



Single-center nonrandomized clinical trial to assess the safety and efficacy of irreversible electroporation (IRE) ablation of liver tumors in humans: Short to mid-term results

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Accepted 15 December 2016

Available online 11 January 2017

Abstract

Introduction: A single-center nonrandomized clinical trial was performed to assess the safety and efficacy of IRE ablation of liver tumors in humans.

Methods: 38 malignant liver tumors on 30 patients were treated with IRE between September 2011 and September 2014. Treatment was with curative intent, and the diagnoses were colorectal cancer with liver metastases (CRLM) (n = 23), hepatocellular carcinoma (HCC) (n = 8) and other metastasis (n = 7). Patients were selected when surgery, radiofrequency ablation (RFA) or microwave ablation (MWA) was not an option, and when they met inclusion criteria (tumor size < 3 cm, 1–2 tumors). Patients were followed-up at 1 and 6 months with a contrast-enhanced computed tomography (CE-CT), and contrast-enhanced ultrasound (CE-US) at 3 months.

Results: Ablation success was defined as no evidence of residual tumor in the ablated area as confirmed by CE-CT and CE-US. At 3 months ablation success was 78.9%, and 65.8% at 6 months. There was no statistically significant difference between tumor volume (<5 cm³ vs >5 cm³, p = 0.518), and between diagnosis (CRLM vs HCC, p = 0.084) in terms of local recurrence. Complications were classified according to the standardized grading system of Society of Interventional Radiology (SIR). A minor complication occurred in six patients (20%), one patient (3.3%) suffered from a major complication (bile duct dilatation and stricture of the portal vein and bile duct). No mortalities occurred at 30 days.

Conclusions: IRE appears to be a safe treatment modality for a selected group of patients with liver tumors and offers high local tumor control at 3 and 6 months.

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Keywords: Liver tumors; Irreversible electroporation; Interventional ultrasonography; Colorectal cancer

Introduction

Surgical resection remains the most effective treatment modality for patients with liver tumors such as colorectal cancer with liver metastasis (CRLM) and in selected cases of hepatocellular carcinoma (HCC).^{1,2} The treatment of

patients with liver tumors is complex, often involving a combination of modalities such as surgery, chemotherapy and some form of ablative method. Radiofrequency ablation (RFA) and microwave ablation (MWA) are widely used in clinical practice, primarily as a complement to surgery or for small tumors in selected patients not suitable for surgery. These modalities, however, can cause thermal injury to structures in the vicinity of the ablated area and can therefore be contraindicated. Moreover, these methods suffer from the ‘heat sink’ effect where heat is lost due to flow of blood in nearby vessels.^{3,4}

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In recent years there have been an increased interest in irreversible electroporation (IRE), a non-thermal ablation method, which increases the permeability of the cell membrane by exposing the cell to electrical pulses.^{5,6} The precise mechanisms of IRE are not yet fully understood but the theory is that high-voltage direct current causes instability of the lipid bilayer by changing the trans-membrane potential across the cell. As a consequence, small, nanoscale pores, are created, which enable micro- and macromolecules to enter and exit the cell.⁷ These changes alter the homeostasis of the cell and contribute to its death.⁴ Since IRE does not use high-temperature-based mechanisms it can be used for tumors close to, or involving vital structures such as blood vessels and bile ducts.^{8–10} The safety and efficacy of IRE ablation of tumors have been studied before, but the studies are relatively small, the inclusion criteria heterogeneous and there is a short follow-up period^{11–17} In contrast to previous studies on IRE treatment of liver tumors, which used guided computed tomography, this study used contrast-enhanced ultrasound (CE-US) to deliver the IRE ablation. The objective of this study is to assess the safety and efficacy of IRE ablation of liver tumors in humans utilizing CE-US and contrast-enhanced computed tomography (CE-CT) presenting short to mid-term results.

Patients and methods

A prospective non-industry sponsored clinical trial was conducted at the department of surgery at Uppsala University Hospital. Patients were recruited between September 2011 and September 2014. The inclusion criteria were a tumor size of <30 mm, a maximum of 2 tumors and performance status according to Eastern Co-operative Oncology Group (ECOG) < 2. In addition, tumors also had to be localized close to large vessels and/or biliary ducts making surgical resection or treatment with other forms of ablation modalities (RFA, MWA or cryoablation) contraindicated. Exclusion criteria were American Society of Anaesthesiologists' (ASA) classification score IV, pacemakers, epilepsy and severe cardiac disease. Severe cardiac disease was defined as Heart failure class IV according to the New York Heart Association (NYHA) functional classification, or when the anesthesiologist thought a general anesthesia was too risky. Patients were deemed suitable for treatment in a multi-disciplinary-team (MDT) conference including liver surgeons, radiologists, hepatologists and oncologists. The study was approved by Uppsala Regional Ethics Committee, Uppsala, Sweden (D nr 2012/191), and all patients signed an informed consent form before the treatment.

Prior to treatment all patients were examined with both a CE-US (to ensure that the tumors were detectable with this modality) and a CE-CT. Subsequently, CE-US was performed the day before the IRE treatment and the day after treatment to identify any complication. The CE-US procedures were performed with Siemens Ultrasound S3000 using

a 6C1 curved array transducer or a 4V1 vector transducer depending on ultrasound access and limiting factors such as patient size, sub- or intercostal approach and/or overlying bowel gas. All needle placements were made using a free-hand technique. CE-US was used to identify the tumor, ascertain the tumor delineation and exclude other lesions not described prior to the ablation. 1 or 2 boluses of 1.5 ml were given using Sonovue (Bracco, Milan, Italy). The actual electrode placement was then performed using B-mode ultrasound alone. Several studies show that CE-US is a modality with high sensitivity and specificity for assessing liver tumors.^{18–21} The volume of the lesions was calculated assuming the tumor had a spherical shape, using the tumor's largest diameter ($V = (4 \times \pi \times r^3)/3$). If anything this would overestimate the volume of the tumor.

Interventional technique and machine settings

The NanoKnife IRE equipment from Angiodynamics System (Queensbury, NY, USA) was used. The electrodes were placed percutaneously under ultrasound guidance using either an intercostal or subcostal approach depending on the position of the tumor. The number of electrodes and the placement configuration was chosen individually in each case so as to cover the entire tumor volume including a safety margin of at least 5 mm, keeping the distance between each 2 electrodes at, or less than, 20 mm and assuming that the ablation zone would extend 5 mm beyond a placed electrode. It has been shown that the distance between the electrodes is more important than the depth of the electrode insertion.²² Time was not recorded for the electrode placement. Typically, a lesion of 20 mm was treated with 3 electrodes in a triangular pattern. Slightly larger tumors were treated with 4 electrodes in a square and in tumors larger than 3 cm the normal pattern would be one electrode in the center of the tumor and the remaining electrodes in the periphery, creating a total of 10 needle pairs with the distance between each 2 needles of 2 cm or less. A maximum number of 6 electrodes were used in each patient, i.e. the number of electrodes allowed by the IRE generator. In all our patients the active electrode length was 20 mm giving an ablation cylinder height of 30 mm. Thus, in order to get a 5 mm safety margin any lesion deeper than 20 mm would require that the electrodes were pulled-back in order to ablate the more superficial parts of the tumor.

All patients were under general anesthesia with deep muscle relaxation and the electrical pulses were synchronized to the patient's electrocardiogram (ECG). A minimum of 90 treatment pulses were delivered between each adequate electrode pair, defined as a distance between the electrodes not exceeding 25 mm. The machine settings were adjusted so that an end electrical current of around 40 A, and never less than 30 A, was achieved. All procedures were carried out by one radiologist. The IRE procedures and machine settings described above are in accordance with the manufacturer's guidelines.

Post-procedural follow-up

After the procedure all patients were monitored in the hospital for a minimum of 24 hours. Routine laboratory studies were taken, including liver and kidney profiles, hemoglobin, c-reactive protein and a white blood cell count. Any adverse events such as pain, fever or abnormal laboratory findings were recorded, and were defined as a major or minor complication according to the standardized grading system of the Society of Interventional Radiology (SIR).²³ A major complication was defined as an event that leads to substantial morbidity and disability, increasing the level of care or substantially lengthens the hospital stay. All other complications were considered minor. A transient self-limiting increase in liver transaminases was not considered a complication. Patients were followed-up within one day (after IRE treatment), and after 3 months with CE-US, and with CE-CT after 1 and ≥ 6 months. The initial CE-US scan at discharge was for patient safety, given the experimental nature of IRE (Figs. 1 and 2). Ablation was assessed using recognized reporting criteria and considered successful if it had an acceptable ablation zone (usually a distance of 10 mm) in the IRE treated area and there was no evidence of residual tumor at follow-up at 1, 3 or 6 months.²⁴ If the ablated zone started to grow or new contrast enhancing areas were seen on follow-up imaging it was considered a local recurrence.

Data analysis

Patient demographics, tumor characteristics, and recurrence at three and six months were studied using descriptive statistics. Median age of patients and median size of tumor

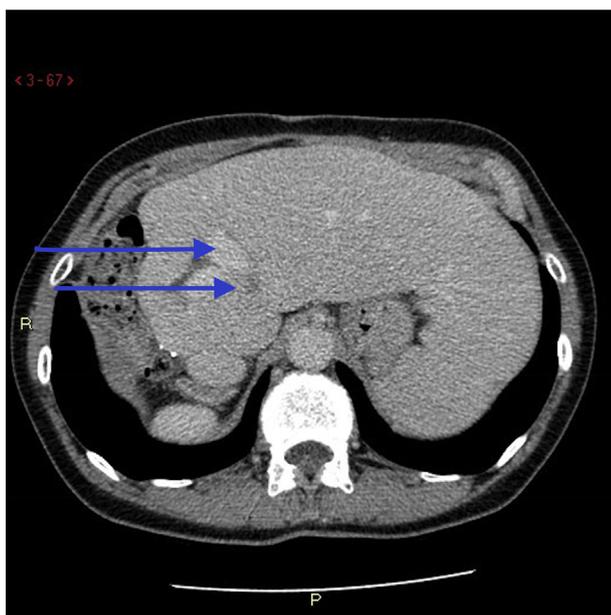


Figure 1. Metastasis (lower arrow) under the remaining left portal branch (upper arrow) in a patient with colorectal cancer and previous right hemihepatectomy.

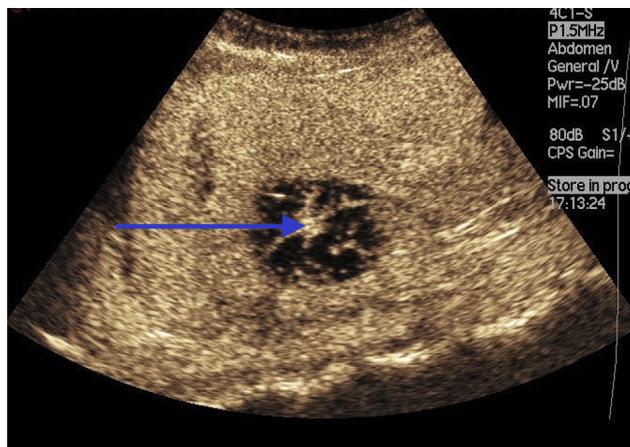


Figure 2. Post-IRE-ablation contrast enhanced ultrasound (CE-US) of the same patient, longitudinal section showing the ablation zone around the intact portal vein (see arrow) including smaller branches.

(both volume and diameter) were calculated, as was a comparison of the first fifteen and last fifteen patients ('learning curve'). The data were analyzed with the help of Statistical Package for the Social Sciences (SPSS) version 22 on a PC. Statistical comparison of recurrence for different variables was calculated using Fisher's exact test.

Results

30 patients (21 male, 9 female) were included in the study and a total of 38 tumors were treated with IRE. Two patients (patients 1 and 6) were treated on two different occasions (24 and 7 months apart) for two separate tumors. 8 patients had two tumors that were treated (Table 1). The median age of the patients was 63 years (46–78 years). The diagnoses were CRLM in 60.5% (23/38), HCC 21.1% (8/38) and 18.4% (7/38) had other metastases (Table 1). 18 patients had undergone previous liver surgery, and 20 had previously received either MWA or RFA. Almost 65% of the patients (20/31) belonged to ASA classification score 1 or 2.

The median size of the tumors was 24 mm (range 8–40 mm). Median volume was 6.79 cm³ (range, 0.11–33.51 cm³), and median diameter 23.50 mm (range, 8–40 mm). Six patients were included with a marginally larger tumor than 30 mm (Table 1).

Complications

The classification of complications followed the standardized SIR grading system, and immediate (up to 6–24 hours following procedure) and peri-procedural complications (within 30 days) were studied. There were no mortalities at 30 days. One patient with CRLM suffered from a major complication (3.3%) in the form of bile duct dilatation and stricture of both the portal vein and bile duct in the IRE ablated area. This patient was treated successfully with a stent in the portal vein, and a percutaneous

Table 1
Patient characteristics, complications and recurrence at follow-up.

Patient	Age/Sex	Diagnosis	Tumor size (mm)	Nights in hospital	Adverse events	Recurrence 3 months	Recurrence \geq 6 months
1	73/M	CRLM	12	1	↑ALAT/ASAT	No	No
			11	2	↑ALAT/ASAT	Yes	Yes
2	60/F	CRLM	13	3	Pain	No	No
			12	3	Pain	No	No
3	74/M	CRLM	34	4	Arrhythmia	Yes	Yes
4	42/F	Adrenal cancer	8	2	Hematoma	Yes	Yes
5	52/F	Midgut carcinoid	9	1	None	No	No
6	72/M	CRLM	20	1	↑ALAT/ASAT	Yes	Yes
			31	1	None	Yes	Yes
7	56/M	HCC	14	1	↑ALAT/ASAT	No	No
8	49/M	NET	10	2	↑ALAT/ASAT	No	No
9	63/M	CRLM	30	3	Pain, SOB	No	Yes
10	78/M	HCC	25	1	↑ALAT/ASAT	No	No
11	68/M	CRLM	24	2	↑ALAT/ASAT	No	Yes
			30	2	pain	No	No
12	59/F	CRLM	25	1	No	No	Yes
			30	1	No	No	No
13	66/F	CC	28	1	↑ALAT/ASAT	Yes	Yes
			8	1	↑ALAT/ASAT	No	No
14	57/M	CRLM	15	1	Pain, VT	No	No
			40	3	↑ALAT/ASAT	Unclear ^a	Died/Yes
16	66/M	CRLM			22	3	Pain
			31	2	No	No	No
17	78/M	HCC	23	3	↑ALAT/ASAT	No	No
18	46/M	CC	25	1	Infection	No	No
19	66/M	HCC	8	2	↑ALAT/ASAT	No	No
20	59/F	CRLM	24	4	↑ALAT/ASAT	No	Yes
			20	4	↑ALAT/ASAT	No	No
21	53/M	HCC	25	1	Pain	No	No
22	56/M	CRLM	35	1	↑BP	No	No
23	57/M	CRLM	30	1	↑bilirubin	No	Yes
24	78/M	CRLM	28	1	None	No	No
25	72/F	HCC	35	1	None	No	No
26	73/M	HCC	15	1	↑ALAT/ASAT	No	No
27	77/F	MM	25	1	None	No	No
28	53/M	HCC	12	2	Pain	No	No
29	60/M	CRLM	22	4	None	No	No
30	71/M	CRLM	10	2	↑ALAT/ASAT	No	No

Abbreviation: CRLM: colorectal cancer with liver metastasis, HCC: hepatocellular carcinoma, MM: malignant melanoma, CC: cholangiocarcinoma, NET: neuroendocrine tumor, Midgut: midgut carcinoid, HEH: hepatic epithelioid hemangioendothelioma. ALAT: amino alanine transferase, ASAT: aspartate aminotransferase. BP: blood pressure, SOB: shortness of breath, M: Male, F: Female, VT: ventricular tachycardia.

^a CT scan was performed without contrast, making an adequate assessment of the imaging difficult.

trans-hepatic biliary drainage catheter in the biliary duct. A minor complication occurred in 6 patients (20.0%), ranging from increased blood pressure, to a self-limiting hematoma in the ablated zone requiring no further action (Table 2). A transient increase in liver transaminases was observed in thirteen patients, which within days returned to baseline without any other intervention. Among the seven patients that reported post-procedural pain only one received a strong opioid in the form of intravenous morphine (Table 1).

Length of stay

The median length of hospital stay was 2 days (range 1–4 days). 19 patients were discharged the day after the procedure, 9 patients were observed for two nights and

10 patients stayed three or more nights. Patients that stayed in hospital beyond 24–48 hours did so because of pain, a short episode of shortness of breath, a transient cardiac arrhythmia or because their liver transaminases were abnormal post-IRE treatment (Table 1).

Follow-up

Follow-up according to the protocol was 100% at 3 and 6 months (Table 1). Radiological assessment of the IRE ablated area followed the well-established reporting criteria by Ahmed and co-workers.²⁴ Local recurrence was defined as evidence of residual tumor in the IRE ablated zone as observed on either CE-US or CE-CT. Considering all tumors that were included in the study, local recurrence

Table 2
Complications post IRE treatment.

Adverse events	Incident and treatment
Patient 3 CRLM. Warfarin treated atrial fibrillation	ECG changes during IRE, and chest pain requiring morphine. Normal troponin measurements. Observation with no further treatment.
Patient 4 Adrenal carcinoma	Hematoma (40 × 60 mm) in ablated zone. No drop in hemoglobin, and patient suffered from no reported pain. No local recurrence of tumor. Hematoma completely reabsorbed as observed on CE-US at 3 months.
Patient 9 CRLM	Episode of shortness of breath. Laboratory findings normal, chest radiograph normal. No further treatment required
Patient 14 CRLM. No previous cardiac history	Transient ventricular tachycardia, which resolved after receiving metoprolol. Discharged the next day without complications.
Patient 15 CRLM	CT scan after 3 months was performed without contrast, making an assessment of recurrence difficult. Patient died 4 months post IRE treatment. The post mortem report concluded pulmonary embolism as cause of death, and that there was evidence of residual tumor in the IRE ablated zone.
Patient 18 CC	Post-operative infection of unknown origin, treated with oral antibiotics. Discharged the day after IRE treatment uneventfully.
Patient 22 CRLM	Episode of increased blood pressure successfully treated with labetalol, and no further follow-up.
Patient 23 CRLM	Portal vein and biliary duct stricture in the IRE ablated zone resulting in increased bilirubin levels. The portal vein stricture was treated with the placement of a stent and the biliary duct stricture with a percutaneous trans-hepatic cholangiography (PTC) drainage catheter.

occurred in 21.1% and 34.2% at 3 and 6 months, respectively. CRLM local recurrence was 26.1% and 47.8% at 3 and 6 months, respectively. There were no local recurrences at either time period for HCC ($p = 0.084$, CRLM vs HCC). For patients with tumors due other form of metastases (e.g. malignant melanoma or cholangiocarcinoma) the recurrence rate was 28.6% after both 3 and 6 months. Follow-up post IRE treatment (Table 3) was 6–48 months (range 181–1466 days, median 680 days). In 9 out of these patients there was no evidence of recurrence. Data extracted from the national patient registry show that 13 patients included in the study have died (median 413 days), none of which died as a consequence of the IRE procedure.

Considering local recurrence and tumor size (using the same cut-off value as Niessen), recurrence was 18.8% for tumors with a volume less than 5 cm³ compared to 45.5% for tumors larger than >5 cm³ ($p = 0.518$).¹³ Local recurrence at 6 months follow-up was for the first 15 patients 50.0% compared with 12.5% for the last 15 patients ($p = 0.348$).

Discussion

This study shows a good safety profile (20.0% minor and, 3.3% major complications), which is similar to the experiences of Dollinger and co-workers (18.8% minor and 7.1% major complications).¹¹ We describe one serious complication with bile duct and portal vein injury, which was successfully treated. These kinds of complications after IRE treatment have been reported in previous clinical studies.^{25,26} Additionally, our experience of the safety of IRE is similar to Scheffer's review of 16 studies and 221 patients.¹⁶ Evidence suggests that IRE is a safe treatment modality for a selected group of patients. One way of

classifying the complications of IRE treatment is to divide them into systemic (e.g. arrhythmias and high blood pressure) and potential complications in the IRE treated area (e.g. bile duct injury).^{11,14,16,27–29} Our experience of a

Table 3
Follow-up data of patients post IRE treatment.

Patient	Age/Sex	Diagnosis	Survival after treatment (days)
1	73/M	CRLM	1692
2	60/F	CRLM	1630
3	74/M	CRLM	861 (died)
4	42/F	Adrenal cancer	1357
5	52/F	Midgut carcinoid	1357
6	72/M	CRLM	825 (died)
7	56/M	HCC	1517
8	49/M	NET	1477
9	63/M	CRLM	1176
10	78/M	HCC	360 (died)
11	68/M	CRLM	1215
12	59/F	CRLM	118
13	66/F	CC	1091
14	57/M	CRLM	1084
15	74/F	CRLM	76 (died)
16	66/M	CRLM	600 (died)
17	78/M	HCC	456 (died)
18	46/M	CC	380 (died)
19	66/M	HCC	844
20	59/F	CRLM	780
21	53/M	HCC	732
22	56/M	CRLM	470 (died)
23	57/M	CRLM	312 (died)
24	78/M	CRLM	413 (died)
25	72/F	HCC	627
26	73/M	HCC	615
27	77/F	MM	402 (died)
28	53/M	HCC	571
29	60/M	CRLM	497 (died)
30	71/M	CRLM	578

self-limiting and rapidly resolving transient increase in liver enzymes is a well-known and expected side effect of IRE treatment since it causes cell death.

In a retrospective analysis of liver function tests before and after IRE treatment in 174 IRE procedures Froud and colleagues noticed that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were often (in nearly 90% of the procedures) strikingly high within a day or two from the procedure, but returned to normal or baseline levels within days. The pattern of elevation was different for both alkaline phosphatase (ALP) and bilirubin compared with ALT and AST. An increase in ALP and bilirubin occurred more seldom (9.8% and 14.4%, respectively) and a return to baseline levels was less common. The conclusion of this study is that although there is a marked increase in liver enzymes post-IRE ablation it is safe and self-limiting.³⁰

Six patients were included in the study despite having a marginally larger tumor than 30 mm. This slight digression from the protocol was discussed and approved in the MDT conference. Since these patients were palliative and no other surgical or ablative intervention was indicated, it was decided that they should be offered IRE treatment, even if the risk of tumor recurrence would be higher.

What makes the methodology of this study unique is the use of CE-US both before and after IRE treatment. Advantages of CE-US include availability, its cost-efficiency, ease-of-use and that it is easily used intra-operatively. Median length of hospital stay was two days, and follow-up at 3 and 6 months was 100%. Local recurrence at 3 and 6 months for all patients together was 21.1% and 34.2%, respectively. This is a higher recurrence rate than reported in studies by for example Kingham, and Cannon et al.^{12,28} This difference can be because of various reasons. First, the number of patients treated with IRE in the three studies combined (the present study and the two aforementioned) is still small. Secondly, the inclusion criteria of these studies are not clearly defined making an adequate comparison of the results of the studies difficult. Finally, the tumors included in this study may have been more challenging to treat given that there was no other treatment option (surgery, MWA or RFA) available, but only palliative care.

Tumor control at 3 months was best achieved for HCC (0% recurrence) compared to CRLM (26.1% recurrence) and other metastases (28.6% recurrence). Volume size less than 5 cm³ had a lower recurrence rate (18.8%) than tumors larger than >5 cm³ (45.5%, $p = 0.518$). There was no difference in size between diagnoses. Local recurrence for the first 15 patients was 50.0% compared with 12.5% for the last 15 patients ($p = 0.348$). This may partly be explained by the fact that 6 out of the last 15 patients compared to 2 among the first 15 patients had HCC. There might also be an element of ‘learning curve’, where acquaintance with the technique may positively influence the outcome.

This study has several limitations. Firstly, the study size is small so the results should be regarded with caution.

Secondly, the assessment of ablation success relies on radiological imaging alone, and the experience of interpreting imaging post-IRE is under development.^{31,32} We used the same radiologist, highly experienced in evaluating post-ablation situations in the liver and therefore we consider this limitation as negligible for this study. In conclusion, IRE offers high local tumor control at 3 and 6 months and appears to be a safe ablative modality with a role to play in the treatment of a carefully selected group of patients with liver tumors close to or surrounding vital structures.

Conflicts of interest statement

All authors declare that there was no conflict of interest.

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