Factors Associated with Short-Term Local Recurrence of Liver Cancer after Percutaneous Ablation Using Irreversible Electroporation: A Prospective Single-Center Study

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ABSTRACT

Purpose: To evaluate the risk factors associated with short-term local recurrence of malignant liver lesions after irreversible electroporation (IRE).

Materials and Methods: Thirty-nine consecutive patients (79 malignant liver lesions) were treated with IRE, of whom 14 were excluded from the analysis (including 12 without 6 mo of follow-up and two with incomplete ablation). The remaining 25 patients (aged 59.4 y ± 11.2) had 48 malignant liver lesions, including 22 hepatocellular carcinomas (HCCs), six cholangiocellular carcinomas, and 20 metastatic liver cancers. Multivariate analyses were used to evaluate the associations of risk factors with early recurrence. The characteristics of patients, lesions, and IRE procedures were assessed by logistic regression.

Results: Fourteen of the 48 treated lesions (29.2%) showed early local recurrence after 6 months. Tumor volume (< 5 cm^3 vs ≥ 5 cm^3; $P = .022$) and underlying disease type (HCC, cholangiocellular carcinoma, or metastatic disease; $P = .023$) were independently associated with early local recurrence. However, distances to the surrounding portal veins (< 0.5 cm vs ≥ 0.5 cm; $P = .810$), hepatic veins ($P = .170$), hepatic arteries ($P = .761$), and bile ducts ($P = .226$) were not significantly associated with local recurrence.

Conclusions: Because short distances to the surrounding vessels were not associated with early local recurrence, percutaneous IRE might provide an alternative treatment option for perivascular tumors. However, patients with larger tumor volumes appeared to be poor candidates for percutaneous IRE. Regarding the different types of treated lesions, patients with HCC had significantly better outcomes.

ABBREVIATIONS

BMI = body mass index, EOB-DTPA = ethoxybenzyl diethylenetriamine pentaacetic acid, HCC = hepatocellular carcinoma, IRE = irreversible electroporation, RF = radiofrequency

Percutaneous ablation techniques, such as radiofrequency (RF) and microwave ablation, have become an established component of multimodal therapy regimens for primary and secondary liver cancer (1,2). However, because these techniques rely on a thermal ablation mechanism, there are some remaining limitations to their use and effectiveness. Indeed, as a consequence of the heat-sink effect, the rate of complete tumor necrosis decreases to less than 50% when there are larger vessels

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abutting the tumor (3,4). In addition, lesions that are proximal to vital structures (ie, major bile ducts, portal vein, and hepatic veins) and liver lesions that are subcapsular or centrally located continue to pose a challenge to the use of thermal modalities, as thermal protection of the adjacent organs or central bile ducts cannot be guaranteed (5,6).

Irreversible electroporation (IRE) is an innovative nonthermal ablation technique that offers certain advantages over other ablation techniques and has gained widespread attention (7). Instead of thermal energy, IRE delivers a number of electrical pulses that have millisecond durations. The pulses disturb the cell membrane potential by creating irreversible nanopores, leading to apoptosis (8,9). Although IRE is believed to destroy all cells within the ablation zone, a number of preclinical animal studies showed that its nonthermal ablation mechanism results in the preservation of proteins in the extracellular matrix of the supportive connective tissue. Therefore, the structural integrity of adjacent or contained vital structures (such as blood vessels, bile ducts, and nerves) appears to be unaffected by IRE (8,10–17). In the past 2 years, the literature reporting clinical experiences with IRE has grown considerably. The first clinical studies have demonstrated promising results regarding its safety and efficacy (18–24).

However, although the risk factors for early recurrence have been extensively evaluated for thermal ablation, the same information has not been available for IRE. Several clinical studies of thermal ablation (1,25–27) identified tumor size and complete ablation with an adequate tumor-free margin as the most important predictors of local recurrence. Other risk factors for local recurrence after thermal ablation include proximity to large vessels and subcapsular location or poor differentiation of the tumor (6,28). Because IRE relies on a fundamentally different mechanism of ablation, the risk factors for early local recurrence after thermal ablation are unlikely to also apply to IRE. Therefore, the aim of the present study was to evaluate the risk factors associated with early local recurrence after percutaneous treatment with IRE.

MATERIALS AND METHODS

A prospective, single-center clinical trial was conducted to evaluate the risk factors associated with early local recurrence within 6 months after an IRE procedure. The study addressed the main hypothesis that several factors influence the frequency of early local recurrence of malignant liver lesions after IRE, but that proximity to vascular structures is not among them. The study received institutional review board approval.

Patients with primary and secondary liver cancer were treated with IRE between December 2011 and March 2013. All patients were poor candidates for surgical options and thermal ablation in view of tumor location and/or preceding surgery. Each case was reviewed in a multidisciplinary tumor conference to ensure that all the treating physicians agreed with the proposed IRE treatment plan before the patient was included in the study. The following inclusion criteria were applied: written informed consent from each patient, age $>$ 18 years, maximum lesion diameter $<$ 5 cm, adequate liver and renal function, and an American Society of Anesthesiologists health status score of 0–3. Before IRE, each patient's disease was staged based on a contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis to rule out extrahepatic tumor manifestation. In addition, dedicated magnetic resonance (MR) imaging of the liver was performed before the ablation procedure to rule out additional malignant liver lesions that might have been undetectable on CT imaging. The MR imaging scan was performed with liver-specific contrast medium (gadolinium [Gd] ethoxybenzyl diethylenetriamine pentaacetic acid [EOB-DTPA]; Primovist; Beyer Schering, Berlin, Germany). Contraindications to IRE treatment in this study were the presence of a defibrillator or a pacemaker, a history or presence of cardiac arrhythmia, recent myocardial infarction, severe heart failure, and severe coagulation disorders (platelet count $>$ 50,000/cm^3; partial thromboplastin time $<$ 50 seconds, or International Normalized Ratio $<$ 1.5). In addition, any characteristics that contraindicated general anesthesia were also contraindications for IRE treatment, as was the presence of extrahepatic or multifocal hepatic disease.

During the study period, a total of 83 patients underwent percutaneous treatment with IRE, microwave ablation, or RF ablation, of whom 39 patients with 79 lesions received IRE. Of these 39 patients, we excluded 12 patients (21lesions) without follow-up imaging at 6 months and two patients (10 lesions) for whom incomplete ablation was documented at the 6-week follow-up examination. Forty-eight lesions were treated in the remaining cohort of 25 patients (four women and 21 men; mean age, 59.4 y ± 11.2 [standard deviation]; age range, 22–80 y; **Table 1**).

The lesions had a mean volume of 6.2 cm^3 ± 8.2 (range, 0.2–37.8 cm^3) and a mean largest diameter of 1.7 cm ± 0.7 (range, 0.7–3.6 cm; **Figs 1** and **2**). Twenty-two lesions were hepatocellular carcinoma (HCC; 45.8%), six were cholangiocellular carcinoma (12.5%), and 20 were metastatic liver cancer (41.7%).

Ablation Procedure and Follow-up

All patients were treated percutaneously with IRE by using the NanoKnife system (AngioDynamics, Latham, New York) and received general anesthesia with deep paralysis to prevent muscle stimulation. All IRE electrodes were percutaneously placed into the target area under CT fluoroscopy (CareVision, Somatom 16;

Table 1. Baseline Patient Characteristics and Baseline Lesion Characteristics

Characteristic	Value
Age (y)	
Mean ± SD	59.4 ± 11.2
Range	22–80
BMI (kg/m^2)	
Mean ± SD	27.9 ± 5.7
Range	19.0–40.0
Sex	
Male	21 (84)
Female	4 (16)
Underlying tumor disease	
Hepatocellular carcinoma	22 (45.8)
Cholangiocellular carcinoma	6 (12.5)
Colorectal metastasis	16 (33.3)
Other metastasis	4 (8.3)
Lesion volume (cm^3)	
Mean ± SD	6.2 ± 8.2
Range	0.2–37.8
Hepatocellular carcinoma	4.6
Cholangiocellular carcinoma	5.6
Colorectal metastasis	6.0
Other metastasis	17.5
Mean longest diameter of lesion (cm)	
Mean ± SD	1.7 ± 0.8
Range	0.7–3.6
Distance < 5 mm to vessels	29 (60.4)
Portal vein	12 (25)
Hepatic vein	17 (35.4)
Hepatic artery	7 (14.6)
Bile duct	5 (10.4)
Localization of lesions	
Segment I	0
Segment II	8 (16.7)
Segment III	1 (2.1)
Segment IV	12 (25.0)
Segment V	7 (14.6)
Segment VI	9 (18.8)
Segment VII	3 (6.3)
Segment VIII	8 (16.7)
Lesion in cirrhosis	
Yes	20 (42)
No	28 (58)
Child–Pugh class*	
Total	20 (100)
A	11 (55)
B	5 (25)
C	4 (20)

Note–Values in parentheses are percentages.
*In cases of liver cirrhosis.

Siemens, Erlangen, Germany) and high-definition ultrasound guidance (1–5 MHz convex multifrequency probe; Logiq E9; General Electric, Fairfield, Connecticut). The treatment parameter for voltage (1,000–3,000 V)

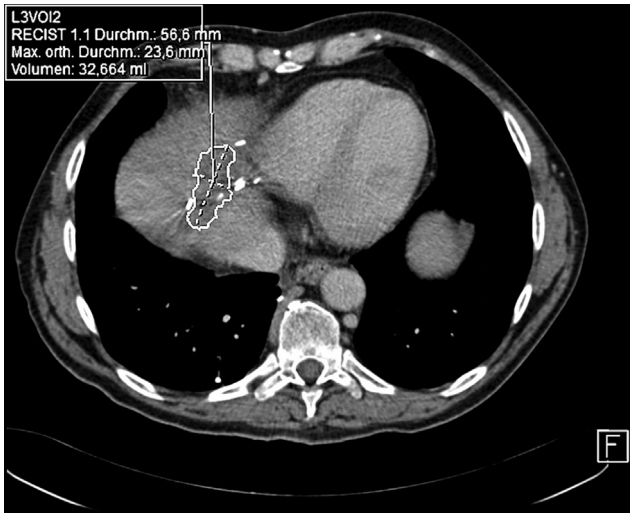

Figure 1. Images from a 69-year-old man with colorectal liver metastases (patient A). Preinterventional CT scan during portal venous-phase volumetry of the target lesion adjacent to the heart and diaphragm shows a volume of 32.7 cm^3 and a maximum orthograde diameter of 2.4 cm.

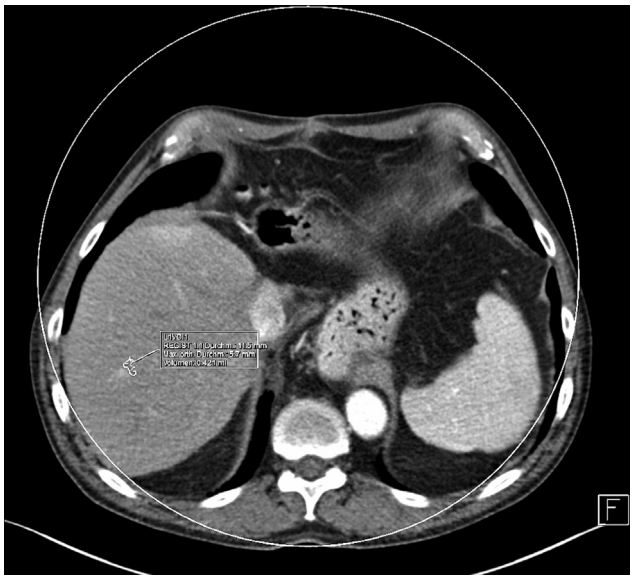

Figure 2. Image from a 66-year-old man with HCC (patient B). Preinterventional CT scan during arterial phase shows an arterially hypervascularized small HCC lesion in segment VII. The lesion's volume is 0.4 cm^3, and its maximum orthograde diameter is 0.6 cm.

depended on the distance between the electrodes (Figs 3 and 4). A total of 70–100 therapeutic pulses were delivered to the target lesion. If the current between two electrodes exceeded 48 A (high-current condition), the delivery of the pulses was aborted to prevent heat induction.

Before being discharged, patients underwent a post-interventional control scan with contrast-enhanced CT (n = 3) or MR imaging (n = 22) to ensure their safety by ruling out any therapy-associated side effects (Fig 5).

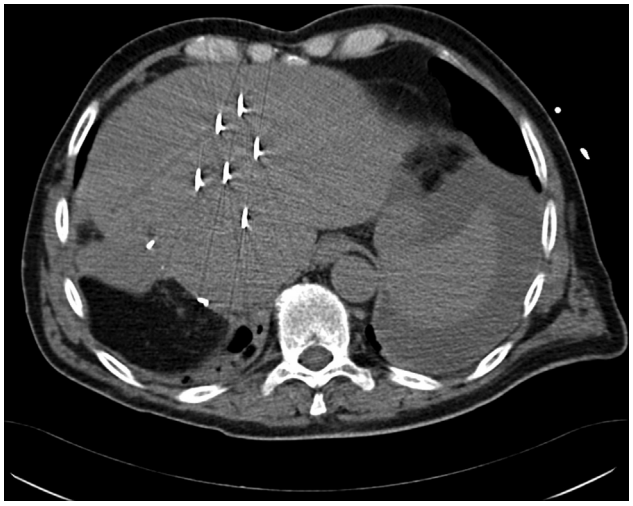

Figure 3. Unenhanced CT scan during IRE ablation of a large colorectal liver metastasis adjacent to the heart and diaphragm (patient A) shows six ablation probes in a parallel direction encompassing the target lesions adjacent to the heart and diaphragm.

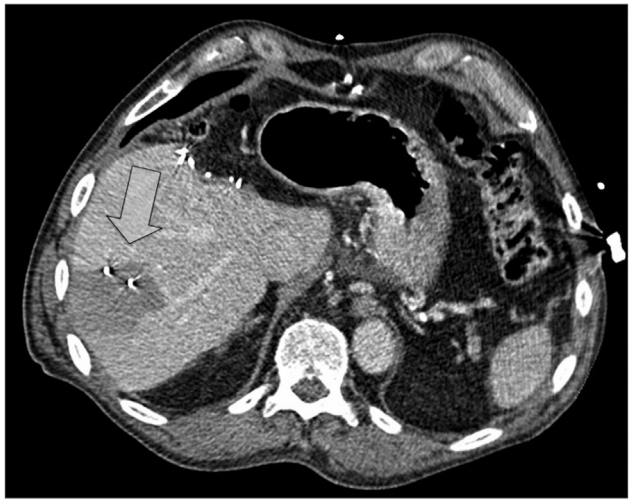

Figure 4. Unenhanced CT scan during IRE intervention for a small subcapsular HCC (patient B) shows two electrode tips that encompass the tumor lesion (arrow), as well as the beginning of the hypodense demarcation of the ablation zone.

After being discharged, all patients underwent follow-up MR imaging with a liver-specific contrast agent at 6 weeks, 3 months, and 6 months after IRE treatment (**Figs 6** and **7**). According to the Society of Interventional Radiology reporting standards for ablation (29), the presence of a persistent viable tumor at the 6-week follow-up examination was defined as incomplete ablation and led to the exclusion of the patient. Because of the particular appearance of the IRE ablation zones—and in accordance with preceding studies (18,30)—complete ablation was defined as a loss of enhancement for hypervascular tumors during the arterial phase and a loss of rim enhancement for hypovascular tumors during the portal venous phase, as assessed by using

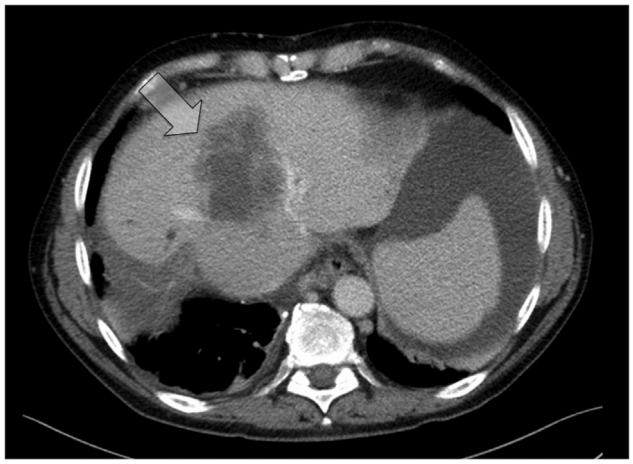

Figure 5. Postinterventional CT scan of patient A obtained before discharge and after ablation of a large colorectal liver metastasis shows complete ablation of the target lesion with hypodense demarcation of the ablation zone and peripheral hyperemia (arrow). The adjacent portal and hepatic veins remain unaffected by IRE.

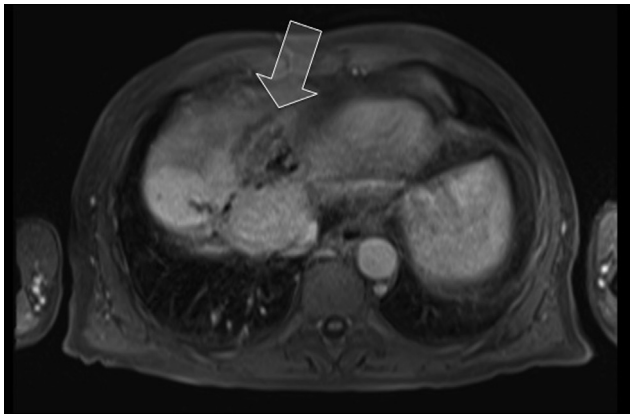

Figure 6. Follow-up Gd-EOB-DTPA–enhanced MR image taken 6 months after IRE ablation of a colorectal liver metastasis (patient A) during the portal venous phase shows hypodense demarcation of the ablation zone (arrow) and adjacent contrast enhancement as a result of a local recurrence.

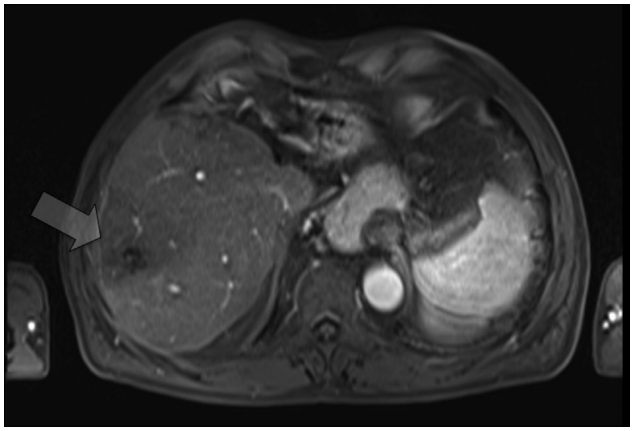

Figure 7. Follow-up Gd-EOB-DTPA–enhanced MR image taken 6 months after IRE ablation of an HCC (patient B) during the portal venous phase shows hypodense demarcation of the ablation zone (arrow) without evidence of local recurrence.

cross-sectional imaging studies at 6-month follow-up. In addition, local recurrence was defined as the presence of an enhancing tumor within 1 cm of the ablation zone at 6-month follow-up. Two radiologists analyzed all follow-up images until a consensus was achieved.

Statistical Analysis

The patient cohort was divided into two groups for statistical analysis: patients with and without early local recurrence (within 6 mo) as defined based on 6-month follow-up cross-sectional imaging. Three groups of variables were assessed. The first group consisted of patient-related risk factors, including age, sex, body mass index (BMI), presence of liver cirrhosis, and degree of chronic liver disease (per Child–Pugh classification). The second group consisted of tumor- or lesion-related risk factors, such as underlying tumor disease, lesion volume, maximum lesion diameter, lesion location (liver segment), distance to the closest portal vein branch, and distance to the nearest hepatic vein, artery branch, or bile duct. Volumetry and maximum diameter were measured by using SyngoVia (Siemens). Distance measurements were dichotomized with a cutoff value of 0.5 cm in all cases. The third group of variables consisted of procedure-based determinants of local recurrence, including the number of electrodes used, the minimum and maximum distances between the electrode probes, and the occurrence of high current during the intervention (ie, more than 48 A of current between the two electrodes). In this situation, the delivery of the planned pulses is automatically aborted by the IRE generator because of the risk of unintended thermal damage. When high-current conditions occur, the overall currents measured between two probes can be reduced by shortening the pulse lengths; however, shorter pulse lengths are less effective as a means of achieving complete ablation.

Several multivariate logistic regression analyses were performed to assess the statistical correlations between local recurrence and independent variables (ie, risk factors). A separate multivariable regression was performed for each risk factor. All binary regression analyses were performed by using a forward selection procedure (likelihood-based) with an exclusion factor of 0.10 and an inclusion factor of 0.07—instead of 0.05—because of the small number of lesions. The statistical influences of nonindependent variables (ie, risk factors) were evaluated by Fisher exact test, χ^2 test, t test, and likelihood-ratio test. All data were statistically analyzed by using SPSS (version 20; IBM, Armonk, New York) and Excel software (Microsoft, Redmond, Washington).

RESULTS

Patient- and Lesion-Based Risk Factors Associated with Early Recurrence

In the logistic regression analysis, tumor volume ($P < .001$) and underlying tumor disease ($P = .009$) were significantly associated with local recurrence (Tables 2 and 3). Local recurrence was observed for three of the 22 treated HCC lesions (13.6%), two of the six cholangiocellular carcinoma lesions (33.3%), six of the 16 colorectal cancer lesions (37.5%), and three of the four treated lesions in patients with other secondary liver cancers (75.0%). Regarding the volumes of the treated liver lesions, 11 of the 14 lesions with local recurrence had volumes of more than 5 cm^3 and 28 of the 34 lesions without local recurrence had volumes of less than 5 cm^3.

The greatest diameter of the lesion and the presence of HCC (vs other cancers) were also significantly associated with early recurrence, but they were not included in the model because they were not independent variables (Table 4): instead of the lesion's diameter, the lesion's volume was included as a variable; and instead of the presence of HCC, the underlying tumor disease was included as a variable. The mean greatest lesion diameters were 1.5 cm ± 0.7 in the group of lesions without local recurrence and 2.1 cm ± 0.8 in the group of lesions with local recurrence. After dichotomizing tumor volume with a 5-cm^3 cutoff value, we observed

Table 2. Tumor Volume and Local Recurrence Rates

Finding	Tumor Volume < 5 cm^3	Tumor Volume > 5 cm^3	Total
No. of treated lesions	31	17	48
No. of local recurrences	3	11	14
Local recurrence rate (%)	9.7	64.7	29.2

Table 3. Underlying Tumor Disease and Local Recurrence Rates

Finding	Hepatocellular Carcinoma	Cholangiocellular Carcinoma	Colorectal Liver Metastases	Other Liver Metastases	Total
No. of treated lesions	22	6	16	4	48
No. of local recurrences	3	2	6	3	14
Local recurrence rate (%)	13.6	33.3	37.5	75.0	29.2

Table 4. Results of Statistical Tests for the Unselected Variables Not Used for Regression Analysis

Comparison	*P* Value	Test
HCC vs other underlying tumor diseases	.030	Fisher exact
Cirrhosis vs no liver cirrhosis	.064	Fisher exact
Child–Pugh class (A vs B vs C)	.072	Likelihood-quotient
Tumor volume (> 5 cm^3 vs < 5 cm^3)	$< .001$	χ^2
Longest lesion diameter	.014	*t* test

HCC = hepatocellular carcinoma.

that it was quite significantly associated with early recurrence ($P < .001$). Larger lesion volumes were also associated with early recurrence ($P = .049$); 11 of the 14 lesions with local recurrence had volumes of more than 5 cm^3, whereas 31 of the 34 lesions without local recurrence had volumes of less than 5 cm^3.

The presence of liver cirrhosis (in 20 of the 48 lesions) and Child–Pugh class also tended to be associated with early recurrence, but these associations were not statistically significant ($P = .064$ and $P = .072$, respectively). Because they were also related to the underlying tumor type (through the associations of cirrhosis and Child–Pugh class with HCC), we also excluded these variables from the model. BMI also tended to be associated with the recurrence rate, but the association was not significant ($P = .064$). The impact of the patient's sex could not be assessed because of the small number of female patients in the study cohort (n = 4).

Patient- and Lesion-Based Risk Factors Not Associated with Early Recurrence

Neither the patient's age ($P = .797$) nor the lesion's location (ie, which liver segment; $P = 0.446$) had a significant association with local recurrence. No significant associations with local recurrence were observed for distances to major vessels (< 0.5 cm vs ≥ 0.5 cm), as assessed for the portal veins ($P = .810$; < 0.5 cm in four of 12 patients), hepatic artery branches ($P = .761$; < 0.5 cm in three of seven patients), hepatic veins ($P = .170$; < 0.5 cm in five of 17 patients), and bile ducts ($P = .226$; < 0.5 cm in three of five patients).

Intervention-Based Risk Factors

A mean of 3.4 electrode probes ± 1.0 (range, 2–6) were used during the 34 analyzed interventions. The mean minimum distance between the paired probes was 11.9 mm ± 5.5 (range, 6–29 mm). A high-current condition occurred in 10 procedures (29.4%).

None of the procedure-based risk factors was associated with early local recurrence. Early local recurrence was not associated with the number of electrodes that was used ($P = .159$), the distance between the electrode probes ($P = .826$), or the occurrence of the high-current condition during the intervention ($P = .178$).

Statistical Validation of Results

By using a second model, we performed a further assessment of the variables that had shown significant associations with local recurrence: lesion volume and underlying tumor disease. BMI, proximity to the portal veins, proximity to the hepatic veins, and proximity to the hepatic artery branches were additionally included in the second model because the hypothesis that IRE is not influenced by blood flow remained to be confirmed. This second multivariable analysis was also performed by using a forward selection procedure with an inclusion factor of 0.07 and an exclusion factor of 0.10.

The second model, which was smaller and more precise, allowed us to confirm the significant findings that were mentioned previously (**Table 5**). Namely, tumor volume ($P = .022$) and tumor entity ($P = .023$) remained significantly associated with local recurrence. In addition, BMI also tended to be associated with local recurrence, but the association was not significant ($P = .022$). In contrast, proximity to vessels was not significantly associated with early local recurrence ($P = .972$).

DISCUSSION

The ablation mechanism of IRE is fundamentally different from that of temperature-based techniques such as RF and microwave ablation. Therefore, IRE may have the potential to overcome the well-known limitations of thermal ablation. For example, the blood flow–mediated cooling effect should not influence the therapeutic efficacy of nonthermal IRE. In a porcine model, Charpentier et al (11) showed that IRE ablation of the liver hilum was safe. The authors concluded that IRE could provide an alternative treatment option for patients who have perivascular or tumors near the liver hilum and who cannot be treated safely or effectively using RF or microwave ablation. Based on their results, Kingham et al (22) conducted a retrospective review of 28 patients who underwent percutaneous treatment of 65 hepatic tumors. This review demonstrated that IRE treatment of perivascular liver malignancies was safe in a clinical setting. In preclinical models, IRE was shown to be unaffected by the heat-sink effect (31). In addition, ablation appeared to be complete to the margins of the blood vessels, but did not compromise their functionality (31). In the present study, we assessed the association

Table 5. Results of Regression Analyses

Parameter	Cases with Local Recurrence	Cases without Local Recurrence	*P* Value	
			All Variables	Selected Variables
Age (y)	55.7 ± 13.9	61.5 ± 9.1	.797	–
Sex			.999	–
Male	9	12		
Female	0	4		
Mean BMI (kg/m^2) ± SD	29.0 ± 5.8	27.2 ± 5.8	.064	.022
Underlying tumor disease	See Table 3	See Table 3	.009	.023
Lesion location			.741	–
Segment I	0	0		
Segment II	3	5		
Segment III	0	1		
Segment IV	2	10		
Segment V	3	4		
Segment VI	3	6		
Segment VII	0	3		
Segment VIII	3	5		
Lesion volume				
< 5 cm^3	3 of 14	6 of 34		
> 5 cm^3	11 of 14	28 of 34		
Mean lesion volume (cm^3) ± SD	12.4 ± 11.6	3.6 ± 4.4	.049	.022
Distance < 5 mm to portal vein	4/12	8/12	.810	–
Distance < 5 mm to hepatic vein	5/17	12/17	.170	–
Distance < 5 mm to hepatic artery	3/7	4/7	.761	–
Distance < 5 mm to bile duct	3/5	2/5	.226	–
Distance < 5 mm to any of these structures	9/29	20/29	–	.972

Note–All binary regression analyses were calculated with forward selection (likelihood), an inclusion factor of 0.07, and an exclusion factor of 0.10
BMI = body mass index, SD = standard deviation.

between local recurrence rates and the presence of larger blood vessels abutting the lesion. Local recurrence did not differ significantly between lesions that were and were not adjacent to blood vessels ($P = .972$).

The results of the present study show that peribiliary tumors were not associated with a significantly increased risk of local recurrence ($P = .226$). Silk et al (32) retrospectively assessed biliary complications after the IRE ablation of 22 hepatic tumors in the immediate proximity of major bile ducts (distance < 1 cm). In their analysis, there were no major biliary complications after IRE ablation, with the exception of two patients. One of these patients had ductal dilation associated with local tumor growth, and the other developed an increase in alkaline phosphatase level (without significant changes in bilirubin levels), which was also associated with local tumor progression at the porta hepatis. Considering the results of Silk et al (32) and the present study, it appears that IRE might be a safe and effective treatment option for liver lesions adjacent to bile ducts.

When performed for tumor lesions with large volumes and diameters, thermal ablation is associated with higher rates of local recurrence, resulting in shorter overall patient survival (33). Cannon et al (21) prospectively assessed 44 patients who underwent 48 IRE procedures with a mixed approach (percutaneous and surgical) for the treatment of mixed hepatic tumors. They found a trend toward higher recurrence rates after nonthermal IRE treatment for tumors with diameters more than 4.0 cm ($P = .178$). Cannon et al (21) recommended IRE as a last-resort therapy that should be applied only when traditional thermal ablation is precluded or for lesions with a maximum diameter of 3.0 cm. In the present study, we therefore decided to assess the impacts of lesion volume and diameter on local recurrence rates. We found that larger lesion volume (≥ 0.5 cm^3) was associated with a significantly higher rate of local recurrence (P[tumor volume] = 0.022; P[longest lesion diameter] = .014). The challenges posed by larger tumors may be explained by the greater number of IRE ablation probes (orientated in a parallel direction) that are required for the complete ablation of larger tumor volumes. If the distances between the tips of the IRE probes are too large, ablation might be incomplete because it might not be possible to establish the required electric field. In contrast, if the distances between the tips of the IRE probes are too short, thermal injury of the target area might result from the high current between

the needle tips. However, even though larger tumor volume was an independent risk factor for local recurrence, the number of IRE probes used per lesion ($P = .159$), the distances between the IRE probes ($P = .826$), and the occurrence of high-current conditions ($P = .178$) were not associated with early local recurrence.

Perfusion-mediated tissue cooling has the greatest effect on the size and shape of thermal ablation. Analogously, the tissue's electrical conductivity may have the greatest influence on the size and shape of IRE ablation zones. Increases in electrical conductivity are associated with increased energy deposition and therefore with larger ablation zones (34). In a porcine model, Ben-David et al (35) assessed the effects of the surrounding microenvironment and local tissue parameters on the electrical parameters and outcomes of IRE in muscle, kidney, and liver tissue. They found that the characteristics of IRE ablation zones were sensitive to electrical conductivity in tissues. The tissue's electrical conductivity is influenced by several tissue properties, such as cell size, fiber orientation, and concentration of membrane proteins. Although the available data on the electric impedance of human tissue are limited—especially for malignant human tissue—computer models have been used to perform extensive simulations and explorations of the behavior of electric fields in normal tissues and tumors. These models have demonstrated that the ratio between the electrical conductivities of normal and malignant tissue has an important influence on treatment outcomes. Previous studies of the liver (36–38) showed that cancerous liver tissue has a higher electrical conductivity than healthy tissue. In addition, the electric conductivity of cirrhotic liver tissue is higher than that of normal liver tissue (36,39). In our analysis of underlying tumor disease, we observed that HCC was less associated with early local recurrence (after 6 mo) compared with other tumor types ($P = .029$). Under the assumption that HCC in cirrhotic livers would lead to a reduced ratio of electrical conductivity, the presence of cirrhosis and the Child–Pugh class were assessed as independent risk factors for early local recurrence. However, neither was observed to be significantly associated with early local recurrence ($P = .068$ and $P = .141$, respectively).

Although BMI was significantly associated with local recurrence ($P = .022$), the role of overweight or obese status as an independent risk factor for local recurrence could not be determined conclusively in the present study. For example, the calculation of BMI incorporates only the patient's weight and height, disregarding important factors such as body fat percentage, muscle percentage, and the presence of ascites, which might lead to a higher BMI despite coexisting (tumor) cachexia.

The results of the present study identify the underlying tumor disease as a risk factor for early recurrence after IRE. Similarly, Cannon et al (21) found that recurrence rates differed according to the underlying tumor entity, observing recurrence rates of 50% for liver lesions from HCC (seven of 14), 58.8% for liver lesions from CRC (13 of 22), and 100% for lesions from other secondary liver cancers (10 of 10). Their results point in the same direction as our own, suggesting that the underlying tumor disease is an independent risk factor for local recurrence. Because of the limited number of lesions in the present study, these results should be regarded as preliminary observations. Further trials that include larger numbers of treated lesions should be performed to confirm or disprove our results.

The present study has multiple limitations, and the reported results should be regarded with caution. The main limitation to the study is the small number of lesions assessed. Accordingly, some of the significant associations with early recurrence may be spurious statistical phenomena, even though they have been confirmed in two separate regression analyses. In addition, some of the factors we identified as having no significant association with local recurrence may be revealed to be significantly associated with local recurrence in larger studies. In addition, the present study may have been limited by the heterogeneity of the included tumors. Moreover, the study lacked long-term follow-up, which would be necessary to establish the efficacy of IRE in a clear manner. Finally, selection bias may have influenced the results of the study because we enrolled only patients who were poor candidates for thermal ablation and surgery, and as previous therapies were disregarded.

In summary, the results of the present study suggest that IRE ablation of perivascular liver lesions is not associated with early local recurrence after IRE. Indeed, the lesions' proximities to hepatic arteries, hepatic and portal veins, and bile ducts were not significantly associated with local recurrence. In this regard, IRE may widen the field of percutaneously treatable liver lesions compared with lesions that are treatable with thermal ablation only. However, similarly to local recurrence after thermal ablation, the present results identify large tumor volume as an independent risk factor for local recurrence after IRE. Our findings also suggest that the risk of early local recurrence after IRE is significantly better in cases of HCC compared with other underlying tumor types.

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