Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation

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Introduction. *Complete tumor extirpation (R0 resection) remains the best possibility for long-term survival in patients with pancreatic adenocarcinoma. Unfortunately, approximately 80% of patients are not amenable to resection at diagnosis either because of metastatic (40%) or locally advanced disease (40%). Recent reports of irreversible electroporation (IRE), a high-voltage, short-pulse, cellular energy ablation device, have shown the modality to be safe and potentially beneficial to prognosis. IRE to augment/accentuate the margin during pancreatic resection for certain locally advanced pancreatic cancers has not been reported.*

Methods. *Patients with locally advanced/borderline resectable pancreatic cancer who underwent pancreatectomy with margin accentuation with IRE were followed in a prospective, institutional review board–approved database from July 2010 to January 2013. Data regarding local recurrence, margin status, and survival were evaluated.*

Results. *A total of 48 patients with locally advanced pancreatic/borderline cancers underwent pancreatectomy, including pancreatoduodenectomy (58%), subtotal pancreatectomy (35%), distal pancreatectomy (4%), and total pancreatectomy (4%), with IRE margin accentuation of the superior mesenteric artery and/or the anterior margin of the aorta. Most patients had undergone induction therapy with 33 patients (69%) receiving chemoradiation therapy and 18 patients chemotherapy for a median of 6 months (range, 4–13) before resection. A majority (54%) required vascular resection. A total of 9 patients (19%), sustained 21 complications with a median grade of 2 (range, 1–3), with a median duration of stay of 7 days (range, 4–58). With median follow-up of 24 months, 3 (6%) have local recurrence, with a median survival of 22.4 months.*

Conclusion. *Simultaneous intraoperative IRE and pancreatectomy can provide an adjunct to resection in patients with locally advanced disease. Long-term follow-up has demonstrated a small local recurrence rate that is lower than expected. Continued optimization in multimodality therapy and consideration of appropriate patients could translate into a larger subset that could be treated effectively. (Surgery 2014;156:910-22.)*

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The poor prognosis associated with pancreatic cancer is often associated with aggressive tumor biology, late clinical presentation, and limited effects of local and systemic therapy. As such, pancreatic cancer is the fourth leading cause of cancer death in the United States and portends a dismal 5-year survival of approximately 5%.[1] Although complete resection offers the best

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Table I. Recent reported series of the effect on overall survival in relation to R1 versus R0 resection in pancreatic adenocarcinoma

Series (y)	n	*Margin status*	*%*	*Median OS (mo)*	*P*
Johns Hopkins (2006)	1,175	R1/R2	42	14	<.0001
		R0	58	20	
University of Leeds UK (2006)	26	R1	85	11	.01
		R0	15	37	
ESPAC-1 (2001)	541	R1	19	11	.006
		R0	81	17	
University of Naples Italy (2000)	75	R1/R2	20	9	.001
		R0	80	26	
Rush-Presbyterian St. Luke's (1999)	75	R1	29	8	.01
		R0	71	17	
MGH	75	R1/R2	51	12	.05
		R0	49	20	

ESPAC, European Study Group for Pancreatic Cancer; *MGH*, Massachusetts General Hospital.

change of long-term control in pancreatic cancer, radical surgery is achievable in <20% of cases. In patients with resectable disease, the 5-year survival rate of patients undergoing curative resection ranges from 15 to 26%.[2-5] The poor overall survival despite complete resection suggests that occult metastatic disease is present in most at the time of resection. Additionally, autopsy studies have demonstrated up to 30% of pancreatic deaths are owing to locally progressive disease.[6]

Aggressive resection aiming for margin-negative (R0) status has been advocated for better overall survival, but a majority (50–80%) of patients with resected pancreatic cancer still develop local tumor recurrence after a presumed R0 resection,[7-10] suggesting that microscopic margin involvement (R1) is underestimated.

The impact of microscopic margin involvement on overall and disease-free survival is not entirely clear, and reported outcomes have varied substantially between published series (Table I). There is increasing interest to identify how the margin status of surgical resection specimens affects outcomes. Some have argued the for negative impact of R1 margins on survival, whereas others have stated that R1 resection is an indicator of the aggressive nature of the tumor biology and, therefore, is an independent prognostic indicator.[5,11] Some contend that R1 margins only influence local recurrence rates and do not have adverse impacts on survival.[12-14]

In patients with advanced pancreatic cancer, which we herein define as both borderline resectable pancreatic cancer and locally advanced pancreatic cancer (LAPC), there are limited curative options. Owing to local extension of tumor to involve vascular structures and the increased likelihood of an R1 resection, patients are usually administered palliative chemotherapy and/or chemoradiation therapy followed by maintenance chemotherapy.

There are select patients, however, with advanced cancers who warrant further investigation. Given the considerable divergence in the frequency of R1 resections in borderline resectable and LAPC, there remains an unmet need to provide tools to enhance or augment the ability of the surgeon to achieve negative surgical resection margins in patients undergoing resection for pancreatic adenocarcinoma.

Irreversible electroporation (IRE) is a technique in which short, high-voltage pulses are applied to soft tissue[15-18] to cause tumor ablation. IRE utilizes non–thermal-based methods to induce permanent nanopores into the cell membrane, leading to cell death. Unlike cryoablation or radiofrequency ablation, which both utilize thermal energy to destroy tissue, IRE does not expose tissue to extreme cold or heat, and therefore, can preserve nearby vital structures, such as the urethra, larger blood vessels, and nerves.[17]

We published recently findings that document the safe use of IRE in the pancreas.[19] Moreover, IRE has been used an operative technique for the palliation of patients with LAPC. There seems to be improved survival rates with the use of IRE in combination with standard chemotherapy and/or chemoradiation therapy compared with standard-of-care chemotherapy or chemoradiation therapy[20] for LAPC. Based on these promising data, we describe the use of IRE for margin accentuation as a means to achieve a microscopic negative margin during resection of either

borderline resectable or LAPC. This study is a comprehensive effort to demonstrate the safety and efficacy of IRE margin accentuation in both borderline or LAPC.

METHODS

Clinical data on patients evaluated for pancreatic resection and IRE margin accentuation for borderline resectable pancreatic cancer and LAPC from July 2010 to January 2013 were retrieved from an institutional review board–approved, prospectively maintained, soft tissue ablation registry.

Standard evaluation of all patients has been described previously,[21] including triple-phase computed tomography with pancreatic protocol with cutes of ≤2-mm at the time of diagnosis. After initial assessment, surgery teams and multidisciplinary pancreatic tumor groups respective to each institution determined radiographic staging.

Borderline resectable disease was defined to include one or more of the after radiographic findings: Tumor abutment (≤180° of the circumference of the vessel) of the superior mesenteric artery (SMA) or celiac axis; tumor abutment or encasement (>180° of the circumference of the vessel) of a short segment of the hepatic artery, short-segment occlusion of the superior mesenteric vein (SMV), portal vein (PV), or SMV–PV confluence amenable to vascular resection and reconstruction.[22] LAPC was defined as >180° encasement of either the SMA, celiac artery, or both without evidence of any type of suspicious metastatic disease.[23,24]

Initial treatment with chemotherapy, chemoradiation, or both were administered to all patients per institutions protocol. Systemic treatment regimens are noted in Table II. Approximately 4–6 weeks after completion of therapy, patients underwent restaging evaluation with repeat triple-phase computed tomography as well as hematologic and serologic markers. Patients found on restaging to have no metastatic disease and primary tumor size that did not exceed the maximum axial diameter 3.5 cm were found to be potential candidates for IRE therapy.

The surgical decision process has been described previously.[19] Succinctly, the decision to perform pancreatic resection with IRE margin accentuation was at the surgeon's discretion based on patient comorbidities, previous therapy, and intraoperative assessment. The dissection and resection technique was carried out as described previously for pancreatic head lesions and by Makary et al[25] for pancreatic body/medial tail lesions. We ink all surgical margins in the operating room to ensure consistency of the pancreatic neck, PV groove, SMA margin, and retroperitoneal/inferior vena cava margin for pancreatoduodenectomy resections and left pancreatectomies with addition of the aortic margin. Standard histopathologic evaluation using hematoxylin and eosin was used for all margins with the knowledge that the use of IRE on ≥1 margins would not affect hematoxylin and eosin staining, because there needs to be a

Table II. Characteristics of locally advanced pancreatic cancer treated with irreversible electroporation

Characteristics	*Value*
n	48
Age, y (median)	61 (27–81)
Sex (male/female)	26/22
Race	
White	42
African American	3
Other	3
Body mass index, kg/m^2 (median, range)	24.1 (17.4–43.4)
Location	
Head	31
Body/neck	17
Lesion size (cm)	
Axial	2.7
Anterior to posterior	2.6
Caudal to cranial	2.6
Performance status*	
100%	37
90%	9
80%	2
Prior chemotherapy (*n*)	
First line	11
Second line	17
>Second line	5
Prior chemotherapy	
Gemzar	21
FOLFOX	3
FOLFIRI	5
Oxaliplatin	1
Cisplatin	2
Taxol	2
FOLFIRINOX	10
Tarceva	5
Xeloda/5FU	16
Gemzar and abraxane	2
GTX	5
Other	22
Prior radiation therapy	
Three dimensional	26
Stereotactic beam radiation therapy	5

*Performance status by Karnofsky performance status.

minimum of 4 hours of perfusion to see IRE histopathologic effects. The use of resection and IRE margin accentuation was performed only in cases where suspected positive margins (R1 resection) might be an issue, and IRE was not performed if there was likely going to be residual gross disease (R2 resection).

Delivery of intraoperative IRE with the Nanoknife system has also been described previously.[26,27] For margin accentuation technique, it is imperative that the IRE energy is delivered before complete transection, because there must be soft tissue in place for the needle(s) insertion. The operative surgeon determines the number of the IRE probes necessary to achieve a certain 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) are placed in a caudal to cranial fashion after appropriate dissection has been performed (Fig 1), usually after the pancreatic neck has been transected and the ligament of Treitz has been taken down, but before any dissection of the SMV/SMA/retroperitoneal tissue. The probes are always placed under direct ultrasound guidance to achieve adequate margin augmentation (Fig 2). Probe position relative to the tumor and/or vessels is evaluated in real time and adjusted to maximize treatment effect.[28] In locally advanced tumors, IRE probes were often readjusted to ablate circumferential areas of the SMA or celiac axis where an R1 resection might persist. In borderline resectable disease, 2 probes positioned in a cephalad and caudal manner were placed in parallel fashion to the posterolateral aspect of the proximal 3–4 cm of the SMA. Given the needle probe exposure is only 1 cm long, a series of pullbacks (approximately 1–3) are usually needed (Fig 3). Delivery of IRE was considered successful based on the combination of intraoperative ultrasonography and real-time assessment of a change of resistance in the ablation zone.[28]

After completion of treatment, patients were evaluated with follow-up imaging at discharge or within 2 weeks of IRE therapy. Thereafter, patients were evaluated every 3–4 months by physical examination and radiographic imaging. Ablation success and recurrence were defined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. All radiographic findings were determined by dedicated body imagers. Development of new, low-density lesions in the region of the resection or near the vasculature 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 omentum or the presence of newly identified ascites.

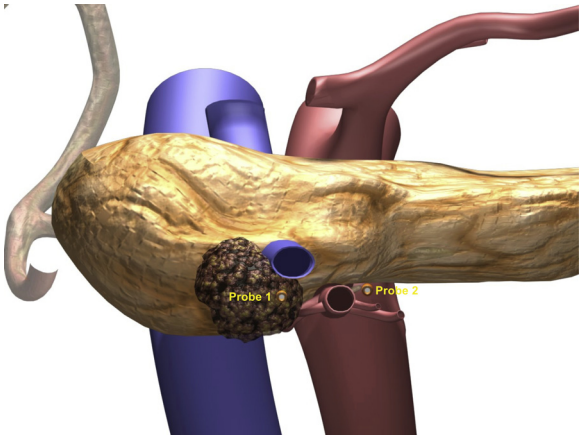

Fig 1. Axial image of the technique for margin augmentation using irreversible electroporation in a borderline/locally advanced pancreatic head cancer. Two needles are placed under continuous ultrasonography visualization either before pancreatic neck transection or after neck transection and before any type of superior mesenteric vein–superior mesenteric artery–retroperitoneal dissection.

IRE-associated variables were also recorded, including operative time, total blood loss, duration 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. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Between July 2010 and January 2013, 48 patients (Table II) with borderline resectable or LAPC were surgical candidates for margin accentuation at the time of dissection before resection, including 26 men and 22 women, with a median age of 61 years (range, 27–81). Patients had similar incidence of comorbidities, body mass index, and racial distribution, as in previous studies for patients with pancreatic adenocarcinoma. Tumors were located in the pancreatic head or uncinate process in 31 (65%; 20 patients on preoperative imaging were borderline and 11 preoperative locally advanced) and the neck or body in 17 (35%; 12 preoperative imaging locally advanced and

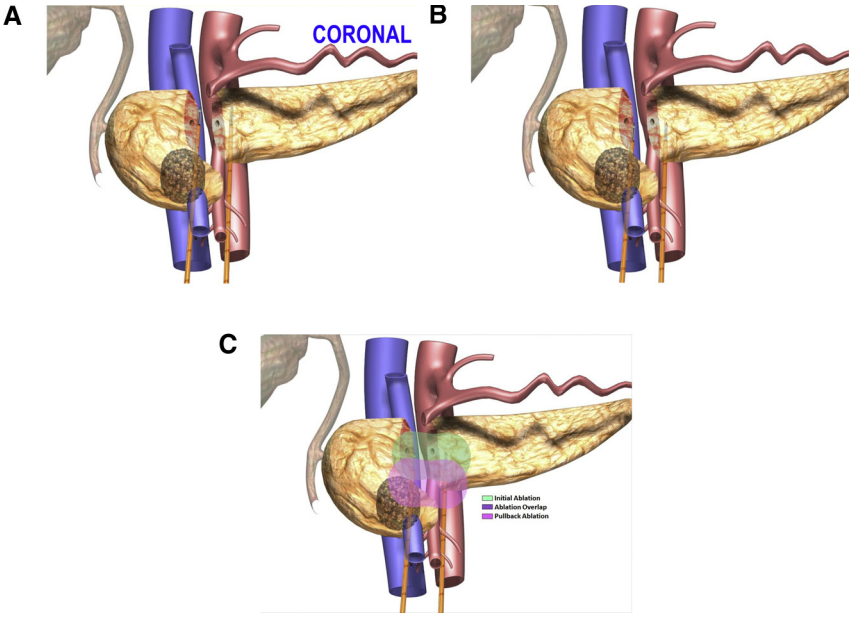

Fig 2. (*A*) Coronal images of technique for margin augmentation using irreversible electroporation (IRE) in a borderline/locally advanced pancreatic head cancer. (*B*) Sequential pullback demonstration because the active IRE probe is 1 cm of exposure and thus, to cover the entire retroperitoneal margin (usually 3–4 cm in length), subsequent simultaneous probe pullback is necessary. (*C*) Ablation examples after subsequent pullback.

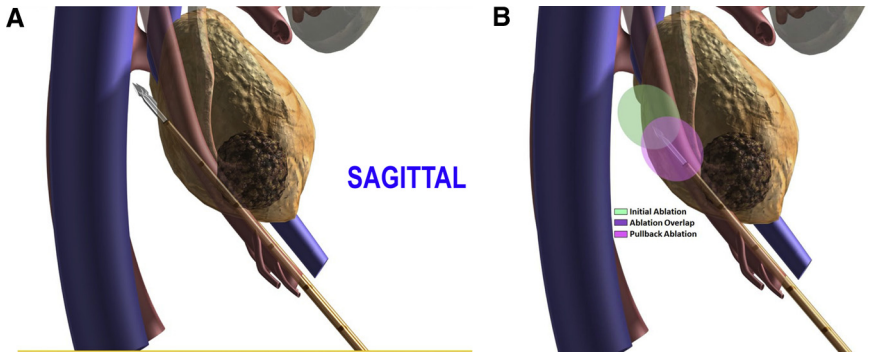

Fig 3. (*A*) Sagittal images of technique for margin augmentation using irreversible electroporation (IRE) in a borderline/locally advanced pancreatic head cancer. (*B*) Sequential pullback demonstration; the active IRE probe is 1 cm.

5 preoperative borderline) of the 48 patients; the median tumor size was 2.7 cm at its longest axis on the axial plane. Of 48 patients, 33 (69%) underwent some form of induction therapy, with 17 of 33 (52%) having already undergone second-line treatment. All patients with locally advanced tumors (n = 11 head and 10 neck/body) underwent induction therapy with the other 12 patients having borderline resectable disease. Of the 48 patients, 31 (65%) had undergone preoperative radiation, including external beam radiation therapy as well as stereotactic beam radiation therapy (SBRT). The median time to IRE from diagnosis was approximately 6 months (Table III).

The operative treatment of all patients is summarized in Table III. All 48 patients underwent an open operation for IRE delivery through a midline celiotomy. IRE was delivered successfully in all 48 patients over a median 12 minutes. En bloc celiac axis resection was performed in 10 of 48 patients (21%) with all 10 patients having arterial invasion. Vein resection was performed in 25 patients (54%; 17 patients had vein invasion on pathology) with 18 of the patients undergoing pancreatoduodenectomy with vein resection (10 segmental resections with primary repair or internal jugular interposition and 8 with lateral venorrhaphy and primary repair) and 7 patients undergoing distal pancreatectomy (4 segmental

Table III. Operative and ablative characteristics of patients with borderline resectable/locally advanced pancreatic cancer treated with IRE

Characteristics	*Value*
n	48
Median time from diagnosis to IRE (mo)	6 (4–13)
Pancreatic operations	
Pancreatoduodenectomy	31
Subtotal pancreatoduodenectomy	17
Margins	
Pancreatoduodenectomy: Preoperative borderline	20
R0	12
R1	8 (6 SMA margin, 2 portal vein groove)
Pancreatoduodenectomy: Preoperative locally advanced	11
R0	5
R1	6 (6 SMA margin)
Left pancreatectomy-subtotal: Borderline	7
R0	6
R1	1 (anterior SMA margin)
Left pancreatectomy-subtotal: locally advanced	10
R0	8
R1	2 (2 aortic margin)
Lymph node status, median (range)	19 (15–48)
N0	10
N1	38
Other operations	
En-bloc celiac axis resection	10
Gastrojejunostomy	3
Partial gastrectomy*	3
Jejunostomy tube	35
No. of IRE probes used	
Bipolar	10
Monopolar	38
No. of probes (median, range)	2 (2–4)
Direction of IRE probes	
Anterior to posterior	9
Caudal to cranial	37
Success of IRE delivery	100%
Total needle placement time (min), median (range)	2 (1–30)
Total IRE delivery time (min), median (range)	12 (2–90)
Total procedure times (min), median (range)	180 (130–740)
No. of pulses delivered, median (range)	90 (70–200)
No. of pullbacks, median	
12 pts	0
10 pts	1
16 pts	2
7 pts	3
3 pts	4
Duration of stay (d), median (range)	9 (4–58)
Complete ablation, *n* (%)	48 (100)
Adverse events, *n* (%)	18 (38)
No. of adverse events	44

*Considered additional organ when performed in conjunction with distal pancreatectomy.
IRE, Irreversible electroporation; *pts*, patients; *SMA*, superior mesenteric artery.

resections with primary repair or internal jugular interposition and 3 with lateral venorrhaphy and primary repair). No patient underwent both segmental vein resection and celiac axis resection. Additional common procedures were the creation of gastrojejunostomy to prevent delayed gastric emptying. The median duration of stay was 9 days (range, 4–58).

Of the 48 patients who underwent successful resection with IRE accentuation, 90-day adverse events (Table IV) were identified in 18 (38%) patients. A total of 44 overall adverse events were recorded; of these, 5 (11%) were possibly IRE device-related complications. Specific to pancreatic surgery, the rates of pancreatic fistulae (5%) and gastroparesis (5%) were relatively low; however, bile leak and ascites comprised 5 (11%) adverse events, and untoward vascular sequelae comprised 6 of 44 adverse events (14%); PV thrombosis (2 patients, 1 with vein resection and 1 without vein resection) and bleeding (2 patients) requiring reoperation made up the majority of these vascular complications. Given that both thrombosis occurred within 90 days of the operation and IRE and both of the patients had undergone preoperative radiation therapy, we documented these 2 events as possibly related to IRE therapy.

At 90-day follow-up for all patients, there was no RECIST criteria of local recurrence. More than half of the patients were able to resume therapy within a median time 2.4 months. Regimens included both chemotherapy (Table V) and/or adjuvant radiation therapy. There were no deaths

Table IV. 90-day adverse events in patients with locally advanced pancreatic cancer treated with IRE

Type of complication (n = *44*)	n	*Grade*
Hematologic	4	3, 2, 2, 1
Ileus	2	1, 2
Bile leak	3	3, 3, 3
Portal vein thrombosis	2	1, 3
Hepatic artery graft failure	1	2
Nonocclusive SMA thrombus	1	2
Deep venous thrombosis	2	2, 2
Pulmonary	2	3, 4
Pancreatic leak	2	
Small bowel leak	1	2
Renal failure	1	3
Ascites	2	3
Wound infection	3	2, 1, 3
Pain	1	1
Delayed gastric emptying	2	1, 1
Gastritis	2	3, 2
Postoperative bleed reoperation	2	4, 3
Hepaticojejunostomy stricture	1	3
Cardiac	2	1, 1
Other	8	1, 1, 1, 1, 4, 2, 2, 1

Other indicates urinary retention, seizure, port infection, and mental status change.
SMA, Superior mesenteric artery.

Table V. Adjuvant chemotherapy or radiation therapy and progression locations

Characteristic	*Value*
n	5
Post resection therapy (yes)	31 (65%)
Time to initiate therapy (mo)	2.4 (range, 1.3–7.5)
Type of additional therapy	
Chemotherapy	23
Radiation	5
Type of adjuvant chemotherapy (52 variations)	
Gemzar	22
Gem-Abraxane	2
Gem-Ox	1
FOLFIRINOX	9
Gem-Cis	4
Gem Tarceva	3
Xeloda-5FU	7
Recurrence, all types (yes)	28 pts
Progression-free survival, all	
Time to local recurrence (mo)	10.7 (range, 3–30)
Locations of recurrence	
Liver	8
Lung	4
Peritoneum	10
Peritoneal lymph nodes	4
Local pancreas recurrence	3

reported during this 90-day span. The decision to utilize radiation therapy in the 5 patients who underwent resection was to provide adjuvant therapy to the lymph node basin and not to the primary resection tumor site.

At 24 months, 28 patients (58%) developed recurrence, with the majority of recurrences identified in the liver (29%) or peritoneum (50%). There were 3 patients who developed local retroperitoneal recurrence at either the SMA or common/proper hepatic artery. The median overall survival in the group was 22 months (95% CI, 17.9–24.9), and progression-free survival was 11 months (95% CI, 3–10).

DISCUSSION

Few effective therapies are available for the treatment and control of pancreatic cancer, thus contributing to the poor prognosis and survival. Only 20% of tumors are resectable at diagnosis, and even in patients with resectable disease, approximately 70% of patients develop distant metastases within 2 years, suggesting that occult metastatic disease is already present in most patients at the time of operative resection. Isolated local recurrences may occur in 10–35% of patients,[29-31] likely associated with underreported positive microscopic resection margins.

In the past several years, additional subsets of patients have been identified as borderline resectable who may benefit from definitive resection. These localized tumors, unlike locally advanced cancers, are thought to be resectable safely with curative intent in specialized treatment centers. Attempts at operative resection, however, can be compromised by margin-positive resection owing to underlying proximity of the primary tumor to major vascular structures, thereby putting patients at high risk for early systemic failure.[22] The tendency toward more local failure of resected borderline resectable pancreatic cancers seems to be the related most frequently to a positive surgical margin and may be associated with a poorer prognosis.[32]

Patients with LAPC have limited options; resection is not an optimal option owing to the inability to achieve negative surgical resection margins. The vast majority of patients develop incurable treatment failure, and median survival is usually <12 months despite the use of chemotherapy alone or in combination with chemoradiation. Although local control is sometimes achievable, the dominant pattern of failure is ultimately metastatic disease.

Autopsy studies confirm that metastatic disease is present in most situations, but there are instances where isolated local recurrence is the only evidence of disease. It is assumed that positive microscopic resection margins (R1) contribute to local recurrence,[32,33] and there has been considerable debate[34-36] on whether R1 resections may play some role in affecting overall survival. It is thought that R1 margins are indicative of biologically aggressive tumors[33] and, thus, contribute to poor outcomes. Other studies, however, suggest that R1 resections are not an independent prognostic factors for long-term survival[15,34,37] and merely affect local recurrence rates.

Nonetheless, it is necessary to stress the importance of attempting to achieve microscopically negative margins for curative intent. Multivariate analysis by the University of Indiana demonstrated that achieving an R0 margin status influences actual long-term survival.[38] Analysis of the European Study Group for Pancreatic Cancer (ESPAC)-1 trials showed a borderline association with R1 resections and survival.[37] These data suggest that the conflicting nature of R1 resections on long-term survival might be, in fact, owing to the underestimation of resection margin involvement. Studies report that true R1 margin rates are underestimated, with rates ranging from 10 to 84%,[34,36,39] owing to a lack of standardized protocol of the reporting of pathologic examination and definition of microscopic margin involvement.[35]

In these situations, where incomplete tumor resection or close margins are at increased risk for local recurrence and ultimately metastatic disease, there is need for aggressive local therapy in attempts to achieve negative margins. To date, there has been little effective therapy to facilitate microscopically negative margin resections outside of patient selection and meticulous operative dissection. Accepting that true margin-positive rates are significantly high (>75%) in resected pancreatic cancers, our study is an attempt to highlight that margin accentuation may help to achieve true R0 margin status. We report the successful implementation of intraoperative IRE to accentuate negative-margin dissection of the retroperitoneal margin and its surrounding perivascular soft tissue, primarily, the perineural and mesenteric tissue adjacent to critical vascular structures.

The adverse event rate of this study is comparable to other reported morbidity with treatment modalities utilized in R1 disease, such as intraoperative radiation therapy (IORT). Additionally, the mortality rate in this cohort of patients was less than the recently published NSQIP data which highlighted a mortality rate of approximately 3% in >4,400 patients undergoing pancreatoduodenectomy.[40] Utilization of IRE did not prolong operative time, requiring an additional 10–15 minutes to effectively deliver therapy the areas of interest.

In comparison with other treatment modalities aimed at addressing advanced pancreatic cancer, the results from this study suggest that IRE for margin accentuation affords similar, if not better, outcomes. Radiation therapy remains an option for patients undergoing an R1 resection and is utilized frequently in patients who achieve an R0 resection for all types of pancreatectomy for pancreatic adenocarcinoma. Variable local recurrence rates have been reported with the use of adjunctive radiation therapy. A recent metaanalysis of all clinical trials identified a local recurrence rate of 11.1%.[41] Other studies have recorded local recurrence rates from as low as 4% to as great as 46%.[42]

Single-institution, retrospective studies have reported variable outcomes with brachytherapy in the treatment of advanced pancreatic cancer. The initial median survivals ranged from 7 to 15 weeks and local control rates (defined as combining stable disease and partial response) in the range of the 65%.[43-49] The complication rates were felt to be unacceptable and have limited the acceptance of brachytherapy in treatment of advanced pancreatic cancer. Attempts at endoscopic ultrasonography-guided brachytherapy have renewed interest in this application, but data are limited at this time, and brachytherapy has not been used with R1 disease.[50,51]

Others have investigated the role of IORT in combination with external beam radiation therapy and chemotherapy for the treatment of pancreatic cancer. Using IORT, the greater dose delivery of radiation than conventional methods provides, at least in theory, improved local control. Although the Japanese incorporate IORT in potentially curative resections, in the United States it is used selectively to treat unresectable pancreatic cancers.[46,52,53] Although some institutions describe the favorable effects of IORT in pancreatic cancer, the context in which IORT has been utilized has not been uniform; most centers use multiple treatment strategies with chemotherapy administered with or without radiation, and most reported experiences were performed in single institutions. Nonrandomized data

suggest that IORT offers no improved benefit in survival or disease-free progression in unresectable pancreas cancer, limiting the indications of this technique.[54,55]

To that end, SBRT is being utilized increasingly in pancreatic cancer, because SBRT potentially improves local control with its precise targeting capabilities and short treatment times. Although some have suggested there may be a role for SBRT in unresectable pancreatic cancer, contradictory studies have shown it to be ineffective or deleterious.[56-60] A report of stage II pancreatic cancer patients who underwent resection with either a R1 or a "close" R0 resection showed a freedom of local progression of 66% at 12-month follow-up.[61,62] Similar results were reported by Chuong et al,[63] who reported the use of SBRT in borderline resectable and LAPC with a resectability rate of only 56%, a progression free survival of 9.8 months, and an overall survival of only 15 months in this single institutional series.

IRE can be implemented successfully as an adjunctive measure for attempting to achieve negative microscopic operative margins in select patients. This treatment is limited to those patients that generally have stable disease at the time of resection. It is our opinion that some form of induction therapy for locally advanced disease and neoadjuvant therapy for borderline resectable should be utilized before resection. We currently utilize 4–6 months of induction chemotherapy alone in locally advanced and now utilize the Alliance-based neo-adjuvant protocol (available from: http://clinicaltrials.gov/show/NCT01821612) for borderline resectable disease. The small number of patients with advanced pancreatic disease precludes meaningful analysis of prognostic factors. In addition, a prolonged course of neoadjuvant therapy likely introduces selection bias of those patients with more favorable tumor biology. Continued research into the utility of IRE margin accentuation of advanced pancreatic cancer should provide additional measures and techniques to prevent as well as treat microscopic positive margins.

In conclusion, in advanced pancreatic cancer, including both borderline resectable and LAPC, operative resection with IRE accentuation may provide an alternative attempt at cure. While metastasis still remains the main challenge for this disease, improvement in local control by IRE may be associated on improved survival of patients or prolonged control of this disease.

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DISCUSSION

Dr Michael House (Indianapolis, IN): I would like to congratulate Dr Kwon and his colleagues from the University of Louisville, The Henry Ford Hospital, and the University of South Florida for successfully conducting a prospective multicenter trial to examine the safety of intraoperative irreversible electroporation (IRE) for patients undergoing pancreatectomy for borderline or locally advanced pancreatic adenocarcinoma. The results of this study support prior reports from your institution that this new technology does not add substantially to the morbidity after pancreatectomy for tumors intimately related to the portomesenteric and celiac vascular anatomy.

To understand better the potential indications and applications for IRE for patients undergoing pancreatectomy for borderline resectable, locally advanced, and possibly even resectable cancers, I ask you to address 4 questions. First, careful histopathologic characterization of the pertinent margins after pancreatic head resections and left pancreatectomy with intraoperative IRE will help us to understand how effectively IRE accomplishes complete macro- and microscopic margin clearance. Could you describe how your margins were processed intraoperatively and how histopathologic examination was conducted? Did you accomplish an R0 margin status in all patients who received IRE? For the 10 patients who underwent celiac axis resection, what was the status of the vessel wall in terms of tumor invasion and treatment effects from IRE?

Second, good outcomes, which you have achieved in this cohort of 48 patients with advanced stages of pancreatic cancer, must follow good patient selection. The pancreatectomy demonstration project of ACS-NSQIP is revealing higher morbidity associated with pancreatectomy combined with vascular resections and venous reconstructions which are often required for locally advanced tumors which received preoperative chemo- and especially chemoradiation therapy. Were patients not candidates for IRE if short-segment portal vein occlusion was present on preoperative imaging? Of the patients in your study, 69% had received preoperative chemo- or chemoradiotherapy. Could you elucidate the factors and issues that precluded preoperative therapy for patients with borderline resectable and locally advanced cancers yet underwent operation? Some centers have utilized responses of serum CA 19.9 levels after induction therapy to select patients for operation. Did you analyze CA 19.9 levels in your patients? Five patients received adjuvant radiation chemotherapy. One putative advantage of IRE is the avoidance of external beam radiotherapy. What factors influenced adjuvant chemoradiation recommendations?

Third, as you have pointed out, we continue to debate the actual impact of margin status and local recurrence on overall survival for patients with gastrointestinal malignancies including pancreatic

adenocarcinoma. With the wide discrepancies that underlie the accurate assessment of pancreatectomy margins, do you feel that there is a potential role for IRE for the retroperitoneal and superior mesenteric artery (SMA) margins for patients with resectable pancreatic head cancer or for the periceliac margin for resectable tumors of the body of the pancreas?

Fourth, in your study, 30% of patients developed peritoneal recurrences, with a median of 24 months. This finding is substantially different than the recurrence patterns, namely hepatic-only and hepatic-first recurrences, which most centers have noted in retrospective and prospective studies of resections for pancreatic cancer. Do you have any concerns that IRE probe placement and manipulations could cause peritoneal dissemination?

Again, congratulations on a nicely presented study and for your group's pursuit of improved, potentially curative, treatments for pancreatic cancer. These presented data certainly attract our interest in studying the efficacy and benefit of IRE for pancreatic cancer with collaborative, randomized, prospective trials.

Dr David Kwon (Detroit, MI): I will try to group some answers together to address things as best as possible.

Intraoperatively, frozen margins were assessed, and they were assessed at areas that we knew based on preoperative imaging that would be areas of concern. When we talk about celiac access resection, we did look at vessels. And ultimately, on our final pathologies, they were all R0 resections.

You asked an interesting question about could we see IRE effects on our final pathology or at the time of examination. And generally, with IRE, we do not see cellular-level effects within a certain time period. Because these resections come out within less than an hour after the IRE is performed, we generally do not see the effects of the actual IRE itself.

In terms of one of the last questions, you asked about whether or not this should be considered in resectable pancreatic cancers as a margin accentuation along the retroperitoneal and SMA margins, this certainly brings up the debate of how our pathology has been read. Uniformly, because there is no consensus on how the retroperitoneal margin is defined or read when we talk as surgeons versus pathologists, there is a discrepancy. That is perhaps why there is such a high positive margin rate.

For such reasons, I certainly would believe, with these interesting data and with the ability to perform IRE successfully, that even in resectable pancreatic head lesions, that this certainly would be an applicable opportunity to use margin-accentuated ablation, especially on the SMA and retroperitoneal margins.

In terms of patient selection, 70% appropriately had either induction chemotherapy or chemoradiation therapy. But, unfortunately, because this is a new device and there are significant data on the Internet, not so much from physicians but from patient experiences, there is a big population of patients that come in directly seeking this. Certainly, at our institution, besides our attempts to encourage them to pursue the traditional route, some are dead set for us to do these procedures. Despite forewarning them that this is not the standard of care, we have had a significant number of patients opt to do this as their definitive standard of care because it takes away the mental anguish of going through induction therapy and then subsequent restaging.

In terms of the vascular resection that we had talked about, if there was a short segment of portal vein involvement that a normal borderline resectable would be resectable with either an internal jugular vein conduit or a saphenous vein skin graft, that did not preclude us from attempting IRE ablation at the time.

Serum CA 19-9 levels were followed, but because some of these patients came in as outside self-referrals, our follow-up was lost subsequently. We could only follow their radiographic imaging. We did not have complete data with CA 19-9 in this entire cohort, but, as we are moving forward, we are getting significantly better at that.

An interesting question that you asked was about the 5 patients who received radiation therapy afterward. You are absolutely correct. The fact that we do the IRE ablation suggests that we would not need it. But, again, because these patients come in as referrals, when they go back to their subsequent treating medical or radiation oncologists despite our rationale for why this would not necessarily be needed, doctors kind of do their own thing, especially if they are not within our health care system.

Last, in terms of the pattern of failure, you certainly bring up a very good point with IRE probes and potentially seeding tumor cells in the peritoneum because the number is significantly greater. I cannot tell you reasonably why, but, in essence, with the IRE ablation, even when we pull back, there should not be tumor seeding, but there certainly could be.

Dr Margo Shoup (Maywood, IL): I congratulate you for continuing to really push the envelope for

this terrible disease and really working for the cutting edge treatment for whatever we can do for pancreatic cancer.

I just have 2 questions. One is a technical question more than anything. I noticed that 20% of your patients had a celiac blockade at the time of surgery. I am just curious how you chose those patients to have that. Were they asymptomatic ahead of time or is it prophylactic? It is just not something we routinely do after our Whipple surgeries.

And the other thing is, I struggle a little bit about how such an attempt for local control can really affect distant metastases. We all realize that pancreatic cancer almost always is a systemic disease at the time of diagnosis, and we are really looking at the local control here with this technology. So I guess I question the role of FOLFOX versus FOLFIRINOX versus adjuvant therapy. I think that is a real important aspect of a study like this, to try to standardize that as much as possible.

I just wonder if you can comment on what you plan on doing in the future for systemic control.

Dr David Kwon: Certainly, you are correct in terms of the dominant pattern of failures with systemic disease. Certainly, what we are doing is local control. If we look at the autopsy reports, it is confirmed that most people die of metastatic disease, but approximately 15–20 patients die of local recurrence. So we believe that, although the data are conflicting on exactly local recurrence and its effect on survival, that this certainly plays a role. That is why we looked at the effects of IRE at local recurrence.

In terms of systemic therapy in terms of this being a systemic disease, certainly, we are seeing very good results with FOLFIRINOX. This is one of the few regimens that now we are seeing at least partial response rhesus criteria. Depending on the patient's functional status, this certainly is a very good first-line drug. But we know a little but not enough to know what is the optimal systemic treatment options.