HOW I DO IT

Irreversible Electroporation in Locally Advanced Pancreatic Cancer: A Call for Standardization of Energy Delivery

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Irreversible Electroporation (IRE) is used to treat locally advanced cancers, commonly of the pancreas, liver, kidney, and other soft tissues. Precise eligibility for IRE should be established in each individual patient by a multidisciplinary team based on comprehensive clinical, imaging, and laboratory assessment. Standardization of IRE technique and protocols is expected to improve safety, lead to reproducible outcomes, and facilitate further research into IRE. The present article provides a set of technical recommendations for the use of IRE in the treatment of locally advanced pancreatic cancer.
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KEY WORDS: pancreatic cancer; irreversible electroporation; technique

INTRODUCTION

Pancreatic cancer is an overwhelming disease that is the fourth leading cause of cancer deaths in the U.S. with a 5-year survival rate below 5%. Although surgical resection offers the best chance at improved survival, less than 20% of pancreatic cancers are resectable. The primary goals when treating this malignancy through any modality are palliation of pain and improved overall survival.

Chemotherapy-based treatments have demonstrated minimal benefit in regards to improvement of quality of life measures as well as overall survival [1]. Local ablative therapies primarily consisting of alcohol injection and radiation therapy have demonstrated improved response rates when compared to chemotherapy-based treatments in some studies, but this had not been reproduced in larger trials [2,3]. Locally ablative therapy with radiofrequency ablation in cases of unresectable disease has been performed, but this technique is restricted by the potential of thermal injury to neighboring vital structures [4].

In contrast to radiofrequency ablation, Irreversible electroporation (IRE) is a technology that utilizes high voltage pulses to create permanent nanopores in the cell membrane, which in turn induces apoptosis of targeted cells [5–8]. Because of IRE's non-thermal mechanism of action, it can be used to target malignancies adjacent to vital structures [6].

IRE is therefore regarded as an attractive treatment option for locally advanced pancreatic cancer, which remain surgically unresectable even after neoadjuvant chemo(radio)therapy, most commonly due to their extensive involvement of vital structures. Unfortunately, there are currently no standardized IRE techniques and protocols, leading to a large variance in the number of probes used, number of pulses, pulse length, and probe exposure. This lack of standardization might negatively affect treatment efficacy, patient safety and hamper further research (Table I). We aim to propose a gold standard for IRE energy delivery that will streamline and standardize IRE use specifically for treatment of locally advanced pancreatic cancer.

Manuscripts detailing IRE delivery demonstrate a lack of standardization in IRE use; most commonly varying number of probes, varying number of pulses delivered, and varying pulse length were seen. Our literature review demonstrated that in just a few studies, the median number of probes used during IRE treatment ranged from two to six probes, with many studies failing to report how many probes were used. This inadequate delivery of energy may lead to incomplete ablation or a zone of reversible electroporation of tumor which has been shown to increase tumor growth rates [9,10]. Our literature review demonstrated that in just a small sample size, there was great variation in probe spacing and its varied reporting by study author. The maximum interprobe spacing used in most studies was 2.0 cm [1,11–18]; however, there were some studies that used as much as a 2.2 cm maximum distance [19–22] and even one group which reported a maximum interprobe distance of 2.9 cm [23]. In addition to these variations, there were two groups that did not report maximum interprobe distance at all [24,25].

Conflicts of interest: Dr. Martin is a paid consultant for Angiodynamics.

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TABLE I. Current Reports on the Use of IRE in the Treatment of Locally Advanced Pancreatic Cancer

Author, year	# Pt	Median energy delivery time (mins)	Voltage setting (V/cm)	Max voltage (V)	Min voltage (V)	Max spacing (cm)	Average spacing (cm)	Min spacing (cm)	Number of pulses (tissue conductivity test)	Median number of pulses (treatment)	Pulse Length (μsec)	Max probe exposure (cm)	Min probe exposure (cm)	Ablation overlap (cm)	IRE endpoint reported
Martin, 2012	27	N/A	1,500	3,000	2,000	2.0	N/A	1.5	10	90	100	N/A	N/A	N/A	90 pulses
Bagla, 2012	1	N/A	N/A	N/A	N/A	N/A	1.8	N/A	N/A	90	N/A	1	1	1	90 pulses
Narayanan, 2012	14	N/A	N/A	3,000	1,500	2.2	N/A	N/A	N/A	90	70	N/A	N/A	N/A	N/A
Philips, 2013	150	28	N/A	N/A	N/A	1.5	N/A	2.3	N/A	90	20–100	N/A	N/A	N/A	All pulses given
Martin, 2013	54	N/A	1,500	3,000	2,000	2.0	N/A	1.5	10	90	100	N/A	N/A	N/A	90 pulses
Mansson, 2014	5	N/A	1,500	3,000	1,000	2.0	N/A	N/A	N/A	90	70	N/A	N/A	N/A	N/A
Dunki-Jacobs, 2014	65	N/A	1,500	3,000	2,000	2.0	1.8	1.5	10	90	100	1.5	1.0	N/A	N/A
Martin, 2014	107	N/A	1,500	3,000	2,000	2.2	N/A	1.5	10	90	20–100	N/A	N/A	N/A	90 pulses
Kwon, 2014	48	12	N/A	3,000	2,000	2.2	N/A	N/A	N/A	90	N/A	N/A	N/A	N/A	Change in tissue resist
Ierardi, 2014	1	N/A	N/A	N/A	N/A	2.9	1.8	1.3	10	90	N/A	1	1	N/A	N/A
Nielsen, 2014	28	N/A	1,500	N/A	N/A	2.0	2.0	2.0	N/A	90	70	1.5	1.5	N/A	N/A
Narayanan, 2014	101	N/A	N/A	3,000	1,500	2.2	N/A	N/A	N/A	90	N/A	N/A	N/A	N/A	N/A
Paiella, 2015	10	N/A	1,500	N/A	N/A	2.0	N/A	1.0	10	90	70	N/A	N/A	N/A	N/A
Scheffer, 2015	1	N/A	1,500	N/A	N/A	2.0	2.0	2.0	10	80	90	2.0	2.0	N/A	N/A
Trueba-Arguinarena, 2015	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	90	N/A	N/A	N/A	N/A
Belfiore, 2015	20	N/A	1,500	N/A	N/A	2.0	2.0	2.0	10	90	70	1.5	1.5	N/A	N/A
Martin, 2015	200	30.5	1,500	3,000	2,000	2.0	N/A	1.5	10	90	100	2.5	1.0	N/A	Change in tissue resist

Number of pulses delivered was more widely reported with the vast majority of studies using a setting of 90 pulses per treatment cycle, as we would recommend as standard. Despite this almost uniform consensus, there was one manuscript that did not report this data, possibly due to the fact that it was a case report of a specific complication [25].

Pulse length is another objective measure that we believe is critical to ensure uniformity in IRE energy delivery, with our recommended pulse length being 70–90 μsec. Of the 17 manuscripts that we evaluated, four did not report this data [21–24], and six reported using pulse lengths that were outside of the recommended 70–90 μsec range [1,11,13,18,20,26].

Finally, one area of reporting that seems to be severely lacking is a defined "endpoint" for the conclusion of the IRE procedure. Almost all of the studies that we examined declared a defined ablation success rate, but the majority failed to give clear and objective measures of how they defined a successfully completed ablation procedural endpoint [12–17,19,22,23,25]. We found that the studies that did report a defined IRE procedural endpoint most commonly used a completed 90 pulses administered as their endpoint [1,11,20,24]. One study defined ablation endpoint as "all scheduled pulses given" and two authors defined their procedural endpoint as the time when there was a definitive change in tissue resistance as measured by the NanoKnife device [18,21,26].

Just as there are standard doses of chemotherapy or Y-90 for a given treatment regimen, we propose that IRE should be subject to the same standardization in regards to energy delivery if we are to expect uniform results. In order to implement and evaluate IRE outcomes based on these proposed guidelines, it is essential that energy delivery metrics be reported uniformly and completely across studies. Because IRE technology is in its infancy relative to other treatment modalities, it is that much more important that adequate and standardized data is collected and reported regarding its use moving forward.

Expert Panel

Our expert panel was comprised of a group of physicians, all of whom have considerable experience in the field of hepato-pancreato-biliary (HPB) surgery and oncology. The recommendations laid out in this manuscript were collaboratively generated during a meeting held in June 2015.

TECHINCAL RECOMMENDATIONS

Patient Selection

The recently proposed algorithm published by Martin et al. [18] provides an appropriate patient selection in order to establish the acceptable biology and stage of the pancreatic malignancy.

It was agreed upon as reported previously (8–10) that the optimal work-up for patients with locally advanced pancreatic cancer must include a 3-phase CT scan with pancreatic protocol with 2.0 mm cuts or less, or a dynamic MRI with pancreatic protocol at the time of diagnosis, and for all follow-up scans (recommend every 3 months). This is imperative to appropriately diagnose and stage patients with locally advanced pancreatic cancer [27,28]. Laboratory work-up is also performed to ensure appropriate hematologic as well as CA19-9 evaluation. Consideration of a staging/diagnostic laparoscopy can be performed at the time of diagnosis so that peritoneal washings can be obtained in order to rule out small occult metastases that are not present on CT/MRI scan. We recommend the use of induction chemotherapy of either a Gemzar-based or FOLFIRINOX-based chemotherapy based on the patient's age and performance status for at least 3–4 months in duration (total of three cycles of Gemzar-based or four to six cycles of FOLFIRINOX) (10). After induction chemotherapy, repeat high-quality 3-phase CT scan/MRI should be obtained with hematologic and serologic markers to ensure locally advanced non-metastatic pancreatic adenocarcinoma still exists. The key goal of this repeat imaging is to ensure that metastatic disease has not occurred, since it is uncommon for a pancreatic cancer to truly respond to induction therapy (chemotherapy alone or chemo-radiation therapy) based on established response evaluation criteria in solid tumors (RECIST) criteria (i.e., reduction in size of >30% of the longest diameter). As long as the patient has not developed metastatic disease and the maximum axial diameter is not above 4.0 cm after induction therapy, then we would recommend proceeding with IRE therapy. Positron emission tomography (PET) scanning can be used as an adjunctive imaging modality prior to IRE if possible.

Approximately 2–4 weeks after the last dose of chemotherapy, open IRE to the pancreatic tumor primary is performed. Based on each institution's management external beam radiation therapy cancer be considered prior to IRE if indicated by their multi-disciplinary team. Patients with pancreatic head tumors that have undergone biliary stenting with a metal stent, should have the stent removed endoscopically and replaced with a plastic stent before IRE; alternatively, a planned surgical removal with a hepatico-jejunostomy should be considered. The reason for this is that the removal of metal stents is critical to patient outcomes (13) [29]. Given that any type of metal is conductive, it has been demonstrated that metal stents lead to significant deflection of energy, which can lead to incomplete ablation, high current conditions, and possible thermal injury since the degree of deflection is not consistent based on the location of the metal, the probe exposure and the fibrotic nature of the tissue to be electroporated (13). We therefore advocate the use of **covered** metal stents in patients with locally advanced pancreatic cancer primarily based on the longer patency which is needed during induction chemotherapy.

Periprocedural Anesthesia

The anesthetic management during IRE of soft tissue deviates somewhat from standard anesthetic medical therapy in regards to depth of neuromuscular blockade and analgesic management during IRE energy delivery. IRE delivery because of the pulse lengths requires a deeper neuromuscular blockade (defined as zero twitches) to ensure that all retroperitoneal muscle excitation is minimized. A standard inhalational agent can be utilized. Additional analgesia and hypertension control should be considered as critical during the energy delivery phase of an IRE procedure. Consideration of a thoracic epidural with local anesthetic and/or narcotic in conjunction with a continuous infusion of a high-dose short-acting narcotic such as remifentanil (0.7–1 μg/kg/min) has been demonstrated to be effective in these cases [30]. The anesthetic management for IRE of soft tissue deviates from standard anesthetic medical therapy in regards to depth of neuromuscular blockade and analgesic management during IRE energy delivery. However, these minor modifications in anesthesia management allow for a safe and efficient patient procedure.

IRE Probe Placement and Optimal Needle Selection

Abdominal approach. All procedures are performed with general anesthesia through midline incision. A midline (defined as 60% of incision above the umbilicus and 40% below) is preferred so that the IRE needles can be placed on as parallel a plane as possible to the superior mesenteric artery (SMA) or celiac or aorta based on the tumor infiltration. The safest method for IRE needle placement is in a caudal-to-cranial approach, so that needle placement can be tracked with ultrasound throughout needle placement. Any occult solid organ liver metastases as well as peritoneal or mesenteric metastases are ruled out before proceeding with IRE of any pancreatic lesion. We recommend not using this device/procedure for anyone with stage 4 disease as well as any patient who is chemo-naïve who is found at the time of exploration to have locally advanced stage 3 disease. This therapy

should not be used as a bailout for patients under-staged on pre-operative CT who have not undergone any type of induction therapy to ensure that the biology of the disease is better established.

The key to safe and effective IRE is to ensure that the operating physician who is placing the needles be an expert in intra-operative ultrasonography as well as work with the highest quality ultrasonography (US) imaging system, with at least a high-definition screen; harmonic imaging is recommended to gain the highest quality imaging as possible. The easiest and most accurate ultrasound technique is performed with minimal to no dissection prior to ultrasound and to use the ultrasound to image on top of the stomach using a trans-gastric technique with either a thin finger probe or a biplane probe. The reason for this is that the stomach provides the most consistent ultrasound crystal apposition and thus the best image quality and accuracy with the least amount of artifact. Intra-operative ultrasound imaging has become our gold standard for elucidating whether a patient has a true locally advanced tumor or a borderline resectable tumor.

Once local advancement is confirmed, in situ IRE is then planned. Detailed intra-operative ultrasound-based measurements of the tumor and the surrounding structures is then performed in order to obtain axial, anterior/posterior as well cranial/caudal maximum tumor diameters. Vital structures that need to be included in those diameters for appropriate needle placement are also assessed. Based on the maximum axial diameter appropriate needles should bracket the entire tumor and are placed at exactly 2.0–2.7 cm apart so that the entire tumor and an approximate 0.5–1.0 cm margin of normal soft tissue is included in the IRE plane.

This most commonly requires four or five needles in a trans-mesocolon approach, two to three needles posteriorly, the other underneath the superior mesenteric vein (SMV) but to the patient's right of the SMA, and the second to the left of the SMA, and a third to the patients left toward the spleen in a row of three probes. One to two additional probes are then placed in a more anterior approach, most commonly 1.5 cm anteriorly such that a triangle or an oblong square is then obtained. We use spacers at 2.0 cm intervals to build off that initial needle to ensure adequate margin posterior to the SMA and place the needles on either side of the SMA to ensure adequate treatment margin(s). Needles are then placed in order to obtain complete bracketing of the tumor.

The optimal placement of the IRE needles is performed through continuous intra-operative ultrasound from the insertion of the needle into the tissue so that the needle tip is followed at all times during needle placement. The transverse mesentery needle approach, with care not to damage the transverse colon vessels, is easier because it allows normal soft tissue to bracket the pancreatic head tumor as well as to allow for appropriate inferior margin to be obtained during pullbacks of the needle (10). Thus, the transverse mesocolon is grasped and raised anteriorly out of the abdomen by an assistant and then the surgeon's dominant hand directs the needle into the tissue, while her/his non-dominant hand utilizes the ultrasound probe to ensure accurate and appropriate needle placement. It cannot be overemphasized that an atraumatic needle placement should be performed to ensure that the needle does not damage the underlying vital structures, namely the SMV, portal vein, SMA, and hepatic artery. Vascular needle trauma may induce underlying vascular thrombosis, especially given the potential hypercoagulable state in a patient with pancreas cancer. In some instances, the tumor is extending superior above the celiac axis and requires an overlapping IRE to be performed with needles placed through the lesser sac superior to the lesser curve of the stomach.

Care should also be undertaken that the maximum probe/needle exposure to perform safe IRE of the pancreas should be 1.0–1.5 cm because of the significant fibrotic nature of these tumors and a larger needle exposure will not be tolerated by the gland or the underlying soft tissue to be treated (14). It has been previously published that a greater probe exposure leads to high current conditions and the potential for thermal damage if these high current conditions are allowed to persist. Thus, the maximum probe exposure should be 1.5 cm or less (14).

Setup, Troubleshooting, and Technical Considerations

Tissue conductivity test. The initial energy delivery settings for the IRE should start at a probe exposure 1–1.5 cm maximum, 1,500 V/cm with pulse length of 90 μsec per probe pair. It is essential that careful attention to probe placement is achieved. This is to ensure that all probe tips are evenly spaced without any convergence or divergence of the probe tip (Table II). Additionally, if there are intra-procedural adjustments that need to be made by probe pull backs, make sure to recheck probe tip placement again to ensure that they are parallel.

TABLE II. Typical Settings for IRE Use in Locally Advanced Pancreatic Cancer

Probe spacing range typically used	1.5–2.0 cm
Absolute minimum probe spacing typically used	1.0 cm
Absolute maximum probe spacing typically used	2.6 cm
Default system pulse length for pulse delivery	90 μsec
Absolute minimum pulse length typically used	70 μsec
Default number of pulses for pulse delivery	70 pulses
Absolute minimum number of pulses typically delivered for each probe pair during pulse delivery	70 pulses
Number of pulses typically delivered between each probe pair during one round of pulse delivery	90–100 pulses
Maximum number of pulses typically delivered for each probe pair after pulse delivery before pull back	180–270 pulses
Default voltage setting	1,500 V/cm
Voltage setting range typically used	1,400–2,000 V/cm
Default maximum voltage output of system	3,000 V
Initial probe exposure typically used for soft tissue (i.e., Liver, Kidney, Lung)	2.0 cm
Initial probe exposure typically used for highly conductive soft tissue (i.e., pancreas)	1.5 cm
Maximum probe exposure typically used for soft tissue	2.5 cm
Pulse timing setting typically used for lesions outside abdominal or thoracic cavities	90 ppm
Pulse timing setting typically reserved for operational verification testing	240 ppm
Default voltage used for test pulse sequence	400 V
Default number of pulses delivered for each probe pair for "test pulse sequence"	1 pulse
Number of pulses typically delivered across each probe pair when performing "tissue conductivity test"	20 pulses
Current range typically displayed after performing a "tissue conductivity test"	20–35 A
Default maximum current limit of NanoKnife	50 A

"Typical" settings represent procedure settings typically seen in use. Any reference made to "typical" settings above do not guarantee improved, enhanced, or favorable outcomes. It is the sole responsibility of the treating physician to determine appropriate device settings using their best clinical judgment.

Once probes are in desired position, a "tissue conductivity test" needs to be performed using 20 pulses per pair of electrodes. Establishing these initial parameters is accomplished by selecting the "edit" button on the probe placement screen. Once the "number of pulses" has been changed to 20 for all probe pairs, select "apply" to save those changes.

Following the aforementioned changes, navigation of the NanoKnife software and energy delivery is resumed in the standard method to begin the "tissue conductivity test." After completion of the conductivity test, a graph will appear on the "results tab." This graph should be evaluated to ensure that the starting amperage level is within a range of 20–35 A for each probe pair. If the amperage level is outside of this range for any probe pair, adjustments should be made and then retested using the "tissue conductivity test" as stated above.

Troubleshooting low amperage. Following the tissue conductivity test, if the amperage is determined to be below the range of 20–35 A, the following steps are recommended for troubleshooting:

First, confirm that the inter-probe spacing is accurate. Low amperage (<20 A) is commonly due to probe spacing that is too wide (>2.5 cm). Once probe spacing is confirmed and only if the spacing is <2.0 cm, the volts per centimeter can be increased by 200–400 V/cm only for the affected probe pairs that were outside (below) the desired amperage range of 20–35. Increasing the Volts per centimeter can be made in the "parameter table" while in "Edit" mode. Finally, consider increasing the probe exposure by 0.5–1.0 cm, especially if the amperage level is found to be low for multiple probe pairs.

Troubleshooting high amperage. Following the tissue conductivity test, if the amperage is found to be above the range of 20–35 A, the following steps are recommended for troubleshooting:

First, confirm that the inter-probe spacing is accurate. The most common cause for high amperage is that probe spacing is too narrow (<1.0 cm). Once spacing is confirmed, consider reducing probe exposure by 0.5–1.0 cm, especially if the amperage is high for multiple probe pairs, keeping in mind that a probe exposure of less than 1.0 cm is typically not used. Once probe spacing is confirmed and probe exposure is already at the "minimum" of 1.0 cm, the next step is to consider reducing the pulse length from 90 to 70 μm, especially if the current is above 40 A and if there is a sharp rise in the amperage seen across each pulse duration. If the current is between 35 and 40 A, and the probe exposure is set at 1.0 cm, consider reducing the pulse length from 90 to 80 μm, especially if there is a sharp rise in amperage seen across each pulse duration. Finally, consider reducing the Volts per centimeter parameter by 200–400 V/cm for the affected probe pairs. This change can be made in the parameter table while in "edit" mode, understanding that this change will likely reduce the size of the IRE zone that is produced by the affected probe pairs.

General Guidelines

Once the "tissue conductivity test" yields an amperage level within the desired range of 20–35 A for all probe pairs, the "baseline" current should be recorded and then referred to throughout the procedure. The "number of pulses" should then be set to 90–100 pulses for each probe pair before continuing with the procedure, then throughout the duration of the procedure, the "Hint" box should be monitored for "high current" warning messages.

Evaluating Adequate Increase in Current

At the conclusion of each treatment sequence, evaluate the current graph in the "results tab" to ensure that an adequate increase in current of at least 12 A from their starting point occurred for each probe pair. If a probe pair did not experience a current rise of at least 12 A from baseline, consider delivering an additional 90 pulses for that probe pair. The parameter table can be modified to deliver energy only to the desired probe pairs that did not undergo an adequate current rise.

It should be noted that the last two to three probe pairs may not achieve a 12 A rise in current due to treatment overlap, signifying that effective electroporation has already occurred. Tissue property changes during an IRE procedure are dependent on a multitude of factors, and thus the decision to re-administer pulse sequences for the probe pairs in question is made at the discretion of the treating physician. The current belief is that additional pulses beyond 270 between a probe pair for a given area of tissue does not add to the treatment zone.

Treatment Completion

Following completion of the IRE procedure, the physician may reposition the probes to target additional tissue. When deciding to pull back on the treatment probes, the physician should consider both the lesion depth along the probe axis and whether a margin is required. If no additional treatment is necessary, the probes can simply be removed from the patient, thus completing the IRE portion of the procedure.

IRE Treatment Follow-Up

It is common to follow patients with CT scan because of their wider acceptance among insurance companies and lower costs as compared to PET-CT and MRI. An immediate 3-phase CT scan can be obtained in the immediate post-operative period (less than 1 month post-operative) to access the patency of vital structures and to establish a baseline of the post-ablation bed. However, no true ablation efficacy can be confirmed at this immediate CT scan since ongoing electroporation effects (most commonly cellular apoptosis) is seen in this immediate phase. Similarly, a false positive PET scan will be seen during these ongoing effects. Subsequent surveillance studies are usually scheduled at 3-month intervals using the same pancreatic imaging protocol. All CT images should be obtained with a helical scanner before and after a bolus injection of 100 ml of nonionic contrast at an intravenous rate of 3 ml/sec. After contrast injection, two spiral CT scans should be obtained during the arterial phase and portal venous phase at 30 and 70 sec, respectively, after the initiation of the injection. Pre-contrast and arterial phase acquisitions should performed of the upper abdomen to include the pancreas and liver; portal venous phase imaging should include the abdomen and pelvis. Contiguously reconstructed sections should be obtained through the pancreas ($5 \times 5\,mm^2$ for non-contrast and $2 \times 2\,mm^2$ for arterial and venous); coronal reconstructions for each phase should also be performed. It is difficult to cross compare CT scans to MRI or CT scan to PET scan unless there are abnormal signs of recurrence. The ability to evaluate response is also different for other ablation modalities within the liver, kidney, and lung, and thus a modification of these response criteria has been proposed here based on our over than 300 cases performed and followed (Table III).

Thereafter, serial imaging over at least 2–6 months must be employed to detect recurrence by comparing with prior studies in conjunction with clinical and serum studies.

FINAL REMARKS

The technical recommendations reported here are aimed at ensuring a consistent use of IRE in the treatment of locally advanced pancreatic cancer. However, given the many patient- and tumor-related variables that play a role in the decision-making process, this document is intended as a guideline. We fully acknowledge that, given the complexity of the disease, individual patient and tumor characteristics may require a different approach from the one recommended here. Few studies have advocated percutaneous IRE [31,32], although we do not necessarily support this, we do feel that energy delivery should be similar regarding an open or percutaneous approach. For no reason should a clinician adhere to the present technical recommendations if, in his/her opinion, a different

TABLE III. Radiologic Criteria for Pancreatic IRE Assessment

	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
Major criteria (1 sufficient for PD)				
Longest diameter in the axial plane of the soft tissue component of the primary tumor (compared to the 1st fu scan acquired >3 months after treatment)	No residual soft tissue primary tumor AND	Decrease >30% AND	Decrease <30%–increase <20% AND	Increase >20% OR
Metastases (non-nodal)[a] (longest diameter >10 mm)	No	No	No	Yes
Minor criteria (>2 needed for PD in absence of major criteria)				
Vessel narrowing (compared to the 1st fu scan >3 months after treatment; >50% diameter reduction; no thrombosis; major vessels)	No			Yes
New-onset biliary obstruction (compared to the 1st fu scan >3 months after treatment; no biliodigestive anastomosis, biliary stents, or endoprosthesis)	No			Yes
Enlarging area of diffusion restriction on MRI (compared to the 1st fu MRI >3 months after treatment)[b] limited cases, difficult to interpret based on individual MRI scanners/magnet strength and protocol	No			Yes
New lymph nodes >15 mm short-axis diameter or pathology proven (compared to the 1st fu scan >3 months after treatment)[a]	No			Yes
CA 19.9 increase >100% (and >74 U/ml[b]) without signs for pancreatitis or biliary duct obstruction (compared to pre-treatment values)	No			Yes

Local site recurrence is defined as (1) the presence of an increase in the longest diameter in the trans axial plane of the soft tissue component of the primary tumor (compared to the 1st fu scan acquired >3 months after treatment) or (2) >2 of the following criteria: vessel narrowing, biliary obstruction or diffusion restriction or (3) >1 of these criteria plus a CA 19.9 rise.
[a]Unequivocal; all other causes excluded (e.g., inflammation, infection, biliary or pancreatic duct obstruction, perfusion induced attenuation differences).
[b]CA 19.9 rise only significant if latest value is at least 2× the upper limit of normal (2 × 37 U/ml).

approach is required in the individual patient to be treated. Finally, it is imperative that physicians are fully aware of the spectrum of potential adverse events associated with IRE to prevent complications or manage them properly.

AUTHORS' CONTRIBUTIONS

All authors listed above provided substantial contributions to the conception/design of the work, acquisition of the data, analysis and interpretation of data. They all provided support in drafting the work and revising it critically for important intellectual content, and gave final approval of the version to be published. They are all in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Martin RC 2nd, McFarland K, Ellis S, et al.: Irreversible electroporation in locally advanced pancreatic cancer: Potential improved overall survival. Ann Surg Oncol 2013;20:S443–S449.
2. Crane CH, Ellis LM, Abbruzzese JL, et al.: Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capecitabine in locally advanced pancreatic cancer. J Clin Oncol 2006;24:1145–1151.
3. Loehrer PJ, Sr., Feng Y, Cardenes H, et al.: Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: An eastern cooperative oncology group trial. J Clin Oncol 2011;29:4105–4112.
4. Varshney S, Sewkani A, Sharma S, et al.: Radiofrequency ablation of unresectable pancreatic carcinoma: Feasibility, efficacy and safety. JOP 2006;7:74–78.
5. Al-Sakere B, Andre F, Bernat C, et al.: Tumor ablation with irreversible electroporation. PLoS ONE 2007;2:e1135.
6. Edd JF, Horowitz L, Davalos RV, et al.: In vivo results of a new focal tissue ablation technique: Irreversible electroporation. IEEE Trans Biomed Eng 2006;53:1409–1415.
7. Davalos RV, Mir IL, Rubinsky B: Tissue ablation with irreversible electroporation. Ann Biomed Eng 2005;33:223–231.
8. Davalos RV, Otten DM, Mir LM, et al.: Electrical impedance tomography for imaging tissue electroporation. IEEE Trans Biomed Eng 2004;51:761–767.
9. Dunki-Jacobs EM, Philips P, Martin RC 2nd: Evaluation of resistance as a measure of successful tumor ablation during irreversible electroporation of the pancreas. J Am Coll Surg 2014;218:179–187.
10. Philips P, Li Y, Martin RC 2nd: Low-energy DC current ablation in a mouse tumor model. Methods Mol Biol 2014;1121:257–265.
11. Martin RC 2nd, McFarland K, Ellis S, et al.: Irreversible electroporation therapy in the management of locally advanced pancreatic adenocarcinoma. J Am Coll Surg 2012;215:361–369.
12. Mansson C, Bergenfeldt M, Brahmstaedt R, et al.: Safety and preliminary efficacy of ultrasound-guided percutaneous irreversible electroporation for treatment of localized pancreatic cancer. Anticancer Res 2014;34:289–293.
13. Dunki-Jacobs EM, Philips P, Martin RC 2nd: Evaluation of resistance as a measure of successful tumor ablation during irreversible electroporation of the pancreas. J Am Coll Surg 2014;218:179–187.
14. Nielsen K, Scheffer HJ, Vieveen JM, et al.: Anaesthetic management during open and percutaneous irreversible electroporation. Br J Anaesth 2014;113:985–992.
15. Paiella S, Butturini G, Frigerio I, et al.: Safety and feasibility of Irreversible Electroporation (IRE) in patients with locally advanced pancreatic cancer: Results of a prospective study. Dig Surg 2015;32:90–97.
16. Scheffer HJ, Melenhorst MC, Vogel JA, et al.: Percutaneous irreversible electroporation of locally advanced pancreatic carcinoma using the dorsal approach: A case report. Cardiovasc Intervent Radiol 2015;38:760–765.

17. Belfiore MP, Ronza FM, Romano F, et al.: Percutaneous CT-guided irreversible electroporation followed by chemotherapy as a novel neoadjuvant protocol in locally advanced pancreatic cancer: Our preliminary experience. Int J Surg 2015;21:S34–S39.
18. Martin RC 2nd, Kwon D, Chalikonda S, et al.: Treatment of 200 locally advanced (Stage III) pancreatic adenocarcinoma patients with irreversible electroporation: Safety and efficacy. Ann Surg 2015;262:486–494.
19. Narayanan G, Hosein PJ, Arora G, et al.: Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. J Vasc Interv Radiol 2012;23:1613–1621.
20. Martin RC, Philips P, Ellis S, et al.: Irreversible electroporation of unresectable soft tissue tumors with vascular invasion: Effective palliation. BMC Cancer 2014;14:540.
21. Kwon D, McFarland K, Velanovich V, et al.: Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation. Surgery 2014;156: 910–920.
22. Narayanan G, Bhatia S, Echenique A, et al.: Vessel patency post irreversible electroporation. Cardiovasc Intervent Radiol 2014;37: 1523–1529.
23. Ierardi AM, Lucchina N, Duka E, et al.: "Vascular lock" causing splenic perfusion defects during irreversible electroporation of a locally advanced pancreatic tumor. JOP 2014;15:604–608.
24. Bagla S, Papadouris D: Percutaneous irreversible electroporation of surgically unresectable pancreatic cancer: A case report. J Vasc Interv Radiol 2012;23:142–145.
25. Trueba-Arguinarena FJ, de Prado-Otero DS, Poves-Alvarez R: Pancreatic adenocarcinoma treated with irreversible electroporation case report: First experience and outcome. Medicine (Baltimore) 2015;94:e946.
26. Philips P, Hays D, Martin RC: Irreversible electroporation ablation (IRE) of unresectable soft tissue tumors: Learning curve evaluation in the first 150 patients treated. PLoS ONE 2013;8: e76260.
27. Callery MP, Chang KJ, Fishman EK, et al.: Pretreatment assessment of resectable and borderline resectable pancreatic cancer: Expert consensus statement. Ann Surg Oncol 2009;16: 1727–1733.
28. Varadhachary GR, Tamm EP, Abbruzzese JL, et al.: Borderline resectable pancreatic cancer: Definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006;13: 1035–1046.
29. Dunki-Jacobs EM, Philips P, Martin li RC 2nd: Evaluation of thermal injury to liver, pancreas and kidney during irreversible electroporation in an in vivo experimental model. Br J Surg 2014;101:1113–1121.
30. Martin RC, Schwartz E, Adams J, et al.: Intra - operative anesthesia management in patients undergoing surgical irreversible electroporation of the pancreas, liver, kidney, and retroperitoneal tumors. Anesth Pain Med 2015;5:e22786.
31. Bagla S, Papadouris D: Percutaneous irreversible electroporation of surgically unresectable pancreatic cancer: A case report. J Vasc Interv Radiol 2012;23:142–145.
32. Narayanan G, Hosein PJ, Arora G, et al.: Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. J Vasc Interv Radiol 2012;23: 1613–1621.