Intra-operative navigation of a 3-dimensional needle localization system for precision of irreversible electroporation needles in locally advanced pancreatic cancer

L. Bond a, B. Schulz b, T. VanMeter b, R.C.G. Martin II a,*

a Division of Surgical Oncology, Department of Surgery and James Graham Brown Cancer Center, University of Louisville School of Medicine, 315 East Broadway − Rm 311, Louisville, KY 40202, USA
b Department of Radiology, University of Louisville School of Medicine, 530 South Jackson Street, CCB-C07, Louisville, KY 40202, USA

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Abstract

Introduction: Irreversible electroporation (IRE) uses multiple needles and a series of electrical pulses to create pores in cell membranes and cause cell apoptosis. One of the demands of IRE is the precise needle spacing required. Two-dimensional intraoperative ultrasound (2-D iUS) is currently used to measure inter-needle distances but requires significant expertise. This study evaluates the potential of three-dimensional (3-D) image guidance for placing IRE needles and calculating needle spacing.

 Patients and methods: A prospective clinical evaluation of a 3-D needle localization system (Explorer™/C212) was evaluated in consecutive patients from April 2012 through June 2013 for unresectable pancreatic adenocarcinoma. 3-D reconstructions of patients’ anatomy were generated from preoperative CT images, which were aligned to the intraoperative space.

 Results: Thirty consecutive patients with locally advanced pancreatic cancer were treated with IRE. The needle localization system setup added an average of 6.5 min to each procedure. The 3-D needle localization system increased surgeon confidence and ultimately reduced needle placement time.

 Conclusion: IRE treatment efficacy is highly dependent on accurate needle spacing. The needle localization system evaluated in this study aims to mitigate these issues by providing the surgeon with additional visualization and data in 3-D. The Explorer™ system provides valuable guidance information and inter-needle distance calculations.

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Introduction

Irreversible electroporation (IRE) is a nonthermal, focal ablation technique that has shown tremendous promise as an effective cancer therapy. Reversible electroporation has long been used as a technique for electotransfection of genetic material or intracellular drug delivery.1 When the energy of the pulses is increased above a certain electric field threshold, the permeabilization becomes irreversible, resulting in apoptosis. The safety and efficacy of IRE has been demonstrated in multiple animal models.2–4 Similarly, early efficacy and safety has been demonstrated in the use of IRE in the treatment of locally advanced pancreatic cancer (LAPC).5,6 However, significant hurdles and limitations remain with the use of IRE not just in LAPC, but in other locally advanced soft tissues. The two most challenging hurdles are the requirement of placing multiple needles (commonly 4) in a bracketing fashion in perfect parallel and with precise spacing (no closer than 1.5 cm and no farther than 2.3 cm apart). These two technical challenges have been responsible for incomplete IRE, local failures, and local recurrences.7–9
These two hurdles—i.e., image accuracy of needle placement and needle spacing—could be addressed with the advent of real-time intraoperative image-guided surgery (IGS). Most IGS has been performed and published within hepatic resection and hepatic ablations. IGS has been utilized in pancreatic surgery; however, no one has utilized this technology for pancreatic ablations. The requirement of any type of IGS system is to utilize high quality preoperative medical images that are appropriate for slice thickness and contrast timing, which are then registered during the operation with 4 intraoperative landmarks (e.g., portal vein, biliary bifurcation, etc.). These landmarks must be distinct and the location accurate in order to provide a 3-D image of the organ of interest. Certain IGS systems allow for the interactive use of the preoperative images to enhance ultrasound localization and targeting.

Thus the aim of this study was to evaluate the use of one of the commercially available IGS units intraoperatively. The goal of this study was to evaluate the feasibility of this intraoperative navigation system and assess if it provided clinically valuable information in the guidance of precise placement of IRE ablation needles.

**Patients and methods**

The study protocol was approved by the University of Louisville Institutional Review Board, and all patients were provided with written, informed consent forms. Our study consisted of a prospective clinical evaluation of 3-D needle localization using a 3-D intraoperative navigation system. This was evaluated in 30 consecutive patients with unresectable pancreatic adenocarcinoma who underwent IRE from April 2012 through June 2013. Data was compared to that of patients treated without the use of 3-D localization. The electroporation system we used was the Angiodynamics NanoKnife irreversible electroporation system (IRE). Preoperative thin-cut, 3-phase, multislice CT scans (pancreas protocol) were obtained as part of the workup and staging protocol in patients with a planned IRE procedure.

Localization and visualization of the pancreas via the 3-D intraoperative navigation system utilizes preoperative imaging with acquired data corresponding to the geometry and anatomy of the area in question. The 3-D image of the patient’s anatomy is then matched with the actual anatomy. The user then identifies tumors and adjacent anatomy on the preoperative scan and their locations are inserted into the 3-D model using the Pathfinder planning software (Scout™ Pathfinder Technologies, Nashville, TN). The processed begins with first obtaining a high quality (defined as thin cut <2 mm triphasic non-contrast, arterial phase, and venous phase) pancreatic protocol CT scan for appropriate staging and tumor localization (Fig. 1). The DICOM images are then uploaded into a either mobile (Laptop version of Scout™) or integrated version of Scout™, where the 3-D reconstruction is performed after identifying key structures (i.e. SMA, SMV, Port Vein, Pancreatic Duct, Pancreatic tumor itself, etc…) Critical to the optimization of this 3-D structure is the quality of the CT scan. The 3-D processed images are then reviewed for clinical accuracy prior to the operation. Once confirmed these processed images are uploaded into a commercially available navigation system (Explorer™, Pathfinder Technologies, Inc., Nashville TN) that is the working system in the OR. Intraoperative surface and anatomical features at different anterior-posterior and cranial-caudal depths (at least 4 to 5) are acquired by manually touching the regions/organ of interest in the patient using an optically tracked probe (Fig. 1) and mark it on the 3-D reconstructed image to establish accurate orientation. Once the desired anatomical features are identified by the user, the Explorer™ device then registers the image for intraoperative use by the surgeon.

The registration accuracy is then calculated an confirmed while using a optically tracked Ultrasound probe and a optically tracked IRE needle. Once these were confirmed to be within 10–12 mm or less of target structures, needle placement was then begun. The IRE needles were placed using both the navigation and US simultaneously.

Inter-needle measurements were taken via intraoperative ultrasound (iUS), which is considered the standard, and compared to the measurement obtained using the Explorer 3-D navigation system. At the completion of each case the surgeon filled out a questionnaire related to the use of the navigation system.

**Literature review**

A literature review was completed after electronic searches were performed using PubMed and EMBASE electronic databases. The search was restricted to studies in English using a human model. The keywords used to search the database were navigation, pancreas/pancreatic, intraoperative and augmented reality. The references used in the studies that were identified were also reviewed.

To be included, studies had to be specifically about navigation surgery techniques involving the pancreas. Additionally, studies had to be from within the past seven years and contain data about patients involved in the study. Duplicate articles were excluded.

The full text articles that met criteria were reviewed, with a focus on the type of navigation system and how it was used intraoperatively, the outcomes noted in each study and the limitations and conclusions found in each study. These points of interest were compiled in a table for simple and quick comparison between articles.

A quality assessment of each article was performed using the Newcastle–Ottawa scale. A score from 0 to 9 is given to the articles based on the selection, comparability and outcome of group(s) involved in the study. A higher
score on the Newcastle—Ottawa scale indicates a higher quality study.

Results

Thirty consecutive patients (15 with 3-D localization and 15 controls) with locally advanced pancreatic cancer were treated with IRE. Both groups were similar in demographics and consisted of 18 males and 12 females.

The results of our study showed that between the groups that used iUS alone or iUS with the 3-D navigation system, the patients were similar for time (i.e. diagnosis to treatment) and type of procedures with IRE. The number of probes was also similar between the groups. However, needle placement time was decreased from 20 to 11 min in the intraoperative navigation group, resulting in an overall shorter operative time by 5 min, as shown in Table 1.

Needle localization error is the millimeter difference between inter-needle measurements obtained via iUS and the intraoperative navigation system. The system averaged a 3.4-mm error per needle pair relative to distances measured by iUS, as indicated in Table 2.

Based on the post-procedure questionnaire, the needle localization system increased surgeon confidence in properly placing the needles and performing the ablation in over 50% of procedures and was felt to reduce needle placement time in 60% of procedures when compared to procedures without 3-D reconstruction, as shown in Table 3. The use of the coronal and axial 3-D models lead to the greatest confidence of needle placement, and enhanced needle safety and accuracy with IRE, according to the surgeons’ questionnaire responses.

Literature related to the use of IGS in the abdomen, specifically the pancreas, was reviewed. Using PubMed and EMBASE databases, seven articles were found with information pertinent to our study. These articles were scored using the Newcastle—Ottawa scale, which gives a publication a score of 0—9 that indicates the quality of the study based on the information included in the study. The median score of these seven articles was 7.14. The primary difference found between these studies was whether or not the

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<th>Comparison of IRE procedures using different navigation techniques for needle placement.</th>
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<td>IRE with iUS alone (N = 15)</td>
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<td>Time from diagnosis to IRE (median)</td>
<td>4.5 months (Range 4—11)</td>
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<td>Additional procedures</td>
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<td>Cholecystectomy</td>
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<td>Jejunal tube placement</td>
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<td>Number of IRE probes (median)</td>
<td>3 (range 3—6)</td>
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<td>Success of IRE delivery</td>
<td>100%</td>
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<td>Total needle placement time</td>
<td>20 min (range 10—33)</td>
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<td>Total IRE delivery time</td>
<td>55 min (range 40—110)</td>
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<td>Total procedure time</td>
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study included information on patient outcome or follow up. Those that did not include this information received a score of 6 and those that did receive a score of 8 (Table 4).

**Discussion**

An IRE procedure uses electrodes to target the delivery of millisecond electrical pulses in a series of short-duration, high-intensity electric pulses through tissue. These pulses cause irreversible structural changes to cell membranes that cause cell apoptosis, differentiating IRE from thermal ablation techniques. This non-thermal technique prevents damage to vital surrounding structures such as nerves and blood vessels while still causing target tissue cell death, which allows for intervention on tumors previously deemed inoperable.

3-D images can be used intraoperatively to improve surgical precision, carry out the preoperative plan accurately, and potentially avoid vital structures. 3-D images of the vascular architecture can be obtained from multislice CT using imaging software that converts 2-D images to 3-D. These images can then be viewed in three different ways intraoperatively: by superimposing the images directly onto the surgical field with a projector beam, by using video assistance where the images are displayed on a monitor for the surgeon to view, or by utilizing a transparent monitor displaying the images between the surgical field and the surgeon’s line of sight. The image must then be matched with the position of the patients’ actual anatomy, a process called registration. This can be done by paired-point matching of anatomical landmarks on the image and on the patient. Fiducials are also used for identification of anatomical landmarks on imaging, which can also be helpful in the registration process. These are markers that are placed in the area of a tumor or lesion and aid in better defining the affected area with millimeter precision. This makes it possible to visualize vasculature and surrounding ductal systems at all angles (Fig. 2).

Building on this technology of 3-D imaging was the development of 3-D image-guidance systems. These systems track instruments intraoperatively and display their positions on the 3-D virtual organ models created from the preoperative imaging. The Explorer intraoperative navigation system is a “GPS” device for the surgeon that fuses preoperative diagnostic images, three-dimensional models of the organ and vessels constructed from preoperative images, and intraoperative ultrasound images of real-time needle positions. Using principles of image registration, this device allows for needle positions identified on 2-D ultrasound images to be transformed to preoperative diagnostic images and 3-D models, thereby allowing for the inter-needle distances to be calculated (Fig. 3).

Pancreatic resections and ablations can be challenging due to the complex and variable anatomy of the pancreas. Surgical imaging by CT scan or MRI helps to delineate the anatomy. Intraoperative ultrasound is also of benefit; however, the images have their limitations. These are primarily dictated based on the quality of the US that is being used in the operative room. There remains a wide range in operative US image quality based on lack of knowledge and lack of device upgrades. Similarly, US training still remains fragmented and lacks standardization among the surgical training associations. Since iUS of the pancreas is not commonly done, the use of this navigation platform in conjunction with it also has the potential to significantly shorten its learning curve. We believe the most important advantage to using an intraoperative navigational system for ablations that require 2 or more needles is the confidence it gives the surgeon in needle spacing and placement. This is especially true when dealing with a stage III pancreatic tumor, which commonly has ill-defined borders and lies in close proximity to vital structures. After each needle is placed, the 3-D model can then be manipulated to determine the trajectory of the next needle. In cases where 4–6 needles are used it is difficult to find a plane on ultrasound where all the needle tips are visible, in order to obtain the final needle spacing measurement. In these cases, the 3-D model becomes even more valuable because it allows the surgeon to verify the distances and make the necessary adjustments, avoiding over or under ablating the tumor.

Image-guided surgery (IGS) provides a 3-D image by using preoperative medical images that are registered to intraoperative landmarks. These images can then be used to precisely identify anatomical landmarks around the pancreas that would otherwise be more difficult and/or time consuming to identify with iUS alone. Thus, IGS allows the surgeon to identify patients’ anatomy quickly...
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<th>Author and year</th>
<th>Type of navigation</th>
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<td>Okamoto et al., 2015</td>
<td>Augmented reality (AR) based navigation system with image overlay display</td>
<td>CT images used to construct a 3-D model which was superimposed on the surgical field</td>
<td>Pancreas</td>
<td>No significant difference in operating time or intraoperative blood loss compared to conventional procedure</td>
<td>The position of each organ in the image created on the surgical field was nearly identical to the actual position of the organ</td>
<td>Registration accuracy, portability and cost</td>
<td>AR based navigation contributed to accurate and effective pancreatectomy, may improve surgical quality, training and education</td>
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<tr>
<td>Okamoto et al., 2015</td>
<td>Augmented reality (AR) based navigation system with image overlay display</td>
<td>Multi-detector CT, reconstructed in 3-D using imaging software which are then viewed on a monitor by the surgeon intra-op</td>
<td>Pancreas</td>
<td>Organ identification and overlay precise to 6.8 mm</td>
<td>The usage of AR based navigation in GI surgery is a topic that needs further testing</td>
<td>Organ deformity, evaluation of utility, portability, cost, time consumption</td>
<td>Can be used as an effective teaching tool, allows for quick identification of structures</td>
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<td>Onda et al., 2014</td>
<td>Augmented reality (AR) based navigation system with image overlay display</td>
<td>Multi-detector CT, reconstructed in 3-D using software suite analyze and displayed on a 3-D monitor intra-op</td>
<td>Pancreas</td>
<td>No significant difference in operating time or intraoperative blood loss between group A who underwent identification of IPDA using AR, group B who underwent early ligation of IPDA without AR, group C who underwent conventional PD</td>
<td>No complications secondary to the navigation system were identified</td>
<td>Limited views of the images, lack of tactile images</td>
<td>Provides precise anatomical information, allows for rapid identification of structures by the surgeon</td>
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<td>Onda et al., 2013</td>
<td>Augmented reality based navigation system using a short rigid scope and stereo-scope</td>
<td>Multi-detector CT reconstructed to overlay images in operative field after paired-point registration</td>
<td>Pancreas</td>
<td>No significant difference in operating time or intraoperative blood loss between cases where short rigid scope is used vs stereo-scope</td>
<td>No complications secondary to the navigation system were identified</td>
<td>Organ shift and deformation</td>
<td>Short rigid scope and stereo-scope suitable for abdominal surgery, system may improve safety, accuracy and efficiency of operations, AR can enhance the ability to safely perform resection during PD</td>
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<td>Marzano et al., 2013</td>
<td>Augmented reality (AR) based navigation system with image overlay display</td>
<td>CT; 3-D model created using software VR-RENDER, IRCAD; superimposed on operative field using Exoscope</td>
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<td>No complications secondary to the navigation system were identified</td>
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<td>AR can enhance the ability to safely perform resection during PD</td>
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<td>Volonte et al., 2011</td>
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<td>AR can reduce intraoperative risks and complications</td>
<td>Organ shift</td>
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and accurately, which can lead to an overall safer procedure. Additionally, studies have been performed using IGS for pancreaticoduodenectomy and distal pancreatectomy, and in these cases, there was no significant difference in operative time or intra-operative blood loss observed in IGS versus conventional surgical technique. These studies also concluded that there were no patient complications secondary to the IGS system itself and that IGS could possibly reduce operative risk. The position of the 3-D model in relation to the patients’ actual anatomy was shown to be nearly identical.
One of the largest obstacles in image-guided surgery is registration. This is demonstrated in Table 2 with an average of 10 mm. When working with IRE probe exposures of 10 mm this can/could lead to ineffective therapy. The current accuracy of optical probe tracking is limited and can be significantly enhanced with the addition of electromagnetic tracking at the probe tip. Currently, there are no navigation systems that merge both of these tracking techniques, and thus this still remains a limitation for wide spread adoption. Additionally, the cost of the software and equipment necessary to construct a 3-D model of patient anatomy can be another obstacle that the surgeon must overcome. This emphasizes that there remains a learning curve with this type of navigation system of at least 4—5 cases, before it can be both optimized for image accuracy and registration efficiency.

Conclusion

IRE needle placement is technically demanding, requiring comprehensive understanding of both IRE technology and advanced iUS techniques. Further, IRE treatment efficacy is highly dependent on accurate needle spacing. The needle localization system evaluated in this study aims to mitigate these issues by providing the surgeon with additional visualization and data in three dimensions. The use of this navigation system does require additional set up time; however, total operative times were slightly less due to the shorter time required for needle placement.

Conflict of interest statement

Dr. Martin is a paid consultant for Angiodynamics. All other authors have nothing to declare.

References