



Original Article

Irreversible Electroporation for Hepatocellular Carcinoma Abutting the Diaphragm: A Prospective Single-center Study

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Received: 8 January 2021 | Revised: 2 April 2021 | Accepted: 21 July 2021 | Published: 10 August 2021

Abstract

Background and Aims: Irreversible electroporation (IRE) is an emerging local ablation therapy which may be effective for unresectable tumors. This study aimed to evaluate the safety and efficacy of percutaneous IRE in the treatment of hepatocellular carcinoma (HCC) abutting the diaphragm. **Methods:** A total of 26 participants with 39 tumors abutting the diaphragm were prospectively evaluated between July 2015 and September 2018. Complications associated with IRE were recorded, and the survival benefit of IRE was analyzed. The factors associated with time to local tumor progression (LTP) were analyzed using univariate and multivariate Cox regression models. **Results:** No major complications or treatment-related deaths occurred. The technical success rate was 96.2% (25/26) and complete ablation rate was 92.3% (36/39). The median follow-up period was 16.7 months (range: 3.0–43.0 months), the LTP occurred in 15.2% of tumors and median time to LTP was 20.4 months. Overall, tumor size (hazard ratio: 1.24 [95% confidence interval: 0.38, 3.81], $p=0.03$) was the only factor associated with time to LTP. **Conclusions:** This study shows for the first time that percutaneous IRE is a safe and effective ablation technology for HCC abutting the diaphragm.

Citation of this article: Ma Y, Chen Z, Liang B, Li R, Li J, Li Z, et al. Irreversible Electroporation for Hepatocellular Carcinoma Abutting the Diaphragm: A Prospective Single-center Study. J Clin Transl Hepatol 2022;10(2):190–196. doi: 10.14218/JCTH.2021.00019.

Keywords: Irreversible electroporation; Hepatocellular carcinoma; Diaphragm; Safety; Efficacy.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha fetoprotein; CI, confidence interval; CR, complete response; CT, computed tomography; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; IRE, irreversible electroporation; LTP, local tumor progression; MR, magnetic resonance; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transarterial chemoembolization; US, ultrasound.

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths globally.^{1–3} In addition, the incidence rate of HCC has been on the rise and is anticipated to continue increasing.^{4,5} The 5-year survival rate of untreated HCC is below 5%.³ Surgical resection and radiofrequency ablation are the recommended therapeutic strategies for early-stage HCC patients.⁶

Treatment of HCC abutting the diaphragm is challenging, due to poor visibility of the target tumor, difficulty in access, and risk of collateral thermal injury to surrounding structures.⁷ Radiofrequency ablation, cryoablation, microwave ablation and other thermal ablation methods are the commonly used local treatment strategies for HCC abutting the diaphragm.^{8–10} A few studies have reported that using conventional radiofrequency ablation resulted in a low local tumor control and high complication rate (mainly pneumothorax or diaphragm injury, lung injury) for HCC abutting the diaphragm.^{11–14} Thus, percutaneous thermal ablation of HCC abutting the diaphragm may result in poor clinical outcomes. However, to date, no reported study has investigated the application of irreversible electroporation (IRE) for treatment of HCC abutting the diaphragm.

IRE is a novel non-thermal ablation technology that uses high-voltage short pulses to influence the target cell membrane, forming irreversible nanopores on the lipid bilayer of the cell membrane. This in turn disrupts the steady state of the intracellular environment, subsequently leading to cell death.^{15–17} Moreover, the main advantage of IRE is that it can treat tumors very close to large blood vessels and bile ducts without affecting blood or bile flow, mainly because it has a non-thermal effect in the treatment zone.¹⁸

Therefore, this study aimed to evaluate the safety and efficacy of percutaneous IRE in unresectable HCC abutting the diaphragm. We hypothesized that IRE could be a better choice for HCC abutting the diaphragm.

Methods

The present prospective study (NCT02329106) was approved by the ethics committee of the Institutional Review Board of Fuda Cancer Hospital. The study was conducted in compliance with the Helsinki Declaration, and written in-

formed consent was obtained from all patients.

Patient selection

A total of 26 patients (median age: 62 years; range: 45–75 years) with 39 tumors were enrolled for the study between July 2015 and September 2018. HCC was diagnosed according to the practice guidelines of the American Association for the Study of Liver Diseases (AASLD).¹⁹ Computed tomography (CT) images were used to measure the shortest distance from the edge of the tumor to the diaphragm. The inclusion criteria were as follows: (1) subphrenic HCC (defined as a tumor adjacent to the diaphragm [<10 mm] on axial or coronal CT or magnetic resonance [MR] imaging); (2) tumor size of ≤ 5 cm; (3) tumor location adjacent to the diaphragm and unable to be subjected to surgical resection or with patient refusal to undergo surgical resection; (4) absence of portal vein tumor thrombus or formation of stubborn malignant ascites; and (5) adequate liver function (Child-Pugh classification of grade A or grade B). The following exclusion criteria were adopted: (1) intolerance to general anesthesia; (2) presence of a pacemaker or biliary metal stents; or (3) diagnosis of arrhythmias, epilepsy and myocardial injury.

IRE procedure

Preoperative preparation involved a 64-slice spiral CT (SOMATOM Definition AS; Siemens Healthcare, Erlangen, Germany), enhanced CT examination and 1.5 T superconducting MR scans, performed to determine whether the tumor was associated with unilateral or bilateral secondary bile ducts, portal veins and other vital structures without distant metastasis, and to confirm that there were no radical surgical resection conditions. Anesthetization included induction medications of midazolam, etomidate, sufentanil and vecuronium under mechanical ventilation of 60% oxygen concentration. Remifentanyl and propofol, in combination with a small amount of isoflurane inhalation, was administered as maintenance medication, and intermittent addition of vecuronium was applied to achieve full muscle relaxation.

After routine aseptic techniques and anesthesia, IRE ablation was performed using the IRE ablation system (NanoKnife; AngioDynamics, Latham, NY, USA) under ultrasound (US) alone or US fused with CT. Electrodes were inserted into lesions under imaging guidance. The number of electrodes used ranged from two to six and was based on the axial maximum tumor size, the distance between adjacent electrodes (1.0–2.0 cm), and exposure length of the ablation electrode (1.0–2.5 cm). To prevent pulse-induced arrhythmias, the IRE generator was synchronized with the patient's cardiac rhythm. Ablation parameters included voltage 1,500–3,000 V in 10 groups of 90 pulses, and the pulse width for each group was 90 μ s. Successful completion of the procedure was defined as the ability to successfully deliver all planned pulses (at least 90) in accordance with the size and dimensions of the lesion as well as to ensure that the current showed a change of at least 5 A from that of the initial 10 pulses delivered. Patient's vital signs were closely monitored during IRE, and the type of anesthesia administered and other surgery-related accidents or complications were recorded.

Patient follow-up

Patients remained hospitalized for at least 24 h after re-

ceiving the IRE ablation treatment. Routine laboratory tests were performed, including liver function test for alpha fetoprotein (AFP) level. The CT and MR imaging were carried out to assess imaging changes. The first assessment was performed 1 month after the IRE procedure, and subsequent assessments were performed every 3 months. Follow-up images were independently interpreted by a senior radiologist with at least 10 years of liver imaging experience. Any tumor observed in the follow-up imaging was reviewed during the weekly multidisciplinary HCC oncology committee meetings.

Evaluation of complications

Adverse events that occurred during the perioperative period, such as pain, fever, or abnormal laboratory results were recorded. Complications were classified as minor and major, in line with the guidelines of the Society of Interventional Radiology Standards of Practice Committee.²⁰ Major complications were defined as any event that led to death or was life-threatening, required surgical or radiological interventions or prolonged hospitalization. All other complications were considered as minor complications.

Evaluation of technical success and treatment effectiveness

Technical success was defined as the evaluation of complete ablation rate observed via CT and MR imaging 1 month after the IRE procedure. Complete ablation was defined as the absence of visible nodules or irregular enhancements near the ablation zone in the arterial phase. During IRE treatment, the technical characteristics of the IRE procedure, including average voltage, number of electrodes, and total number of pulses delivered between each combination of electrodes for each procedure, were recorded.

Evaluation of tumor control

After administration of IRE ablation treatment, the presence of irregular regional enhancement within 1 cm of the ablation area in the arterial phase, nodule enlargement or identification of new contrast enhancement areas during the follow-up period reflected local tumor progression (LTP). Time to LTP was defined as the date from IRE ablation administration to the date of the first observation of LTP.

Evaluation of tumor response

Treatment response was evaluated using contrast-enhanced CT or MR imaging and the guidelines of the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Arterial phase enhanced imaging revealed that the target lesions were not observed in complete response (CR). Partial response (PR) was reflected by a $\geq 30\%$ decrease in the sum of diameters of the target lesions. Progressive disease (PD) was reflected by a $\geq 20\%$ increase in the sum of diameters of target lesions or new lesions. Stable disease (SD) manifested target lesions that were not decreased to PR or increased to PD.

Statistical analysis

Data analyses were performed using SPSS version 20.0

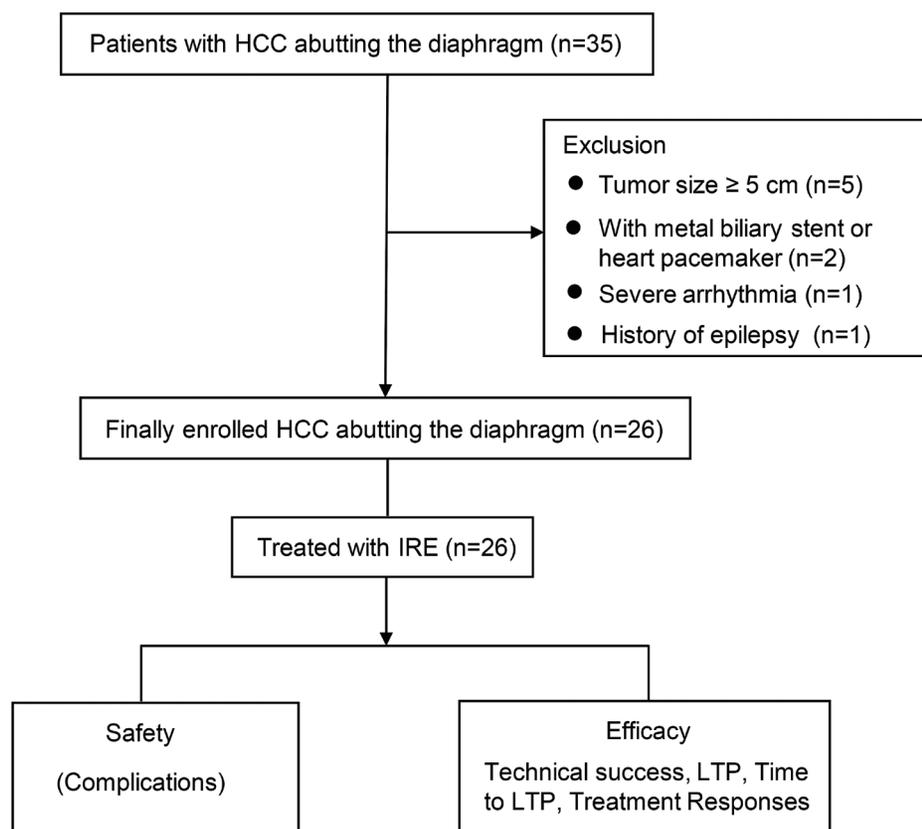


Fig. 1. Flowchart of patient selection.

(IBM Corp., Armonk, NY, USA). Patient demographics, tumor characteristics, and recurrences were analyzed using descriptive statistics. The median time to LTP was analyzed using the Kaplan-Meier method. Univariate and multivariate Cox regression models were used to estimate crucial baseline tumor parameters for time to LTP. A p -value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 35 patients with HCC abutting the diaphragm were evaluated by the multidisciplinary tumor board between July 2015 and September 2018. Among them, nine patients were excluded due to tumor size ≥ 5 cm ($n=5$), the presence of a metal biliary stent or heart pacemaker ($n=2$), presence of arrhythmias ($n=1$), or history of epilepsy ($n=1$). All 26 patients (16 males, 10 females) with 39 tumors underwent the IRE procedure (Fig. 1). Baseline characteristics of the patients are summarized in Table 1. The median age of patients was 62 years (range: 45–75 years). The median size of the tumors was 2.4 cm (range: 1.3–4.2 cm). All tumors were located adjacent to the diaphragm, with a median distance from the diaphragm of 0.56 cm (range: 0.16–1.0 cm). Of the 20 (76.9%) patients who underwent surgery, 11 (42.3%) received transarterial chemoembolization (TACE) before IRE. Representative CT images of HCC abutting the diaphragm before, during, and 40 months after performance of the IRE procedure are displayed (Fig. 2). No patient was lost to follow-up.

IRE procedure characteristics

During IRE ablation, two to six electrodes (median of three electrodes) were inserted into the ablation area under the guidance of CT coupled with US. Electrodes were placed at 10–20 mm intervals (median interval: 15 mm). Median energy delivery time was 20 m (range: 10–30 m) (Table 2).

Safety

No major complications or deaths associated with IRE occurred. During the follow-up period, all postoperative complications were minor, with adverse reaction levels ranging from 1 to 2 (Table 3). Five patients (19.2%) developed IRE treatment-related cardiac arrhythmia during IRE, eight patients (30.7%) showed elevated blood pressure which was controlled with nicardipine, and six patients (23.1%) developed pneumothorax without chest drain. All patients were in remission after general symptomatic treatment.

Efficacy

The technical success rate was 96.2% (25/26) for the initial session. Thirty-six tumors (92.3%) achieved complete ablation (Table 4). The median follow-up period was 16.7 months (range: 3.0–43.0 months). LTP occurred in 6 of the 39 tumors (15.4%); among these, LTP occurred in 2 of the 25 tumors (8.0%) with size of <3 cm and 4 of the 14 tumors (28.6%) with size of >3 cm. The median time to LTP was 20.4 months (range: 3.0–41.2 months) (Fig.

Table 1. Baseline characteristics of eligible patients

Characteristic	Value, <i>n</i> =26
Median age in years, mean (range)	62 (45–75)
Sex, <i>n</i> (%)	
Male	16 (61.5)
Female	10 (38.5)
Number of tumors	39
Tumor size, median (range)	2.4 (1.3–4.2)
AFP level in ng/mL	86.2 (2–1,562)
Median distance from diaphragm in cm, mean (range)	0.56 (0.16–1.0)
ECOG performance status >1, <i>n</i> (%)	8 (30.7)
Child-Pugh class, <i>n</i> (%)	
A	20 (76.9)
B	6 (23.1)
Tumor location, (%)	
S8	16
S7	11
S5	7
S4	3
S2	2
Prior therapy	
Surgery	20
TACE	11

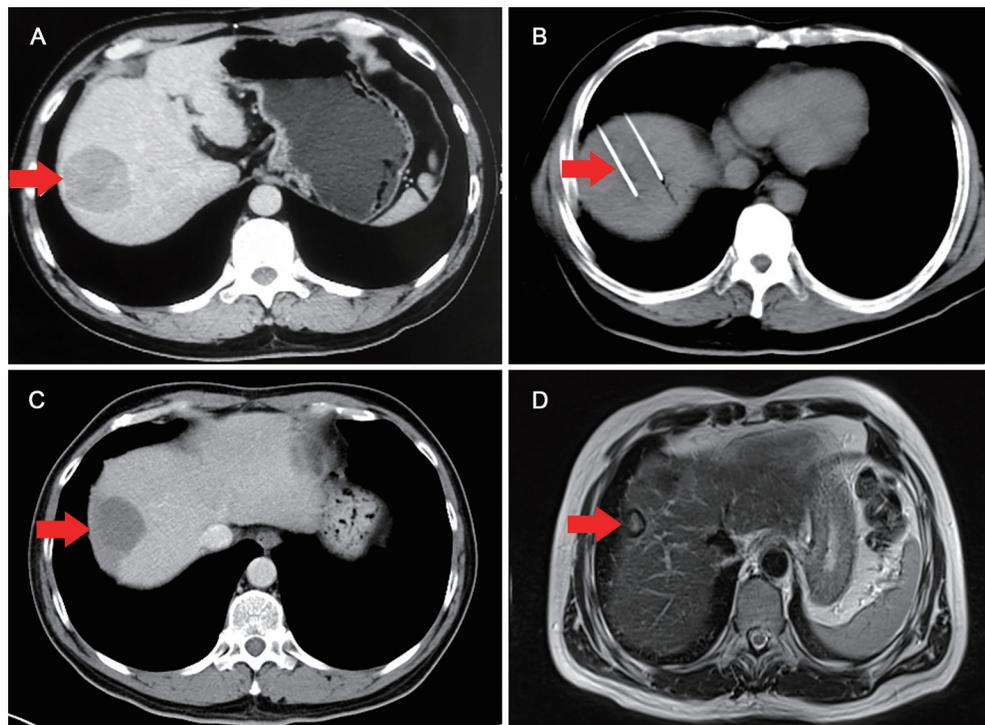


Fig. 2. A 49 year-old male with HCC abutting the diaphragm. (A) Preoperative enhanced CT illustrating location of the tumor adjacent to the diaphragm (arrow). (B) Two ablation electrodes inserted into the tumor area under the guidance of enhanced CT. (C) 6 months after IRE. (D) 40 months after IRE. The ablation zone has shrunk (arrow).

Table 2. IRE characteristics

Characteristic	Value
No. of electrodes, median	3 (2–5)
Pulse length in μ s	70–90
No. of pulses (range)	1,800 (180–3,800)
Electrode exposure length in mm	20 (15–25)
Median voltage	2,600 (1,500–3,000)
Median electrode spacing in mm (range)	15 (10–20)
Median length of active tip in mm (range)	20 (10–25)
Median energy delivery time in m (range)	20 (10–30)

Table 3. Adverse reactions after treatment

Adverse event	Grade (n, %)				Total (n, %)
	I	II	III	IV	
Pneumothorax	2 (7.7)	4 (15.4)	0	0	6 (23.0)
Cardiac arrhythmia	2 (7.7)	2 (7.7)	0	0	4 (15.3)
Pleural effusion	0	1 (3.8)	0	0	1 (3.8)
Elevated blood pressure	2 (7.7)	6 (23.0)	0	0	8 (30.7)
Partial portal Thrombosis	0	1 (3.8)	0	0	1 (3.8)
Abdominal pain	1 (3.8)	2 (7.7)	0	0	3 (11.5)
Fever	1 (3.8)	0	0	0	1 (3.8)
Vomiting	1 (3.8)	1 (3.8)	0	0	2 (7.7)
Decreased platelet count	0	1 (3.8)	0	0	1 (3.8)

3). Results of univariate analyses revealed that AFP level (hazard ratio [HR]=8.72 [95% confidence interval (CI): 2.97, 13.30]; $p=0.03$), vascular invasion (HR=2.58 [95% CI: 1.10, 4.21]; $p=0.02$), and overall tumor size (HR=0.78 [95% CI: 0.45, 1.86]; $p=0.01$) were significantly associated with time to LTP. However, multivariate analyses results revealed that only overall tumor size of >3 cm (HR: 1.24 [95% CI: 0.38, 3.81]; $p=0.03$) was significantly associated with time to LTP (Table 5).

Discussion

The results of the present study indicated that IRE ablation was a safe and effective treatment method for HCC abutting the diaphragm. About 92.3% of the tumors achieved complete ablation and 15.4% of the patients experienced LTP. Moreover, the median time to LTP was 20.4 months, and multivariate analyses revealed that only overall tumor size (>3 cm) was associated with time to LTP.

No IRE-related deaths occurred in the present study. Diaphragmatic perforation and other serious adverse events were not observed in the study. Five patients developed

cardiac arrhythmia, which resolved once the released pulse ended and after nicardipine treatment. The cases of arrhythmia were caused by the high-voltage electric field which induced bioelectrical disturbance in the body. This underscores the need for cardiac synchronization in such patients.²¹ Two patients had pneumothorax caused by electrode puncture of the lung. These results suggested

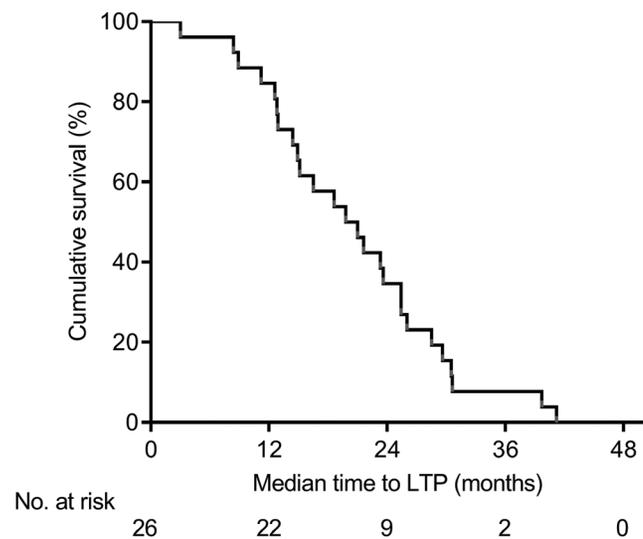


Fig. 3. Graph representing time to local tumor progression in 26 patients with 39 tumors after IRE.

Table 4. Treatment responses of the tumors

Treatment responses	Total	CR	PR	SD	PD
Number of tumor	39	36	2	1	0
Percentage	100	92.3	5.1	2.6	0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 5. Factors associated with time to local tumor progression after IRE

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age >60 years	0.82 (0.51–1.45)	0.67		
Cirrhosis	1.40 (0.51–2.87)	0.71		
No prior treatment	1.21 (0.49, 3.04)	0.86		
AFP level >200 ng/mL	8.72 (2.97, 13.30)	0.03	1.263 (0.789–2.354)	0.06
More than one nodule	0.76 (0.23, 3.20)	0.61		
Vascular invasion	2.58 (1.10–4.21)	0.02	2.48 (0.79–4.96)	0.22
Overall tumor size >3 cm	0.78 (0.45–1.86)	0.01	1.24 (0.38, 3.81)	0.03

that IRE could be considered as a treatment option in the treatment of patients with HCC abutting the diaphragm.

Surgery is the standard treatment procedure for early-stage HCC. However, only less than 20% of the patients are suitable for surgery.^{2,22} For patients who are not suitable for surgery, radiofrequency ablation is considered as a safe and effective therapy for early-stage HCC.²³ However, radiofrequency ablation has heat-sink effect and hence cannot protect vital structures well.^{24,25} To avoid these limitations, IRE has been proposed as a safer alternative, as it does not cause damage to bile ducts or blood vessels and vital structures.^{26,27} Moreover, radiofrequency ablation with infusion of artificial ascites creates a buffer zone and isolates vital structures, such as the diaphragm, stomach, bowel loops and gallbladder. However, artificial ascites increases the risk of additional trauma during radiofrequency ablation. The technical success rate of artificial ascites has been low. More importantly, artificial ascites themselves may increase the risk of peritoneal seeding.²⁸ Therefore, IRE ablation could be a potential treatment option for HCC abutting the diaphragm.

Tumor location is an important factor affecting local tumor control. In the present study, the LTP was achieved for 15.4% of lesions. Kang *et al.*¹³ retrospectively analyzed 80 patients who underwent a percutaneous radiofrequency ablation with tumor diameters of <4 cm and abutting the diaphragm. LTP was observed in 29% of the lesions. Makovich *et al.*²⁹ retrospectively analyzed 38 HCC patients who underwent a percutaneous microwave ablation of lesions (≤ 5 mm from diaphragm) abutting the diaphragm. LTP occurred in 23.7% of the lesions. Yang *et al.*³⁰ reported on 61 patients (with 77 lesions) who were treated with percutaneous cryoablation. LTP was observed in 41.9% of the lesions. To sum up, all these results suggested that the rate of LTP from IRE was significantly lower than that from radiofrequency ablation, microwave ablation, and cryoablation. Hence, percutaneous IRE appears to be a better choice for HCC abutting the diaphragm.

In the present study, the complete ablation rate was 92.3%. Sutter and his colleagues³¹ retrospectively analyzed 58 patients with HCC and 75 lesions who underwent IRE ablation. They found the complete ablation rate to be 77.3%, which was nearly 81.8% for lesions with diameters <30 mm. Fruhling *et al.*³² found a complete ablation rate of 78.9% at 3 months after receipt of IRE and 65.8% at 6 months after. These preliminarily clinical data indicate that IRE ablation can effectively treat HCC-abutting diaphragm tumors, with good complete ablation rates.

In summary, this is the first study to demonstrate that IRE is a safe and effective treatment option for HCC abutting the diaphragm. Furthermore, compared with other ablation techniques, IRE has a lower LTP rate and higher survival benefit for HCC abutting the diaphragm. However, this study has some limitations, such as the small sample

size. Future multicenter studies are advocated to validate the present findings.

Acknowledgments

We thank all the patients and their families for supporting the study. We also thank the staff in our hospital for their assistance.

Funding

This study was supported by grants from the International Science Foundation of Affiliated Fuda Cancer Hospital, Jinan University (No. Y2018-ZD-01).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Designed the research (LN, ML), conducted the research (ZC, JZ, YM), analyzed the data (YM, ML), wrote the paper and took primary responsibility for its final content (YM, ML). All authors read and approved the final manuscript.

Data sharing statement

All data are available upon request.

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