Adverse effects of irreversible electroporation of liver malignancies under CT fluoroscopic guidance: a single-center experience

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Received 29 January 2015; revision requested 3 March 2014; revision received 15 March 2015; accepted 8 April 2015.

Published online 31 August 2015
DOI 10.5152/dir.2015.14442

This is a preprint version of the article; the final version will appear in the November-December 2015 issue of the Diagnostic and Interventional Radiology.

About 70% of hepatic metastases are nonresectable because of their anatomic location, the presence of comorbidities, or limited hepatic functional reserve (1). In these patients and in case of nonresectable primary liver tumors, percutaneous thermal ablation procedures, such as radiofrequency (RF) and microwave ablation, have become effective tools for treating hepatic malignancies (2–4). However, the effectiveness of RF and microwave treatment may be limited, either because of thermal damage to temperature-sensitive structures located in close proximity to the target tissue (5) or because of incomplete ablation of tumors adjacent to major hepatic vessels due to a phenomenon commonly termed “heat-sink effect” (6–10) which describes the loss of the applied thermal energy through the blood flow in those major vessels, whereby the effective energy application remains inadequate to ablate the target lesion.

Irreversible electroporation (IRE) is a theoretically nonthermal ablation technique that delivers a series of high-voltage millisecond electrical pulses to the surrounding tissue, thus leading to irreversible disruption of the integrity of cell membranes and subsequent cell death by apoptosis (11–14). IRE may overcome the problems raised with thermal ablation: previous animal studies reported that bile ducts, blood vessels, nerves, and connective tissues are affected by IRE; however, regeneration is possible to some extent due to preservation of the tissue architecture (12, 13, 15–19). Moreover the feasibility of inducing cell death up to a vessel wall without any perivascular sparing was shown with IRE (12, 13, 18). The safety of IRE in the treatment of humans has been described (20). First reports have described potential complications after IRE, such as hemorrhage requiring blood transfusion (1.2%, two of 167 ablation procedures), portal vein thrombosis (3.2%, one of 31 ablation procedures), injury to bile ducts (1.8%, three of 167 ablation procedures), and infection (3.6%, six of 167 ablation procedures) (21, 22).
However, few data are available for evaluating the potential risk factors associated with the occurrence of post-IRE complications.

The purpose of this study was to review the frequency of mortality and morbidity after computed tomography (CT) fluoroscopy-guided liver IRE conducted at a single center and assess the factors influencing the occurrence of major complications.

### Methods

**Patients**

In this study, 85 IRE procedures in 56 patients with 114 malignant liver tumors (nonresectable and not suitable for thermal ablation) were retrospectively analyzed. The patient group consisted of 42 men (75%) and 14 women (25%) with a median age of 61 years (range, 22–81 years). There were 28 patients with 52 lesions of primary liver tumors and 28 patients with 62 lesions of secondary liver tumors (Table 1). The median follow-up period was 10 months (range, 0–28 months).

The median tumor diameter was 2.2 cm (range, 0.2–6.3 cm). In 61.2% of ablative procedures (52/85), the radiographic margins of index tumors were located within 1 cm to a major hepatic vessel, in 55.3% (47/85) within 1 cm to the liver capsule, and in 4.7% (4/85) within 1 cm of the diaphragm.

The median number of IRE sessions per patient was one (range, 1–4). The median procedure time was 172 min (range, 55–561 min), and a median of four electrodes (range, 2–6) were used. Twenty of 56 patients (35.7%) underwent two or more IRE treatments.

**Study design and ablation procedure**

The study was approved by the local ethics committee. Patients underwent IRE ablation (52/85), the radiographic margins of index tumors were located within 1 cm to a major hepatic vessel, in 55.3% (47/85) within 1 cm to the liver capsule, and in 4.7% (4/85) within 1 cm of the diaphragm.

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**Complications**

Complications were documented for each IRE session by evaluating medical records and radiologic images. Complications were defined as events that, if untreated, threatened the life of the patient, led to substantial morbidity and/or disability, or resulted in a lengthened hospital stay. All other complications were considered minor. Complications were categorized as immediate (within 24 hours after ablation), periprocedural (1–30 days after ablation), and delayed (more than 30 days after ablation) according to the time point of diagnosis (23). According to the SIR grading system, common procedural side effects such as periprocedural pain, fever, and transient elevation of liver enzyme levels were excluded from the evaluation.

**Statistical analysis**

Risk factors influencing the occurrence of major complications were assessed by means of logistic regression models. Variables included previous liver therapy (status post liver resection or chemotherapy), the number of tumors treated, the number of IRE needles, tumor location (subcapsular or subphrenic), distance to major vessels (<1 cm vs. >1 cm), duration of the ablation procedure, liver cirrhosis, hemoglobin levels (<12.0 g/dL vs. ≥12.0 g/dL), platelet count (<150 /µL vs. ≥150 /µL), creatinine level (<1.2 mg/dL vs. ≥1.2 mg/dL), partial thromboplastin time (≤40 s vs. >40 s), anticoagulation, and biliary anastomosis. Odds ratios and corresponding 95% confidence intervals (CI) are reported as effect estimates. An exact unconditional test based on the Pearson’s chi-squared statistic was used for a group-to-group comparison regarding the occurrence of postablative abscess formation between patients with biliary anastomosis and patients without this condition. Statistical significance was set at P ≤ 0.05. Data entry and calculations were made with the software package SPSS 22.0 (IBM Corp.) and R 3.0.3.

**Results**

The results of major complications are presented in Table 2. In six of 85 IRE sessions...

### Table 1. Tumor types in 56 patients treated with irreversible electroporation of malignant liver tumors

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>No. of treated lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary liver tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>Cholangiocellular carcinoma</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal tumor</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pancreatic tumor</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

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(7.1%) seven major complications occurred, with two major complications developing within a single IRE session. No patient died due to IRE ablation. The most frequent major complication was hepatic abscess (4.7%), which occurred in four patients. The abscesses detected during the periprocedural postablative period were located within the ablation zone and required intravenous antimicrobial and drainage therapy. A group-to-group comparison showed that postablative abscess developed significantly more often in patients with bilioenteric anastomosis (three of seven ablation procedures in three of four patients) than in patients without this condition (one of 78 ablation procedures in one of 52 patients) ($P = 0.010$). Logistic regression models showed that only bilioenteric anastomosis presented a significant risk factor for the occurrence of a major complication ($P = 0.002$; odds ratio, 18.75; 95% CI, 2.76–137.28). One of the patients with postablative hepatic abscess formation additionally developed renal failure after IRE and thus required transient hemodialysis during the periprocedural postablative period (preinterventional glomerular filtration rate, 77 mL/min/1.73 m$^2$).

Two patients developed bleeding (2.4%). One patient sustained injury to the right mammary artery during the intervention, and the resulting acute hemorrhage was treated by arterial embolization during angiography (Fig.); no blood transfusion was required. Another patient required blood transfusion because of diffuse intraperitoneal bleeding with decreasing hemoglobin levels; bleeding stopped spontaneously, so that no surgical or interventional therapy was necessary.

Minor complications according to the SIR grading system occurred in 18.8% of procedures (16/85). In three cases, two minor complications were found within a single IRE session. The most frequent minor complications were hemorrhage without requirement of any further therapy (5.9%, 5/85) and portal vein branch thrombosis (5.9%, 5/85). Further complications were pneumothorax without requirement of a chest drain (3.5%, 3/85), hepatic arteriovenous shunt (3.5%, 3/85), and neurologic deficits of the right upper limb due to peri-interventional positioning (2.3%, 2/85), which completely resolved at discharge from hospital. One patient developed partial liver infarction associated with the above-mentioned portal venous thrombotic changes (1.2%, 1/85).

Table 2. Major complications after 85 irreversible electroporation procedures

<table>
<thead>
<tr>
<th>Complication</th>
<th>Immediate</th>
<th>Periprocedural</th>
<th>Delayed</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic abscess</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hemorrhage requiring blood transfusion</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhage requiring arterial embolization</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Figure. a–d. A 66-year-old male patient with hepatocellular carcinoma. T2-weighted MRI image six days before intervention shows a hyperintense HCC lesion (a, arrow) in segment V of the liver located within a perimeter of 1 cm of a segmental portal vein branch (not shown on the figure). A peri-interventional contrast-enhanced CT scan shows extrahepatic hematoma (b, thick arrow) with active extravasation of contrast medium (b, arrowhead) due to active bleeding. The ablation zone (b, thin arrow) contains intralesional gas bubbles (b, curved arrow). Immediate digital subtraction angiography with selective angiography of the right internal thoracic artery (c) shows extravasation of contrast medium (arrowhead) from one of its branches (thin arrow). Consecutively, the vessel was successfully embolized with an ethylene vinyl alcohol copolymer (Onyx, ev3 Inc.) (d). K, kidney (a, b).
In three patients, complete thrombosis of a portal vein branch or segmental portal vein branch was detected during the periprocedural follow-up by means of CT imaging. In the first patient, preinterventional imaging showed the left portal vein branch to be 0.5 cm distant to the target lesion, and the follow-up image after 13 months showed persistent branch thrombosis and a reduced volume of the left liver lobe. In another patient, preinterventional imaging showed radiographic margins ablated tumor located within 0.5 cm to a segmental branch of the left portal vein. This patient developed segmental portal vein branch thrombosis leading to infarction of parts of the left liver lobe and received low-intensity anticoagulation therapy. The preinterventional images of a third patient showed a segmental branch of the left portal vein located 0.9 cm from the target lesion that was completely occluded on the first follow-up images. The patient received anticoagulation therapy, and thrombosis resolved after seven days without any evidence of liver infarction.

In two patients, partial thrombosis of portal vein branch was detected in periprocedural follow-up imaging. In both patients, the left portal venous system was affected. The preinterventional images of the first patient showed the left portal vein branch abutting the target lesion. At three-month follow-up, thrombosis persisted with consecutive volume reduction of the left liver lobe. In the other patient, the affected part of the left portal vein was 0.8 cm distant to the ablation zone on the first postablative day; at six-month follow-up thrombosis resolved, and no liver infarction occurred. Since thrombosis within the portal venous system and liver infarction were detected by means of imaging and were clinically unapparent, they were considered to be minor complications. Logistic regression models did not show any risk factors for the occurrence of minor complication.

Discussion

Although percutaneous tumor ablation procedures are generally considered to be minimally invasive, published data suggest that such techniques carry some degree of risk. Since IRE ablation represents a rather new ablation technique, possible risks factors in IRE have yet to be evaluated. The current results show that IRE of hepatic tumors using CT fluoroscopy has a major complication rate of 7.1% (6/85) without any mortality, which is an acceptable safety profile comparable to other ablative treatments.

Livraghi et al. (5) reported six deaths (0.3%) and 50 additional major complications (2.2%) in a multicenter study in which more than 3,500 hepatic tumors in 2,320 patients were ablated by internally cooled RF ablation. Additional major complications predominantly consisted of peritoneal hemorrhage, neoplastic seeding, intrahepatic abscesses, and intestinal perforation (5). In the current study, the major complication rate after IRE ablation was higher than that after RF ablation. However, the selection bias of patients should be taken into consideration because patients were only treated with IRE ablation if they were unable to undergo thermal ablation or surgery.

The most frequent major complication in the current study was hepatic abscess which occurred during the periprocedural postablative period. This is in line with previous studies reporting a time range from eight days to five months between hepatic RF ablation and abscess formation (25–27). Those percutaneous RF ablation studies reported rates of abscess formation of 0.4% to 3.1% (6/1500 to 7/226) (25, 28). Thus, the rate of 4.7% found in the current study is higher compared to the above-mentioned results after RF ablation. However, the development of postablative abscesses was significantly associated with the presence of biliaryenteric anastomosis compared to patients without this condition. In the current study, three of four patients with postablative abscess had biliaryenteric anastomosis, and this condition has been reported to be a risk factor for infectious complications after loco-regional hepatic tumor treatment such as RF ablation (5, 25), microwave ablation (29), and embolization (30–33). In case of chemoembolization in patients with biliaryenteric anastomosis, prophylactic therapies have already been proven to be successful (34).

Hemorrhage requiring therapy has been described as one of the common major complications after hepatic RF ablation with a frequency of 0.5% to 1.1% (5, 28). In the current study, the rate of this complication was slightly higher (3%). Since two to six electrodes are used in IRE ablation compared to one electrode in thermal ablation techniques, hemorrhage may occur markedly more often after IRE ablation than after RF or microwave ablation. The nonthermal effect of IRE does not allow cauterization of the needle tracts, which represents another theoretical risk factor. On the other hand, the relative small size of IRE electrodes of just 18G compared to that of RF probes of up to 15G would imply a decreased risk of hemorrhage.

Thrombotic changes within the portal venous system, especially of small vessels, are known complications after thermal ablation (10). However, according to de Baere et al. (25) thrombosis of larger hepatic vessels is mainly associated with vascular occlusion (Pringle maneuver) in cirrhotic livers, which is used as supplement to RF ablation to avoid heat sink phenomena. The narrowing of hepatic vessels immediately after IRE ablation due to edematous and inflammatory changes has already been described previously (39.1%, 9/23 hepatic veins) (18), and even postablative portal vein thrombosis is a well-known complication after IRE ablation (3.2%, 1/31 ablation procedures) (22). The thrombotic alterations within the portal venous system in the current study may have been due to portal vein narrowing with reduced blood flow.

The current study has several limitations such as the low number of patients and IRE interventions and its retrospective nature. Consequently, other types of complications may be described in future studies. The current patient series was also too small to find risk factors for each respective complication. Another limitation is the heterogeneity of the study population consisting of patients with and without liver cirrhosis.

In conclusion, the current study suggests that IRE ablation of liver tumors may be a well-tolerated and rather safe ablative technique with a 7.1% rate of major complications and no deaths. Intratumoral abscess was the most frequent postablative complication, and it was significantly associated with the presence of biliaryenteric anastomosis.

Acknowledgement

The authors thank Dietlinde Ulspunger for editing the figures.

Conflict of interest disclosure

All authors have read the journal’s policies, and the following conflicts have emerged: Philipp Wig-germann received travelling assistance from Angio-dynamics®. In response to this conflict, the authors state that this assistance does not alter adherence to any of the policies of the Diagnostic and Interventional Radiology on sharing data and materials. Angiodynamics® was neither involved in the study design, data collection and analysis, nor in the decision to publish or the preparation of the manuscript.
References


