

Irreversible electroporation in primary and metastatic hepatic malignancies

A review

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Abstract

Background: Liver cancer makes up a huge percentage of cancer mortality worldwide. Irreversible electroporation (IRE) is a relatively new minimally invasive nonthermal ablation technique for tumors that applies short pulses of high frequency electrical energy to irreversibly destabilize cell membrane to induce tumor cell apoptosis.

Methods: This review aims to investigate the studies regarding the use of IRE treatment in liver tumors and metastases to liver. We searched PubMed for all of IRE relevant English language articles published up to September 2016. They included clinical trials, experimental studies, observational studies, and reviews. This review manuscript is nothing with ethics issues and ethical approval is not provided.

Results: In recent years, increasingly more studies in both preclinical and clinical settings have been conducted to examine the safety and efficacy of this new technique, shedding light on the crucial advantages and disadvantages that IRE possesses. Unlike the current leading thermal ablation techniques, such as radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, IRE requires shorter ablation time without damaging adjacent important vital structures.

Conclusion: Although IRE has successfully claimed its valuable status in the field of hepatic cancer treatment both preclinical and clinical settings. In order to systemically test and establish its safety and efficacy for clinical applications, more studies still need to be conducted.

Abbreviations: CT = computed tomography, HCC = hepatocellular carcinoma, IRE = irreversible electroporation, LRFS = local recurrence free survival, MWA = microwave ablation, RFA = radiofrequency ablation.

Keywords: hepatocellular carcinoma, irreversible electroporation, liver metastases, primary liver tumor, tumor ablation

1. Introduction

Liver cancer can be divided into 2 categories based on the primary tumor site: primary liver cancer and metastatic cancer to liver (liver metastases). Primary liver cancer is the 3rd leading cause of cancer mortality worldwide^[1] and the 7th leading cause of cancer-related death in the United States.^[2] Among the types of

primary liver cancers, hepatocellular carcinoma (HCC) is the predominant histologic form^[3] and has an incidence similar to the US liver cancer mortality rate, indicating a poor prognosis for HCC patients.^[4] According to the data from Surveillance, Epidemiology, and End Results Program of National Cancer Institute, both the HCC incidence rate and the US liver cancer mortality rate increased over recent years, from 3.1 to 5.1 per 100,000 persons and from 3.3 to 4.0 per 100,000 persons, respectively.^[5] Furthermore, survival rate in patients with advanced HCC is not significantly improved by systemic chemotherapy.^[6,7] Only 20% to 30% of patients are eligible candidates for surgical tumor resection when they are diagnosed. Safer and more efficient procedures are desperately needed for liver tumors and metastases treatment.^[8] This review compares irreversible electroporation (IRE) with other traditional ablation techniques and includes research studies in both preclinical and clinical settings published in recent years focused on investigating safety and/or efficacy of IRE technique, aiming to summarize these studies to provide an update of IRE application and improve the clinical practice of this new technique.

We searched PubMed for all of IRE relevant English language articles published up to September 2016. This review manuscript is nothing with ethics issues and ethical approval is not necessary.

2. IRE and other local ablation techniques

Local ablation techniques have been crucial and useful for treating benign or malignant tumors in the past several decades.

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Partial liver resection or liver transplantation is still the most preferred method for treating malignant tumors for its potential of curing the cancer. However, the application of liver resection or transplantation is largely affected by several factors including patient's general condition, liver function reserve, and tumor stage and so on. Also, it is constrained by the location of the tumor. In this case, few patients can be eligible candidates for this primary treatment. IRE is a comparatively new minimally invasive nonthermal ablation therapy for hepatic tumor where high frequency electrical energy is applied in short pulses to ablate tissue.^[9,10] Electroporation induces increased permeability of cell membrane.^[11,12] This can lead to an abnormal transmembrane electrical potential across the plasma membrane which will irreversibly open the plasma membrane leading to cell apoptosis.^[13,14] However, while electroporation technology has been utilized for decades,^[15–17] IRE is still an emerging field in clinical application.

In addition to IRE, several other alternatives have been developed for ablating liver cancer, such as cryoablation, radiofrequency ablation (RFA), and microwave ablation (MWA). Every technique has been proven effective under certain circumstances and possesses its own advantages and disadvantages. Cryoablation freezes malignant tissue with a low temperature probe, which can be guided accurately by intraoperative ultrasonography and thermally monitored precisely with thermocouple.^[18] However, it is difficult to use cryoablation when the lesion is close to large vessels because the relative heat of circulating blood may warm cryoprobe and decrease treatment efficacy.^[18] Also, cryoablation can cause variable damage at the margin of ablation zones and injury to adjacent structures.^[19] RFA is another popular local ablation technique that thermally destroys the malignant tissue by placing a small electrode into the tumor to deliver directed radiofrequency energy. MWA is a form of thermal ablation used in interventional radiology to treat cancer. It uses electromagnetic waves in the microwave energy spectrum to produce tissue-heating effects. RFA and MWA are both widely used techniques, and in both techniques, the generated heat is difficult to control due to thermal fluctuation from blood circulation which affects the local heat.^[18,20,21]

Unlike the other alternative techniques, IRE requires minimal energy input into the system and can induce cell death in a nonthermal way, giving IRE an unique advantage in treatment of liver cancer.^[19,22,23] Typically, RFA procedures run in 375 to 500 kHz and MWA functions at 915 MHz or 2.45 GHz, while cryoablation requires cooling tumors to cytotoxic temperatures.^[23,24] Compared to other alternatives, IRE only applies several series of electrical pulses (typically 90 pulses) ranging from 1500 to 3000 V. The nonthermal electrical characteristic of IRE prevents collateral damage to other tissues, such as vessels, ducts, and nerves, which often occur in thermal ablation techniques.^[25,26] Furthermore, IRE creates a sharp edge between the treated and untreated tissues, thus providing a higher regional specificity in ablation which allows relatively easier monitoring and controlling.^[27] In addition, IRE requires shorter time to operate than other traditional ablation techniques because of its nonthermal characteristic, making it a more efficient technique than others. Recently, Tam and Abdelsalam^[28] evaluated the intratumoral uptake of nanoparticles used in combination with IRE or RFA in rabbit VX2 models, they found the nanoparticles in the tumor was most intense after RFA at 1 hour time point. However, the uptake of nanoparticles increased at 18-hour time point in IRE group, higher than RFA group, whose uptake

decreased during the time range. This study suggested that IRE might have ability to accelerate the cellular internalization of molecules.

3. IRE of hepatic tumors in preclinical settings

In recent years, more and more animal models have been built to evaluate the safety and efficacy of IRE. Different approaches were created to test the effects of different parameter settings on animal models. Summary of recent animal liver models of IRE in preclinical settings is shown in Table 1.^[25,29–34]

In 2012, Lee and Tafti^[33] corroborated the safety and efficacy of IRE in treating large tumor models in vivo by a rabbit model. They implanted VX2 tumors in 35 New Zealand White Rabbits and divided them into control, single IRE (IRE-S), and multiple IRE (IRE-M) 3 groups. The rabbits in IRE-S group underwent single IRE application, and those in IRE-M group were treated with multiple IRE applications. Before IRE treatment, the intrahepatic VX2 tumors were allowed to grow up to 1 to 1.5 cm. The mean longest diameter of ablation zones in IRE-S group was 3.6 cm and in IRE-M group was 3.9 cm. Contrast-enhanced computed tomography (CT) scans were performed on all the animals before the procedure at 24 hours, 3 days, and 21 days after treatment. Outcomes from both IRE-S and IRE-M group showed a significant decrease in tumor volume compared with control group. Furthermore, complete ablation of tumor was observed in IRE-M group 21 days after procedure, indicating a promising efficacy of IRE. No complication was observed in the experiment either during or after IRE sessions. Lee and Prieto^[25] also created another animal liver model in 16 Yorkshire pigs, which demonstrated IRE as a safe and effective ablative method. Fifty-five ablations were performed with real-time monitoring with ultrasound and followed by ultrasound, MRI, and CT. The mean longest diameter of the ablation zones was 3.4 ± 0.3 cm. Tumor cell death was observed with no complication in any of 16 animals and with full preservation of periablative zone structures including blood vessels, bile ducts, and neighboring tissues. The treatment areas were sharply demarcated, and areas of complete cell death stained positive for apoptotic markers (TUNEL, BCL-2 oncoprotein), suggesting involvement of the apoptotic process in the pathophysiology of cell death caused by IRE. In another swine model built by Charpentier et al,^[32] 16 liver ablations and 4 ablations in the liver hilum were performed in 8 healthy pigs using 2 monopolar electrodes spaced 2 cm apart. The longest diameter of ablation zones ranged from 2.95 ± 0.31 cm to 4.45 ± 0.07 cm. Hemorrhagic necrosis of the hepatocytes in the ablation zone were found with no evidence of heat sink and no major complication. Bile ducts, portal veins, and hepatic arteries were well-preserved. According to the ablation results of these studies, IRE may have the potential to be superior to conventional thermal ablation for the treatment of small, unresectable liver tumors.

In addition to swine models, 30 Sprague-Dawley rat models were built by Guo et al^[29] to examine the efficacy of IRE. In this model, significant differences in tumor size was found between the treated and untreated groups of HCC rat models with no postoperative complications in the treated group (Fig. 1). MR images showed a significant tumor size reduction within 15 days posttherapy, and histology correlation studies showed a clear progression from poorly differentiated viable hepatoma tissue pretherapy to extensive tumor necrosis and complete tumor regression in 9 of 10 treated rats 7 to 15 days after treatment.

Table 1**Summary of recent animal liver models of IRE in preclinical settings.**

Year	Authors	Animal model	Number	Voltage, V	Duration, μ s	Outcomes
2010	Guo et al ^[29]	Rat HCC	30	2500	100	Showed potential efficacy of IRE as an ablation technique for the treatment of HCC
2010	Zhang et al ^[30]	Rat Normal	18	1000/1500/2500	100	Showed MR imaging permits immediate depiction of ablated tissue zones for monitoring of IRE ablation procedures
2010	Lee et al ^[25]	Pig Normal	16	2000–3000	100	Examined the safety and efficacy of IRE and found complete tissue death without complication
2011	Guo et al ^[31]	Rat Normal	15	500–1000	100	Demonstrated IR-prepared contrast-enhanced MR imaging could be used to quantitatively measure IRE ablation zones in the liver
2011	Charpentier et al ^[32]	Pig Normal	8	2500–3000	100	Demonstrated IRE could be performed safely efficiently in liver hilum for liver tissue ablation
2012	Ben-David et al ^[53]	Pig Normal	25	2250–3000	50–100	Proved zones of tissue destruction could be predictable by adjusting different parameters in IRE sessions
2012	Lee et al ^[33]	Rabbits HCC	20	2500	100	Examined the safety and efficacy of IRE and validated the potential of IRE as a clinically translatable treatment
2014	Zhang et al ^[34]	Rat HCC	24	2500	100	Found IRE induced rapid changes on imaging tools, suggesting the possibility of delineating ablation zones from the unablated surrounding parenchyma

HCC = hepatocellular carcinoma, IRE = irreversible electroporation.

4. IRE of hepatic tumors in clinical settings

To date, 9 published case series have evaluated the safety and efficacy of IRE on human liver tumors. All of them adopted the NanoKnife system (AngioDynamics, New York), which consists of a footswitch, a control panel with a screen and a cardiac synchronizer, and a direct current generator connected with unipolar or bipolar needle electrodes. Table 2 shows summary of recent IRE studies on liver tumor treatment in clinical settings.^[35–42]

In 2010, Ball et al^[43] published a clinical trial report of IRE on evaluating the complications associated with IRE procedure which is the first report of IRE intervention in human subjects. They found IRE to be an encouraging new technique and most importantly, it spared adjacent tissues with no vascular damage. All complications were manageable and largely predictable.

Later, a single-center prospective nonrandomized cohort study was published by Thomson et al in 2011,^[44] which included 38 patient volunteers with advanced liver, kidney, or lung malignancy. Clinical examination, biochemistry, and CT scans were obtained before, immediately after, 1 month after, and 3 months after IRE to examine the treated area. A total of 63 IRE ablations of liver tumors were performed in 25 patients, and immediate postprocedure CT scans showed rim enhancement with no enhancement of the ablated areas. Subsequent 1- and 3-month follow-up CT scans showed nonenhancement in both the ablated areas and the rims. Fifteen out of the 18 targeted tumors were successfully ablated in HCC patients. The IRE response rate reached 50% in liver metastases group. However, progressive disease was found in all individuals in this group and all metastases larger than 5 cm showed no response compared to control group. According to this study, Thomson found IRE to be safe for human clinical use when ECG-synchronized delivery was

used. The author also suggested that there was no evidence of major vessel or bile duct injury when these structures were included in the IRE procedure zones.

A retrospective review study of patients treated with a total 31 separate IRE procedures over a period of 10 months was reported by Kingham et al.^[45] The study included 28 patients with 65 tumors ranging from 0.5 to 5 cm with a median of 1 cm. The majority of patients had colorectal cancer liver metastases (75%), and HCC patients made 7% of the study population. Contrast-enhanced CT scans or MRI was performed in the immediate perioperative period at 1 to 3 months and 6 months. Overall, there were 3 local recurrences and 1 tumor with persistent disease – a combined local failure rate of 7.5%. Within the study, 41 tumors were located within 1 cm of a major hepatic vein or portal pedicle. Complications included 1 case of intraoperative arrhythmia and 1 case of postoperative portal vein thrombosis. The mortality rate was 3% with no treatment-associated mortality. As a result, the authors concluded that IRE technique was a safe treatment option for patients with perivascular malignant hepatic tumors.

Similar results were found by Cannon et al,^[46] who published a study representing a multiinstitutional prospective registry of 44 patients undergoing 48 IRE procedures near vital structures in a period of 2 years for liver tumors including 20 colorectal metastases, 14 HCCs, and 10 other metastases. The study was specifically focused on the tumors which were in proximity to vital structures. Patients were followed up at the time of discharge or within 2 weeks of IRE procedure for safety consideration and then at 3-month intervals with CT or MRI evaluations. Initial success was achieved in 100% of the procedures, with an overall local recurrence free survival (LRFS) rate of 97.4%, 94.6%, and 59.5% at 3, 6, and 12 months, respectively. In addition, a trend toward higher recurrence rates was found for tumors larger than

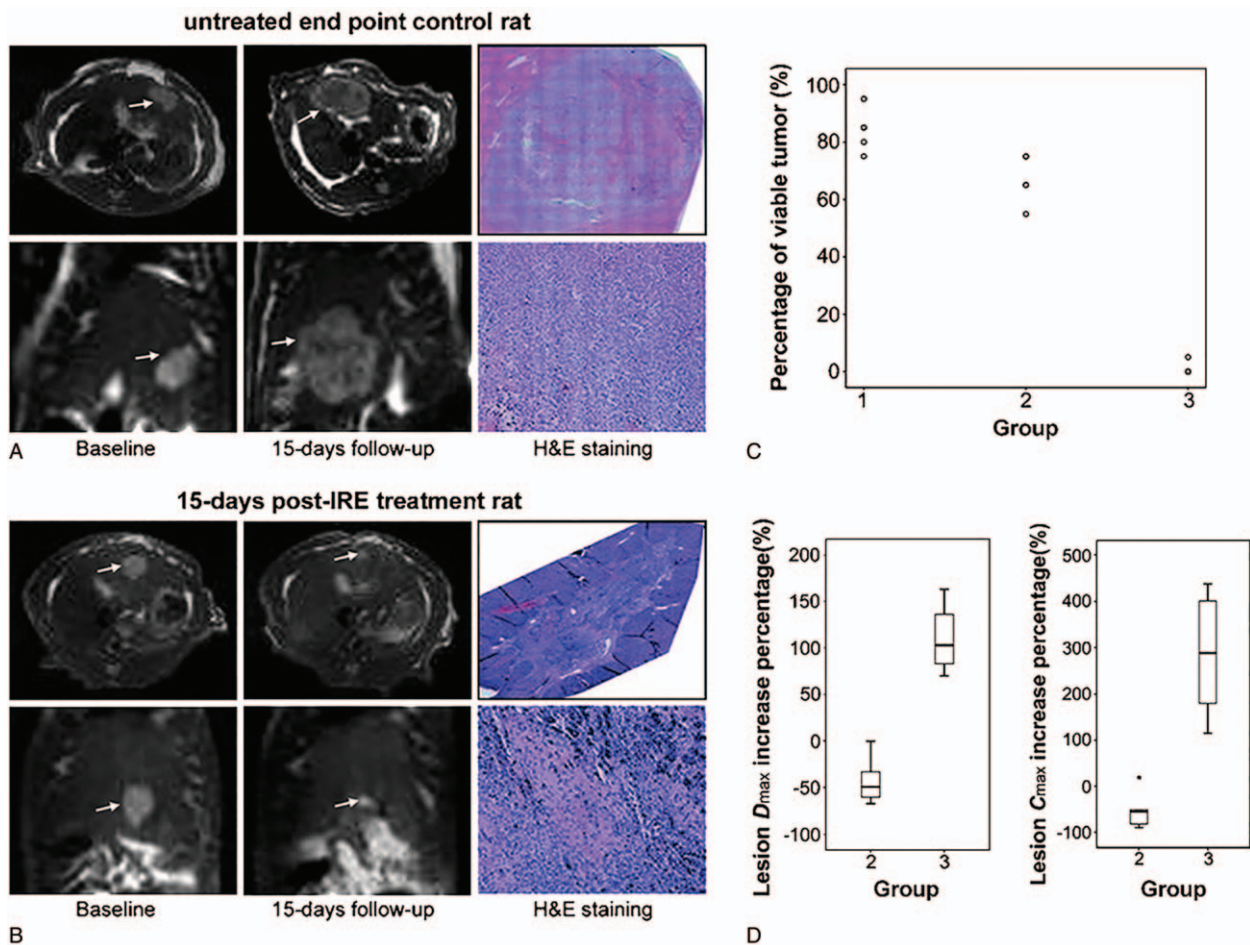


Figure 1. MRI images in axial and coronal orientations along with corresponding pathologic H&E slide images for an untreated 15-d end point control rat (A) and a 15-d post-IRE treatment rat (B).^[29] A significant reduction of tumor size in IRE-treated animal (B) is shown compared to the untreated rat (A). Arrows indicate tumor positions. H&E pathology slides showed 70% viable tissue within the untreated tumor (A) and completed tumor regression within the IRE-treated rat (B). Scatter plot (C) shows the percentage of viable tumor tissue for 6 rats at baseline control interval (group 1), 6 untreated control rats following a 15-d growth period after original baseline scan (group 2), and 6 IRE-treated rats following the same 15-d growth period (group 3). Box plots (D) show the D_{max} increase (left) and C_{max} increase (right) for 15-d follow-up animals in untreated control group 2 and IRE-treated group 3. D_{max} and C_{max} increase for group 2 rats were significantly greater than D_{max} and C_{max} increase for group 3 rats ($P = .004$ for both comparisons using nonparametric Mann–Whitney U test). D_{max} , along the orientation bearing the largest tumor diameter; C_{max} , the cross-product of the maximum lesion diameter D_{max} and largest diameter measured perpendicular to D_{max} . IRE=irreversible electroporation, MRI=magnetic resonance imaging.

4 cm (hazard ratio: 3.236, 95% CI: 0.585–17.891; $P = .178$) and a slight difference between the surgical and percutaneous approaches of IRE was observed 3 and 6 months postprocedure. There were 9 adverse events after 5 procedures. Three of these 9

adverse events including neurogenic bladder, abdominal pain, and flank pain may have been procedure related. All complications resolved within 30 days, and there were no treatment-related deaths.

Table 2

Summary of recent IRE studies on liver tumor treatment in clinical settings.

Year	Authors	Patients	Tumor	IRE sessions	Tumor size, mm	Voltage, V	Duration, μ s	Complete ablation rate		LRFS	
								HCC	Metastases	Rate	Time
2011	Thomson et al ^[35]	25	N/A	63	10–80	1500–3000	70	.83	.50	N/A	N/A
2012	Kingham et al ^[36]	28	65	31	5–50	1500–3000	70	N/A	N/A	.93	6 months
2013	Cannon et al ^[37]	44	44	48	11–110	1500–3000	100	1.00	1.00	.95	6 months
2014	Hosein et al ^[38]	28	58	36	12–70	N/A	N/A	N/A	.97	.79	2 years
2015	Cheng et al ^[39]	6	6	6	6–26	1500–3000	90–100	1.00	N/A	1.00	3–17 months
2015	Sugimoto et al ^[40]	5	6	6	11–28	1500–1800	70	.83	N/A	1.00	244 ± 55 days
2016	Padia et al ^[41]	20	N/A	N/A	10–33	1500–3000	20–100	.90	N/A	1.00	1 year
2016	Niessen et al ^[42]	34	65	N/A	2–71	1500	90	1.00	.95	.80	6 months

HCC=hepatocellular carcinoma, IRE=irreversible electroporation, LRFS=local recurrence free survival, N/A=not available.

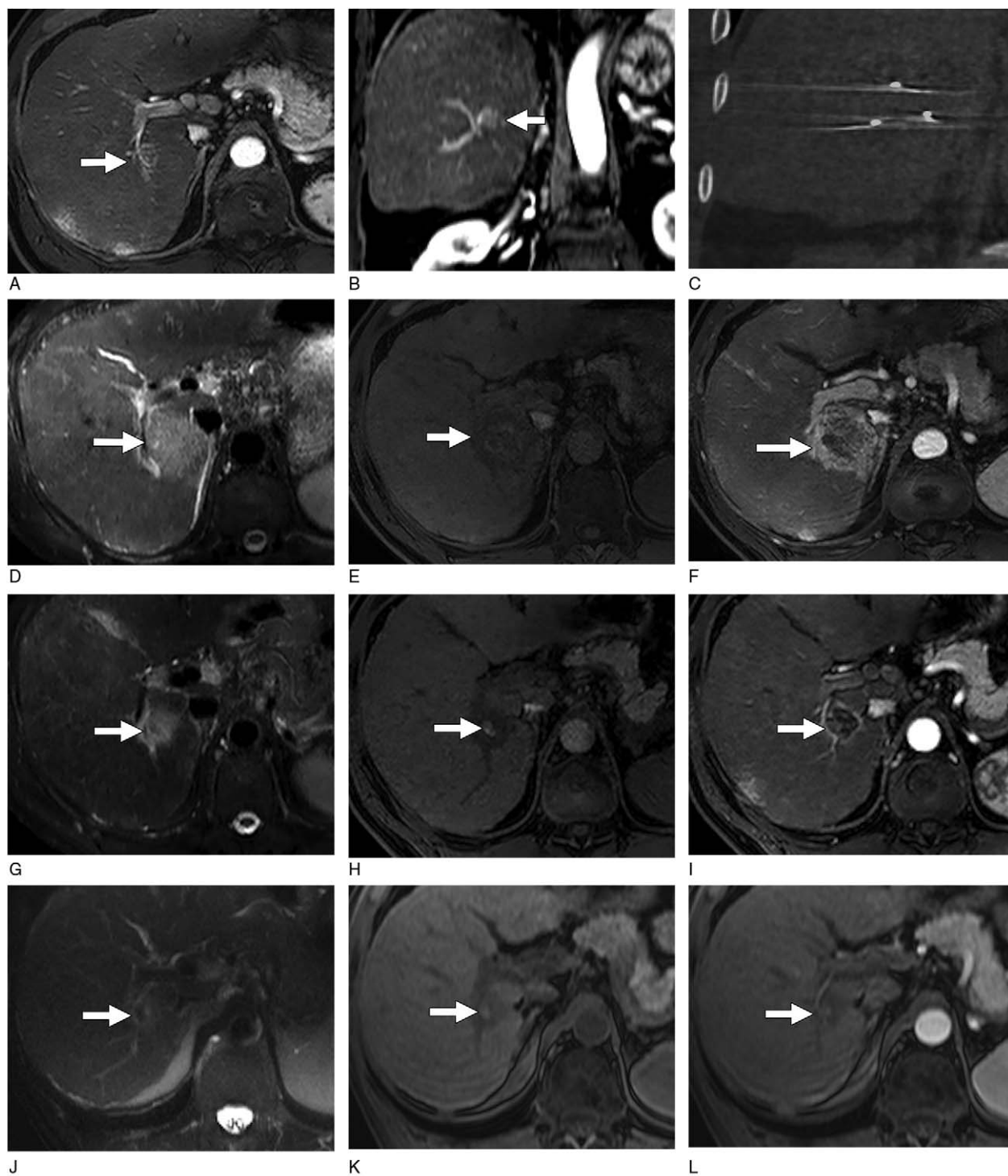


Figure 2. MR images of HCC after IRE in a 63-year-old man.^[49] Baseline axial (A) and coronal (B) gadolinium contrast-enhanced T1-weighted MR images obtained in the arterial phase show a 2-cm HCC lesion (arrow) in the right hepatic lobe adjacent to the right portal vein. (C) Unenhanced coronal CT image obtained after percutaneous IRE shows 3 electrodes in a parallel configuration. (D) T2-weighted MR image obtained 24 hours after IRE shows a large ablation zone (arrow) of diffuse increased signal intensity. (E) Unenhanced T1-weighted MR image obtained 24 hours after IRE shows slight hyperintensity of the ablated tumor with associated decreased signal intensity in the ablative margin (arrow). (F) T1-weighted MR image obtained in the arterial phase 1 day after IRE shows marked persistent enhancement of the ablative margin (arrow). The tumor itself demonstrates no enhancement. (G) T2-weighted MR image obtained 30 days after IRE shows a marked reduction of the ablation zone (arrow). (H) Unenhanced T1-weighted MR image obtained 30 days after IRE shows that the increased signal intensity of the tumor (arrow) persists. The size of the tumor decreased compared with day 1 after IRE. (I) T1-weighted MR image obtained in the arterial phase 30 days after IRE shows a substantial decrease in the size of the ablation zone compared with day 1 and thinning of the ablative margin (arrow). Unenhanced (J) T2- and (K) T1-weighted MR images obtained 120 days after IRE show further involution of the ablation zone and persistent slightly increased signal intensity of the tumor (arrow). (L) MR image obtained in the arterial phase shows a lack of enhancement in the entire ablation zone. CT = computed tomography, HCC = hepatocellular carcinoma, IRE = irreversible electroporation, MR = magnetic resonance.

Another retrospective study reported by Hosein and Loaiza-Bonilla^[47] analyzed 29 patients (28 evaluable) who underwent 36 IRE sessions on 58 tumors for the management of colorectal liver metastasis between March 2010 and February 2013. All patients were assessed by CT scan immediately after IRE treatment, most had subsequent CT scans after 30 days according to patients' condition. No biliary strictures, vessel stenosis, thrombosis, or shunting within or near the treatment zones were observed in the CT scan results. Two adverse events related to IRE procedures were found in 2 patients (7%) including 1 case of ventricular arrhythmia and 1 case of atrial fibrillation; both resolved without sequelae. According to the study, LRFS reached 79% at the 2-year time point. However, all patients (n=19, 100%) showed progressive disease within 2 years.

Cheng et al^[48] published a similar retrospective study in the following year focusing on 6 HCC patients who underwent a total of 6 IRE procedures before liver transplant. All tumors showed a complete response on follow-up cross-sectional imaging performed at 1 month and every 3 months until liver transplant. Complete pathologic necrosis was observed in 5 of 6 treated tumors with sharp edges and well-preserved bile duct.

Recently Padia and Yeung^[49] published a retrospective study with 20 HCC patients treated with IRE which aimed to assess the postprocedure findings of IRE with MRI. The study reported a trend of decreasing signal intensity in the peripheral ablation zone on both T2-weighted ($P=.01$) and T1-weighted ($P<.08$) images acquired on postprocedure day 1, 30, and every 90 days thereafter. Complete response was observed in 18 patients (90%) with the other 2 patients showing a partial response (Fig. 2).

In 2015, Sugimoto and Kobayashi^[50] conducted a prospective clinical trial to assess the safety of IRE in Japan including 5 patients with 6 HCCs enrolled. Within the study, 5 of the 6 tumors were successfully treated and no local recurrence at 244 ± 55 days of follow-up. No procedure-related complications were seen during or after IRE intervention but an increase of 78 and 36 mmHg in systolic and diastolic blood pressure were observed as a minor complication.

In another prospective single-center study, Niessen and Pregler^[51] found promising results on the therapeutic efficacy of IRE treatment for hepatic tumors. The study included 65 malignant tumors in 34 patients, of which 33 were HCCs, 22 were colorectal cancer metastasis, 5 were cholangiocellular carcinoma, 3 were neuroendocrine cancer metastasis, and 2 were testicular cancer metastasis. The primary follow-up imaging was performed within 24 hours via both contrast-enhanced CT scans and MR imaging after the IRE procedure. Twelve tumors were treated with a 2nd IRE procedure for incomplete ablation and local recurrence observed by follow-up imaging. LRFS was 87.4%, 79.8%, and 74.8% at 3, 6, and 12 months. However, the complication rate was 27.5% with 6 major complications including 1 diffuse intraperitoneal bleeding, 1 partial thrombosis of the portal vein, and 4 liver abscesses. The high complication rate drew significant concerns to its safety.

5. Discussion

As discussed above, IRE processes its own advantages especially including avoiding the heat sink and sparing vital structures adjacent to tumor. The tumor ablation efficacy is promising, especially for those tumors smaller than 5 cm. Vital structures were all well-preserved in the studies although they were really close to the ablated area.

However, IRE is still not the first preferred choice among the various ablation procedures for HCC patients due to its limitations. In most situations, only patients who have limited volume hepatic tumor and who are not candidates for liver transplantation or other thermal ablation surgeries will be enrolled in IRE treatment. As one of its shortcomings, IRE always requires general anesthesia and adequate neuromuscular blockade for its potential to cause muscle stimulation from high current during the procedure. Another important shortcoming of IRE is the inability to completely ablate large tumors, especially those larger than 5 cm, without repetition or repositioning the electrodes, which limits the number of qualified candidates.^[52] In addition, IRE can cause unintended injury to other structures when electrodes are placed. Ball et al^[43] reported 3 instances of pneumothorax during their study. One of these cases occurred after transabdominal placement of electrodes in the liver. No treatment was required for the other 2 cases and none of the 3 cases required urgent treatment. Also, the same group found 3 cases of pneumothorax in another clinical trial published in 2011.^[44] One of them was caused directly by an electrode but resolved spontaneously with no delay in discharge. Authors suggested that electrodes could be placed during periods of apnea to minimize diaphragmatic movement if the procedure carried the risk of pneumothorax. Cardiac arrhythmia is also a notable serious complication from IRE due to the presence of high current close to the heart. Ventricular bigeminy, ventricular tachycardia, and atrial fibrillation were reported by Ball et al and Thomson et al.^[43,44] According to the study, the most serious cardiac rhythm disturbance occurred during the ablation of a very large hepatic tumor which was directly beneath the diaphragm and close to the inferior cardiac border.^[43]

In conclusion, although IRE has been introduced in the clinical arena within the past decade, it has successfully claimed its valuable status in the field of hepatic cancer treatment though it possesses its own disadvantages as discussed above. In order to systemically test and establish its safety and efficacy for clinical applications, more studies still need to be conducted.

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