Effectiveness and safety of irreversible electroporation for recurrent hepatocellular carcinoma ineligible for thermal ablation after surgery

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ABSTRACT

Objectives: To preliminarily evaluate the clinical effectiveness and safety of computed tomography (CT) image-guided irreversible electroporation (IRE) for the treatment of recurrent hepatocellular carcinoma (HCC) after surgical resection.

Methods: From January 2016 to February 2018, 18 patients diagnosed with recurrent HCC after surgical resection received IRE under CT image guidance for 22 tumors. Patients were enrolled for IRE when ineligible for thermal ablation due to tumor location. Clinical records and imaging data were reviewed to assess complete ablation rate, local tumor progression free rate (LTPFR), local tumor progression free survival (LTPFS) and complications after a median follow-up time of 14 months.

Results: Successful complete ablations were achieved in 20/22 (90.1%) tumors. Mean LTPFS was 10.5/± 9.4 months. Overall 3-, 6- and 12-months LTPFR in 22 tumors following IRE were 68.2% (95% confidence interval [CI]: 45%–83%), 59.1% (95% CI: 33%–76%) and 36.4% (95% CI: 17%–56%), respectively. Complications included pneumothorax (2/18, 11.1%), localized pain (3/18, 16.7%), bile duct dilation (1/18, 5.6%) and transient hypertension (1/18, 5.6%). No major complications or treatment-related deaths were observed. The alphafetoprotein levels of two patients decreased to the normal range at 3 and 4 months, respectively.

Conclusions: This study showed that percutaneous CT image-guided IRE can serve as a safe and effective treatment for recurrent HCC not suitable for thermal ablation.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death in the world.¹,² Surgical resection is one of the curative treatments for HCC. However, recurrence rate after hepatectomy is more than 70%,³,⁴ and intrahepatic tumor progression, vascular invasion and extrahepatic metastasis are more serious. Ablative therapies have played a significant role in the treatment of recurrent HCC after hepatectomy, achieving high rates of successful ablation and low complication rates.³ Notwithstanding the advantages of ablation, sometimes incomplete ablation occurs, and thermal injury to structures, such as vessels, bile ducts and important organs, can occur when the tumors are located in dangerous sites.⁴

In the last decades, the concept of applying irreversible electroporation (IRE) to induce tumor cell death has been verified both in vitro and in vivo. Unlike thermal ablations, the rationale of IRE is a high-density electrical field applied to form an irreversible nanoscale pore across the cell lipid bilayer that alters transmembrane potential, disrupts cellular homeostasis, and finally leads to cell death.⁵,⁶ IRE induces neoplastic cell apoptosis, rather than necrosis, which means that the extracellular matrix integrity is preserved, and the ablated liver tissue quickly regenerates. IRE has been demonstrated as an effective non-thermal ablation for several malignant solid tumors.⁷-¹² The applications of IRE are further expanded to HCC in dangerous locations since it can be used to treat HCC adjacent to vital structures, including large blood vessels, bile ducts and important organs.⁷-¹⁰
However, there is no report focusing on IRE for the treatment of recurrent HCC located close to critical structures and that are ineligible for thermal ablation. In this context, we report here that computed tomography (CT) image-guided percutaneous IRE for the treatment of special-site recurrent HCC shows good local treatment efficacy and low complication rates.

Methods

Ethical approval

This retrospective study was approved by the Institutional Review Board of Sun Yat-sen Memorial Hospital (W2017NJ007). All clinical practices and observations were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all 18 patients before IRE ablation.

Patients

From January 2016 to February 2018, 18 patients were enrolled in this study. All participating patients were initially treated with hepatic resection and HCC was confirmed by pathological examinations. Patients were ineligible for thermal ablation due to the location of their tumors, and thus, IRE was performed as an alternative treatment. Clinical information and imaging data were obtained from our hospital database.

Inclusion and exclusion criteria

From January 2016 to February 2018, 18 patients who met the following inclusion criteria and underwent percutaneous CT image-guided IRE to treat recurrent HCC were included in our study.

Inclusion criteria: age of 18–75 years; recurrent intrahepatic lesion after surgery; not suitable for thermal ablation due to tumor anatomic location, adjacent <10 mm to large vessels, bile ducts, diaphragm and digestive tract; liver function classified as Child-Pugh A or B; tumor diameter <5 cm; tumor number <3; with tumor thrombus invading portal vein branch confirmed by radiological examination; patient accepted IRE as an alternative treatment. Exclusion criteria: patients with ventricular arrhythmias or cardiac pacemaker history; multiple organ failure. Patients who were lost to follow up or had incomplete clinical or imaging data were also excluded from the study.

The decision to use IRE treatment was made after discussion among multidisciplinary experts, including the oncologist, hepatobiliary surgeon, interventional radiologists, diagnostic radiologists, and anesthesiologist. Recurrent HCC was diagnosed in the context of classical radiological imaging (contrast-enhanced CT and magnetic resonance imaging [MRI]) and previous HCC history. For uncertain tumors, positron emission tomography (PET)/CT or biopsy was performed. The baselines of aspartate transferase (AST), alanine transferase (ALT), total bilirubin (TBIL), and alpha-fetoprotein (AFP) were calculated.

IRE procedure

The IRE device (AngioDynamics, New York, USA), approved by China Food and Drug Administration in June 2015, was used on all enrolled patients. IRE procedures were conducted as per the equipment manufacturer’s guidelines and our department’s established standard operating procedures. The ablation entry site and path were planned according to contrast-enhanced CT within 4 weeks prior to IRE ablation. All procedures were performed percutaneously under CT image guidance and general anesthesia with a complete neuromuscular blockade by a sophisticated operator (L.F. Xu) with more than 20 years of experience in percutaneous tumor ablation. Depending on tumor size and shape, 2 to 6 19-gauge monopolar electrode needles with a 10–20 mm active tip length were inserted around the entire tumor, parallel to each other and separated by a distance of 11–25 mm. The size of the ablation zone could be predicted via the IRE device. Parameters were 80–90 pulses, 70–90 us pulse length, 50, and a maximum voltage of 3000 V. Post-IRE CT scan was immediately performed to determine whether the procedure had been successful and to check for any potential complications. Electrical pulses were applied during the absolute myocardial refractory period according to synchronism electrocardiography to prevent cardiac arrhythmia. If incomplete ablation was suspected, the electrode needles were pulled back for repositioning, and another IRE procedure was carried out.

Local treatment efficacy and complications

The primary endpoint of the study was to assess the safety and local treatment efficacy of IRE for the treatment of recurrent HCC. Safety was assessed based on complications and abnormal laboratory values. Local treatment efficacy included complete ablation and local tumor progression-free survival. Complete ablation was defined as the tumors being totally overlapped by the ablation zone with a 5–10 mm safety margin and the absence of enhancement within the ablation area at a 1-month follow-up imaging study. For completely ablated lesions, local tumor progression (LTP) was defined as an abnormal enhancement or increase in size within the ablation zone and recorded per lesion.17 Local tumor progression-free survival (LTPFS) was defined as the interval between the date of the IRE procedure and radiologic progression on imaging, death, or the last follow-up by May 2019. Radiologic progression of tumors included initial incomplete ablated tumors. The size of the tumor was assessed by the longest diameter of the ablated tumor.18 Contrast-enhanced CT was performed within 4 weeks before IRE ablation and routine laboratory tests were examined within 1-week prior to the IRE procedure. Colonoscopy was performed to exclude disruption of the digestive tract wall by tumor invasion.

Complications were categorized as major and minor complications.19 Major complications were defined as events that resulted in substantial disability or mortality. This included any case in which additional interventional treatment was required. All other events were defined as minor.

Table 1

Baseline characteristics of 18 patients with 22 tumors.

| Parameter                                      | Value (Number, Percentage) |
|------------------------------------------------|-----------------------------|
| **IRE (18 patients/22 tumors)**                |                             |
| Age * 51.6 ± 11.5                              |                             |
| Sex                                             |                             |
| Male                                           | 13 (72.2)                   |
| Female                                         | 5 (27.8)                    |
| HBsAg                                          | 18 (100)                    |
| Cirrhosis                                      | 18 (100)                    |
| Hepatic resection history                      | 18 (100)                    |
| Biopsy (HCC)                                   | 18 (100)                    |
| Child-Pugh classification                      |                             |
| A                                              | 17 (94.4)                   |
| B                                              | 1 (5.6)                     |
| Tumor longest diameter (cm)                    |                             |
| > 3 cm                                         | 9 (40.9)                    |
| < 3 cm                                         | 13 (59.1)                   |
| Tumor number                                   |                             |
| Solitary                                       | 14 (77.8)                   |
| Multiple (≥2)                                  | 4 (22.2)                    |
| Tumor location                                 |                             |
| Tumor adjacent to hepatic portal               | 8 (36.4)                    |
| Tumor adjacent to hepatic vein                 | 7 (31.8)                    |
| Tumor adjacent to inferior vane cava           | 2 (9.1)                     |
| Tumor adjacent to subcapsular                  | 3 (9.1)                     |
| Abdominal metastasis lymph node                | 2 (9.1)                     |
| Portal vein tumor thrombus                     | 1 (4.5)                     |

Except for * indication, values are presented as Number (percentage). Indicated * data are expressed as means ± standard deviation.

IRE = irreversible electroporation, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, AFP = alpha-fetoprotein.
Follow up

For all patients, blood tests, including liver function and tumor biomarker AFP were tested on days 3 and 7, and then every month after IRE ablation. Contrast-enhanced CT or MRI was performed 1 week, 1 month, and then every 2–3 months post IRE treatment. Follow-up imaging studies were examined by 2 senior abdominal radiologists.

Statistical analysis

All statistical analyses were conducted using SPSS software package (version 21.0, SPSS Inc, Chicago, USA). Continuous data were expressed as the means ± standard deviation. Categorical data were expressed as numbers and percentages. The curve for local tumor progression-free survival was analyzed using the Kaplan-Meier method. GraphPad Prism 5 software (GraphPad Software, Inc, La Jolla, CA, USA) was used for data imaging.

Results

Eighteen patients (13 males, 5 females) were included in our study between January 2016 and February 2018. Mean age was 51.6 ± 11.5 years. The Eastern Cooperative Oncology Group performance status score was 0–1. The liver functions of these patients were Child-Pugh A or B with cirrhosis. Median time from initial surgical resection to IRE was 13 months. Mean tumor size was 2.8 ± 1.1 cm; 9 tumors were larger than 3.0 cm. Fourteen patients had a single tumor, and 4 patients had 2 tumors that were treated with IRE. Mean follow-up period was 14.3 ± 11.1 months. Among the 22 tumors, 8, 7, 2 and 2 were located close to the hepatic portal, hepatic vein, inferior vena cava, and subcapsular areas, respectively; 1 tumor was portal vein tumor thrombus (PVTT); and 2 tumors had abdominal lymph node metastases in the vicinity of the digestive tract or splenic vein. The baseline characteristics of patients and tumors are summarized in Table 1.

After 1 month, contrast-enhanced CT revealed that 20/22 (90.1%) tumors had achieved complete ablation (Fig. 1). Incompletely ablated tumors were retreated with transcatheter arterial chemoembolization (TACE), but subsequent imaging exams still revealed residual tumors which resulted in massive intrahepatic progression.

Mean LTPFS was 10.5 ± 9.4 months. The 3-, 6-, 12-months LTPFR of completely ablated tumors were 75% (15/20), 65% (13/20) and 40% (8/20), respectively. The overall 3-, 6-, 12-months LTPFR were 68.2% (95% confidence interval [CI]: 45%–83%), 59.1% (95% CI: 33%–76%) and 36.4% (95% CI: 17%–56%), respectively (Fig. 2). At the last follow-up, 9 patients were alive, of which 5 were still clinically well without LTP.

Median AFP levels before and 1 month after IRE treatment were 12,398.8 ng/ml and 3369.9 ng/ml, respectively. In 2 patients AFP levels returned to normal range at 3 and 4 months after IRE, with LTPFS of 33 and 31 months, respectively.

There were no IRE-related mortalities and major complications within 1 month after the IRE procedure. The most common minor complications in 18 patients.

| Event                          | Patients (n) |
|-------------------------------|--------------|
| Mortality                     | 0            |
| Pneumothorax                  | 2 (11.1)     |
| Bile duct dilation            | 1 (5.6)      |
| Transient hypertension        | 1 (5.6)      |
| Localized pain                | 3 (16.7)     |
| ALT and AST elevation         | 8 (44.4)     |
| TBIL elevation                | 6 (33.3)     |

Values are presented as Number (percentage).

IRE = irreversible electroporation.

ALT = alanine transferase.

AST = aspartate transferase.

TBIL = total bilirubin.
complication was localized pain. Pneumothorax in the right lung lobe occurred in 2 patients (2/18, 11.1%) during the IRE procedure that did not require any interventional treatment. There was 1 intrahepatic bile duct dilation (1/18, 5.6%) that recovered by conservative treatment. One patient experienced fatigue, vomiting and dizziness due to narcotics (1/18, 5.6%). Transient increase in blood pressure occurred during the IRE procedure in 1 patient (1/18, 5.6%). No other complications were observed during or after IRE ablation. Serum ALT and AST were increased obviously on the days 3 and 2 in 8 (8/18, 44.4%) patients, and then decreased to baseline on days 5 and 3, respectively. Highest median ALT and AST levels after IRE were 320.1 U/L and 307 U/L, which gradually reduced to 75.7 U/L and 57.6 U/L, respectively. The TBIL level was elevated on day 3 in 6 patients, fell to baseline within 1 month in 5, and decreased to a basic level at 3 months post IRE in one patient. In our study, most complications were easily controlled. Table 2 shows IRE-related complications during and after the IRE procedure.

Discussion

Our study showed that IRE achieved high LTPFS rate with no major complications in recurrent HCC. We believe IRE could serve as a safe and effective treatment modality for recurrent HCC that is unsuitable for thermal ablation.

In clinical practice, the function of recurrent HCC treatment is not only to control tumor progression, but also to protect the remnant hepatic parenchyma from injury. Thermal ablations have an associated risk of vital structure damage, high local recurrence, ablation tissue necrosis, and the consequent effect on liver function, especially when the tumor is located close to vital organs. Due to the preservation of the extracellular matrix integrity, IRE ablation could effectively destroy tumor cells, while simultaneously protecting critical structures, such as vessels, bile ducts, stomach and intestinal tract. The quick regeneration of ablated liver tissue following IRE30 is another advantage for recurrent HCC after surgical resection. Thus, IRE was performed for recurrent HCC tumors in this study.

In our study, IRE was applied for recurrent HCC adjacent to vital structures, including hepatic portal, hepatic vein, inferior vena cava, subcapsular position, or operated directly on the abdominal metastasis lymph node and PVT. LTPFS was 10.5 ± 9.4 months. No major complications or IRE-related deaths occurred.

Regarding the tumor adjacent to large vessels, bile ducts and important organs, one of the reasons due to which thermal ablation can lead to incomplete necrosis is the heat-sink effect. However, Fan et al. showed that radiofrequency ablation and microwave ablation were safe and effective for HCC located closely to the second porta hepatitis. In their study, 65 tumors were completely ablated following no more than 3 sessions of thermal ablation. The 1-year LPSF rate was 86.2%. No treatment-related deaths were observed. LTP was observed in 32.2% patients. The major complication was tumor seeding (1/84, 1.2%, 84 was total ablation sessions), while the minor complication rate was 20.2% (17/84). In our study, the 12-month LTPFR of the completely ablated tumors was 40% (8/20). No IRE-related mortality or major complications were observed. According to the standardization of minor complication of Fan’s study, the minor complication rate of our study was 18.2% (4/22). However, the baseline of the selected patients in these two studies were different from each other. Tumor location was more complex in our study (hepatic portal, hepatic vein, inferior vena cava, and subcapsular areas, PVT, abdominal lymph node metastases) and the patients were all treated with hepatectomy before IRE. Therefore, a larger scale study is needed to compare whether IRE is better than thermal ablation for tumor treatment in different dangerous locations.

In 2017, Frühling et al. reported results on the use of IRE for the treatment of 8 HCC patients. In their study, no tumor progression was observed at 3 or 6 months, which was better than the 3- and 6-month LTPFR reported in our study (75%, 65%, respectively). However, the tumor sizes in their study were between 8 and 35 mm (7 tumors < 30 mm, only one tumor > 30 mm). In our study, the tumor size was much larger (40.9% > 30 mm). Thus, the LTPFR result may be associated with tumor size. Indeed, Niessen et al. verified that tumor size affected the treatment outcome.

To our knowledge, AFP is an important prognostic factor closely associated with recurrent HCC.24,25 High-level AFP expression indicates carcinogenesis and is correlated with poor clinical outcome of HCC after local treatment.26 Our results showed that the median AFP level descended from 12,398.8 ng/ml to 3369.9 ng/ml post 1-month follow up. Further, the AFP of two patients decreased to normal range, and their LTPFS was much longer than 30 months.

As far as we know, there is no research focusing on the clinical safety and local treatment efficacy of IRE for recurrent HCC. Our study is the first report on this issue. However, our study had several limitations. First, based on the fact that patients evaluated in our study were highly selective, it was difficult to directly compare the results of our study with those of previous treatments. Second, due to the insufficient number of patients enrolled in this study it was difficult to make definitive conclusions. Third, this is a retrospective study.

In conclusion, our study provides preliminarily evidence that IRE is a safe and effective regional treatment for recurrent HCC. Herein, IRE could be considered as a palliative treatment for recurrent HCC unsuitable for thermal ablation. However, to obtain more representative data, larger studies with longer follow ups are needed, which is our next aim.

Declaration of competing interest

All authors declare no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence our work.

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