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. (J Am Coll Surg 2014;218:179−187. © 2014 by the American College of Surgeons)

Electroporation is a phenomenon in which the cell membrane permeability to ions and macromolecules is increased by exposing the cell to short (microseconds to milliseconds) high-electric-field pulses.[1] The permeabilization can be temporary (reversible electroporation) or permanent (irreversible electroporation) as a function of the electric field magnitude (voltage) and duration (pulse length), period, and number of pulses. Both reversible and irreversible electroporation have been demonstrated to have important applications in biotechnology and medicine.[2] Reversible electroporation is now commonly used with microorganisms and cells in culture for transfection or for introduction or removal of macromolecules from individual cells.

Irreversible electroporation has historically been used for sterilization of liquid media from microorganisms. During the last 2 decades, reversible electroporation has started to be used in living tissues for in vivo gene therapy (electrogenetherapy)[3,4] and to enhance the penetration of anticancer drugs into undesirable cells (electrochemotherapy, ECT).[5] Recently, we and other authors have reported on the use of irreversible electroporation in the treatment of locally advanced pancreatic cancer.[6-8]

True in vivo electroporation efficacy depends on too many factors to be reliably applied in an open-loop procedure.[9,10] Real-time feedback from the outcome of the applied pulse or pulses is a requirement if it is desired to obtain complete IRE by means of the magnitude of

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Abbreviations and Acronyms
DFS = disease-free survival
IRE = irreversible electroporation
LAP = locally advanced pancreatic cancer
LFR = local failure or recurrence
RR = relative risk

energy delivered and/or the number or duration of the pulses.[11,12]

A set of possible methods for assessing the effects of electroporation could be based on measurements of the passive electrical properties of the electroporation-affected cells or tissues.[10,13-16] As a matter of fact, the electroporation phenomenon was first described in electrical terms.[17,18] Measuring changes in electrical properties of cells has been proposed for determining the effectiveness of electroporation protocols in individual cells and in cell cultures.[10,12] Similarly, changes in electrical properties were proposed for detecting electroporation in tissues,[19] including creation of images of the electroporated tissue volumes by means of electrical impedance tomography.[20]

This study is part of a comprehensive effort to obtain definitive IRE endpoints at the time of energy delivery to better enhance efficacy and maintain safety through fully characterizing the changes in electrical properties of tissues with reversible and irreversible electroporation.

In another previous study,[21] the efficiency of different electroporation protocols for ablating tumors by IRE was assessed. Here we have used some of those protocols and we have compared the results in terms of impedance properties and of tissue damage.

METHODS

A prospective evaluation of patients undergoing irreversible electroporation for locally advanced pancreatic cancer (LAP) from December 2009 to November 2012 was performed, using an IRB-approved prospective data entry of a soft tissue ablation registry (http://www.ablationregistry.com) for patients treated with either an open surgical technique[22] or a percutaneous approach.[23,24] Locally advanced pancreatic cancer was defined as per the 7th edition of the American Joint Committee on Cancer (AJCC) staging system for pancreatic cancer, described as arterial encasement of either the celiac axis or the superior mesenteric artery, or both.[25,26] Irreversible electroporation was not used on patients with borderline resectable lesions.

We compared intraprocedural IRE therapy in patients who developed a local failure or electroporation failure or local recurrence against those patients who did not develop recurrence after each patient's data were entered prospectively at the time of initial IRE evaluation and IRE treatment. Local failure or electroporation failure was defined as the ability to bracket the entire tumor with appropriate needles and deliver at least 90 pulses to the target lesions and without 3-month imaging confirmation of ablation success. Local recurrence was defined as above, but with 3-month confirmation and then subsequent recurrence of the target lesion.

Comparisons were made between the groups in terms of patient demographics, short-term outcomes, and overall (OS) and disease-free (DFS) survivals. Baseline comorbidities were assessed using the Charlson Comorbidity Index. Surgical complications were graded according to our standard scale, which has been previously published.[27,28]

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

Surgical and percutaneous electroporation technique

The surgical decision making has been described previously,[27] but in short, the ultimate 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.[27] The technique for IRE alone has been recently published describing needle placement and IRE energy delivery.[22] The surgical technique was carried out as described by Martin and colleagues[27] for pancreatic head lesions and by Makary and associates[29] 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.

The percutaneous IRE approach to LAP was up to the treating physician and the multidisciplinary team to which the patient was referred for evaluation. The percutaneous IRE approach for LAP has been extensively described by both Bagla and colleagues[24] and Narayanan and associates.[23] However, in short, using general anesthesia commonly 2 to 3 15-cm monopolar probes in 2 separate sessions is one of the established techniques to avoid using more than 4 probes. The probes are commonly placed into the central and lateral aspect of the tumor under ultrasound guidance in a square configuration, with average probe spacing of 1.8 cm.[24] Computed tomography imaging with contrast medium was performed to evaluate needle position relative to vessels and measure interprobe distance. All probes had 1 to 1.5 cm of electrode exposure, and in certain instances, 1 or more probes may have had to be placed by using a