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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

Irreversible Electroporation in Locally Advanced Pancreatic Cancer: Potential Improved Overall Survival

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ABSTRACT

Background. Locally advanced unresectable pancreatic adenocarcinoma (LAC) is characterized by poor survival despite chemotherapy and conventional radiation therapy. We have recently reported on the safety of using irreversible electroporation (IRE) for the management of LAC. The purpose of this study was to evaluate the overall survival in patients with LAC treated with IRE.

Methods. A prospective, multi-institutional evaluation of 54 patients who underwent IRE for unresectable pancreatic cancer from December 2009 to October 2010 was evaluated for overall survival and propensity matched to 85 matched stage III patients treated with standard therapy defined as chemotherapy and radiation therapy alone.

Results. A total of 54 LAC patients have undergone IRE successfully, with 21 women, 23 men (median age, 61 (range, 45–80) years). Thirty-five patients had pancreatic head primary and 19 had body tumors; 19 patients underwent margin accentuation with IRE and 35 underwent in situ IRE. Forty-nine (90 %) patients had pre-IRE chemotherapy alone or chemoradiation therapy for a median duration 5 months. Forty (73%) patients underwent post-IRE chemotherapy or chemoradiation. The 90 day mortality in the IRE patients was 1 (2 %). In a comparison of IRE patients to standard therapy, we have seen an improvement in local progression-free survival (14 vs. 6 months, $p = 0.01$), distant progression-free survival (15 vs. 9 months, $p = 0.02$), and overall survival (20 vs. 13 months, $p = 0.03$).

Conclusions. IRE ablation of locally advanced pancreatic tumors remains safe and in the appropriate patient who has undergone standard induction therapy for a minimum of 4 months can achieve greater local palliation and potential improved overall survival compared with standard chemoradiation–chemotherapy treatments. Validation of these early results will need to be validated in the current multi-institutional Phase 2 IDE study.

INTRODUCTION

Locally advanced pancreatic cancer—stage III (LAP)—is a devastating disease with mortality rate and overall 5 year survival rate lower than 5 %. The primary goals of treatment for LAP are palliation of intractable pain and improved overall survival. Most studies of single-agent or combination chemotherapy in patients with LAP have documented limited response rates (RR) with little reproducible impact on patient's survival or quality of life. Recent reports have demonstrated an increasing incidence and increasing death rate from 9.28 per 100,000 in 1991 to 9.48 per 100,000 in 2006.[1]

More established, local ablative therapy, including alcohol injection and radiation therapy, have reported RR as high as 15–30 % occasionally seen in pilot studies of novel combination agents but generally have not been reproduced in larger trials.[2,3] Radiofrequency ablation of the pancreas in the setting of unresectable disease has been described in a few case series, but implementation of that technology is limited by concerns about thermal injury to adjacent organs and vessels.[4]

Irreversible electroporation (IRE) is a technique in which short, high-voltage pulses are applied to tissues to

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permeabilize the cell membranes.[5–8] 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.[6] We have recently published our findings regarding safety of IRE in the pancreas.[9] 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. We published recently our initial human use in the first 27 LAP patients treated with IRE and concluded that IRE ablation of locally advanced pancreatic tumors is a safe and feasible primary local treatment in unresectable, locally advanced disease.[10]

The purpose of this study was (1) to evaluate the overall survival of IRE in LAP patients and (2) to compare IRE to standard therapy of chemotherapy and chemoradiation therapy.

METHODS

A prospective evaluation of patients who underwent irreversible electroporation for locally advanced pancreatic cancer (LAP) from December 2009 to March 2012 was performed. 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.[11,12] IRE was not utilized on patients with borderline resectable lesions.

These patients were compared with a cohort of patients who underwent standard therapy of chemotherapy or chemoradiation therapy alone during a similar time period (12/2008 to 3/2012) who were matched on a 1.5:1 basis. Matching was performed after 4 months of induction therapy by propensity scoring, with scores based on patient age, size of tumor, performance status, cardiac comorbidities, and pulmonary comorbidities (to confirm similar surgical fitness). These variables were chosen empirically based on factors that we felt would be important contributors to selection bias and to confirm that all patients could undergo a surgical procedure after 4 months of induction chemotherapy and did not have metastatic disease, which also was in the control group. The other variables were thought to contribute to operative difficulty or risk of complications/mortality. More granular measures, such as specific lesion location were not included, because this would make achieving an adequate matching difficult. The reason that the control group did not undergo IRE was based on the decision of the medical oncologist, radiation oncologist, surgeon, and/or patient.

Briefly, a propensity score represents the probability that a patient underwent IRE of the pancreas based on a logistic regression model, including the factors outlined above as covariates. Non-IRE patients (standard therapy only) with the closest propensity score (and a maximum difference in propensity score of no >0.1) to each IRE patient were chosen as the comparison group. The purpose of propensity score matching is thus to achieve balance (equal distributions) on the covariates included in the model between the IRE patients and non-IRE patients.

Comparisons were made between the matched groups in terms of patient demographics, short-term outcomes, and overall (OS) and disease-free (DFS) survival. Baseline comorbidities were assessed using the Charlson Comorbidity Index.[16] Surgical complications were graded according our standard scale which has been previously published.[17]

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), and p values <0.05 were considered significant.

Surgical and Electroporation Technique

The surgical decision making has been described previously,[10] but in short 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.[10] The surgical technique was performed as described by Martin et al.[13] for pancreatic head lesions and by Cameron et al.[14] for pancreatic body-medial tail lesions. The use of resection and IRE in these unique cases was performed to treat suspected positive margins and was not performed when gross residual disease would be left behind. Patients who were found to have metastatic disease at the time of planned IRE were not treated with IRE ($n = 3$ patients in this study). All postoperative complications to 90 days were monitored and graded prospectively according to a previously published 5-point scale.[13]

Chemotherapeutic adverse events were recorded and graded as per Common Terminology Criteria for Adverse Events version 3.0 AFTER the initial 4 months of therapy to only capture similar patients who had received adequate pre-IRE chemotherapy or chemoradiation therapy (defined as at least 4 months form diagnosis to better establish the biology of the disease and rule out early stage 4 disease).

The delivery of IRE was performed via the Nanoknife system (Angiodynamics, Lanthan, NY) as described in our previous manuscript of IRE in the porcine pancreas[9] and patients with LAP.[10] The cost of the IRE probes is approximately $2,000.

Follow-up imaging was performed at the time of discharge or within 2 weeks of IRE therapy for safety evaluation and then at 3 month intervals. Ablation

recurrence was defined as per RECIST criteria with either persistent viable tumor as defined by dynamic imaging in comparison to pre-IRE scan, persistent hypermetabolic activity if hypermetabolic 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 (1) the ability to obtain a preoperative PET scan, and (2) that the primary lesion in question had PET activity. Those imaging modalities, CA 19-9 values, as well as the clinical values were all utilized to determine local recurrence. All images were read by dedicated body imagers, none of which were IRE proceduralists. Post-IRE imaging of the pancreas is challenging given the acute inflammatory changes seen from postoperative day 1 through day 10, as well as the soft tissue inflammation that occurs during the apoptotic process as described by Bower et al.[10,15] that persists 6–8 weeks postablation. Thus involvement of a dedicated body imager is recommended when initiating a pancreatic IRE ablation program.

RESULTS

A total of 139 patients were included in this observational review of 54 patients treated with standard therapy and IRE therapy compared with 85 patients who underwent standard chemotherapy and/or chemoradiation therapy alone and who because of either decision of treating physician or patient, or both, did not wish to undergo IRE during this timeframe (Table 1).

In an evaluation of their overall oncology care, patients had an even distribution of both locally advanced pancreatic cancers located in the head versus the body and neck with a similar overall lesion size in both the axial, anterior, posterior and cranial caudal planes (Table 1). Prior systemic chemotherapy was variable based on the wide use of Gemzar-based chemotherapy, oxaliplatin-based chemotherapy, as well as the recent and increasing use of Folfirinox. A majority of patients underwent a combination of Gemzar-based or oxaliplatin-based chemotherapy as demonstrated in Table 1. The utilization of either 5-FU and radiation therapy or Gemzar and radiation therapy also was similar in both groups.

In evaluating the 54 patients who underwent IRE alone, the median time to undergo surgical ablation from the time of diagnosis was 5.1 months with a range of 1 to 32 months (Table 2). The reason for the range is predominantly based on the timing of either patient self-referral, treating oncologist referral, or both. Patients who had undergone IRE at an earlier stage were predominantly either refractory to systemic chemotherapy or refused systemic chemotherapy at the time of diagnosis. The most common approach was through an open supine midline incision with two patients treated in a laparoscopic fashion. Nineteen patients at the time of exploration were found to have less extensive arterial encasement and because of this underwent a combination of IRE for margin accentuation and margin extension and en bloc resection of the entire celiac axis with a subtotal pancreatectomy or pancreaticoduodenectomy. The most common placement for needle placement was predominantly in a caudal-to-cranial fashion parallel to vital structures in order to avoid needle damage at needle placement.

TABLE 1 Characteristics of 139 LAP cancer patients treated with either IRE and chemotherapy and/or radiation (N = 54) therapy versus chemotherapy/radiation therapy alone (N = 85)

Characteristics (n = 139)	Chemotherapy and/or radiation therapy (n = 85)	IRE with chemotherapy and/or radiation (n = 54)	p value
Location			
Head	58 (68 %)	35 (65 %)	0.11
Body/neck	27 (32 %)	19 (35 %)	
Lesion size			
Axial	3.1 (1.9–5)	3.2 (1–5.5)	0.13
Anterior–posterior	2.6 (1.1–5.1)	2.6 (1–4.7)	
Caudal to cranial	2.8 (1.5–5)	2.9 (1–4.9)	
Performance status			
100 %	60 (70 %)	34 (64 %)	0.07
90 %	18 (16 %)	10 (18 %)	
80 %	17 (14 %)	10 (18 %)	
Charleston comorbidity index (median, IQR)	4 (1)	4(1)	0.1
Prior chemotherapy			
Gemzar	44	26	0.09
FOLFOX	7	3	
FOLFIRI	3	1	
Oxaliplatin	7	4	
Avastin	2	1	
Cisplatin	5	2	
Taxol	4	2	
FOLFIRINOX	13	9	
Abraxane	5	3	
Tarceva	9	6	
Other	48	26	
Prior radiation therapy			
5FU and radiation	42 (50 %)	15 (28 %)	0.06
Gemzar and radiation	15 (18 %)	9 (17 %)	

TABLE 2 Operative and ablative characteristics of patients with locally advanced pancreatic cancer treated with IRE

Characteristics	Chemo- XRT and IRE
Median time from diagnosis to electroporation	5.1 months (range 1–32.1)
Approach	
Open—supine midline	52
Laparoscopic	2
Pancreatic operations	
Whipple	9
Subtotal pancreatic	10
Other operations	
Hepaticojejunostomy	10
Gastrojejunostomy	19
Partial gastrectomy*	6
Celiac plexus block	9
Other	27
No. of IRE probes used	
Bipolar	6 patients
Monopolar	48 patients
No. of probes	4 (3–6)
Direction of IRE probes	
Anterior to posterior	7
Caudal to cranial	47
Success of IRE delivery	98 %
Total IRE delivery time	16 min (2–189)
Total procedure times	180 min (40–500)
Length of stay	7 days (1–58)
Complete ablation	51 of 54
Adverse events	32 patients had 67 complications
Follow-up recurrence (median 12 months)	(27 patients recurred)
6 weeks	0
3 months	8 (6 local)
6 months	5 (3 local)
9 months	11 (6 local)
12 months	2 (0 local)

*Considered additional organ when performed in conjunction with distal pancreatectomy

In the same 54 patients, IRE success—defined as the minimum ability to deliver at least 90 pulses at appropriate voltage—was achieved in 53 of 54 patients (Table 2). The time for IRE delivery was variable based on the size of the lesion to be treated and the number of probes necessary to cover that lesion. Total procedure times were a median of 180 min with an overall median length of stay of 7 days. Thirty-two of the 54 patients treated suffered a total of 67 different adverse events during their minimum 90 day follow-up. After a median follow-up of 15 months, a total of 15 of 54 patients have had local recurrences (Table 2).

TABLE 3 Adverse events in patients with locally advanced pancreatic cancer treated with irreversible electroporation or with standard chemotherapy and/or XRT alone

Type of complications	Standard therapy: chemotherapy and/or radiation		IRE with chemotherapy and/or radiation	
	85 patients		54 patients	
	No. patients	Grade	No. patients	Grade
Hematologic	20	2–4	4	
Ileus			2	2
Bile leak			2	
Portal vein thrombosis/ graft failure	8	3–4	4	2, 5
Deep venous thrombosis	9	1–2	2	2
Pulmonary	9	2, 3	3	
Renal failure	8	1–3		
Ascites	8	1–3	3	1, 3, 4
Wound infection	6	1, 2	7	1–2
Dehydration/failure to thrive/nausea	45	1–4	8	
Bleeding	8	1–3	3	2, 4
Diarrhea	25	1–4	3	1
Duodenal leak			2	4, 4
Liver insufficiency	19	2, 3	1	2
Pancreatic leak			2	3, 3
Other	35	1–5	10	1–3

Adverse event capture was stopped when patients developed progression of disease

With respect to overall adverse events in the patients treated with IRE followed by additional chemotherapy compared with standard chemotherapy alone, the comparison of adverse events was initiated after the initial 4 months of standard therapy (Table 3). Because we did not wish to bias the results by including those initial 4 months of therapy, the evaluation of adverse events in the standard chemotherapy group occurred after what was felt to be an appropriate length of time to initiate standard chemotherapy. Forty-seven of the 54 patients who underwent IRE received some form of post-IRE therapy—most commonly gemcitabine-based chemotherapy, with 10 of these 47 patients also received radiation therapy after IRE per their treating oncologist. Compared with those groups, there were similarities especially in regards to incidents of nausea, dehydration, as well as underlying liver insufficiency and hematologic adverse events occurring in patients who were under continuous chemotherapy or chemoradiation therapy after an initial 4 months of therapy. The adverse events in the IRE group included two patients with bile leaks, as well as two patients who had

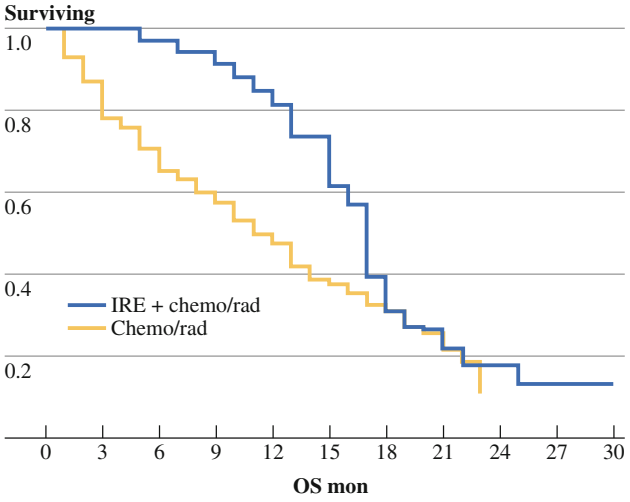

FIG. 1 Overall survival of the 54 patient with LAP treated with IRE and standard chemotherapy and/or radiation therapy versus the 85 patients treated with just chemotherapy and/or radiation therapy alone

duodenal leaks. One duodenal leak occurred after a duodenotomy needed to remove the patient's stent; the other occurred early on in the evaluation when the needles were placed in a transduodenal approach and the patient leaked from those needle puncture sites. One patient in the IRE group died during the 90-day follow-up. There were no deaths from specific chemotherapeutic adverse events in the standard chemotherapy or chemoradiation therapy group.

Compared with overall survival, there was the local progression-free survival in the chemotherapy and IRE group (14 vs. 6 months, $p = 0.01$), and distant progression-free survival (IRE with therapy 15 vs. 9 months with therapy alone, $p = 0.02$) was increased as well as in overall survival in the IRE and chemotherapy group (20.2 vs. 11 months, $p = 0.03$) compared with the standard chemotherapy group (Fig. 1). However, as the overall survival graph demonstrates, when patients did recur, they most likely recurred because of metastatic disease, such that with a follow-up the survival graphs quickly overlap at approximately 20 months due to rapid progression of disease in a distant fashion in the IRE group. In a subset analysis of the patients who were resected with IRE, versus IRE alone, there was a trend to improved overall survival (IRE with resection 23.1 months vs. IRE alone 17.2 months, $p = 0.1$), again because of systemic recurrence as the most common site of failure.

DISCUSSION

At the time of diagnosis, 30–35 % of patients with pancreatic cancer present with LAP. Recently, the biologic aggressiveness and the natural history of this stage of cancer have been questioned and are believed to have a different history compared with metastatic disease. Recently, an autopsy series of patients with pancreatic cancer identified 30 % who succumbed to locally destructive disease without evidence of progression at distant sites.[16] Historically and nihilistically, with little foundation, little evidence, and with limited success chemoradiotherapy alone has been and remains a component of LAP therapy subsequent to a few small studies in the 1980s that used ineffective systemic therapies and older radiation techniques.[17–19]

Further investigation of the seemingly modest benefit for chemoradiation therapy from previous studies with gemcitabine and from earlier reports on fluorouracil combined with radiation remains an unmet need in the management of LAP.[3,17,18] Because pancreatic cancer has so many systemic manifestations, it is not hard to see that radiation therapy, when given over 5–6 weeks, would not have a significant impact on the natural history of this disease. Therefore, there is an urgent need to test newer and novel systemic strategies in combination with efficient local therapies that could work to treat LAP.

We have previously reported on the safety of the use of IRE in LAP,[10] and this report is the first to demonstrate superior local progression, distant progression, and overall survival compared with current standard therapies of chemotherapy and/or chemoradiation therapy (Fig. 1). We have similarly demonstrated that even in the patients who did not undergo IRE, after 4 months of induction therapy, there remains significant morbidity in those patients, which in some instances is as severe as in surgical patients, or even worse (Table 3). Thus, the rationale that patients with LAP are spared surgical therapy is unsubstantiated and should continue to be evaluated even after initial diagnosis. It is imperative that all oncologists realize that a declaration of unresectability only has a 3 month expiration date and should be reevaluated at each 3 month interval with appropriate clinical and radiologic review. Similarly, our results in the chemoradiation-therapy-only group are similar to the most recent reports, with consistent, median, overall survival of 11–13 months (Table 4).

The use of any type of ablative therapy in the pancreas has the potential for unique complications. The pancreas surrounds or abuts several vital structures, including the common bile duct, pancreatic duct, superior mesenteric artery and vein (SMA and SMV), portal vein, stomach, and duodenum. However, with a clear understanding of all of these potential complications we have not seen any of these in our chronic animal studies, other investigators' animal studies or in our previous short-term clinical evaluation of the use of IRE in LAP.[10,15,20]

There are inherent limitations of this study; specifically, the type and duration of chemotherapy before IRE was not

TABLE 4 Recently reported overall survival in locally advanced pancreatic cancer

Study	No. patients	Therapy	90 day mortality	Overall survival (months)
Crane, 2011	69	Gem-Ox–Cetux	5 %	11.6
Melnik, 2010	40	Gem–Etoposide	9 %	8.8
Didolkar, 2010	85	Sterotactic XRT-then Gem	9 %	8.65
Arnoletti, 2011	16	Gem–Cetux with XRT	0	10.5
Milandri, 2011	33	GEMOX–XRT	0	10.2
Shibuya, 2011	19	Gem–XRT	0	16.6
Oberic, 2011	18	5-FU–DCT–CDDP–XRT	4 %	10.1
Mamon, 2011	81	Gem–XRT	5 %	12.2
Maluta, 2011	66	XRT–Hyperthermia–Gem-Ox	4 %	11
Brunner, 2011	93	5FU–Gem–Mito–XRT	5 %	12.7
Loehrer, 2011	69	Gem versus Gem–XRT	6 %	9.2
Lee, 2012	53	Gem–Xeloda	3 %	16.6

standardized and was highly variable based on patient self-referral as well as medical oncologist referral with the groups receiving various durations of oxaliplatin or Gemzar-based chemotherapy. However, this degree of variability was similar in both groups, further demonstrating that there is no current standard chemotherapeutic regime that is universally approved in the United States. In addition, the standard chemotherapy/chemoradiation group did not undergo definitive repeat laparoscopy staging and there is a potential that small-volume peritoneal disease may have existed in some of this group of patients, because they were only followed with standard high-quality pancreatic protocol axial imaging. Lastly, quality-of-life scores were not captured. Significant decreases in overall narcotic use has been reported previously, which has continued to maintain in the IRE group, but specific quality of life has not been captured in this subset.

CONCLUSIONS

We believe that IRE ablation of locally advanced pancreatic cancer is safe, provided that the appropriate patient has undergone standard chemotherapy of a minimum of 4 months. Patients who undergo IRE in conjunction with standard chemotherapy and chemoradiation therapy achieve greater local palliation and improved overall survival compared with chemoradiation therapy/chemotherapy treatments alone. Further validation of this initial observational study is necessary in a prospective, randomized, phase II trial planned for mid 2012 to validate these initial, encouraging results.

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