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Irreversible Electroporation for Unresectable Hepatocellular Carcinoma: Initial Experience

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Abstract
Purpose To evaluate the efficacy and safety of irreversible electroporation (IRE) in the treatment of unresectable hepatocellular carcinoma (HCC).
Materials and Methods A retrospective study was conducted from September 2014 to June 2017. A total of 21 HCCs in 21 patients with cirrhosis were treated with IRE. There were eight subcapsular or exophytic, ten perivascular and three peribiliary tumors. The median tumor size was 26 mm (range 14–40 mm). The technical success of the procedure was recorded. Median follow-up, median time to local recurrence, median local tumor progression-free survival (PFS) and complications were recorded.
Results Technical success was achieved in all the patients. The median follow-up was 10 months (range 2–30 months). The median time to local recurrence and local tumor PFS were 4 months (range 3–4 months) and 7 months (range 3–30 months), respectively. The tumor-related factor that was significantly associated with local PFS was the size. Maximum tumor diameter < 25 mm was significantly associated with local tumor PFS ($p = 0.045$). Other parameters including tumor location, segmental portal vein thrombosis, baseline alpha-fetoprotein level and underlying etiology did not affect local tumor PFS. Complications were noted in nine patients and were classified as grades 1 and 2. No procedure-related mortality was encountered.
Conclusion IRE is an effective treatment for ablation of small HCCs. Larger prospective studies with strict selection criteria will establish the safety and efficacy of IRE in the treatment of unresectable HCC in patients who cannot undergo thermal ablation.

Keywords Hepatocellular carcinoma · Irreversible electroporation · Radiofrequency ablation

Introduction

Thermal ablation methods, particularly radiofrequency ablation (RFA) and microwave ablation (MWA), are the most popular ablation methods, achieving the therapeutic effect by thermal damage and necrosis [1]. The risk of damage to the critical surrounding structures (central bile ducts, gallbladder, colon and diaphragm) is inherent to these techniques. Not only this, these techniques are effective when the tumor nodules are less than 3 cm and away from a major vessel [1]. Irreversible electroporation (IRE) is a recently introduced ablation technique. It acts at the level of the cell membrane and achieves apoptotic cell death by creating irreversible pores [2]. This effect is achieved via delivery of ultrashort pulses of high voltage and high-intensity current [3]. The connective tissue

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framework and the adjacent vital structures are not damaged. As IRE works by nonthermal mechanism, it is not affected by the heat sink effect. These distinct advantages have allowed interventional radiologists to use IRE for treatment of HCCs that are otherwise candidates for curative treatment but the location renders them unfit for other ablative methods. A number of studies with small cohorts have already explored the safety and feasibility of IRE in the management of HCC [4–11]. Few studies have also demonstrated the efficacy of IRE in the management of HCC with variable characteristics [4, 7, 10, 12, 13]. However, the data regarding the tumor selection and effectiveness of IRE are still sparse. We conducted this study with the aim of determining the safety and efficacy of IRE in patients with HCC. To the best of our knowledge, this is the first study of its kind from Southeast Asia.

Materials and Methods

Patients

This was a retrospective study of consecutive IRE procedures conducted between September 2014 and June 2017. The study was approved by the Institute Ethics Committee. All patients gave informed written consent for the procedure. The diagnosis of HCC was based on American Association for Study of Liver Diseases (AASLD) guidelines. All the patients underwent a multiphase contrast-enhanced computed tomography and/or magnetic resonance imaging within prior 2 weeks of the IRE session. The therapeutic decisions were decided by a team comprising of interventional radiologists, hepatologists and gastroenterologists. Inclusion criteria for IRE were single nodules up to 4 cm in close proximity to vital structures, limited vascular invasion, Child–Pugh class A or B disease, lack of invasion of main portal vein and absence of nodal and distant metastases. The nodules were defined as peribiliary if they were within 1 cm of the common, right or left hepatic ducts and perivascular if they were within 0.5 cm of the major hepatic or portal venous branches or major hepatic arterial branches [11, 13]. Patients with cardiac pacemakers, history of cardiac arrhythmias and uncorrectable coagulopathy constituted the exclusion criteria.

IRE Procedure

All the IRE procedures were performed by a single interventional radiologist having 12 years experience in percutaneous ablative treatment of HCC with RFA. IRE procedures were performed on a commercially available system (NanoKnife, AngioDynamics). This system is capable of generating high voltage (up to 3000 V) and high intensity (up to 50 A) pulses of direct current. The IRE electrodes are monopolar 19 G electrodes with adjustable active tip length (5–40 mm). IRE procedures were performed under general anesthesia with muscle relaxation. All the electrical pulses were delivered during the refractory phase of the myocardium (ST segment). This was achieved by cardiac synchronization using a commercially available device (Accusync, Accusync Medical Research). The planning of ablation zone was done based on tumor size and location in the contrast-enhanced CT (CECT) scan done on the day of procedure. All the electrodes were placed parallel to each other (± 20°) using CT fluoroscopy. The distance between each electrode pair was less than 2.5 cm and more than 1 cm. The number of electrodes was determined by the size of the nodule. For lesions less than 2 cm, three electrodes were placed in the periphery of the lesion (Fig. 1). For lesions between 2 and 3 cm, four electrodes were placed in the periphery of the lesion. For lesions larger than 3 cm, 4–6 electrodes were placed and included 1–2 electrodes in the center of the lesion. The subcapsular lesions were approached through the normal liver using this multineedle technique of IRE. The electrodes used in IRE are relatively thinner (19-gauge) as compared to the electrodes used in most of the thermal ablation techniques. As IRE is not known to cause any damage to the collagenous structures, we did not use artificial ascites to create a buffer or displace vital structures like diaphragm, stomach, bowel loops and gallbladder in our subset of patients with subcapsular lesions. Initially, test pulses were delivered (20 pulses of 1500 V–1850 V/cm, duration 90 μs). This was followed by delivery of 70–90 target electrical pulses of 2300–3000 V and 20–50 A. For complete ablation, pullback application and/or reinsertion of electrodes were performed as deemed necessary by the interventional radiologist. The technical success was defined as the ability to deliver the complete set of electrical pulses as planned.

Assessment of Treatment Response and Patient Follow-Up

Immediately following the procedure, a CECT of the upper abdomen was performed to exclude local puncture-related complications (hematoma, hemoperitoneum, pneumothorax and pleural effusion). A multiphase contrast-enhanced CT scan was performed 4 weeks following the IRE procedure. Further follow-up CT scans were performed at 12 weeks and then at 3-monthly interval. The CT scans were reviewed by radiologists with 7 years and 5 years experience in abdominal imaging.

Complete tumor ablation was defined by the lack of any arterial hypervascularity or washout in portal venous or

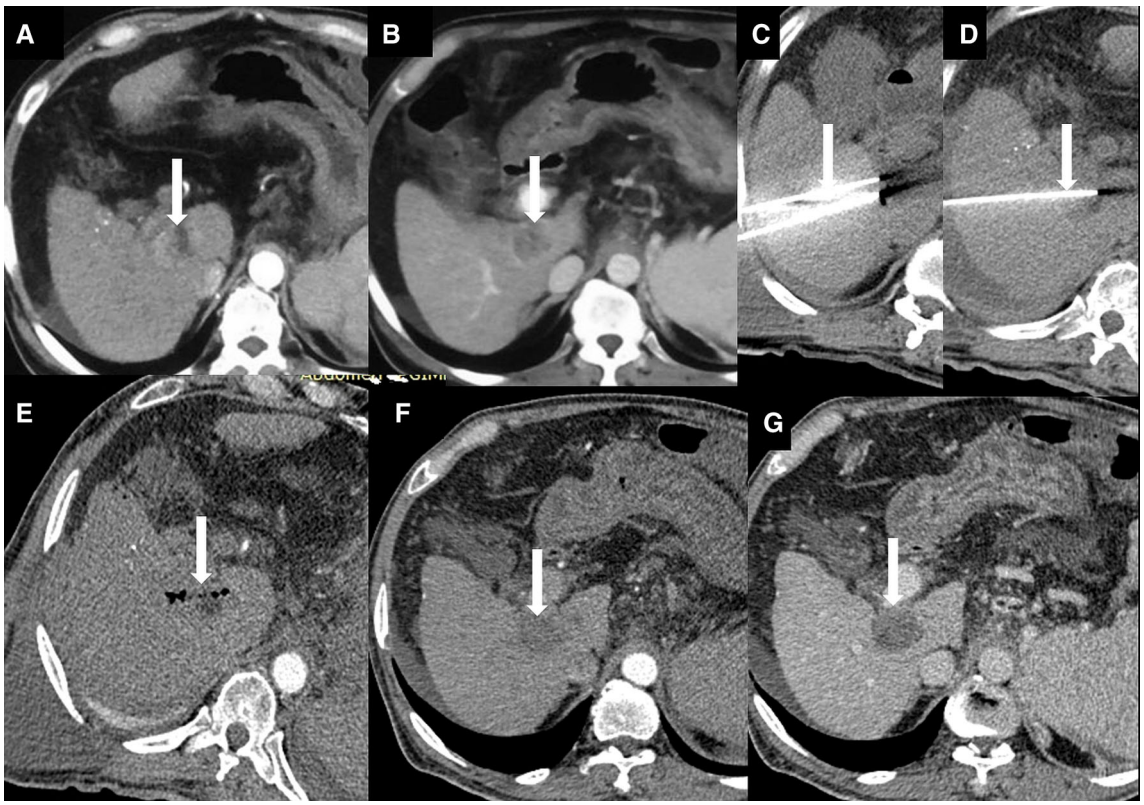

Fig. 1 IRE in a 52-year-old male with NASH-related cirrhosis and HCC in caudate lobe. **A** Axial arterial phase CT image shows a peripherally enhancing nodule (arrow). **B** Venous phase image shows washout (arrow). **C** Two IRE probes are inserted into the lesion (arrow). **D** Another IRE probe is inserted into the lesion at a slightly cranial level (arrow). **E** Axial arterial-phase CT image obtained immediately after IRE shows complete necrosis of the lesion with few air foci (arrow). **F** Axial arterial phase image obtained 6 months after the IRE procedure shows no hypervascularity within the lesion (arrow). **G** Axial venous phase image of the same study shows no abnormal enhancement (arrow)

delayed phase at the CT performed after 4 weeks (Figs. 1, 2). Residual disease or incomplete ablation was defined as the presence of tumor adjacent to the site of ablation on CT during the initial 1-month follow-up. Recurrent disease was considered to be present when there was no disease at initial 1-month CT, but tumor was identified at or adjacent to the ablation site (local recurrence) or away from the ablation site (distant recurrence) on subsequent follow-up CT scans. Local tumor progression-free survival (PFS) was defined as the time elapsed between the last IRE procedure and tumor progression or death.

Safety

Major and minor procedure-related complications were assessed in accordance with the CIRSE recommendations for evaluation of complications [14]. According to this classification, in grade 1 complications, there is no deviation from the normal posttherapeutic course, no additional therapy is required and there are no postprocedure sequelae. Grade 2 complications on the other hand mandate prolonged observation. However, no additional therapy is required and there are no postprocedure sequelae.

Statistical Analysis

Continuous data were expressed as median and ranges and categorical variables were expressed as proportion and frequency. Univariate and multivariate regression models were employed to assess significant clinical characteristics and nodule parameters affecting local tumor PFS. Cumulative survival rates were expressed using Kaplan–Meier analysis. $p < 0.05$ was considered statistically significant. Statistical analysis was done using SPSS IBM software version 17.

Results

A total of 21 HCCs in 21 cirrhotic patients treated with IRE were included in the study. During the same period, 250 HCCs in 240 patients were treated with transarterial chemoembolization (TACE) (n = 155), RFA (n = 75) and

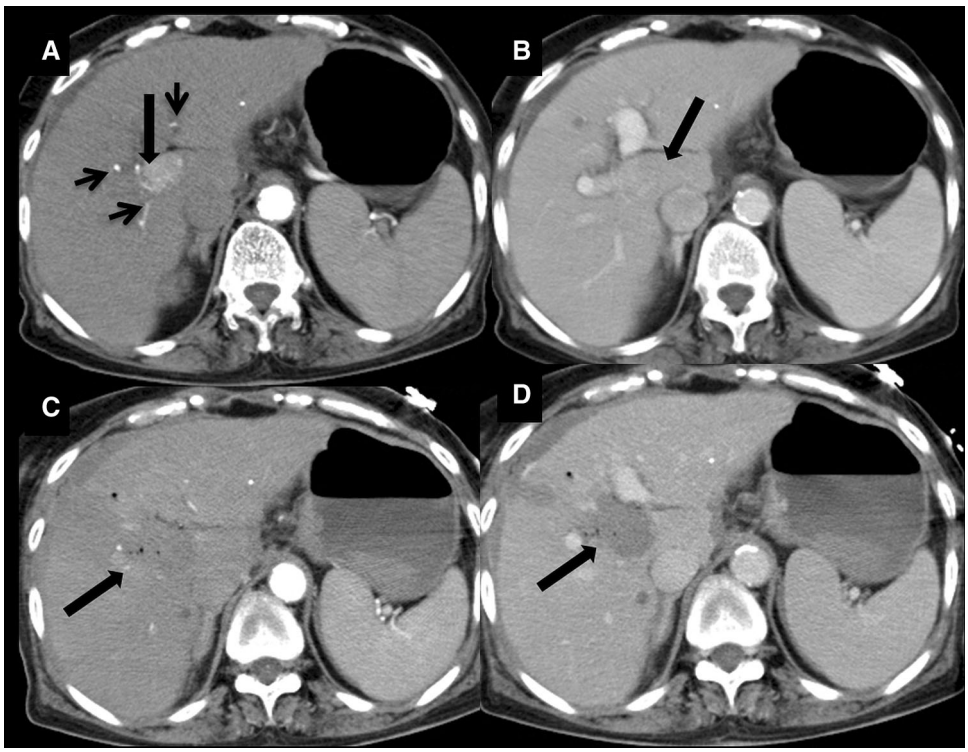

Fig. 2 IRE in a 72-year-old female with HCV-related cirrhosis and HCC adjacent to major vascular structures. **A** Axial arterial phase image shows a centrally placed enhancing nodule (arrow) adjacent to major arteries (short arrows). **B** Venous phase image shows washout within the nodule (arrow). The nodule is in close relation to the right and the left branches of the portal vein. **C** Arterial phase image immediately after completion of IRE procedure shows lack of any residual enhancement within the lesion and no injury to the adjacent arteries (arrow). **D** Venous phase image of the same study also shows complete necrosis of the lesion (arrow) with no injury to the adjacent veins. Mild hemoperitoneum was noted that resolved with conservative management

selective intra-arterial radiation therapy (SIRT) (n = 20). During this period, our center was not performing MWA for HCCs. Baseline characteristics are given in Table 1. There were eight subcapsular or exophytic, ten perivascular and three peribiliary tumors. Sixteen patients had Child–Pugh class A disease, and five patients had Child–Pugh class B disease. The median age was 64 years (range 40–84 years). There were 14 men and seven women. The median tumor diameter was 26 mm (range 14–40 mm).

Technical Parameters

Technical success was achieved in all the patients. A median of four probes (range 3–6) were used. The median number of pulses per nodule was 180 (range 90–270). The median energy deposited per nodule was 2600 V (range 2300–3000 V). The pullback application was employed for 12 nodules. The technique-related parameters are given in Table 2.

Residual Disease, Recurrence and Local Tumor Progression-Free Survival (PFS)

Complete tumor ablation was seen in all patients at 1-month follow-up. Local recurrence occurred in five patients (24%). The median time to local recurrence was 4 months (range 3–4 months). Repeat session of IRE was done in three patients. The remaining two patients with local recurrence did not opt for repeat IRE treatment. Both the patients underwent TACE. The median local tumor PFS was 7 months (range 3–30 months) (Fig. 3). After a median follow-up of 10 months (range 2–30 months), 13 patients were alive. Eight deaths occurred during this period after a median duration of 5 months (range 2–15 months). Distant recurrence was seen in three patients. Extrahepatic disease progression was seen in one patient. The 6-month PFS was 71.4%. If we exclude the six patients who died before or at 6 months, the PFS increases to 93.3%. The tumor-related factor that was significantly associated with local tumor PFS was the size of the lesion. Maximum tumor diameter < 25 mm was significantly associated with local tumor PFS ($p = 0.045$). Other parameters including location, segmental portal vein thrombosis, baseline alpha-fetoprotein level, underlying etiology, BCLC and CTP scores did not affect local tumor PFS.

Subgroup analysis of BCLC-A and BCLC-C is given in Table 3.

Complications

Complications were noted in nine patients (42.9%) and were classified as grades 1 and 2. Grade 1 complications included fever (n = 3). Grade 2 complications included mild hemoperitoneum (n = 4), mild pneumothorax (n = 2) and mild right pleural effusion (n = 2). In none of these patients, drainage was required and all patients improved on conservative treatment. No procedure-related mortality

Table 1 Demographics and salient parameters (n = 21)

Median age (years)	64 (40–84)
Males:females	14 (67%):7 (33%)
No. of previous treatments	5 (24%)
Etiology of cirrhosis	
Alcohol	7 (33%)
Hepatitis C virus	7 (33%)
Hepatitis B virus	5 (24%)
NASH	2 (10%)
Child–Pugh class	
A	16 (76%)
B	5 (24%)
C	–
BCLC stage	
0	–
A	17 (81%)
B	–
C	4 (19%)
D	–
Portal vein invasion	3 (14%)
Median longest diameter (mm)	26 (14–40)
Tumors with longest diameter > 30 mm	9 (43%)
Location	
Central	13 (62%)
Peripheral	8 (38%)
Proximity to large vessels	10 (48%)
Proximity to hilar bile duct/gallbladder	3 (14%)
Proximity to diaphragm	7 (33%)
Median α-FP level (ng/mL)	19.2 (5–3437)
α-FP level > 100 ng/mL	3 (14%)
Median follow-up (months)	10 (2–30)
Local recurrence	5 (24%)
Median progression free survival (months)	7 (3–30)
Median time to local recurrence (months)	4 (3–4)
Deaths	8 (38%)
Median time to death (months)	5 (2–15)
Additional treatment	5 (24%)
RFA	1
TACE	3
TAE	1

BCLC Barcelona clinic for liver cancer; α-FP alpha-fetoprotein; *NASH* non-alcoholic steatohepatitis; *RFA* radiofrequency ablation; TACE transarterial chemoembolization; *TAE* transarterial embolization

was encountered. Eight deaths that occurred during the follow-up period were due to liver failure not related to the procedure (n = 4) and due to distant intrahepatic and extrahepatic spread of the disease (n = 4). Table 4 highlights the complications encountered during the IRE procedures.

Table 2 Technical details of IRE procedure

Median number of probes	4 (3–6)
Median exposure length of probe (cm)	1.5 (1–2.5)
Median voltage (V)	2600 (2300–3000)
Median spacing (cm)	1.7 (1–2.5)
Number of tumors where pullback was done	12 (57%)
Median number of pulses per session	180 (90–270)

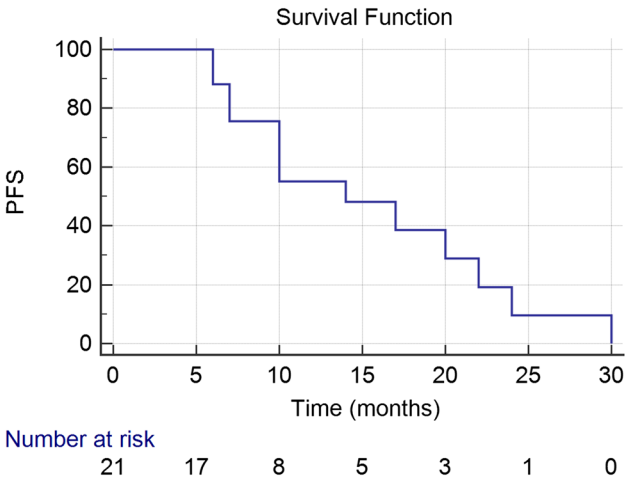

Fig. 3 Kaplan–Meier curve showing local tumor progression-free survival following IRE in 21 patients

Discussion

We performed IRE in 21 patients with unresectable HCC over a period of approximately 3 years. The tumor selection was based on the location that precluded safe and effective treatment with thermal ablation. IRE has been shown to be safe, because of its nonthermal mechanism of action. Technical success was achieved in all the patients. None of the patients suffered major complications. No procedure-related mortality was encountered. Local recurrence occurred in five patients (24%) over a median period of 4 months. Overall median local tumor PFS was 7 months. The only factor that was found to significantly affect local tumor PFS was nodule size (< 25 mm, p = 0.045). These results suggest that IRE is an effective therapeutic option for small HCCs in locations where other ablation therapies can cause collateral damage.

There are few studies with small cohorts that have evaluated the effectiveness of IRE in HCC in similar setting [12, 15]. Sutter et al. [15] reported results of IRE in 58 patients with 75 HCCs. The patients were divided into two

Table 3 Subgroup analysis of BCLC-A and BCLC-C disease

	BCLC-A (n = 17)	BCLC-C (n = 4)
Median age (years)	58 (40–84)	64.5 (52–66)
Sex distribution (M:F)	10:7	4:0
Median longest diameter (mm)	25 (14–40)	31 (24–36)
Location		
Central	12	1
Peripheral	5	3
Proximity to large vessels	10	0
Proximity to hilar bile duct/gallbladder	2	1
Subcapsular/exophytic	5	3
Median α-FP level (ng/mL)	21 (7–3437)	18.5 (5–120)
Local recurrence	4	1
Median progression-free survival (months)	10 (3–30)	7 (6–24)
Median time to local recurrence (months)	4 (1–4)	3
Deaths	7	1

Table 4 Acute complications of IRE procedure

CIRSE grade	Details of complications
1	Fever (n = 3)
2	Hemoperitoneum (n = 4); pleural effusion (n = 2), pneumothorax (n = 2)
3	0
4	0
5	0

groups based on the indication for IRE. One group comprised patients where IRE was chosen due to the tumor location being adjacent to the critical structures (n = 48). The other group comprised patients with poor general condition (n = 10). The technical success was reported in all the cases. A complete ablation was achieved in 77.3, 89.3 and 92% tumor nodules after one, two and three sessions of IRE. Local tumor progression (LTP) was reported in 15 patients (20%) after a median follow-up of 9 months. The 6-month and 12-month local tumor PFS was reported to be 87% and 70%, respectively. Local recurrence in our study (24%) was similar to this study but occurred earlier (median 4 months; range 3–4 months). Median local tumor PFS in our study compared well with this study. We found that tumor size < 25 mm significantly affected the local tumor PFS. Other parameters did not significantly affect local tumor PFS. However, the study by Sutter et al. found the pre-ablative α-FP (> 200 ng/mL) to significantly affect local tumor PFS. The size of the HCC nodule did not significantly affect local tumor PFS in their study. In a smaller study comprising five patients with six HCCs, technical success of 83% was reported. After a median follow-up of 244 ± 55 days, no LTP was noted (excluding the initial technical failure and residual tumor detected on the day of procedure) [12]. The results indicate that IRE is an effective ablative method for small HCCs. In a study comprising 14 patients, eight with large- (> 5 cm) and six with medium-sized (3–4.1 cm) primary liver cancers (including seven HCCs and seven intrahepatic cholangiocarcinomas), complete ablation was achieved in only 25% patients with large-sized tumors and 66.6% patients with medium-sized tumors [16]. This indicates that complete ablation is difficult to achieve in larger tumors.

Although the time to local recurrence and local tumor PFS are lower than those reported for thermal ablation methods (RFA and MWA), this comparison is not justified as IRE is usually selected for patients with tumors in challenging locations for other ablative techniques [17]. Going by the size criteria, poor results are expected with most of the thermal ablative methods than those reported with IRE [18, 19]. Efficacy of IRE seems to be better than that reported after TACE with drug-eluting beads for patients within the Milan criteria [20]. This is important as it obviously favors IRE as a better treatment option in this group of patients as well. However, prospective studies are needed to confirm this. A recent study reported promising results with combination therapy using IRE and allogenic natural killer cell immunotherapy [21].

Complications were reported in 19% of patients in a recent study [15]. However, most of these complications were grades 1 and 2. Only two patients had grade 4 and one patient had grade 5 complications. Two of the higher grade

complications occurred in patients with poor liver function. One procedure-related death was also reported. Though we report a higher complication rate (42.9%), all patients had grade 1 and grade 2 complications. No patient developed clinical jaundice or decompensation following the procedure. Mild to moderate cholestasis, believed to be due to the damage to the bile ducts by local heating, was reported in 24% patients in a study [13]. In the same study, needle tract seeding was reported in 26% cases [13]. We did not observe cholestasis secondary to thermal damage to bile ducts or needle tract seeding in any of our patients.

There were limitations in our study. First was the retrospective design of the study. Secondly, the sample size was small. The lack of a comparative arm was another significant limitation of our study. The inclusion of few patients with segmental portal vein invasion was another limitation. These patients had tumors less than 4 cm and did not agree to undergo SIRT.

In conclusion, IRE is an effective ablative treatment for small HCCs. However, large prospective studies and randomized control trials are required to establish the safety and efficacy of IRE for the ablation of HCC.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Procedural informed consent was obtained from all individual participants included in the study.

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