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 treatment of locally advanced pancreatic cancer (LAPC). Irreversible Electroporation (IRE) is an energy delivery system, effective in ablating tumors by inducing irreversible cell 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 IRB-approved registry. Perioperative 90-day outcomes, local failure, and overall survival were recorded and compared to standard of care data for stage III LAPC.

RESULTS
200 patients with LAPC underwent IRE of tumor (In-Situ, n=150) or IRE with pancreatic ± arterial resection (Margin, n=50). All patients underwent induction chemotherapy, with an additional 52% receiving chemo-radiation, for a median of 7 months (range, 5-13) prior to IRE (Figure). IRE was successfully administered to all patients. 19% sustained complications with a median grade of 2 (range, 1-3). Median length of stay was 6 days (range, 4-58). With a median follow up of 25 months, 6 (3%) had local recurrence. Median overall survival (OS) in both groups was 23.5 months (Figure).

CONCLUSIONS
In stage II LAPC, the addition of IRE with established chemotherapy and/or radiation therapy can provide a significant survival advantage. These early outcome metrics and overall survival begin to establish the minimal standards in which to establish future comparative studies.

*Robert CG Martin is a consultant for AngioDynamics.

The link to the abstract on the American Association of Surgery website http://meeting.americansurgical.org/abstracts/2015/13.cgi
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/accentsuate 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.

CONCLUSIONS
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.

*Robert C Martin is a consultant for AngioDynamics. All other authors have nothing to declare. Partial support of the Soft Tissue Ablation Registry has come from an unrestricted educational grant from AngioDynamics.

The link to the article on PubMed at http://www.ncbi.nlm.nih.gov/pubmed/25239345
Irreversible Electroporation of Locally Advanced Pancreatic Head Adenocarcinoma

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ABSTRACT
Irreversible electroporation of locally advanced pancreatic adenocarcinoma has been used to palliate appropriate patients with locally advanced pancreatic adenocarcinoma. The setting was at a university tertiary care center. Subjects are patients with locally advanced pancreatic adenocarcinoma who have undergone appropriate induction chemotherapy for at least 3 to 4 months in duration. Technique of open irreversible electroporation of locally advanced pancreatic adenocarcinoma is described. The technique of open irreversible electroporation with continuous intraoperative ultrasound imaging and consideration of intraoperative navigational system is described. Irreversible electroporation of locally advanced pancreatic adenocarcinoma is feasible for locally advanced unresectable pancreatic cancer.

*Robert C Martin is a consultant for AngioDynamics.

The link to the article on PubMed at http://www.ncbi.nlm.nih.gov/pubmed/23929188
Irreversible Electroporation in Locally Advanced Pancreatic Cancer: Potential Improved Overall Survival.

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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.

*Robert CG Martin is a consultant for AngioDynamics. All other authors have nothing to declare. Partial support of the Soft Tissue Ablation Registry has come from an unrestricted educational grant from AngioDynamics.

The link to the article on PubMed at http://www.ncbi.nlm.nih.gov/pubmed/23128941
Evaluation of Thermal Injury to Liver, Pancreas and Kidney During Irreversible Electroporation in an In Vivo Experimental Model

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BACKGROUND
Irreversible electroporation (IRE) is a new technique for tumour cell ablation that is reported to involve non-thermal-based energy using high voltage at short microsecond pulse lengths. In vivo assessment of the thermal energy generated during IRE has not been performed. Thermal injury can be predicted using a critical temperature model. The aim of this study was to assess the potential for thermal injury during IRE in an in vivo porcine model.

METHODS
In vivo continuous temperature assessments of 86 different IRE procedures were performed on porcine liver, pancreas, kidney and retroperitoneal tissue. Tissue temperature was measured continuously throughout IRE by means of two thermocouples placed at set distances (0.5 cm or less, and 1 cm) from the IRE probes within the treatment field. Thermal injury was defined as a tissue temperature of 54°C lasting at least 10 s. Tissue type, pulse length, probe exposure length, number of probes and retreatment were evaluated for associations with thermal injury. In addition, IRE ablation was performed with metal clips or metal stents within the ablation field to determine their effect on thermal injury.

RESULTS
An increase in tissue temperature above the animals’ baseline temperature (median 36.0°C) was generated during IRE in all tissues studied, with the greatest increase found at the thermocouple placed within 0.5 cm in all instances. On univariable and multivariable analysis, ablation in kidney tissue (maximum temperature 62.8°C), ablation with a pulse length setting of 100 μs (maximum 54.7°C), probe exposure of at least 3.0 cm (maximum 52.0°C) and ablation with metal within the ablation field (maximum 65.3°C) were all associated with a significant risk of thermal injury.

CONCLUSIONS
IRE can generate thermal energy, and even thermal injury, based on tissue type, probe exposure lengths, pulse lengths and proximity to metal. Awareness of probe placement regarding proximity to critical structures as well as probe exposure length and pulse length are necessary to ensure safety and prevent thermal injury. A probe exposure of 2.5 cm or less for liver IRE, and 1.5 cm or less for pancreas, with maximum pulse length of 90 μs will result in safe and non-thermal energy delivery with spacing of 1.5–2.3 cm between probe pairs.

*R.C.G.M. is a consultant for AngioDynamics. The authors declare no other conflict of interest.

Evaluation of Resistance as a Measure of Successful Tumor Ablation During Irreversible Electroporation of the Pancreas

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BACKGROUND
Intraoperative evaluation of successful pancreatic tumor ablation using irreversible electroporation (IRE) is difficult secondary to lack of visual confirmation. The IRE generator provides feedback by reporting current (amperage), which can be used to calculate changes in tumor tissue resistance. The purpose of the study was to determine if resistance can be used to predict successful tumor ablation during IRE for pancreatic cancers.

STUDY DESIGN
All patients undergoing pancreatic IRE from March 2010 to December 2012 were evaluated using a prospective database. Intraoperative information, including change in tumor resistance during ablation and slope of the resistance curve, were used to evaluate effectiveness of tumor ablation in terms of local failure or recurrence (LFR) and disease-free survival (DFS).

RESULTS
A total of 65 patients underwent IRE for locally advanced pancreatic cancer. Median follow-up was 23 months. Local failure or recurrence was seen in 17 patients at 3, 6, or 9 months post IRE. Change in tumor tissue resistance and the slope of the resistance curve were both significant in predicting LFR (p = 0.02 and p = 0.01, respectively). The median local disease-free survival was 5.5 months in patients who had recurrence compared with 12.6 months in patients who did not recur (p = 0.03). Neither mean change in tumor tissue resistance nor the slope of the resistance curve significantly predicted overall DFS.

CONCLUSIONS
Mean change in tumor tissue resistance and the slope of the resistance curve could be used intraoperatively to assess successful tumor ablation during IRE. Larger sample size and longer follow-up are needed to determine if these parameters can be used to predict DFS.

* Dr Martin received an unrestricted education grant from AngioDynamics; the company had no access or ability to review or influence any of the data presented here. All other authors had nothing to disclose.

Link to the article at http://www.journalacs.org/article/S1072-7515%2813%2901173-3/abstract
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