 2 = 4	7	Grade 1 = 1 Grade 2 = 2 Grade 3 = 3 Grade 5 = 1
Wound	3	Grade 1 = 2 Grade 4 = 1	3	Grade 1 = 2 Grade 2 = 1
Other	7	Grade 1 = 4 Grade 2 = 1 Grade 3 = 1 Grade 4 = 1	16	Grade 1 = 8 Grade 2 = 7 Grade 3 = 1

Cardiovascular includes postoperative atrial fibrillation, GI included anorexia, dehydration, gastritis, heartburn, nausea, vomiting, liver included ascites, biliary anastomotic stricture, liver dysfunction and failure. Neuro equaled mental status changes. Pancreatic included pancreatic leak, clinical pancreatitis, and pancreatic failure. Vascular included deep venous thrombosis, pseudoaneurysm, hepatic arterial thrombosis, and nonocclusive superior mesenteric vein/portal vein thrombosis.

GI indicates gastrointestinal; superior mesenteric vein.

to be from ulcerated tumor, which could not be operatively corrected. The second presented with liver failure 45 days post-IRE. This patient already had complete portal vein thrombosis/SMV occlusion before IRE, recovered well immediately post-IRE, but then presented later with liver failure that failed to respond to therapy. The third patient died 50 days post-IRE from pulmonary embolism after being found down at home. We did not see any pancreatic-related complications in the IRE in situ group, and there was no evidence of a pancreatic leak or clinically significant pancreatitis in the 90-day post-IRE follow-up interval.

After a median follow-up of 29 months, 3 patients had IRE failure at 3 months (all IRE-alone patients) and 6 patients had local recurrence at the ablation site after IRE success (Table 5). A total of 58 (29%) patients have developed recurrence, with a median

TABLE 5. Recurrence and Progression-free Survival—All LAPC Treated With IRE

Progression Characteristics	**Time or Incidence of Recurrence**
No. patients with recurrence	58
Overall progression-free survival	Mean: 12.4 (range: 4.4–38.9)
IRE electroporation failure at 3 mo	N = 3
Local recurrence after IRE success	N = 6
Local progression-free interval	Median: 10.7 (range: 4.4–12.4) mo
Distant progression	
Liver	N = 34
Peritoneum	N = 7
Lymph nodes	N = 11
Time to distant progression	Median: 16.8 (range: 1.3–55)

progression-free survival (PFS) of 12.4 months and distant PFS of 16.8 months. The liver was the most common site of disease recurrence. The median overall survival for all patients with LAPC was 24.9 months (range: 12.4–85 months): 28.3 months (range: 9.2–85 months) for the resection + IRE group and 23.2 months (range: 4.9–76.1) (P = ns) for the IRE in situ group (Fig. 1). The median overall survival from the day of IRE treatment for resection + IRE was 23 months (range: 8.3–36.3 months) and for IRE in situ was 18 months (range: 4.9–55.4 months).

DISCUSSION

Recently, there have been encouraging trends in the oncologic management of stage III LAPC, with improved response rates to current chemotherapeutic combinations,[10,22] enhanced radiation delivery,[23,24] and enhancements in molecular marker diagnosis (KRAS, TP53, ACTN4, and SMAD4)[25–27] and, thus, potentially better prediction of underlying cancer biology. Current optimal systemic chemotherapy regimens that include either FOLFIRINOX-based chemotherapy or gemcitabine-Abraxane-based chemotherapy have enhanced response rates or improved PFS.[28–31] Enhanced radiation delivery has continued to evolve to allow a larger dose-per-fractions to be delivered safely with less toxicity and hypothetical enhanced efficacy.[32,33] The use of IRE in the consolidative management of patients with LAPC further augments the benefits seen with chemotherapy and chemoradiation therapy and has allowed us to demonstrate a longer-term disease control than has ever been reported within the literature. The appropriate and precise use of IRE in appropriately selected patients with LAPC can result in a median overall survival of close to 24 months, which is nearly double the survival rate with the best new chemotherapy and chemoradiotherapy.[28,30,32–34]

The management of LAPC according to National Comprehensive Cancer Network guidelines is confusing because there are currently 6 different chemotherapeutic regimen options. This variability as to the optimal first-line systemic chemotherapy regimen confounds the overall outcomes for patients with LAPC. This chemotherapeutic heterogeneity allows for many oncologists to utilize therapies that may be better tolerated but have been proven to have limited efficacy. We believe that appropriate induction chemotherapy should consist of either FOLFIRINOX-based chemotherapy or a gemcitabine-based chemotherapy regimen as the initial induction therapy for approximately 4 months. This allows an assessment of the biology of the disease and confirmation that the patient truly has stage III pancreatic adenocarcinoma. Recent reports from Blazer et al[28] have further shown that a modified FOLFIRINOX-based chemotherapeutic regimen can be delivered in most patients with good tolerance and equivalent disease control. It is this type of active chemotherapeutic regimen that is essential to obtaining disease control and, thus, selecting out patients with truly locally advanced stage III pancreatic adenocarcinoma who can benefit from local consolidative therapy. However, the poor quality of life and longer-term tolerance of these active therapies are well established and should not be underestimated in this stage of patients.[14]

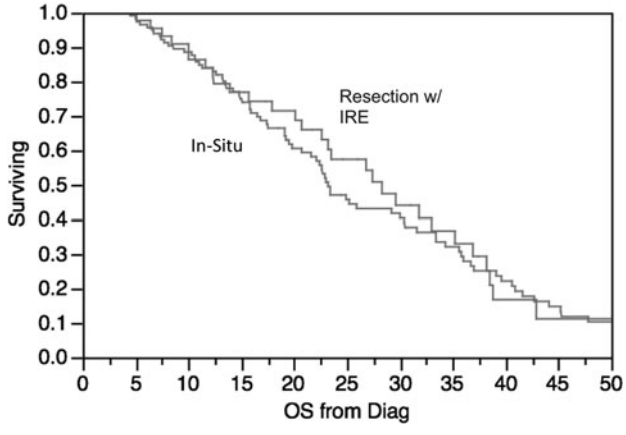

FIGURE 1. Overall survival of the entire 200-patient locally advanced pancreatic cancer group broken down by the patients who underwent resection with IRE and patients who underwent IRE in situ. IRE indicates irreversible electroporation; OS, overall survival.

This report of our 200-patient review is the single largest evaluation to date and further confirms the smaller series that have been published with the use of this treatment in patients with pancreatic adenocarcinoma. Our initial report of 27 patients by Martin et al[1] demonstrated the safety and feasibility of the use of this IRE treatment in patients with LAPC. The optimization of the technique was variable and the patient selection was even more variable because of the significant amount of referral biased in this initial series. A larger series of 54 patients who were matched and compared prospectively to another 85 patients who underwent chemotherapy and radiation alone further demonstrated the role of a consolidative local therapy that can be beneficial in patients with LAPC. These 54 patients who were treated with chemotherapy, IRE, and/or radiation therapy did demonstrate a significant improvement in overall survival and local PFS.[2] That report also demonstrated that the morbidity of this additional surgical treatment (IRE treatment) was similar to continued systemic chemotherapy after the 4-month induction treatment time interval. Thus, there were equally severe complications with continuing chemotherapy after the 4 to 6 months of induction period when compared with the IRE group. These findings were significant because it demonstrates that continued chemotherapy has similar morbidity when compared with IRE treatment delivery. The morbidity of IRE treatment delivery seems to be mitigated by the significant improvement in overall survival and local PFS. This report, however, also demonstrated that when patients do experience recurrence, they commonly experience recurrence with metastatic disease, and the ability to salvage that metastatic disease is minimal. Further reports with the use of IRE both as a margin accentuation in patients with borderline resectable tumors[20] and larger series with the uses of IRE around vital vascular structures[7] have demonstrated the safety and efficacy of this treatment provided the procedure is done precisely with a high degree of technical ability and skill set.

Additional benefit with the advent of IRE use has been in the greater surgical confidence that a preoperative LAPC can be resected with either electroporation or electroporation alone. This has become more apparent with the recent study by Ferrone et al,[8] who found that 48% patients with preoperative LAPC on CT scan were able to undergo resection. These encouraging results presented here and with the ability to perform IRE as the time of exploration could lead to a greater number of LAPCs having appropriate consolidation local therapy after induction therapy with subsequent survival improvements. However, the results that we present here with IRE treatment demand that complete electroporation be achieved through precise biology understanding, precise tumor size selection, and precise IRE energy delivery. It cannot be understated the need to avoid incomplete electroporation based on the recent results from Philips et al,[35] in which this effect of incomplete electroporation can lead to a change in the biology of a local tumor.

The technical demands with the use of IRE currently should not be minimized. The requirements to place these multiple monopolar probes in precise spacing (plus or minus 5.0 mm maximum),

precise depth (plus or minus 5.0 mm maximum), and in appropriate bracketing of the soft tissue retroperitoneal tumor that is commonly seen with pancreatic adenocarcinoma can be difficult. There is an essential learning curve,[36] and the optimal access for the placement of these devices for both pancreatic head tumors[6] and pancreatic neck tumors[15] has been published and is currently reproducible. Additional research into the optimal efficacy endpoints and validation that the use of IRE is performed via a nonthermal injury technique have also been validated and confirmed, which is essential to the safe and efficacious use of IRE around LAPC.

Radiation therapy has also been a mainstay of treatment of LAPC. The challenges in radiation therapy have been predominantly around the lack of any type of any true response to the tumor (defined as reduction in 20% of the maximum diameter) as defined by RECIST 1.1. Thus, we have relied on radiation response being defined as disease control and have utilized multiple serologic and some functional imaging (positron emission tomography) as a way to assess efficacy and potential optimal response. However, as has been outlined, in multiple borderline resectable tumors that have been treated with chemotherapy and chemoradiation therapy, either Xeloda-based chemoradiation or gemcitabine-based chemoradiation, the complete response rate and eradication of the tumor is less than 2% in most series.[34,37] There is also concern that after induction chemotherapy and/or radiation therapy, a molecular change in the tumor can occur through the persistence of stellate cells, or the activation of any remaining living tumor cell growth occurs from the cleavage of caspases 3, 7, and protein kinase Cd while cells undergo apoptosis.[38] The lack of complete eradication has been further demonstrated regardless of the type of radiation therapy that is delivered, whether IMRT, stereotactic body radiotherapy, or other variations of radiation delivery. Thus, some form of additional consolidative therapy before or after radiation therapy is necessary simply based on the fact that local progression of the primary tumor or systemic progression of persistently viable local tumor is not salvageable, with a median survival of 2 to 4 months.[39,40] It is this aggressiveness at the time of "recurrence" or "return of active" growth that a simple "watch and wait" should not be utilized after initial therapy, regardless of the degree of partial response or stable disease that is obtained with either chemotherapy alone or in combination with chemoradiation therapy.

Limitations of this study include likely selection bias (patients who did not progress on systemic therapy, with good performance status, few comorbidities, able to withstand a major surgical procedure, and often travel significant distances to tertiary care centers). If this selection bias of not treating patients with IRE at the time of diagnosis but after the biology of the tumor is better understood (ie, through induction chemo for 4–6 months), then these 23- to 28-month median survival rates in these patients with LAPC can be possible. This was a registry and not a prospective study; there was some variability in the post-IRE imaging protocols between centers. Local recurrence or persistent disease based on RECIST criteria may be underestimated, as conventional imaging has significant limitations in detecting viable tumor. These results need to be confirmed through a randomized trial of chemotherapy and radiation therapy compared with chemotherapy, IRE, and radiation therapy.

This study was conducted in a small number of centers that have optimized this technique and overcome the learning curve. The technical demands of this therapy are one of the reasons for the slow adoption, which could be viewed as both a benefit and a limitation. However, the increasing enthusiasm for the percutaneous approach

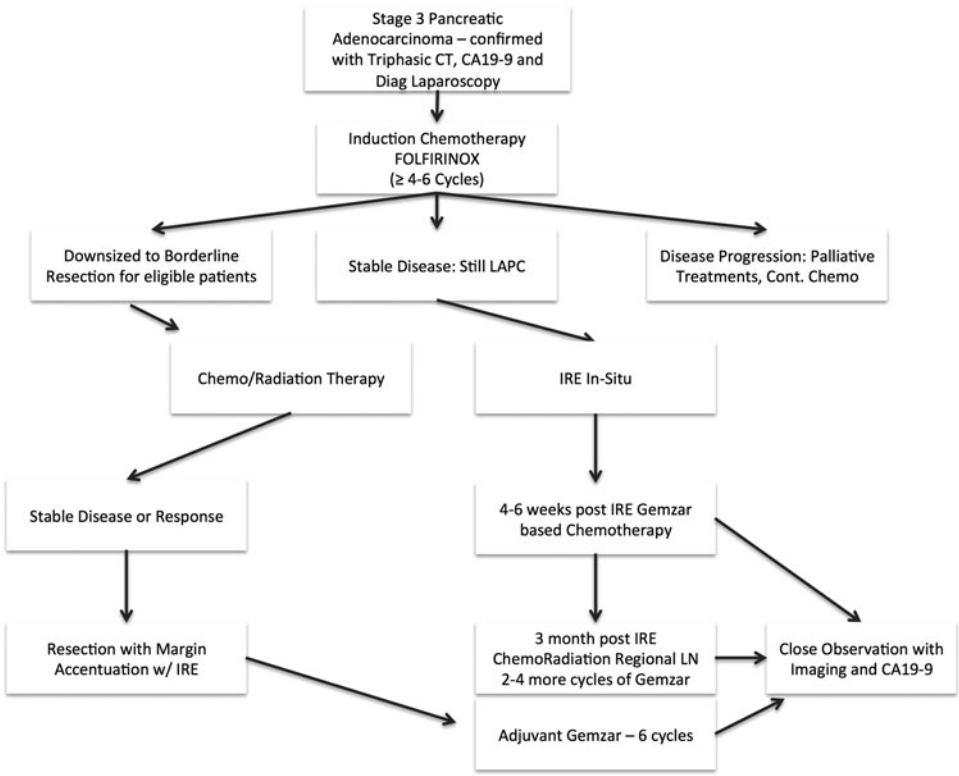

FIGURE 2. Potential treatment algorithm for LAPC that utilizes trimodality therapy for improved overall survival. IRE indicates irreversible electroporation; LAPC, locally advanced pancreatic cancer.

for IRE by interventional radiology access needs to be evaluated critically and compared with the results of this open series.

CONCLUSIONS

We believe that this report demonstrates that IRE results in substantially prolonged survival of patients with LAPC compared with historical controls. This suggests that improved local disease control, in conjunction with systemic therapy, translates into prolonged survival for patients with LAPC (Fig. 2). The optimal use of radiation therapy either before or after IRE remains to be determined. A true trimodality therapy of chemotherapy, radiation therapy, and IRE treatment does seem to provide the optimal disease control which has translated into optimistic and impressive overall survival results.

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DISCUSSANTS

J. Drebin (Philadelphia, PA):

Pancreas cancer is a relatively uncommon cancer but a common cause of cancer death. It's predicted that in the next 5 years, it

will become the second most common cause of cancer death in this country. Dr Martin and colleagues are to be congratulated in studying a novel technology, irreversible electroporation, in a multidisciplinary treatment plan for the approximately one-third of patients with pancreas cancer who present with locally advanced disease. They have demonstrated both reasonable safety and excellent local control with this approach.

I have several questions.

First, given the chemotherapy lead-in and requirement for stable disease for an average of 6 months before IRE treatment, not all of the initial locally advanced patients are going to be eligible for this treatment. Randomized trials of both FOLFIRINOX and gemcitabine-Abraxane chemotherapy combinations show an approximately 6-month median progression-free survival in metastatic patients. If the same is true in locally advanced disease, half or more of patients might never become eligible for IRE because they will progress in that 6-month interval.

What fraction of potentially eligible patients dropped out because of disease progression before ever getting to IRE in your series? If one includes those patients in an intention-to-treat analysis, what's the median survival for the entire cohort? It will certainly be less than the 24 to 28 months that you've presented.

Second, the DPC4 tumor suppresser gene is mutated in about half of pancreas cancers, and mutation has been linked to extensive and early metastatic disease. In contrast, tumors with wild-type DPC4 are oligometastatic and may result in death due to extensive local infiltration without significant metastases. Do you know the DPC4 status of patients in your study, and might this be a useful biomarker; that is, should patients with normal DPC4 get IRE since they are more likely to benefit from an aggressive regimen aimed at improving local control?

Finally, what about costs? How much do the generators cost? I'm assuming the probes are disposables. What do they cost? What's the cost per case?

Response From R.C.G. Martin:

Dr Drebin, thank you for your review and thoughtful questions. You bring up a key point in that those trials that demonstrated a median progression-free survival with gemcitabine, Abraxane, and FOLFIRINOX combined both metastatic (stage IV) and stage III together. I do believe that there is potential for significantly increased progression-free survival of stage III LAPC with consolidative IRE therapy.

To answer your first question, in our institution, the patients who presented with stage III pancreatic adenocarcinoma, only approximately 75% of those were eligible. The main reason for that is clearly tumor size; tumors larger than 5 cm are not eligible for IRE in situ and only eligible for resection with IRE if microscopic margins would be positive. Thus, approximately 25% are not eligible at diagnosis.

From percentage of patients, second step of ineligibility is then after that induction chemotherapy. We lose approximately 10% to 15% because of progression. Progression either locally or systemically.

The third reason is that patients ultimately just don't maintain or improve their performance status. As you know, a lot of these patients can come to you fairly frail. Some of them get better on chemotherapy; some of them just never improve and then obviously would never be able to tolerate this type of procedure, which requires the patient to be able to undergo general endotracheal anesthesia and recover from the electroporation. Of that subset that are eligible for IRE initially at diagnosis but do not undergo IRE have a median survival of 6.8 months at our institution.

You bring up a great question about the DPC4. Ultimately, we have begun to study this molecular marker. One of our biggest challenges is our tertiary referral center. A lot of these patients are diagnosed with an fine needle aspiration (FNA) at an outlying facility and begin their therapy before referral. It has been very difficult for our pathologists to be able to run DPC4 on just that FNA, because there's just not enough tissue.

However, of the subset of patients who have undergone resection, we have been able to do DPC4 expression, and we are seeing that there is potentially a signal in about 60% of those patients who are wild type with DPC4. It's a little early for us to postulate on that; but, yes, we are very interested in that as a potential surrogate molecular marker of which patients potentially could benefit from this trimodality therapy—chemotherapy, IRE, and radiation therapy.

Last is cost. Currently now, the machine is a capital equipment cost, which I know is the ultimate 6–letter word in any hospital system. It runs approximately about $150 to $200,000. The probes themselves run at a market value of about $2000. We have run this cost-benefit ratio specifically around our patients who were unable to undergo Whipple operations or pancreatectomies. Ultimately, those charges—I need to be careful about that—the charges that the hospital is willing to give me, since they won't give me true cost—the charges are about the same. That runs at a median of about $75 to $80,000 for those types of resections or IRE in our institution.

DISCUSSANTS

K. Lillemoe (Boston, MA):

This is an important paper offering new and exciting options for the management of an increasingly important problem that we face as pancreatic surgeons: locally advanced pancreatic cancer.

As you know and have referenced in your manuscript, we have had an increasing experience with exciting favorable results with the use of FOLFIRINOX in the treatment of these patients. Not only have we reported excellent tumor response with the ability to obtain R0 resection but at least our early survival results are encouraging.

One thing we have learned is that the findings on postneoadjuvant therapy imaging have become almost useless in predicting who can and cannot undergo resection. Only careful operative dissection and checking of potential margin frozen sections has helped decide when to abort attempts at resection. What this means is that we are now taking patients to the OR whom we might never have attempted resection in the past.

Thus, my first question is whether you are finding more candidates for IRE as better neoadjuvant therapies have become part of routine management of locally advanced pancreatic cancer.

My second question relates to the intraoperative decision making to perform IRE as a sole procedure versus for margin enhancement. It would seem to me that performing IRE upfront on all patients and then attempting to resect with continued dissection and taking biopsies from the areas of concern for major visceral vessel involvement seems like the optimal strategy. Will this work? Does IRE make this already difficult dissection more or less challenging? Is the IRE delivered to the margins adequate or, in those whom you can't resect, do you need to go back and provide more treatment?

Next, with regard to the other palliative procedures potentially necessary in these patients, I understand the metal stents that most of these patients have must be removed before IRE treatment. This buys them all a biliary bypass. Do you add routine gastrojejunostomy in most or all patients with cancer of the head of the pancreas?

Finally, have you had any experience with a percutaneous approach for pancreatic tumors? I know this has been done with liver and renal tumors.

Thank you, Rob, for pushing this technology forward and training so many surgeons from around the country, including my partners. I know your paper is not definitive as to the role of this exciting new therapy for locally advanced pancreatic cancer; it does give us hope that follow-up studies, perhaps even a multicenter randomized trial might someday follow.

Response From R.C.G. Martin:

To your first question, yes, we are taking far more patients to the operating room. We echo what obviously Christina Ferrone and you all published in *Annals of Surgery*. We are finding that preoperative computed tomography or even magnetic resonance imaging is not as definitive, and we are strengthened more with these patients to take them to the operating room for possible resection, because we have the use of IRE either for margin accentuation or for IRE in situ if indeed they are unresectable at exploration.

To that end, the need for defining unresectability at the time of operation must be extensively evaluated. I believe that this can be performed in 2 ways either through extensive dissection or with the use of high-quality, high-definition, and motion compensated angular compound ultrasound imaging to truly define vessel invasion versus abutment. We utilize intraoperative ultrasound extensively through that incision, before we extend it, if we think there's a greater degree of surgical resectability.

We do believe that ultrasound alone or with contrast enhancement is a required surgical adjunct device when performing operations on patients with LAPC and with the use of IRE.

To answer your second question, when you perform IRE and then follow with intraoperative biopsies, you will not see anything histologically. The method of action and thus the true histologic changes for IRE require approximately 4 hours of in vivo perfusion. Thus, it is impossible pathologically to see any true effect of IRE unless you leave the tumor profused for that amount of time.

A huge issue, because of our training and because of our push to educate surgical endoscopist and gastroenterologists, is to utilize only the fully covered 6- or 4-cm metal stents for biliary stenting. The main reason is that these stents are endoscopically removable. So, what we do is we will put this type of stent in, allow them to get their induction therapy, take the stent out before IRE and place a plastic stent in for targeting, and then at 3 months post-IRE, another metal stent can be placed. Thus, avoiding the need for a bypass and reducing some of the underlying surgical complications that can occur with a hepaticojejunostomy.

The percutaneous approach I think is exciting. I think the level of enthusiasm among our interventional radiology colleagues is significantly greater than their technical ability. And my concern with this technique is that there are very thin windows that they have to be able to get into to completely bracket the tumor. We have recent data demonstrating the deleterious effects of partial electroporation in pancreatic adenocarcinoma and thus unless the entire radiologic tumor based on computed tomography or magnetic resonance imaging can be treated, a percutaneous approach should not be utilized. Right now, I know only about 4 interventional radiologists in the world who are consistently able to do this procedure completely.

The other problem I have with percutaneous ablation is that their overall survival is significantly less than what we have presented here, and I do believe that's because of understaging. We still do see approximately 20% to 25% of patients who think they are eligible for IRE but at staging laparoscopy, at the beginning of the operation, find peritoneal disease that they are not finding. So, I have significant trepidation at this time about the use of percutaneous unless this type of optimal outcome can be achieved.