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ORIGINAL ARTICLE

Evaluation of tolerability and efficacy of irreversible electroporation (IRE) in treatment of Child-Pugh B (7/8) hepatocellular carcinoma (HCC)

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Abstract

Introduction: Few studies have assessed the tolerability and efficacy of irreversible electroporation (IRE) in the treatment of Child-Pugh B (7/8) patients with hepatocellular carcinoma (HCC). Based on its mechanism of action, we hypothesized that IRE would be superior to microwave (MW) ablation and compared the liver tolerance and ablation success rates of these therapies in Child-Pugh B patients with HCC.

Methods: 55 patients with Child-Pugh B (7/8) HCC were treated with either MW ablation (n = 25) or IRE (n = 30). Tolerance and ablation success were evaluated at 30 and 90 days and 90 days and 6 months, respectively. Tolerance was defined as stable liver function and absence of increased ascites or worsening portal hypertension. Ablation success was defined as tumor eradication on triple phase contrasted computed tomography (CT).

Results: Patients undergoing IRE had shorter length of stay (p = 0.05) and 90 day readmission rate (p = 0.03) than those undergoing MW ablation. Additionally, IRE was better tolerated than MW ablation at 30 and 90 days. IRE and MW ablation resulted in 6 month success rates of 97% and 100%.

Conclusion: Treatment of Child-Pugh B (7/8) HCC with IRE results in equivalent ablation success with improved liver tolerance compared with MW ablation and other ablative modalities.

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Introduction

Complete anatomic surgical resection represents optimal therapy for patients with hepatocellular carcinoma with no or minimal (Child-Pugh A) liver dysfunction. Meanwhile, for patients with Child-Pugh B or C liver disease, optimal treatment of HCC involves liver transplantation. Among this latter group of patients, failure to fulfill the Milan or expanded University of California San Francisco criteria often experience poor post-transplant outcomes. For patients with large (>6.5 cm) tumors, multiple tumors with the largest >3–4.5 cm, or diffuse disease not amenable to resection, various ablative modalities have been utilized for treatment of HCC in the palliative setting or as a bridge to transplantation.

Currently, several therapies exist for patients with unresectable HCC, including transarterial hepatic therapy, external beam radiation, and ablation (generally thermal or cryoablation). The optimal treatment modality for these patients remains unclear and largely depends on patient and tumor specific variables.[1] The safety and efficacy of radiofrequency ablation (RFA), microwave ablation (MW), and cryoablation have all been demonstrated for treatment of HCC in patients with mild to moderate liver dysfunction (Child-Pugh A/B), with ablation success rates between 90 and 98%, complication rates of 6–10%, and 3 year

survival between 43 and 73%.[2–14] These modalities have several limitations, however. In tumors greater than 4 cm, the above mentioned ablative modalities fail to achieve >50% tumor necrosis.[15] Furthermore, the heat sink effect prevents thermal ablative modalities from inducing adequate tumor necrosis in situations where blood vessels abut tumors or when tumors lie in a subcapsular position.[16,17] Thermal spread and the coagulative necrosis induced by these ablative modalities damages surrounding hepatic parenchyma, potentially worsening pre-existing moderate hepatic dysfunction. Indeed, the majority of studies evaluating the safety of ablative treatment in HCC, particularly MW ablation, contain very few Child-Pugh B patients and fail to report complications specific to this group. When reported, severe complication rates approach 30% for these patients.[18]

In comparison, few studies have assessed the tolerability and efficacy of irreversible electroporation (IRE) in the treatment of such patients and none have directly compared IRE to ablative modalities. IRE acts at the cellular level, delivering electrical pulses that induce apoptosis via creation of pores in the cell membrane.[19,20] Unlike thermal ablation, it does not disrupt the extracellular matrix, protecting surrounding vascular and biliary structures.[19–21] Additionally, because of its mechanism of action, it results in less damage to surrounding hepatic parenchyma than that induced by thermal spread.[19,20]

Owing to these factors, we sought to compare the tolerability and efficacy of IRE ablation to MW ablation in treatment of HCC in patients with Child-Pugh B (7/8) HCC. We hypothesized that IRE tolerance among Child-Pugh B (7/8) patients with HCC should be superior to MW ablation in this same patient population. Additionally, we believed that IRE ablation efficacy would be equivalent or superior to MW ablation.

Methods

A University of Louisville IRB approved prospective multi-institutional double arm treatment registry was evaluated from 1/2010–4/2015 in which 55 patients presenting with Child-Pugh B (7/8) HCC[22] were treated with either MW ablation or IRE. The study was also conducted in compliance with the protocol and the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP). Informed consent was obtained from the subject prior to evaluation and screening. The registry was initiated to satisfy the strict criteria for critical appraising of the quality of a registry study with (i) a well described patient population, (ii) hypothesis generating and answering questions, (iii) high quality data, with good quality control, (iv) independent assessment of outcomes, (v) good clinically relevant follow up with minimal loss of patients, and (vi) comparable patient evaluation across all participating institutions.

Inclusion criteria were confirmed diagnosis of Child-Pugh B (7/8) HCC that was deemed unresectable or as a bridge to transplantation. Unresectability was determined based on tumor characteristics, baseline hepatic function, and predicted post-operative functional liver remnant. Exclusion criteria included general unfitness to undergo general anesthesia, extensive extrahepatic disease, and multifocal hepatic disease not amenable to surgical ablation. Decision regarding treatment with MW ablation or IRE was determined based on anatomic tumor location and proximity to major vascular and biliary structures.

Patients underwent open or laparoscopic microwave ablation utilizing the Microsulis 2450 Hz Microwave ablation system (Angiodynamics, Marlboro MA). Two types of microwave probes were used for this study: the open surgical antenna, which is 19 cm in length, 1.8 mm, with a 2-cm radiating active tip; and the laparoscopic antenna, which is 29 cm in length, 1.8 mm, with a 2-cm active tip. The laparoscopic approach was utilized when possible. The MW ablation size was performed in order to obtain at least a 1 cm margin surrounding the entire tumor. Overlapping ablations were performed when intra-ablation liver ultrasound demonstrated the lack of hyper-echoic spread of the energy or to obtain an adequate margin. The instructions for use were used as a guide with the most common wattage being 140 and the most common time being 4 min being utilized.

IRE ablations were performed either open or laparoscopically using 19-gauge monopolar electrodes as we have previously described.[19,23–25] The electrodes were placed within the liver using continuous ultrasound guidance. Monopolar electrodes were spaced at varying intervals of between 1.5 and 2.4 cm using an attached spacing device, per the manufacturer's modeling algorithm. Probe spacing was confirmed using ultrasound. The depth of exposed electrode was also varied depending on the vascular anatomy.

Expected ablation dimensions were generated using a proprietary algorithm developed by AngioDynamics® using exposure time and probe spacing.[26] The IRE current generator (NanoKnife™; AngioDynamics®: Queensbury, NY, Energy output – 3 kV, 50-amp maximum energy output) was synchronized to deliver electrical pulses coordinated with the patient's cardiac rhythm in order to prevent cardiac dysrhythmias. Each ablation began with a test pulse at 10% planned energy output to assess that an adequate current was achieved. Following successful test pulse, the therapeutic pulses were then delivered. As has been previously reported, the goal of treatment is to deliver 90 electrical micro-second pulses in groups of 10, with a pulse duration of 20–100 μsec and a pulse interval of 250 msec.

The *a priori* primary end points were: (i) rate of complete ablation of liver tumors (ablation success); (ii) ablation recurrence defined as recurrent disease within 1 cm from ablated site(s); (iii) hepatic recurrence at nonablated sites; and (iv) morbidity and mortality associated with the surgical procedure. We used CT confirmed complete ablation as our primary end point for sample size determination. All adverse events were recorded per standards and terminology set forth by the Cancer

Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 3.0. Follow-up assessments included a triple-phase CT scan of the liver at 30, 90, and 180 days from the treatment completion. All CT scans were read by radiologists who were blinded regarding patients' ablation status. Tolerance of treatment was assessed based on whether or not patients demonstrated increases in liver function tests and ascites volume. Increases in transaminase levels, total bilirubin, and ascites were evaluated at 30 and 90 days post-treatment. Determination of increased ascites was determined by blinded radiologists based on comparison to a patient's previous CT scans. Total hospital length of stay as well as 90 day readmission were recorded for each patient. Reasons for readmission were recorded and graded for severity according to the Clavien-Dindo classification of complications.[27]

Table 1 Baseline characteristics of Child-Pugh B (7 and 8) patients with HCC treated with Microwave Ablation (MW) or Irreversible Electroporation (IRE)

	MW (N = 25)	IRE (N = 30)	P-Value
Age	60 (49–81)	61 (51–75)	NS
Gender (Male/Female)	23/2	28/2	NS
Race			
White	25	27	NS
African American	0	3	NS
Body mass index	24.5 (21.3–34.2)	24.8 (21.4–31.5)	NS
HCC Etiology			
NASH	4	2	NS
Hepatitis	7	9	NS
ETOH	12	14	NS
Other	2	5	NS
Past medical history			
Cardiac	4	1	
Vascular	0	0	
Pulmonary	6	3	
Diabetes	3 (2 non-insulin)	1	
Smoking	16	12	
Hypertension	21	26	
Other	18	13	NS
Portal HTN			
Yes	19	27	NS
Median MELD	9 (6–14)	10 (7–19)	NS
Prior Therapy			
Surgical resection	3	0	
Prior Y-90 therapy	6	7	
Prior DEBDOX	6	8	
Prior therapy ablation	2	2	
Prior Nexavar	4	4	NS
Median AFP	34 (2–2389)	29 (3–1987)	NS

Data entry was monitored for completeness and accuracy at University of Louisville and data was queried when it was required. All data was maintained in a secure database accessible only by members of the research team. Data source documents were requested and monitored for at least the first 5 patients from each site. A central assessment of tumor response was performed for all patients by the Principal Investigator at University of Louisville. When there was a discrepancy the Registry PI and the site PI reviewed again for concurrent agreement.

Patients were grouped according to the ablative modality used in their treatment. Analysis was subsequently performed to assess the tolerability and efficacy of each modality at 30 days, 90 days, and 180 days post-treatment. The Student *t* test was used for continuous data. The Fisher's exact and chi-square tests were used for categorical data comparison (two-tailed). *P* values less than 0.05 were considered statistically significant. All statistics were calculated using JMP software (JMP, SAS Institute Inc, Cary, NC).

Results

A total of 55 patients underwent either microwave ablation (n = 25) or IRE ablation (n = 30) for Child-Pugh B (7/8) HCC. These patients received ablative treatment owing to the fact that they were not candidates for transplant or resection, as a bridge to transplant, or because they had a single remaining lesion after treatment with hepatic arterial drug eluting bead therapy. Median age for patients undergoing MW ablation was 60 compared to 61 for those undergoing IRE ablation. HCC etiology was similar comparing the two groups. Pre-existing comorbidities, presence of portal hypertension, MELD scores

Table 2 Operative and ablative characteristics of Child-Pugh B (7/8) patients with HCC treated with IRE

	MW (N = 25)	IRE (N = 30)	P-Value
Size	3.2 (1.9–3.5)	3.0 (2–3.3)	NS
Radiographic characteristic			
Pusher	17	5	<0.0001
Invader	8	24	0.0002
Hanger	0	1	NS
Number (median, range)	1 (1–3)	1(1–2)	NS
Location			
Segment 7/8	8	12	NS
Segment 5/6	10	9	NS
Segment 4	7	9	NS
Proximity to hepatic veins	4	17	0.0015
Proximity to major portal inflow	0	19	<0.0001
Approach			
Laparoscopic	15	20	NS
Percutaneous	10	10	NS

and AFP levels were comparable between the two groups (Table 1).

Most patients in both groups (84 vs. 70%) had undergone at least one previous line of hepatic therapy prior to evaluation for MW or IRE ablation. Specifically 12%, 48%, and 8% of patients undergoing MW ablation underwent prior hepatic resection, received prior hepatic arterial therapy, or underwent prior liver ablation. This approximately mirrored numbers in patients undergoing IRE ablation (0%, 50%, and 7%, respectively). Distribution of tumors within the left and right lobes of the liver were comparable between groups (Table 2). The majority of tumors treated with IRE were more often classified as "invaders" based on radiographic characteristics ($p = 0.0002$) and were close to hepatic and/or portal vascular structures. Meanwhile only 16% and 0% of tumors treated with MW ablation were adjacent to hepatic or portal vascular structures, respectively ($p = 0.0015$; $p < 0.0001$), and most were more often classified as "pushers" based on radiographic characteristics ($p < 0.0001$).

Patients undergoing MW and IRE ablation demonstrated similar tumor burden in terms of number and size. Median tumor size was 3.2 cm (range 1.9–3.5 cm) and median tumor number was 1 (range 1–3) for patients treated with MW ablation. Meanwhile, patients treated with IRE ablation had median tumor size 3.0 cm (range 2.0–3.3 cm) and median tumor number 1 (range 1–2) (Table 2). Laparoscopic ablations were able to be performed in the majority of patients. Average length of stay for patients undergoing MW ablation was 2 days (range 1–5) compared to 1 day (range 1–4) for patients undergoing IRE ablation ($p = 0.05$) (Table 3). Furthermore, only 4 patients (13%) patients undergoing IRE ablation required readmission for procedure related issues within 90 days of treatment compared with 9 patients (36%) undergoing MW ablation ($p = 0.03$). In patients undergoing both IRE and MW ablation, reasons for readmission most frequently consisted of transient liver failure, dehydration, and/or uncontrolled ascites. Rates of uncontrolled ascites and transient liver failure requiring readmission were slightly higher among patients undergoing MW ablation, though the differences were not statistically significant ($p = 0.11$, $p = 0.14$, respectively). Additionally, patients undergoing MW ablation tended to have more severe uncontrolled ascites than those undergoing IRE ablation (4 patients with grade III ascites versus 1 patient with grade II ascites; Table 3).

Regarding treatment safety and tolerability, there were no treatment related deaths observed in either group. Major and minor complication rates were 76% for patients undergoing MW ablation and 27% for patients undergoing IRE ablation. Complications most often consisted of pleural effusion and portal vein thrombosis in both cases. Rates of pleural effusion and portal vein thrombosis were lower among patients treated with IRE (16% and 3%) compared with those treated with MW ablation (56% and 20%, $p < 0.01$ and $p = 0.03$, respectively). IRE resulted in lesser increases in AST (0 fold vs. 2 fold, $p = 0.05$), ALT (0 vs. 2 fold, $p = 0.05$), and total bilirubin (1 vs. 1.5 fold, $p = 0.07$) as well as fewer incidences of increased post-ablation ascites (5 vs 13 fold, $p = 0.02$) at 30 days compared with MW ablation. A similar pattern was evident at 90 days, though the differences were not statistically significant (Table 3).

Regarding treatment success, both treatments exhibited a 90 day success rate of 100%. IRE ablation resulted in 180 day success rate of 97% compared to 100% for MW ablation ($p = 0.37$).

Table 3 Adverse events and post-procedural characteristics of Child-Pugh B (7/8) patients with HCC treated with MW ablation vs. IRE

	MW (N = 25)	IRE (N = 30)	P-Value
Intra-operative complications			
Arrhythmia	0	0	NS
High Current	0	2	0.10
Failure to deliver	0	0	NS
Length of stay (days; median, range)	2 (1–5)	1 (1–4)	0.05
30 day tolerance (median, range)			
AST (fold increase)	2 (1–4)	0 (1–2)	0.05
ALT	2 (1–4)	0 (1–2)	0.05
Total bilirubin	1.5 (1–2)	1 (1–1)	0.07
Increased ascites	13 (52%)	5 (16%)	0.02
90 day tolerance (median, range)			
AST (fold increase)	1 (1–4)	0 (1–2)	0.09
ALT	1(1–4)	0 (1–2)	0.09
Total bilirubin	0 (1–2)	0 (0–1)	0.12
Increased ascites	5 (20%)	2 (6%)	0.05
Pleural effusion (90 day)	14	5	<0.01
Portal vein thrombosis (90 day)	5	1	0.03
Readmission (90 day)	9 (36%)	4 (13%)	0.03
Reasons for readmission			
Uncontrolled ascites	4 (all grade III)	1 (grade II)	0.11
Dehydration	2 (all grade II)	1 (grade II)	0.46
Liver failure	5 (four grade II, one grade III)	2 (all grade II)	0.14
Ablation success			
90 day	25 (100%)	30 (100%)	NS
180 day	25 (100%)	29 (97%)	0.37

Discussion

There remain multiple treatment options for patients with hepatocellular carcinoma who are unable to undergo primary hepatic resection liver transplant. These options all have various effectiveness based on response rates and overall outcomes For thermal based ablation, radiofrequency ablation (RFA) has historically been the ablative modality of choice for HCC, Advances

in technologies over the past five to ten years have resulted in the development of other modalities, namely microwave (MW) ablation and irreversible electroporation (IRE), with theoretical advantages to RFA. Several groups, including ours, have demonstrated the safety and efficacy of both MW ablation and IRE in treatment of hepatocellular carcinoma.[12,14,19,28,29] However, studies of IRE have been limited in size (N < 15), and none have directly compared IRE ablation to thermal ablative modalities. Here, we present what represents, to our knowledge, the first direct comparison of IRE with MW ablation in treatment of HCC.

This study comparing MW ablation with IRE in treatment of HCC in the setting of Child-Pugh B (7/8) hepatic dysfunction demonstrated equivalent initial, 90 day, and 180 day treatment success as well as comparable procedural complication rates between the two groups. IRE, however, offered superior hepatic tolerability, faster procedural recovery time, and lower readmission rates compared with MW ablation. Our work mirrors previous findings that IRE is safe and well-tolerated in treating patients with HCC and underlying liver dysfunction.[19,29,30]

MW ablation represents an attractive thermal ablative modality in treatment of HCC owing to its large zone of active tissue heating, its lack of limitation by charring of surrounding tissue, and its resistance to the "heat sink" effect as a result of its efficiency and energy deposition in surrounding tissues.[28] However, as a result of the high amounts of energy imparted to tissues and temperature increases it induces in surrounding tissues, it is known to result in transaminase and bilirubin elevation.[31] As our data shows, IRE ablation produces minimal, if any, transaminitis, hyperbilirubinemia, or ascites increase. We believe this derives from two factors: the fact that IRE does not rely on thermal energy for its effect and its preservation of extracellular tissue structure. As previously mentioned, IRE results in a sharply defined region of cell killing compared with thermal ablative modalities, including MW ablation.[21,20] This results in less collateral damage to surrounding non-malignant hepatocytes during ablation of primary hepatic tumors and, as a result, lesser increases in transaminases. Similarly, decreased damage to biliary structures and proximate vascular structures by IRE compared with thermal ablative modalities causes lesser increases in bilirubin and portal hypertension (and, by extension, ascites), respectively.

The implications of underlying cirrhosis or fibrotic hepatic tissue on tissue conductivity, energy distribution, and ablation efficacy have been reviewed by several groups in the literature. Multiple groups have assessed the effect of cirrhosis on thermal ablation, namely radiofrequency ablation (RFA).[32,33] For thermal ablation, a surrounding ring of fibrotic hepatic parenchyma produces an "oven effect," causing thermal energy retention in the surrounding hepatic tissue. This increases thermal ablation's ability to result in complete tumor necrosis for a given amount of thermal energy. However, this can also result in complete destruction of normal hepatocytes in uninvolved surrounding tissue. Meanwhile, Abdelsalam, *et al.* showed that, in a porcine model, while fibrosis increases hepatic tissue resistivity and impedes conductance, IRE effectively achieves effective ablation, with no significant difference in ablation volume compared with that achieved in normal liver.[34] Similarly to normal liver, there was little inflammation in hepatic tissue surrounding the ablation area nor was there significant evidence of apoptosis in normal hepatocytes in said area.

One aspect of ablation comparison not addressed in our study is ablative efficacy with respect to tumor diameter. All but one of the tumors in our study was smaller than 3.5 cm in maximal diameter, and our previous work has demonstrated the efficacy of both IRE and MW ablation in treatment of such lesions.[19,28] However, treatment of tumors greater than 3–4 cm in maximal diameter with IRE results in decreased rates of complete ablation and higher likelihood of recurrence.[35] The one lesion with maximal diameter larger than 3.5 cm included in our study was a 3.8 cm tumor located in segment 5/8. IRE ablation of the lesion initially resulted in success at 3 months, though local recurrence was noted on follow-up imaging at 6 months. For tumors larger than approximately 3–3.5 cm in maximal diameter, 4 or more probes would be required for IRE treatment.[19] Significant precision is required in probe placement to create an ablation region that would ablate all viable tumor, and such precision is not easily achieved with 4 or more probes. In contrast, MW ablation has been shown to effectively ablate large tumors, regardless of size.[12] This likely stems from its reliance on active tissue heating and the current ability to employ an increasing number of probes to generate the desired ablation volume. As the ability to accurately utilize probe arrays consisting of at least 4 probes with IRE evolves, further studies will be required to determine if it retains its efficacy in treatment of larger (>4 cm diameter) tumors.

It is important to emphasize that effective ablation stems from accurate lesion localization and probe placement. Currently, IRE and MW ablation can be performed via percutaneous, laparoscopic, and open approaches. Percutaneous ablation holds significant appeal owing to its minimal invasiveness. However, laparoscopic and open approaches offer important advantages over percutaneous ablation. They allow for improved tumor staging with intraoperative ultrasound by allowing for confirmation of the presence of a true single lesion rather than multifocal lesions within the liver. Additionally, real time use of intraoperative ultrasound improves lesion targeting and optimizes probe placement and safety. Finally, open and laparoscopic ablation allow for performance of post-ablation contrast ultrasound to confirm ablation of the entire target region as well as vital structure patency and flow.

Our current study has several limitations. First, as a single-institution study, it suffers from surgical bias in the use of ablation as an adjunct to surgical resection. Additionally, both groups in our study consist of relatively few patients (25 and 30, respectively). While the differences noted between MW and IRE ablation in terms of treatment tolerability are significant, further

studies on larger patient groups should be performed to assess whether then trends observed in our study persist with increasing sample size. Finally, our study does not address long-term efficacy of IRE compared with MW ablation in Child-Pugh B (7/8) patients. Continued data collection on local recurrence, disease free survival, overall survival, and recurrence post-transplant, if applicable, will allow for assessment of long-term therapeutic benefit of IRE compared with MW ablation in treatment of HCC.

In conclusion, irreversible electroporation represents a safe, effective ablative modality for treatment of hepatocellular carcinoma in the setting of Child-Pugh B (7/8) liver dysfunction. Its safety and efficacy compare favorably with other treatment modalities for Child-Pugh B (7/8) hepatocellular carcinoma. Compared with microwave ablation, it affords improved liver tolerability as well as overall procedural tolerability evidenced by shorter length of stay and decreased readmission rates.

Disclosures

Dr. Martin is a paid educational consultant for AngioDynamics.

Conflict of interest

None declared.

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