Safety and Early Efficacy of Irreversible Electroporation for Hepatic Tumors in Proximity to Vital Structures

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Introduction: Irreversible electroporation (IRE) has shown promise for ablation of lesions in proximity to vital structures in the preclinical setting. This study aims to evaluate the safety and efficacy of IRE for hepatic tumors in the clinical setting.

Methods: An IRB approved prospective registry of patients undergoing IRE for hepatic tumors over a 2-year period. Factors analyzed included patient and tumor characteristics, treatment related complications, and local recurrence free survival (LRFS) for ablated lesions. LRFS was calculated according to Kaplan–Meier, with secondary analyses stratified by procedural approach (laparotomy, laparoscopy, and percutaneous) and tumor histology.

Results: There were 44 patients undergoing 48 total IRE procedures, 20 colorectal mets, 14 hepatocellular, and 10 other metastatsis. Initial success was achieved in 46 (100%) treatments. Five patients had 9 adverse events, with all complications resolving within 30 days. LRFS at 3, 6, and 12 months was 97.4%, 94.6%, and 59.5%. There was a trend toward higher recurrence rates for tumors over 4 cm (HR 3.236, 95% CI: 0.585–17.891; $P = 0.178$).

Conclusions: IRE appears to be a safe treatment for hepatic tumors in proximity to vital structures. Further prospective evaluation is needed to determine the optimal effectiveness of IRE in relation to size and technique for IRE of the liver.

KEY WORDS: irreversible electroporation; hepatic metastasis; hepatocellular carcinoma

INTRODUCTION

Complete surgical resection remains the most effective therapy for hepatic malignancy; however, delays in diagnosis or poor underlying liver function mean that the number of patients who are candidates for this potentially curative approach is relatively small. In hepatocellular carcinoma (HCC), for example, only 30–40% of patients are eligible for surgical resection [1]. In light of the limited applicability of surgical resection to many patients with hepatic tumors, a number of ablative technologies have been developed to provide liver directed therapy. Amongst these are radiofrequency ablation (RFA) [2–4], ethanol ablation [5,6], laser ablation [7,8], cryoablation [9], high intensity focused ultrasound (HIFU) [10], microwave ablation [11,12], and stereotactic body radiation therapy [13].

These thermal ablative technologies all rely on transfer of thermal energy to the surrounding tissue for its effect. Similar limitations in relation to size and location have limited the use and effectiveness of these modalities. Studies of livers explanted after RFA have demonstrated that the rate of complete tumor necrosis falls below 50% when there are vessels larger than 3 mm abutting the tumor, a consequence of the heat sink effect [14]. Lesions in a subcapsular location or in close proximity to the gallbladder demonstrate similar difficulty in achieving complete ablation [15,16]. Similar limitations around safety have also been demonstrated with the other thermal modalities in relation to lesions in proximity to vital structures (i.e., major bile ducts, portal vein, and hepatic veins). For patients not candidates for these thermal modalities, three-dimensional conformal radiation therapy has also been utilized [17,18], although the median time to local recurrence with these modalities has been reported as early as 6.8 months [18], with complete response rates in small HCC as low as 44.3% [17].

Irreversible electroporation (IRE) is a promising new technology that may be able to overcome the problem of difficult tumor location faced by current ablative technologies. Rather than relying on thermal energy to induce necrosis, IRE delivers a series of electrical pulses of millisecond duration that create irreversible pores in cell membranes, leading to apoptosis [19,20]. The great promise of IRE is that the extracellular matrix is left unperturbed, thus sparing the structural integrity of surrounding structures such as bile ducts and blood vessels [21]. Preclinical studies have demonstrated the potential efficacy of IRE in ablation of HCC in an animal model [22]. The goal of this study is to present the first large evaluation of IRE for ablation of hepatic tumors in a clinical setting, to evaluation safety and efficacy, as well as to assess lessons learned from this early experience that could serve as selection criteria for future protocolized studies.

METHODS

An IRB approved multi-institutional registry of patients undergoing IRE for hepatic tumors from 2009 through 2011. As this study represents a treatment registry, there was no standardized protocol dictating patient selection criteria, which were left to the discretion of the treating physician. General exclusion criteria, however, would include general unfitness to undergo general anesthesia, extensive extrahepatic disease, or multifocal hepatic disease not amenable to complete ablation.

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Ablation Procedure

IRE was performed using the Angiodynamics Nanoknife system (Angiodynamics, Latham, NY). The Nanoknife system consists of a computer controlled pulse generator that delivers 3,000 V pulses to the IRE probes. Typically, 90 pulses are delivered which last from 20 to 100 μsec each. The most common pulse duration is 100 μsec, although shorter durations may be utilized in cases where high electrical resistance is encountered. The pulse voltages and duration are based on preclinical studies [20,23,24]. Treatment planning is based on preoperative imaging with CT scanning in which the tumor dimensions and morphology are measured. From the preoperative scan, the tumor dimensions are input into the pulse generator, which will calculate the number and spacing of probes needed to create the desired ablation zone based on a computer algorithm. Either a single bipolar, or multiple monopolar probes may be used, with greater numbers of probes needed for larger ablation zones. Probe spacing typically varies from 0.5 to 2 cm apart, with the specific distance determined by computer algorithm as specified above. The probes themselves are 19 gauge diameter and radio-opaque to aid in intraprocedural identification of the probe tip.

The actual IRE procedure itself may be performed either percutaneously or in the operating room at the time of laparotomy or laparoscopy. Percutaneous cases are performed with CT guidance. In all cases, the patient must be under general anesthesia with deep neuromuscular blockade, which requires close collaboration with the anesthesiologist to achieve paralysis to 0 twitches out of a train of 4. This level of paralysis is needed to prevent patient movement when the high voltage pulses are delivered. For procedures performed via laparotomy or laparoscopic, the Pathfinder (Nashville, TN) intraoperative navigation system is used to guide probe placement in order to achieve the ablation zone determined on preoperative planning. The Pathfinder system provides stereotactic guidance in which the position of the probe tip is overlaid on the preoperative images in real time, with additional incorporation of intraoperative ultrasound images. This guidance system allows precision probe placement. The proper distance between probes is measured at the tip, and the probes must be placed within 10° of parallel for irreversible electroporation to occur. Small deviations in probe placement can lead to areas of *reversible* electroporation which are likely to result in tumor recurrence. When multiple probe arrays are utilized, a mechanical guide is employed to maintain proper spacing and alignment. The probes are placed in a manner as to bracket the tumor, rather than violate the tumor itself. The probes must also be completely encased in tissue to prevent arcing.

Delivery of the pulses is synchronized to the patient's ECG, which is an incorporated feature of the Nanoknife pulse generator. The pulses are timed as to be delivered during the absolute myocardial refractory period 50 msec after the R-wave in order to prevent generation of arrhythmias. Because of this synchronization, the patient must have a pulse rate of under 115. Higher pulse rates will cause the pulse generator to believe an arrhythmia is occurring and cease to deliver further pulses. During the procedure, the progress of the ablation is followed by tracking the actual current delivered, which should increase throughout the procedure, as ablated tissue has lower resistance.

Ablation technical success was defined as the ability to successful deliver all planned pulses (at least 90) in accordance with size and dimension of the lesion, as well as on at least 8-week axial scanning to demonstrate a complete ablation without evidence of enhancement. The definition of proximity to major vascular/biliary structures or adjacent organs was defined as <5 mm in distance (Fig. 1). Adverse events were recorded as per the established CTCAE scale version 3.0. All complications were recorded prospectively at all institutions.

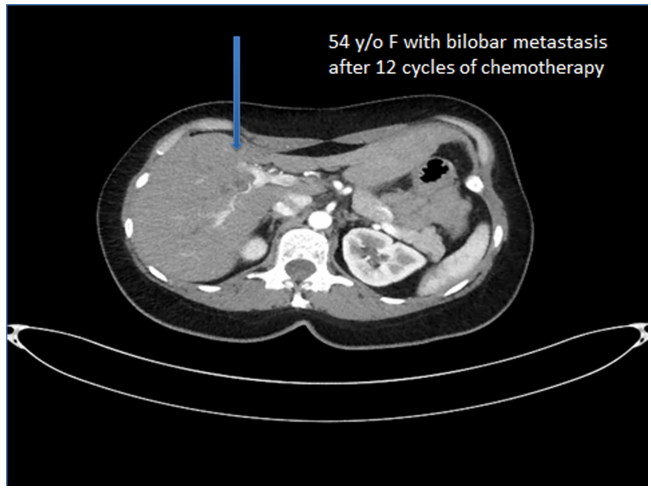

Fig. 1. CT scan demonstrating a colorectal metastasis situated at the bifurcation of the right and anterior and posterior sectoral inflow vessels. This patient had bilobar metastases and underwent left hepatectomy at the time of IRE.

Post-Procedural Followup

Follow up imaging was performed at the time of discharge or with 2 weeks of IRE therapy for safety evaluation and then at 3-month intervals. The initial scan at discharge was primarily for patient safety. Given the experimental nature of IRE, it as of yet unknown whether early complications result from the procedure. Thus, the early scans were obtained to look for complications such as portal vein thrombosis. They were not intended to provide any indication of treatment efficacy. Imaging was ordered by the treating physician and/or the multidisciplinary team caring for the patients. Ablation recurrence was defined as persistent viable tumor as defined by dynamic imaging in comparison to 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. In cases where preoperative PET scan was obtained and the lesion was PET avid, persistent, or recurrent PET avidity was evidence for tumor recurrence. Specific cutoffs for SUV to determine recurrence were not utilized. The use of CT versus MRI imaging for followup was left to the discretion of the treating physician. Radiologic interpretation of recurrence was made by dedicated body-imaging radiologists, who were not blinded to treatment. As noted above, general radiologic criteria for recurrence are new or persistent enhancement on multi-phase imaging such as defined by the RECIST criteria [25].

In addition to imaging, standard tumor markers including CEA for colorectal metastases, AFP for hepatocellular carcinoma, and CA 19-9 were followed where appropriate. Although a diagnosis of recurrence was not made based on tumor markers alone, rising levels would lead to an imaging study. In cases where imaging was equivocal, biopsies were obtained at the discretion of the treating physician.

Statistical Analysis

Patient demographics, tumor characteristics, in hospital outcomes, and local recurrence free survival were examined. Continuous

variables were summarized by median and interquartile range (IQR) and compared using the Wilcoxon–Mann–Whitney test while categorical variables were summarized as count (percentage) and analyzed using the chi-squared or Fisher's exact test, where appropriate. Local recurrence free survival (LRFS) was determined from the time of ablation to radiographic recurrence of the treated lesion. Patients without evidence of recurrence were censored at the time of last followup. Survival estimates were determined according to the method of Kaplan and Meier, with survival curves compared by the log rank test. The relation of target lesion size to LRFS was determined according to Cox proportional hazards regression. To determine whether there was an appropriate cutoff in tumor size related to increased risk of LRFS, plots of martingale residuals versus tumor size were examined as described by Therneau et al. [26]. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), with $P < 0.05$ considered significant.

RESULTS

There were 44 patients undergoing 48 total IRE procedures. The majority (n = 24) of patients were male at a median age of 60 years. Tumors were centrally located in proximity to major vascular/biliary structures or adjacent organs in all 40 (100%) patients. The most frequent diagnosis was colorectal metastasis (45%, n = 20), followed by hepatocellular carcinoma (35%, n = 14). Other hepatic metastases included in Table I include two each of non-small cell lung cancer and breast cancer, three carcinoid/neuroendocrine tumors, one melanoma, one renal cell carcinoma, and one soft tissue tumor. The ablation procedure was most often performed percutaneously (76.5%, n = 39). Technical success was achieved in 48 (100%) procedures. Further description of patients and procedures is outlined in Table I.

The majority of patients (72%) had received and failed at least one other form of therapy prior to being referred for IRE. Details of prior treatments are outlined in Table II. The remaining 12 patients who had not undergone prior therapy included 5 with HCC, 2 with metastatic non-small cell lung cancer, 2 with colorectal metastases, 1 with a carcinoid metastasis, and one with a renal cell carcinoma metastasis. For the patients with colorectal metastases who had been previously treated, all had received chemotherapy, most commonly with FOLFOX (80%). Two patients were continuing to receive chemotherapy concomitant with the IRE procedure, one with 5FU/Avastin/Irinotecan and one with Xeloda/Irinotecan/Erbitux. Ten of CRC patients previously treated had prior liver directed therapy, including three with RFA, four with hepatic resection, three with three-dimensional conformal radiotherapy, and three with hepatic arterial therapy. Some patients were treated with multiple modalities.

TABLE I. Baseline Patient and Tumor Characteristics, Treatment Technique, and Early Success

Age	60 (14)
BMI (kg/m^2)	24.9 (5.2)
Gender	
Male	23 (53%)
Female	21 (47%)
Race	
Caucasian	35 (80%)
African American	6 (13%)
Other/unknown	4 (7%)
Karnofsky score	Median 90 (range: 80–100)
Comorbidities	
Cardiac/peripheral vascular	4 (10%)
Pulmonary	4 (10%)
Diabetes mellitus	4 (10%)
Hypertension	22 (50%)
Chronic hepatitis	8 (20%)
Cirrhosis	6 (15%)
Diagnosis	
Colorectal metastasis	20 (45%)
HCC	14 (32%)
Other metastasis	10 (23%)
Procedural approach	
Percutaneous	28 (63%)
Laparoscopic	2 (5%)
Laparotomy	14 (32%)
Concurrent abdominal procedure performed	7 (16%)
Complete ablation	48 (100%)

Continuous variables are presented as median (interquartile range) and categorical variables as count(percentage).

TABLE II. Prior Treatment Details

Any prior treatment	32 (72%)
Systemic chemotherapy	26 (60%)
Any liver directed therapy	22 (55%)
Hepatic resection	10 (23%)
Radiofrequency ablation	5 (12%)
Hepatic arterial therapy	10 (23%)
Three-dimensional conformal radiation	6 (15%)

For the patients with HCC, the majority (75%, n = 10) were Okuda stage I, while the remaining 25% (n = 4) were Okuda stage II. Hepatic function was Childs–Pugh class A in 9 (75%) patients and class B in the remaining 4 (25%) patients. Half (n = 7) patients had received other therapy prior to IRE. This consisted of liver directed therapy in all cases, while two of the patients also had received systemic therapy. Both patients who had systemic therapy received sorafenib, while one also received additional Avastin/Erlotinib. Liver directed therapies consisted of RFA in two patients, hepatic resection in three, and hepatic arterial therapy in five. As with the CRM group, some patients had undergone multiple prior liver directed therapies. One patient was concurrently receiving Avastin and Erlotinib at the time of the IRE procedure.

The median length of stay following ablation was 1 (0.5) days. Analysis of adverse events within 90 days of the procedure included total of 9 adverse events occurred after 5 (10%) procedures. Two were deemed unrelated to the ablation (leukocytosis, urinary tract infection), four were categorized as indirectly related (dehydration, biliary stent occlusion, cholangitis due to biliary stent occlusion, and acute renal failure), and the remaining three were possibly procedure related (neurogenic bladder, abdominal pain, and flank pain). There were no treatment related deaths. There have been no late occurrences of biliary stricture or portal vein thrombosis.

Tumor size, adverse events, and initial technical success were similar when procedures were stratified by histology (Table III). Overall local recurrence free survival at 3, 6, and 12 months was 97.4%, 94.6%, and 59.5%. In addition to the local recurrences, there were four distant recurrences: two in the lung, one in the peritoneum, and one in the scalp and gluteal soft tissue. There were no significant differences in local recurrence rates when patients were stratified by tumor histology or whether IRE was performed via surgical or percutaneous technique (Table IV). The overall local recurrence free survival at 3, 6, and 12 months for lesions <3 cm was 100%, 100%, and 98%. Median LRFS was not reached in any analysis. Examination of a plot of Martingale residuals versus tumor size indicated asharp increase at 3 cm, with maximum risk being attained at a tumor size of 4 cm (Fig. 2). When Cox regression was comparing LRFS in patients with tumors >4 cm versus <4 cm, the increased hazard ratio (HR) for larger tumors did not reach statistical significance (HR 3.236, 95% CI: 0.585–17.891; $P = 0.178$).

TABLE III. Comparison of Tumor Size and Treatment Characteristics by Tumor Histology

	Metastatic CRC (n = 22)	Hepatocellular carcinoma (n = 14)	Other (n = 10)	P-value
Tumor size (cm, median, range)	2.7 (1.2–11)	2.1 (1.3–4.5)	2.5 (1.1–5.0)	0.290
Probes uses per Tx (median, range)	3 (2–5)	3 (2–4)	4 (3–5)	0.111
Adverse events (n, %)	2 (10%)	1 (7%)	2 (20%)	0.706
Technical success (n, %)	21 (95.0%)	14 (100.0%)	10 (100.0%)	1.000

TABLE IV. Comparison of Local Recurrence Free Survival at 3, 6, and 12 Months Stratified by tumor Histology (Top Half) and by Probe Placement Technique (Bottom Pane, Surgical Includes Laparotomy and Laparoscopy)

	3 months (%)	6 months (%)	12 months
Tumor histology			$P = 0.537$
Colorectal metastasis	100	94.10	58.80%
Hepatocellular carcinoma	90.00	90.00	50.00%
Other	100	100	100%
IRE technique			$P = 0.344$
Surgical	100.00	100.00	80.00%
Percutaneous	96.40	92.70	50.70%

DISCUSSION

Irreversible electroporation has shown significant promise in the preclinical setting. In a rodent model of poorly differentiated hepatocellular carcinoma, Guo was able to demonstrate complete regression in 90% of treated tumors [22]. The major benefit of IRE compared to thermal ablative strategies has been the ability to achieve ablation without damage to surrounding vital structures. Bower and colleagues performed ablation of pancreatic tissue in six swine, with the probes placed within 1 mm of either the portal vein or superior mesenteric artery. Postoperatively, all animals recovered without any evidence of pancreatic necrosis or vascular thrombosis [20]. Charpentier and colleagues demonstrated the preclinical use of IRE in proximity to the hepatic hilum in another swine model. In this study, there was no evidence of heat sink effect despite close proximity to major vascular structures. Furthermore, there was no evidence of damage to the portal triad structures [23].

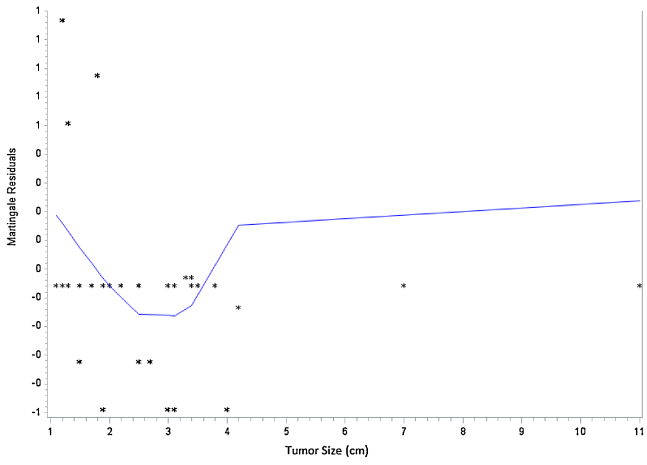

Fig. 2. Plot of Martingale residuals (*y*-axis) versus tumor size (*x*-axis). Inflection points in the curve indicate potential cutpoints in the risk of recurrence with increasing tumor size. Positive inflections indicate an increased risk while negative inflections indicate potentially decreased risk. The sharp increase from 3 to 4 cm demonstrates a greater risk for recurrence once tumors reach this size.

These preclinical studies provide a background of evidence suggesting that IRE may have a suitable role in the treatment of patients who are less than ideal candidates for current thermal ablation modalities due to tumor location in proximity to vital structures. Thus far, the literature on clinical application of IRE has been sparse. Bagla has reported a single case of locally advanced unresectable pancreatic adenocarcinoma treated with IRE. The tumor encased both the splenic and superior mesenteric arteries, and was successfully ablated in two treatment sessions. Importantly, patency of both arteries was demonstrated on followup imaging, and the patient was free of local recurrence at the ablation site 3 months after the procedure [27].

The only series of patients currently reported in the literature was described by Thompson et al. [28], in which 38 patients with malignancies of the liver, kidneys, and lungs were treated by IRE. Initially, the procedure was performed without ECG synchronization, but resulted in transient ventricular arrhythmias in four patients. Following the introduction of ECG synchronization for the remaining 30 patients in the series, there was one case of transient supraventricular tachycardia and one case of transient atrial fibrillation. The other two treatment related complications were transient hypertension resulting from inadvertent direct ablation of the adrenal gland, and ureteral obstruction. There was no other evidence of adjacent organ damage in the 69 tumors treated with IRE. Complete ablation was achieved in 46 of 69 patients (66%), with most of the treatment failures occurring renal and lung tumors. Of the 18 cases of hepatocellular carcinoma, complete ablation was achieved in 83% of treated lesions. Notably, there was no evident response in liver metastases larger than 5 cm in any dimension.

We were not able to determine any statistically significant differences in local tumor recurrence after stratifying by tumor type or by procedural approach (operative vs. percutaneous), which is most likely a function of limited statistical power in this small series. There are possible trends towards decreased recurrence with the ''other'' metastatic tumor histologies and when the IRE procedure performed via an operative approach. These trends, if they bear out to be significant in the future, may result from patient selection. Given the greater potential morbidity of an operative rather than percutaneous procedure, there may have been a bias to perform operative IRE in patients with more indolent disease than those who underwent a percutaneous procedure. This same effect could be present with the ''other'' tumor histologies, in that these more uncommon hepatic metastases could have been more indolent. The lack of randomization and a standardized protocol for patient selection make these questions impossible to answer with the study at hand, however, and will require future prospective, protocolized studies.

The series reported in this manuscript represents further evolution in the learning curve for clinical application of IRE, and is the largest to date. From our experience, there are two important lessons to be learned. First is the importance of ECG synchronization, which was employed for all patients, with no reported cases of treatment

related arrhythmias. Another is the role of tumor size. Thomson demonstrated no significant treatment effect for liver metastases larger than 5 cm [28]. In this report, we demonstrate an increase in the risk of recurrence for tumors larger than 3–4 cm. That this difference did not reach statistical significance is likely a function of low statistical power. We have also found that precise intraprocedural imaging is paramount to achieving complete ablation of target lesions, as misplacement of the probes by a margin of millimeters will result in viable tumor being left behind. A likely reason for the higher recurrence with tumors larger than 3–4 cm is the number of probes required to treat these large lesions. A 3 cm tumor is the largest that can be treated with a 3 probe array. We do not currently believe that larger probe arrays can be placed with the precision necessary to treat these larger tumors.

Because of the small number of patients in this series and the multiple operators and approaches, it would not be feasible to statistically asses for a learning curve, though we believe that for the open approach at least five cases are required for the operating surgeon to be facile in both the technique, but just as important the patient selection. A further five cases (10 total) would be required for a laparoscopic approach, which is more difficult. As far as the percutaneous approach, given the requirement to be able to place multiple (at least three or more) needles in perfect parallel and at precise spacing it is our feeling that five to seven cases were needed to gain comfort with the procedure.

At this time, IRE appears to be best suited as salvage therapy tumors <3–4 cm in diameter which are situated in locations that make them poor candidates for treatment with thermal ablation. Although 29% of patients in this series had no prior treatment, these were treated earlier in our experience and we would no longer recommend IRE as first line therapy in patients who are candidates for other modalities. As such, the most appropriate comparator therapy to IRE is probably radiation therapy. In a study of 61 patients undergoing three-dimensional conformal radiation therapy for HCC under 5 cm in diameter, Lim et al. [17] demonstrated an initial complete response rate of only 44.3%, with 32% experiencing nausea or vomiting and 4.9% experiencing radiation induced liver injury. In a study of radiation therapy for colorectal metastases in 17 patients, Krishnan's group demonstrated 6-month local recurrence free survival of 62%, with 29% experiencing diarrhea and 47% experiencing nausea [18]. The median time to local recurrence in Krishnan's study was 6.8 months.

The results presented here for IRE compare favorably to those presented above for radiation therapy, however the local recurrence rate of 40% at 12 months that is reported in our series is un-acceptable in our opinion and needs to be improved through—better patient selection, smaller tumors, improved technique, improved image guidance, and further understanding of intra-ablation IRE success prior at the completion of the energy delivery. Having captured the early lessons in this preliminary report, we expect that results in future patients will improve as a result of improved experience and knowledge regarding the proper application of IRE. To summarize, such proper application would limit be to limit treatment to tumors under 3 or 4 cm which can be adequately ablated with a 3 probe array. Furthermore, accurate intraoperative image guidance is critical to the necessary precision probe placement. Finally, patients who are candidates for established ablative modalities such as RFA should not undergo IRE as first line therapy because of the higher recurrence rates witnessed in this series. This study serves to provide preliminary data to guide future prospective clinical trials with this experimental technology. Based on the lessons learned here, appropriate inclusion criteria would be patients with hepatic tumors <3 cm in diameter who are not candidates for more traditional liver directed therapies due to tumor location or have failed previous attempts with other therapies.

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