Percutaneous Ablation of Peribiliary Tumors with Irreversible Electroporation

Mikhail T. Silk, BS, Thomas Wimmer, MD, Kyungmouk S. Lee, MD, Govindarajan Srimathveeravalli, PhD, Karren T. Brown, MD, Peter T. Kingham, MD, Yuman Fong, MD, Jeremy C. Durack, MD, Constantinos T. Sofocleous, MD, and Stephen B. Solomon, MD

ABSTRACT

Purpose: To assess biliary complications after irreversible electroporation (IRE) ablation of hepatic tumors located < 1 cm from major bile ducts.

Materials and Methods: A retrospective review was conducted of all percutaneous IRE ablations of hepatic tumors within 1 cm of the common, left, or right hepatic ducts at a single institution from January 2011 to September 2012. Computed tomography imaging performed before and after treatment was examined for evidence of bile duct dilatation, stricture, or leakage. Serum bilirubin and alkaline phosphatase levels were analyzed for evidence of biliary injury.

Results: There were 22 hepatic metastases in 11 patients with at least one tumor within 1 cm of the common, left, or right hepatic duct that were treated with IRE ablations in 15 sessions. Median tumor size treated was 3.0 cm (mean, 2.8 cm ± 1.2, range, 1.0–4.7 cm). Laboratory values obtained after IRE were considered abnormal after four treatment sessions in three patients (bilirubin, 2.6–17.6 mg/dL; alkaline phosphatase, 130–1,035 U/L); these abnormal values were transient in two sessions. Two patients had prolonged elevation of values, and one required stent placement; both of these conditions appeared to be secondary to tumor progression rather than bile duct injury.

Conclusions: This clinical experience suggests that IRE may be a treatment option for centrally located liver tumors with margins adjacent to major bile ducts where thermal ablation techniques are contraindicated. Further studies with extended follow-up periods are necessary to establish the safety profile of IRE in this setting.

ABBREVIATION

IRE = irreversible electroporation

Nearly 70% of hepatic metastases are unresectable because of anatomic location, limited functional liver reserve, or comorbidities (1,2). Without treatment, the 5-year survival for metastatic liver disease is < 1% (3). Percutaneous thermal ablation techniques have been shown to be an effective tool for treating tumors, increasing 5-year survival of hepatocellular carcinoma to 33%–54% and colorectal metastasis to 25%–46% (4). However, a large population remains ineligible for thermal techniques because of tumor proximity to main biliary tracts (5).

Irreversible electroporation (IRE) is a nonthermal ablation technique that uses pulsed direct current to induce cell death (6). Although cell death is believed to occur via the formation of permanent nanopores in the cell membrane, the extracellular matrix appears to remain intact (7). It is hypothesized that although tumor cells near bile ducts treated with IRE may die, bile ducts in the ablation zone may retain their structural integrity secondary to intact extracellular matrix. Additionally, the efficacy of IRE is not limited by heat sink effects (8,9). Previous clinical studies suggested the safety and efficacy of IRE in the liver and pancreas. Thomson et al (10) investigated the safety of IRE in humans including hepatic ablations. Narayanan et al
needles at any one time. Ablation zone size can be any number of electrodes can be used to enclose a target either 16-gauge or 18-gauge needle electrodes. Although this study was primarily focused on the effects of IRE ablation on hepatic blood vessels, effects on the biliary ducts and liver function were also evaluated. Cannon et al (13) examined the general safety of centrally located hepatic IRE ablations.

The purpose of this clinical study was to examine specifically the safety of IRE for larger, more centrally located liver tumors with tumor margins in close proximity to major bile ducts where thermal techniques are contraindicated. We assessed possible complications and the safety of IRE ablation for hepatic tumors located within 1 cm of the common, left, or right hepatic ducts. We retrospectively examined serum bilirubin, alkaline phosphatase, and computed tomography (CT) imaging studies for evidence of bile duct dilatation or leakage.

MATERIALS AND METHODS

We obtained institutional review board approval to perform a retrospective review of all patients who underwent ablation using IRE for hepatic tumors with margins within 1 cm of the common hepatic duct or the first-order branches of the common duct (the left and right hepatic duct before further branching) performed at our institution from January 2011 to September 2012. The shortest distance between the tumor margin and the closest bile duct was measured on CT images (LightSpeed 16/LightSpeed VCT; GE Medical Systems, Milwaukee, Wisconsin) obtained before ablation using axial, coronal, or sagittal reformations. Distance measurements were performed independently by two radiologists (T.W. with 7 y of experience, K.S.L. with 4 y of experience) (Fig 1a–d).

IRE Procedure

The tumors were targeted with IRE because of concern for duct stricture if a thermal technique was used. In all cases, the planning of the ablation zone was performed in a way that a minimum electric field of 680 V/cm would be achieved throughout the tumor, which would result in cell death by IRE (6).

IRE was performed using a commercially available direct current pulse generator device for clinical application (NanoKnife; AngioDynamics, Queensbury, New York). The device can deliver 3,000 V and 50 A through either 16-gauge or 18-gauge needle electrodes. Although any number of electrodes can be used to enclose a target fully with IRE, pulses are delivered through only two needles at any one time. Ablation zone size can be influenced by length of the active tip (0.5–4 cm), pulse number (typically 70–90), duration of pulses (typically 90–100 μs), distance between probes, and voltage applied.

All procedures were performed under general anesthesia with complete muscle blockade (paralysis) to reduce muscle stimulation from the treatment (although even with complete muscle blockade, local muscle stimulation in close proximity to the area treated by IRE is common). The patient’s electrocardiogram was synchronized to the IRE device such that pulses were delivered during the complete refractory period (50 ms after the R wave) to prevent arrhythmias.

ELECTRODE PLACEMENT

Needle placement was performed under CT (LightSpeed 16) or positron emission tomography (PET)/CT (Discovery PET/CT 690; GE Medical Systems) guidance. Electrodes were placed such that the active exposed needle tip of each probe was approximately parallel to its companion. Image reconstructions along the electrode axis were performed to measure distance between the tips of the electrodes to adjust treatment parameters on the IRE planning console accordingly. The number of electrodes used depended on the size of the tumor and the operator. Needles were placed in a way to ensure complete coverage of the tumor, while avoiding direct puncture of critical structures such as blood vessels and bile ducts. The individual planning of electrode trajectories was at the discretion of the interventional radiologist performing the ablation. In this cohort of patients, the median number of probes used was three (range, two to six), with a median distance between probes of 1.6 cm (range, 0.8–3 cm), and an active exposure of 2.5 cm (range, 1.5–3 cm).

Device Setting

The median voltage applied per electrode pair was 2,370 V (range, 1,800–3,000 V) achieving an electrical field strength of 1,510 V/cm (range, 904–1,982 V/cm) between the electrodes. A minimum of 70 pulses (range, 70–90 pulses) applied in trains of 10 pulses with a minimum pulse length of 90 μs (range, 90–100 μs) was applied via each electrode pair. Repeat treatments were given until an increase of current was observed between the first pulse of each pulse set (indicating successful electroporation owing to pore formation represented as a reduction in electrical resistance). Technical treatment success was confirmed with split-dose PET/CT through resolution of fluorodeoxyglucose activity as previously described (14) or contrast-enhanced CT with a hypodense ablation zone encompassing the tumor.
Follow-up Imaging  
A CT scan was obtained immediately after ablation in all cases to indicate that the ablation zone covered the targeted lesion with margins. The first CT scan after ablation was obtained 4–8 weeks after treatment and was independently reviewed (by T.W. and K.S.L.) without knowledge of diagnosis, laboratory values, and patient outcomes. A contrast-enhanced portal venous acquisition phase axial CT scan (120 kV, 89–377 mA, pitch 0.984–1.375, slice thickness 3–5 mm, 115–150 mL Omnipaque 300 contrast agent, 1–4 mL/s injection, portal venous delay 60–90 s) obtained before treatment was examined for baseline appearance of the bile ducts. CT scans obtained immediately after ablation and 4–8 weeks after ablation were examined for signs of biliary duct strictures, leakage, or dilatation. An increase of 2 mm in bile duct width was considered bile duct dilatation. Follow-up imaging performed after 4–8 weeks was examined for treatment efficacy. Local treatment failure was defined as abnormal enhancement at the periphery of an ablation defect on contrast-enhanced imaging performed after the procedure.

Laboratory Values  
For all patients, baseline serum bilirubin and alkaline phosphatase levels measured within 4 weeks of treatment were recorded and compared with values 24 hours and 4–8 weeks after treatment. To identify patients with possible bile duct injury, elevated bilirubin or alkaline phosphatase values after treatment were investigated. To account for normal variance in laboratory values (15), an increase in bilirubin $\geq 1$ mg/dL or an increase in alkaline phosphatase $\geq 60$ U/L from baseline related to IRE treatment at any point 8 weeks after treatment was considered clinically significant and identified as abnormal.
RESULTS

From January 2011 to September 2012, 11 patients with at least one hepatic tumor with radiographic margins located within 1 cm of a major bile duct were treated with IRE in 15 sessions. Patient demographics are listed in Table 1. Eight patients had more than one liver metastasis and were concurrently treated in one session with additional IRE (n = 4), radiofrequency ablation (n = 3), and microwave ablations (n = 1). Radiofrequency ablation and microwave ablations were performed in different hepatic segments from the IRE ablation in more peripheral locations and not in proximity to major bile ducts. One patient received transarterial embolization after the IRE procedure. Tumor characteristics are summarized in Table 2. Tumor size, as measured by the largest dimension, ranged from 1.0–4.7 cm (median, 3.0 cm; mean 2.8 cm ± 1.2).

Average time between IRE treatment and first CT imaging after IRE was 43 days ± 6. The average follow-up for all patients was 9 months ± 6. Four patients exhibited bile duct dilatation on imaging performed before treatment, and two patients had metal biliary stents located in the ablation zone. In three patients, we observed either an increase in biliary duct width or new onset of biliary duct dilatation on follow-up CT. One patient with preexisting bile duct dilatation showed an increase in duct dilatation after treatment (Fig 2a, b) with an increase in alkaline phosphatase but no change in bilirubin thought to be secondary to tumor progression and ultimately required bile duct stent placement. One patient showed new onset of left hepatic duct dilatation (Fig 3a–c) with a transient increase in serum bilirubin levels and alkaline phosphatase. Another patient with preexisting bile duct dilatation showed an increase in duct dilatation after treatment (Fig 2a, b) with an increase in alkaline phosphatase but no change in bilirubin thought to be secondary to tumor progression and ultimately required bile duct stent placement.

Figure 2. A 55-year-old woman with colorectal metastatic disease and previous right hepatectomy underwent IRE ablation in the caudate lobe. (a) Initial contrast-enhanced CT scan (portal venous phase) performed before treatment shows the tumor (asterisk) and bile ducts (arrows). (b) Follow-up scan performed 34 days after the procedure shows unsuccessful ablation (asterisk) with new growth of the tumor (arrowhead) and increasing width of bile ducts (arrows).

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<th>Table 1. Patient Demographics</th>
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patient with no laboratory signs of bile duct injury developed subsegmental bile duct prominence (Fig 4a–c).

Baseline laboratory values were measured on average 12 days ± 5 before treatment and recorded in 15 of 15 sessions. Laboratory levels measured 24 hours after treatment were recorded in 10 of 15 sessions. The average time to the second laboratory follow-up evaluation was 38 days ± 5 after treatment and recorded in 14 of 15 sessions (Figs 5, 6). There was a median increase in serum bilirubin of 0.3 mg/dL (mean, 1.15 mg/dL ± 1.8; range, 0–5.4 mg/dL) 24 hours after treatment and a median increase of 0.1 mg/dL (mean, 0.2 mg/dL ± 0.4; range, −0.1 to 1.5 mg/dL) in serum bilirubin 38 days ± 5 after treatment. There was a median increase in alkaline phosphatase of 3 U/L (mean, 25 U/L ± 54; range, −29 to 145 U/L) 24 hours after treatment and a median increase of 22 U/L (mean, 92 U/L ± 248; range, −49 to 940 U/L) in alkaline phosphatase 38 days ± 5 after treatment.

Laboratory values obtained after IRE were considered abnormal after four treatment sessions in three patients. The elevations after two of these sessions were transient and returned to baseline by the 1-month follow-up. The two prolonged increases in laboratory values were seen in patients who had local tumor progression after IRE.

One patient underwent a combined IRE and microwave ablation after a previous IRE treatment failed to ablate the entire tumor, bilirubin levels increased from a baseline of 0.9 mg/dL to a maximum of 17.6 mg/dL after 4 days, and alkaline phosphatase increased from a baseline of 100 U/L to a maximum of 412 U/L after 6

Figure 3. A 46-year-old man with colorectal metastatic disease and previous right hepatectomy underwent two IRE treatment sessions and had a transient abnormal serum bilirubin level after both treatments. (a) Initial contrast-enhanced CT scan (portal venous phase) performed before treatment shows the tumor (arrowheads). (b) Follow-up scan performed immediately after the procedure shows the ablation cavity (asterisk). The patient received a second IRE treatment for progression of metastatic disease. (c) Follow-up CT scan shows unsuccessful ablation with viable tumor (arrowheads) and new onset of bile duct dilatation (arrows).

Figure 4. A 52-year-old man with colorectal metastases underwent IRE treatment for two tumor locations. (a) Initial contrast-enhanced CT scan (portal venous phase) performed before treatment shows baseline duct width. (b) Follow-up CT scan performed immediately after the procedure shows ablation cavity and a prominent segmental duct (arrowheads). (c) Follow-up CT scan performed 1 month later still shows bile duct dilatation (arrowheads).
days. Bilirubin and alkaline phosphatase trended down to 2.4 mg/dL and 218 U/L 49 days later; however, serum bilirubin levels increased again, and follow-up imaging showed local tumor recurrence obstructing bile ducts. This patient had no biliary ductal dilatation before treatment, and imaging performed after treatment showed the new onset of ductal dilatation associated with tumor growth and progression of disease. 

**DISCUSSION**

IRE is assumed to work by creating permanent nanopores in cell membranes that lead to an increased influx of extracellular ions. These ions are cleared by adenosine triphosphate-dependent ion pumps resulting in intracellular depletion of adenosine triphosphate, which subsequently leads to cell death by apoptosis (16) with tissues reaching a maximum apoptotic rate after 24 hours (17). Animal studies investigating IRE in the liver have shown minimal effects on the biliary tree with no long-lasting effects on bilirubin levels in pig models (9,18). Previous studies have investigated the safety of IRE in general as well as in hepatobiliary and pancreatic settings (10–12,19–21). In this study, we specifically followed patients undergoing treatment of liver metastases located within 1 cm of major bile ducts to assess the safety of IRE in locations considered contraindicated to thermal techniques.

IRE is believed to be safe in close proximity to vital structures because the proposed mechanism of action is nonthermal, although more recent articles have pointed out a thermal potential for IRE (22–24). Faroja et al (22) showed IRE can have a thermal effect but only with device settings that are not used clinically (ie, unusual high pulse repetitions and voltage settings).

Our results agree with previously published observations suggesting the safety of IRE in proximity to hepatic veins and the portal pedicle (12), and our study adds to the existing literature on hepatic IRE ablation with a series of larger, more centrally located liver tumors. In our cohort of patients, there was a single case that showed new onset of subsegmental bile duct prominence with no laboratory findings of bile duct injury. Retrospective review of CT images showed the needle path going through the area where the bile duct became prominent and could be a result of a thermal effect owing to direct contact of the bile duct with the needle. Long-term imaging follow-up of this patient after 316 days showed persistent subsegmental duct prominence with no progressive dilatation or segmental atrophy. Currently in our practice, electrode placement is planned in a way that no part of the active tip is in contact with a vital structure.

Local tumor recurrence was evident in 6 of 11 patients. The median time to imaging first showing local recurrence was 132 days (range, 34–258 d) after the procedure. Two of the four patients with pretreatment bile duct dilatation and both patients with metal biliary stents had local recurrence.
ducts contributing to bilirubin and alkaline phosphatase elevation. Electroporation itself could induce leakage of bilirubin through membrane pores from hepatocytes and alkaline phosphatase from cells lining the bile ducts because of reversible electroporation at the border of the ablation zone. Finally, liver cells that undergo apoptosis or necrosis from irreversible electroporation would release bilirubin or alkaline phosphatase as well (25).

In this cohort of patients, 6 of 11 patients exhibited local recurrence, which is comparable to the reported efficacy of IRE in the liver with longer follow-up periods (10,13). Tumors treated in the current study were larger than previously reported with a median size of 3.0 cm, known to represent a group that is more difficult to control (27).

Ben-David et al (28) observed IRE ablation zone changes secondary to local environment influences. They reported alteration to the ablation zone margins when IRE was performed close to metal plates, which may have influenced the treatment outcome in the two patients with metal biliary stents.

Limitations of this study include the retrospective nature of the analysis. Time points of bilirubin and alkaline phosphatase measurements and imaging follow-up were not standardized, and we were unable to deduce the expected increase in bilirubin from the size of the ablation zone. In addition, many patients received prior and concurrent multimodal local and systemic treatment, which may have influenced laboratory values in addition to the IRE procedure. It is plausible that the prior treatment history could have been a major contributing factor for the abnormal laboratory values seen transiently in two patients. One patient had an ablation next to a surgical resection margin, and the less compliant scar tissue could have caused a transient stasis in the duct secondary to edema after ablation. Another patient had a significant section of the liver concurrently treated by microwave ablation, which could have caused the abnormal increase in laboratory values. Nonetheless, the purpose of this investigation was not to explain transient elevation of liver function tests but to use elevation in these parameters in an effort to identify patients who may have developed IRE-related bile duct injury.

In conclusion, our clinical experience suggests that IRE may be a treatment option for centrally located liver tumors with margins adjacent to major bile ducts where thermal ablation techniques are contraindicated. Further studies with extended follow-up periods are necessary to establish the safety profile of IRE in this setting.

REFERENCES


