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Initial experience with irreversible electroporation of liver tumours

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ABSTRACT

Introduction: Thermal ablation of liver tumours is an established technique used in selected patients with relatively small tumours that can be ablated with margin. Thermal ablation methods are not advisable near larger bile ducts that are sensitive to thermal injury causing strictures and severe morbidity. Irreversible electroporation (IRE) has the possibility to treat these tumours without harming the bile tree. The method is relatively new and has been proven to be feasible and safe with promising oncological results.

Methods: 50 treatments were performed on 42 patients that were not resectable or treatable by thermal ablation (12 women and 30 men) with 59 tumours in total. 51% were colorectal cancer liver metastases (CRCLM) and 34% were hepatocellular carcinomas (HCC). 70% of the treatments were performed using stereotactic CT-guidance for needle placement.

Results: 81% of the treatments were performed with initial success. All patients with missed ablations were re-treated. Local recurrence rate at 3 months was 3% and 37% at one year. The complication rate was low with 2 patients having major complications (Clavien-Dindo grade 3b-5) and without 30-day mortality.

Conclusion: IRE is safe for treating tumours not suitable for thermal ablation with 63% of patients being without local recurrence after one year in a group of patients with tumours deemed unresectable. IRE has a role in the treatment of unresectable liver tumours close to heat-sensitive structures not suitable for thermal ablation.

Level of Evidence: Level 4, Case Series.

1. Introduction

Local ablative therapy of liver tumours is an established technique in colorectal cancer liver metastases (CRCLM) and primary liver cancer (Hepatocellular Carcinoma, HCC) [1,2]. Ablation for tumours smaller than three centimetres is acknowledged as an alternative to resection in recent international guidelines [3,4]. The methods most frequently used are thermal, where the goal is to create coagulative necrosis of the tumour. The most commonly used methods are Radiofrequency Ablation (RFA) and Microwave Ablation (MWA) [5,6]. These methods are limited by the risk of collateral damage to adjacent structures such as bile ducts and bowel, as well as risk of insufficient heating caused by cooling from larger blood vessels, the so-called heat-sink effect [5].

Irreversible electroporation (IRE) is a relatively new method for non-thermal local ablation. By applying short pulses of direct electrical current an electric field is created across the tumour cells, inducing nano-pores in the cell membranes and thereby disturbing the cells' homeostasis, causing the cells to undergo apoptosis. As there is no thermal effect in the treatment zone it is possible to treat tumours very close to larger vessels and bile ducts without affecting the blood or bile flow [7]. The endothelial cells, as well as cholangiocytes, are also affected by the electrical field, but the collagen matrix in the vessel walls and bile ducts is not, allowing for re-epithelization and preservation of vessel and duct function after treatment [8,9].

Previous publications on IRE in the liver are case series of 5–71 patients and a variety of diagnoses and indications. These studies have mainly focused on safety and short-term results [10–18]. One study presents long-term survival analyses with a median follow-up of 35.7 months [16].

The aim of this study was to report feasibility, short-term outcome and complications in 50 consecutive liver IRE treatments where resection or thermal ablation was not possible, focusing on patients with HCC and CRCLM. This article follows the updated standardization of terminology and reporting criteria stated by Ahmed et al. [19].

2. Materials and methods

2.1. Patient selection

All patients were discussed at a multidisciplinary team (MDT)

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conference. Patients considered not eligible for surgery or transplantation were potential candidates for ablative therapy. These patients were treated with MWA if possible. Tumours that were located too close to central bile ducts and/or portal branches to allow for safe thermal ablation were instead treated with IRE and were included in the present retrospective single centre study.

2.2. Procedure

All procedures were performed under general anaesthesia and full muscle relaxant. The respiratory movement of the liver was minimized by using high frequency jet-ventilation (HFJV). HFJV uses high-flow, short-duration pulses of air through a small catheter placed inside the normal endotracheal tube resulting in very little movement of the liver [20–23]. A single oral dose of 800 mg. Sulfamethoxazole and 160 mg. Trimethoprim was given as preoperative antibiotic prophylaxis two hours before the intervention. Postoperative thrombosis prophylaxis was given for 10 days with 4500 units of Tinzaparin daily.

The procedures were performed in the radiology department when using a percutaneous approach and in an operating room (OR) when using an open approach. One percutaneous, ultrasound-guided procedure was performed in the OR due to logistical problems with access to the CT-lab.

The methods for image guidance were either ultrasound, ultrasound fused with computer tomography (CT) and/or magnetic resonance imaging (MRI) or with stereotactic CT-guidance (CAS-ONE, CAScination AG, Switzerland). CAS-ONE is a stereotactic CT-guided navigation system that allows the interventionist to have a 3D view of the liver. Using the two infrared cameras in combination with retro-reflective skin-markers, the applicator can be guided in this 3D view with high accuracy as has been previously described [24]. New functionality was added to the software with possibilities of positioning multiple applicators in pre-set patterns at predetermined offsets and also evaluate the actual electrode positions with precise measurements of distances (Fig. 1). With these software modifications, CAS-ONE was the image guidance of choice.

When the positions of the electrodes were accepted, 10–20 test pulses were delivered between each pair and the graph of delivered current was analysed and the voltage was adjusted if needed. A minimum of 70 treatment-pulses were delivered between each electrode pair and the graph showing the delivered current was analysed. The delivered current was accepted if there was an increase in amperage between the first and last set of 10 pulses. The increase of current is a sign of decrease in tissue resistance according to Ohms law.

All patients underwent an immediate post-interventional radiological investigation, with a second contrast dose when kidney function allowed for it, otherwise without contrast, to evaluate the immediate ablation result and to detect early complications such as bleeding or pneumothorax. If there was suspicion of residual tumour and the scan was done directly after the ablation, a second treatment was done during the same procedure.

After recovery the patients were discharged on the same day or after an overnight stay, mostly for urinary retention problems or because of long transports home.

The treatment result was evaluated every three months, with CT-scans for HCC, and MRI for CRCLM, for the first year or until recurrence. In case of recurrence, the patients were assessed for additional ablative treatment or re-referred to the MDT conference for further discussion. Further follow-up after this time-period was at the discretion of the referring physician.

2.3. Data collection

A retrospective follow up of all patients treated with hepatic IRE was performed by reviewing electronic patient records regarding pre-operative investigations, prior treatments in the liver, per- and post-

Fig. 1. a) CAS-ONE, reprint with permission from CAScination AB, Bern. b) Planning the electrode trajectory. Coloured lines show the planned electrode paths. c) 3D view of the patient with retro-reflectant skin markers (green) and planned electrode positioning.

operative complications using the Clavien-Dindo classification [25], length of hospital stay, additional treatments (liver resection, ablation, trans arterial chemo embolization (TACE) or liver transplantation) and mortality. All relevant radiological examinations were retrospectively reviewed by one radiologist (MB). Pre- and per-operative images were reviewed to determine correct tumour size and segmental location. All post-operative images were reviewed to determine if and when local recurrence occurred, or if tumours were detected in non-treated parts of the liver. Local tumour recurrence was defined as a recurrence within 1 cm of a previously treated tumour.

All patients were followed for at least 12 months.

2.4. Statistical analyses

Descriptive statistics were used for presentation of patient and tumour characteristics using medians (range) for non-normally distributed data. Differences between groups were analysed using the Mann-Whitney U test or Fisher's exact test as appropriate. The threshold for statistical significance was set to $\alpha < 0.05$. Survival, time to local recurrence and time to loss of control was illustrated using Kaplan-Meier graphs. STATA 15 (StataCorp, College Station, Texas 77845 USA) was used for the statistical analyses.

2.5. Ethical approval

Ethical approval was obtained from the regional ethical review board in the Stockholm-Gotland region (EPN Dnr2016/2212-31/2)

3. Results

The IRE procedures were performed from February 2014 until May 2017. 50 treatments were done on 59 tumours in 42 patients, consisting of 12 women (29%) and 30 men (71%). The majority of the patients had CRCLM (20 patients, 48%) or HCC (17 patients, 40%). Of the tumours 30 (51%) were CRCLM and 20 (34%) were HCC. Two thirds of patients had at least one prior intervention done in the liver, the most common procedure being liver resection (18 patients, 43%) followed by MWA (15 patients, 36%). There was a primary curative intent in 36 patients (86%), while 6 patients (14%) were treated as a first stage before liver surgery, mainly with the intent to clear the future liver remnant of liver metastases.

One patient has been excluded from the full analysis. This was a 20-year-old man with primary biliary cirrhosis with a 15 mm nodule in segment 2. After discussion at the MDT conference, the decision was to perform a biopsy followed by IRE-treatment at the same intervention. The pathological report did not show any signs of malignancy in the biopsy specimen, and thus the patient is not included in the analyses of recurrence. This patient was discharged on the day of the procedure and did not have any 30-day complications.

The patient characteristics are summarized in Table 1.

The first procedure with stereotactic CT-guided IRE was performed in September 2014, and following this initial experience, over 80% of the treatments has been performed with CT-guidance using the CAS-ONE system. Two patients were treated with an open surgical approach due to tumours being too close to the bowel, where organ displacement by infusion of glucose solution was thought to be ineffective because of previous open surgeries. The median procedure time was 167.5 min overall and 135 min when using CT-guidance. A software update for placing multiple needles and a new electrode holder were developed and brought into use in December 2015, reducing the procedure times significantly (mean procedure time for the first 11 procedures with CAS-ONE were 198 min compared to 95 min for the last 20, $p < 0{,}001$), but part of this improvement is also due to the learning-curve for the procedure. No difference in recurrence rates was seen between the two groups.

There was one intra-operative complication with a peak in blood pressure over 200 mmHg due to the treated tumours proximity to the right adrenal gland. The blood pressure was normalized immediately when the pulse delivery was aborted. Despite the increase in blood pressure all the pulses could be delivered.

Table 1
Patient and tumour characteristics in 50 interventions. Cholangio carcinoma (CCC), Microwave (MW), Radio frequency (RF), Hepatocellular carcinoma (HCC), Irreversible electroporation (IRE), Trans arterial chemo embolization (TACE).

Sex, no.of treatments (%)	
Male	34 (68%)
Female	16 (32%)
Age (y), median (min-max)	63 (38–86)
Tumour type, no (%) of tumors	
Colorectal livermetastases	30 (50,8%)
Hepatocellular carcinoma	20 (33,9%)
Cholangiocarcinoma	2 (3,4%)
Livermetastes from CCC	2 (3,4%)
Leiomyosarcoma	1 (1,7%)
Sarcoma	1 (1,7%)
Adrenocortical carcinoma	4 (6,8%)
Tumour diameter (mm), median (min-max)	20 (5–60)
Previous interventions, no. (%) of patients	
Resection	24 (46,2%)
MW ablation	23 (46,0%)
RF ablation	3 (6,0%)
IRE	8 (16,0%)
TACE (if HCC)	4 (21,1%)
Purpose no. (%), tumours	
Curative	50 (84,7%)
Stage 1	8 (13,6%)
Debulking	1 (1,7%)

One patient had a sub-capsular bleeding on a CT scan done to verify the needle positioning and received no treatment. Eventually her HCC was treated with MWA, now possible because the hematoma had displaced the tumour from the bile duct, before going to a successful liver transplantation.

Procedural complications within 30 days were seen in 10 patients (20%). Eight of the complications were Clavien-Dindo grade 1-3a and two were grade 3b-4b. Three patients had a pneumothorax, but none needed indwelling pleural drains.

There was no 30-day mortality, but one patient suffered from liver failure due to his underlying cirrhosis and died from this condition 46 days after the procedure.

Procedural characteristics and complications are summarized in Table 2.

11 treated lesions (19%) had signs of residual tumour on the first radiological investigation following the initial intervention. One patient with a rectal cancer metastasis received chemotherapy after the IRE treatment and went on to hemi-hepatectomy three months after the IRE. One patient with HCC received TACE two months after the IRE, then had another recurrence that was treated with MWA and went on to liver transplant one year after the initial IRE treatment. The remaining nine patients all received additional ablative treatment, three with IRE and six with MWA. This illustrates the multimodal approach to these patients where tumour recurrences for various reasons are common but often re-treatable.

For the remaining patients, local recurrence rate, defined as recurrence within 1 cm of the ablated tumour, was 3% at three months, 26% at six months and 37% at one year. Graphs of a first recurrence after IRE treatment in patients with HCC and CRCLM are shown in Fig. 2. Subsequent IRE treatments of previously IRE treated tumours are not included in this analyses that is based on the first IRE treatment for the specified tumour.

The number of patients with liver metastases of non-colorectal origin are too few for any meaningful tumour-specific analysis.

No signs of local recurrence along the electrode tracts (seeding) were found in this material.

Table 2
Procedure characteristics and list of complications. Patients radiation dose for patients that underwent CT-scan during the procedure. Computer Assisted Surgery (CAS), Dose-length product (DLP).

Image guidance	
CAScination	35 (70,0%)
Ultrasound-fusion	11 (22,0%)
Ultrasound	2 (4,0%)
Open surgery	2 (4,0%)
Procedure time, All 50 treatments, (min), median (min-max)	167,5 (44–324)
Procedure time, CAS 35 treatments, (min), median (min-max)	135 (44–304)
Procedure time, non-CAS 15 treatments, (min), median (min-max)	210 (102–324)
Number of needles, median (min-max)	4 (2–7)
DPL, CAS n = 35 (mGy x cm), mean (± SD)	1399,4 ± 515,6
DPL, radiated non-CAS n = 10 (mGy x cm), mean (± SD)	906,6 ± 404,2
Length of hospital stay (days), median (min-max)	1 (0–10)
Complications, 30 days	
pneumothorax	3
bleeding	1
liverfailure	1
portal vein thrombosis	2
infection	1
brachial plexus injury	3
Clavien-Dindo	
1-3a	7
3b-5	2

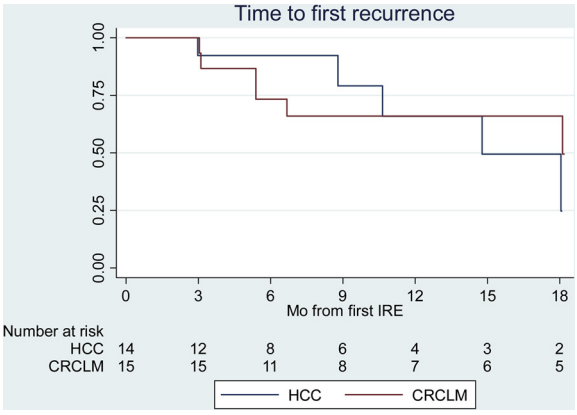

Fig. 2. Kaplan-Mayer estimates showing time from first IRE treatment to first local recurrence for patients with HCC (Hepatocellular carcinoma) and CRLM (Colorectal liver metastases). IRE (Irreversible electroporation).

Re-intervention was performed on all patients with local recurrence. Two patients had a new IRE treatment, one with additional MWA, five patients had MWA treatment, two underwent hemi-hepatectomy, one had TACE and one was treated with alcohol injection.

Following local ablative therapy, the need for re-intervention is not uncommon, 15 patients (36%) had prior MWA treatment. All patients with local recurrences were re-treated, with the aim to keep on treating with curative intent until the disease was out of control. Loss of control was defined as a situation where curative treatment was no longer possible due to overwhelming liver tumours or distant metastases that were categorized as not treatable with curative intent. Time to loss of control is presented in Fig. 3.

Six patients were treated as a first step before additional treatment, all with CRCLM. Three of these patients went on to hemi-hepatectomy. One patient went through with portal vein embolization, but when surgery was performed six weeks later he had wide-spread metastatic disease. One patient received IRE as a first step and continued in a second stage with MWA before surgery of the primary tumour and is still alive two years after the initial IRE treatment. One patient had

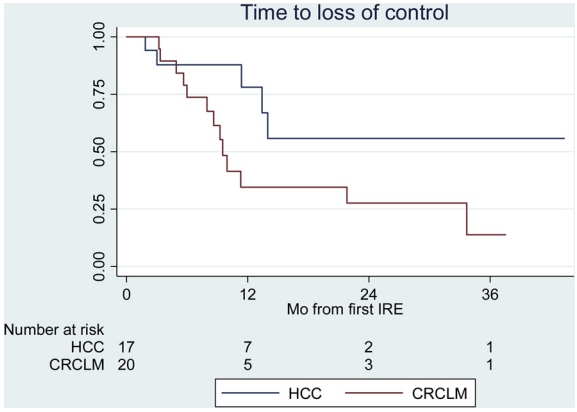

Fig. 3. Kaplan-Mayer estimates showing time from first IRE treatment until the patient is no longer candidate for curative intended treatment. IRE (Irreversible electroporation). HCC (Hepatocellular carcinoma). CRMLM (colorectal liver metastases).

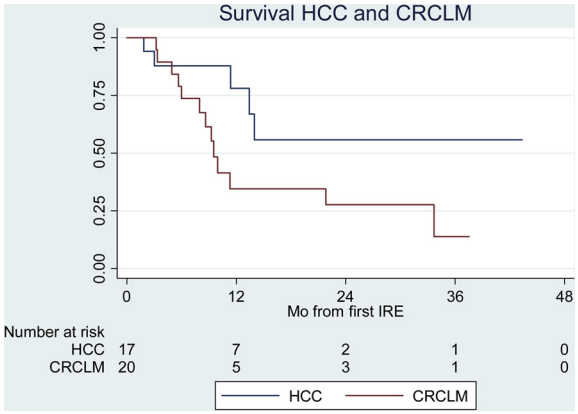

Fig. 4. Kaplan-Mayer estimates showing overall survival after first IRE treatment for patients with HCC (Hepatocellular carcinoma) and CRCLM (colorectal liver metastases). IRE (Irreversible electroporation).

developed multiple metastases on follow-up and further treatment was not possible.

Survival analyses on patients with HCC and CRCLM were performed separately and is presented in Fig. 4.

4. Discussion

This study presents the results from the first 50 IRE treatments at a dedicated specialized unit. The most important result is that the treatment is safe and that the recurrence rate is acceptable with 61% of patients being without local recurrence within 12 months.

Seventy percent of all treatments were performed with stereotactic CT-guidance, using the CAS-One system to assist in electrode placement. A significant software improvement in combination with streamlined team-work has led to significantly shorter procedural times. The procedural time is important mainly because of the risk for the patients, e.g. brachial plexus injury after prolonged time with extended shoulders in the CT gantry, but also for a logistical point of view where time in the CT-lab is limited.

The high incidence of incomplete ablations, 19%, could be explained by the location of the treated tumours. All of them were adjacent to larger bile ducts or the bowel making electrode placement more demanding. The rate of incomplete ablations is similar to other studies. Thomson et al. showed complete tumour ablation at follow up after one and three months in 83% (15 of 18) of HCC patients and 50% in liver metastases [26] and Nissen et al. showed that 18,5% of tumours

required retreatment due to incomplete ablation or early recurrence [27]. Of the eleven patients with incomplete ablations, nine received new ablative therapy. Six of these could receive MWA, as the primary IRE treatment had succeeded in ablating the part of the tumour close to the heat sensitive structure. This could be an important role for IRE in the future, ablating only the most difficult part of the tumour and then using MWA or other thermal ablation techniques to treat the larger bulk of the tumour.

Local recurrence in the whole group was 26% at 6 months and 37% at one year. In the two largest groups of patients, HCC and CRCLM, the local recurrence rate at 12 months is 17% and 38%. The 3 and 6-month recurrence rates are similar to previously published data [18,26,27].

Distelmaier et al. published data showing local recurrences along the electrode paths [28]. Because of this all radiological exams of patients with local recurrence were reviewed and no sign of local recurrence along the electrode paths could be found. An explanation could be that in the present series, care was taken to put electrodes around the tumour rather than within, whenever this was possible.

30-day complication rates are similar to previously published data [16,18] with few severe complications.

In this report we use a new term: “time to loss of control”. In the nature of local ablative therapy, re-ablation is common. One can argue that this is a weakness of the methods used, but on the other hand these procedures are done percutaneously with few complications and short hospital stays on groups of patients with high risk of recurrence of new tumours, even after major hepatic surgery. The term “time to loss of control” shows how long time a curative intention is held, despite recurrence of new tumours.

The survival of metastasized colorectal cancer has increased in the last decade [29,30]. This is believed to be because of better multidisciplinary treatments with resections, ablations and new oncological treatments. About 17–25% of patients with liver metastases from colorectal cancer are candidates for liver resection with a three-year survival of 80% compared to 12% for patients with unresectable disease [29,30].

The patients in this study were all considered unresectable. The follow-up time for most of the patients has not yet reached three years, but for those who have, the survival is over 30%.

One strength of this study is the complete and meticulous follow-up of the patients. All patients are followed regularly for one year after the treatment and thereafter the electronic patient records allow for further follow-up of patients, both regarding clinical as well as radiological reports.

An obvious weakness is the retrospective nature of the study, with data originating from only one institution.

Based on these results, IRE has its role in treatment of liver tumours close to heat-sensitive structures where thermal ablative methods are unsuitable. For this group of patients, where in many cases no other ablative or surgical treatment is an option, IRE can be a valuable tool in the multi-modal treatment strategies available.

Funding

This study was not supported by any funding.

Conflict of interest

None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

This study has obtained approval from the regional ethical review board in the Stockholm-Gotland region (EPN Dnr2016/2212-31/2) and the need for informed consent was waived.

Consent for publication

For this type of study consent for publication is not required.

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