Ultrasound-guided percutaneous irreversible electroporation of hepatic and abdominal tumors not eligible for surgery or thermal ablation: a western report on safety and efficacy

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Abstract

Purpose To report our first results on sixteen patients affected by liver and abdominal malignant tumors, unfit for surgery or thermal ablation, treated with US-guided percutaneous irreversible electroporation (IRE).

Methods From June 2014 to December 2016, all patients meeting the inclusion criteria (malignant hepatic or abdominal tumors not eligible for resection or thermal ablation) and not meeting the exclusion criteria (heart arrhythmia, pro-hemorrhagic hematological alterations, tumor size > 8 cm, presence of a biliary metallic stent) referred to our institutions were prospectively enrolled to undergo percutaneous US-guided irreversible electroporation (IRE). Sixteen patients (age range 59–68 years, mean 63; 7 females) with 18 tumors (diameter range 1.3–7.5 cm) fulfilled the inclusion criteria and were included in the study. Data concerning efficacy (tested by a 1-week CEUS and a 4-week enhanced CT and/or enhanced MRI) and safety were recorded during a 18-month follow up.

Results All patients completed a 35–50-min procedure without complications. One patient with 6 cm Klatskin tumor also underwent a second session for 1 month. A 1-week CEUS and a 4-week e-CT and/or e-MRI arterial phase contrast enhancement analysis showed an overall reduction of arterial flow with confirmation of unenhanced lesions for seven nodules. After 1–18 months of follow up, no major complications were recorded and no tumor-related death occurred. The lesions of two patients disappeared 3 and 6 months after their treatment, respectively.

Conclusions IRE is a promising ablation modality in the treatment of malignant hepatic and abdominal tumors unsuitable for resection or thermal ablation.

Keywords Irreversible electroporation · Hepatic tumors · Abdominal tumors

Introduction

Thermal ablative techniques are highly effective in treating liver tumors; however, there is still a significant population of patients whose tumors are either adjacent to large (> 3 mm) blood vessels or major bile ducts such that thermal ablation would be ineffective or dangerous. Irreversible electroporation (IRE) may potentially be an ideal ablation modality for those tumors where thermal techniques are contraindicated [1]. In contrast to thermal ablation techniques, IRE is a new non-thermal ablation technique that—instead of heat—uses electric impulses to cause an irreversible disruption of cell membrane integrity, resulting in cell death in the ablated region. Through the use of a high-voltage, low-energy direct current, electrons passing between electrodes pass through intervening cells and cause “nanopores” in the cell membrane. When the repair of nanopores cannot match

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the frequency with which they are produced, and the number of nanopores reaches a critical number, damage to the cell membrane can no longer be reversed, cellular homeostasis is disrupted, and apoptotic cell death is triggered [2–7].

The safety of IRE has been evaluated in several animal models. In animals, the radiologic–pathologic correlation of IRE-induced cell death showed that the treatment areas were sharply demarcated and bile ducts' and vessels' integrity was completely preserved [5]. The areas of complete cell death stained positive for apoptotic markers (TUNEL, BCL-2 oncoprotein) suggest the involvement of the apoptotic process in the pathophysiology of cell death caused by IRE [5, 6].

Rubinsky et al. demonstrated that IRE ablation in porcine liver can completely ablate target tissue up to the margin of blood vessels without vascular insult [7]. The vessel-preserving effect of IRE is believed to be due to the fact that the vessel wall contains a higher proportion of collagenous connective tissue and elastic fiber, and it lacks a normal cellular membrane [7].

In the literature, most of the first reports on IRE applicability were from Eastern authors, however, there are recently quite a large series of patients treated with IRE in the Western world mainly from USA and Germany [8–10].

Therefore, the aim of the present study is to report our preliminary results on the first 16 patients with liver and abdominal malignant tumors unfit for surgery or thermal ablation treated with percutaneous US-guided IRE.

Materials and methods

Patients

From June 2014 to December 2016, all patients admitted at our institutions (Tortorella Clinical Institute, Athena Clinical

Institute and Ostuni Hospital) presenting with malignant hepatic or abdominal tumors and that were not eligible for resection or thermal (radiofrequency or microwaves) ablation, were prospectively enrolled into the study. Sixteen consecutive patients (age range 59–68 years, mean age 63 ± 4 ; 7 females) with 18 primary or secondary malignant lesions met the aforementioned criteria and represent the study population. In particular, here following are the characteristics of the patients. Two hepatocellular carcinoma (HCC) patients presenting with two metastatic abdominal lymph nodes had achieved complete radiologic necrosis after percutaneous radiofrequency ablation of two parenchymal nodules (2.5 and 2.8 cm, respectively), both located in the 5th segment of the liver. Thereafter, two sub-hepatic hypervascular (3 cm in diameter) lymph nodes were noted and both patients were treated with sorafenib for 2 months. Despite the medical treatment, the two lymph nodes increased in volume up to 6 cm with no change in hypervascularity on dynamic imaging. Therefore, IRE was proposed and performed. Two patients with Klatskin tumor, before IRE underwent the placement of a plastic biliary stent and two cycles of chemotherapy without improvement. Three patients with neuroendocrine tumor were unfit for resection and had been treated with chemotherapy for 3 months before IRE. One patient with metastasis from colon carcinoma was resected for the first tumor and the liver metastasis located at the confluence of the middle and hepatic veins was judged unresectable by our surgery team, and was not approachable percutaneously by microwaves due to the deep position of the nodule and the fear of large bore microwave antenna to be used for ablation. Finally, one patient with hepatic metastasis and locally biliary dilatation from gallbladder carcinoma was previously radically resected, but during surgery there was an abundant hemorrhage and IRE was proposed and performed for treatment of the hepatic nodule. In all cases, the treatment intent was palliative (Table 1).

Table 1 Tumor characteristics and ancillary findings of our series

Tumor	Patients no.	Diameter of tumor (mean and range)	Other characteristics
Hilar HCCs	4	3.2 (2.2–4.5) cm	Six nodules Moderate/severe dilatation of intrahepatic biliary tree in all patients
Metastatic abdominal lymph nodes from HCC	2	5 cm (4–6 cm)	
Klatskin tumors	4	3.9 (3.7–4.0) cm	
Hepatic metastases	3	3.6 (1.3–7.5) cm	Primary tumor: pancreatic neuroendocrine carcinoma
Hilar hepatic metastasis	1	5 cm	Primary tumor: colon carcinoma. Presence of intrahepatic biliary tree dilatation.
Hepatic metastasis of colon carcinoma located at the confluence of middle and right hepatic veins	1	3.6 cm	Primary tumor: colon carcinoma
Hepatic metastasis	1	4.5 cm	Primary tumor: gallbladder carcinoma

The inclusion criteria were: (1) age over 18 but not over 90 years; (2) presence of histologically proven malignant hepatic or abdominal tumor unfit for surgery or thermal ablation with radiofrequency or microwaves (evaluated by the multidisciplinary oncologic team of our institutions). Patients with the presence of a pre-positioned biliary plastic stent were considered eligible for IRE.

Exclusion criteria were: (1) presence of heart arrhythmias; (2) prothrombin time lower than 50% and platelet count $< 50,000/\text{mm}^3$; (3) tumor size not > 8 cm; (4) presence of a biliary metallic stent.

Elevated bilirubin in non-cirrhotic patients as well as the presence of ascites in cirrhotics were not exclusion criteria. Diagnosis of malignancy was based on the results of percutaneous US-guided core biopsy (18 G needle) of the lesions in all cases. Before the procedure, all patients underwent contrast-enhanced ultrasound (CEUS) of the lesions, contrast-enhanced abdominal CT (e-CT) and/or contrast-enhanced abdominal MRI (e-MRI). CEUS was also performed immediately before IRE to evaluate the arterial enhancement of the lesions (when present), and soon after the IRE procedure to assess its disappearance so as to obtain a map of the ablated areas induced by IRE. CEUS, clinical assessment and laboratory tests were also performed 1 week after IRE. Evaluation of efficacy of IRE was based on findings of e-CT and/or e-MRI 1 month after IRE according to the mRECIST criteria [11]. Patients were followed up with clinical, laboratory and CEUS examinations every month for

the first 6 months and every 2 months thereafter. e-CT and/or e-MRI were performed every 3 months.

The mean bilirubin value was 1.9 mg/dl (0.7–8 mg/dl) and the mean platelet count was 112,000 cells/mL (89,000–188,000 cells/mL). Prothrombin time ranged from 62 to 100% (mean 73%). Alfa feto-protein, Ca 19.9 and Ca 125 were also evaluated.

Technique

IRE was performed using the NanoKnife system (AngioDynamics, Latham, NY, USA). Because the current generated by IRE is known to cause whole-body muscle contractions, general anesthesia with the use of neuromuscular blockage was performed in all patients.

In all cases, IRE was performed percutaneously under US guidance. Nodules located in the left lobe were punctured with patients in a supine position. Nodules located in the right lobe were usually punctured in the intercostal space. In case of Klatskin tumors, the probes were inserted using a subcostal scan. Two bipolar 19 G needles (probe n. 1 and probe n. 2) 20 cm length in each session were employed. The exposure length of the active tip was determined according to the depth of the lesions and varied between 1.5 and 3 cm.

The probe number 1 was first inserted generally at the left margin of the nodule on the US monitor (Fig. 1d, e) and thereafter the needle number 2 was inserted at a distance of 1.5, maximum 2 cm from needle number 1, so that the two

Fig. 1 **a, b** Hilar hepatocellular carcinoma without cirrhosis with marked dilatation of the biliary tree. **c** Before IRE, CEUS shows homogeneous arterial enhancement of the lesion. **d, e** US appearance

of the needles inserted into the tumor during the procedure. **f** CEUS performed soon after IRE shows complete necrosis of the HCC nodule that appears hypovascular

Fig. 2 **a** Large NEC of the left lobe of the liver (diameter 7 cm); **b**, **c** two needles are inserted within the tumor; **d** 3 months later, on CEUS the tumor appears completely hypovascular and decreased in volume. **e** 6 months later the tumor is no more visible on US

tips were clearly visible in the same scan on US monitor. Soon after, the first ten test electric pulses were delivered. Thereafter, if the computer of the system's generator gave the consent (i.e., pulses appeared as symmetric waves on the generator's monitor) other 80 high-voltage (3000 V) direct current (40 Å) electrical pulses were delivered between the two paired bipolar electrodes. During the procedures, the target lesion became hyperechoic especially around the needles (Fig. 2b, c). In case of small nodules, only one insertion of the two needles was performed and the procedure was judged enough after delivering 90 electric pulses.

In case of large nodules (more than 4 cm), the two needles (2.5–3 cm tip exposure) were inserted deeply within the nodules up to the inferior margin of the tumor and after delivering the first 90 pulses, a pull back was performed so as to treat the remnant untreated portion of the tumor along the same axis in the US scan. Thereafter, the two needles were repositioned in the remnant untreated portion of the tumor and the pull back technique was repeated.

In the same patient, no more than one repositioning was performed. Before the repositioning of the needles, CEUS was performed again to assess the hypovascularity of the treated area and the needles' repositioning was performed in the remnant untreated hypervascular zone of the tumor.

Results

In all patients, the IRE procedure was completed. The duration of procedures ranged from 35 to 50 min (mean 40 min) and no complication occurred after delivering the electric pulses. No alterations in cardiac rhythm occurred.

No complications due to general anesthesia were observed. All patients but one were treated in a single session and all patients were discharged 2 days after the procedure. Only one patient with a Klatskin tumor (diameter 6 cm) underwent a second session of IRE 30 days after the first one to obtain complete necrosis on imaging.

The follow up ranged from 1 to 18 months (mean 10 months). Table 2 reports the CEUS findings of hypervascularity of the tumors before treatment and 1 week after IRE. All 1-week CEUS findings were confirmed at 1-month e-CT and/or e-MRI. In particular, e-CT and/or e-MRI confirmed 60 and 90% necrosis in the two HCC metastatic lymph nodes and 100% necrosis in all six hilar HCCs, one Klatskin tumor, two metastases from colon carcinoma and one metastasis from gallbladder carcinoma. Partial necrosis (60–90%) was observed in three Klatskin tumors. One of these patients underwent a second session of IRE and the 1-month e-CT showed complete necrosis. Two of the three hepatic metastases from neuroendocrine tumors (1.7 and 3 cm) showing a thin enhancement at 1-week CEUS after IRE had complete necrosis at 1-month eCT; the third one (7.5 cm) showed complete necrosis and decreased volume (4.2 cm). This patient showed complete disappearance of the tumor during the follow up. No death occurred. No major complication was observed.

In particular, in patients with dilatation of intrahepatic biliary tract and elevated total bilirubin level, no increase in the bilirubin level and grade of biliary tree dilatation was observed. No vascular injuries occurred. Only one patient (large mesenteric lymph node metastasis from HCC) presented with mild fever after IRE and, 1 week later, CEUS showed a small peri-lesion haematoma that healed

Table 2 Changes in arterial phase enhancement on CEUS 1 week after treatment

Type of nodule	N	Pre-IRE	1-week post-IRE
Hilar HCCs	6	Homogeneous hyperenhancing	Unenhanced all
Metastatic abdominal lymph nodes from HCC	2	Inhomogeneous hyperenhancement	60–90% unenhanced
Klatskin tumors	4	Inhomogeneous hyperenhancement	One lesion unenhanced 3: 60–90% unenhanced
Hepatic metastases from neuroendocrine carcinoma	3	Homogeneous hyperenhancement	Unenhanced with thin (5 mm) rim enhancement
Hepatic metastasis from colon carcinoma of hilar and venous confluence tissue	2	Thick rim-like hyperenhancement	Increased hypovascular volume No rim enhancement
Hepatic metastasis from gallbladder carcinoma	1	Inhomogeneous hyperenhancement	Unenhanced

spontaneously. No needle tract seeding was observed during the follow up.

Two patients (one with hepatic metastasis from neuroendocrine carcinoma—diameter 7.5 cm—and one patient with 4.5 metastases from gallbladder carcinoma) showed disappearance of the lesions on US and reconstitution of liver parenchyma after 3 and 6 months, respectively. One patient treated for hilar HCC died 6 months after IRE because of stroke. All the remaining treated patients were alive at the end of the follow up. After IRE, local tumor progression was observed in three patients (18.75%). On CEUS, eCT and/or MRI, new appearance of both arterial hypervascularity and increased volume was noted. In particular, in one 4.5 cm hilar HCC patient, the former findings appeared 1.3 years later; in one patient with Klatskin tumor (4 cm) 11 months later and in one patient with hilar colon carcinoma metastasis (5 cm) 9 months later, respectively. Thereafter, the first patient was treated with sorafenib, the second one was lost to follow up and the third patient was treated with second-line chemotherapy with FOLFIRI plus aflibercept regimen.

Discussion

Our results confirm the main advantages of IRE in terms of uncommon injury of biliary tree, stomach or bowel loops. On the other hand, this new technique presents some disadvantages compared to other thermal ablation techniques currently used in clinical practice such as RF and MWS, because IRE needs general anesthesia, has more complexity and is much more expensive compared to RF and MWS. These disadvantages should indicate IRE to be used in well selected patients.

Furthermore, our results are similar to the recent data in the literature [12–16].

Sugimoto treated five patients with six tumors with a diameter ranging from 11 to 28 mm [13]. Five of the six tumors (83%) were successfully treated, with no local recurrence after a follow up of 244 days. In one lesion located in the caudate lobe, a residual tumor was diagnosed 7 days

after intervention by follow-up EOB-MRI. No serious complications related to the IRE procedure were observed. The authors concluded that image-guided percutaneous IRE can achieve satisfactory local disease control, particularly for small HCCs, and is well tolerated by patients [13].

Niessen reported the results of IRE on 35 consecutive patients with 48 malignant liver lesions [16]. There were 22 hepatocellular carcinomas, 6 cholangiocellular carcinomas, and 20 metastatic liver cancers. Fourteen of the 48 treated lesions (29.2%) showed early local recurrence after 6 months. Tumor volume and the underlying disease type (HCC, cholangiocellular carcinoma, or metastatic disease) were independently associated with early local recurrence. However, distance to the surrounding portal veins, hepatic veins, hepatic arteries, and bile were not significantly associated with local recurrence.

Cheng et al. reported full explant pathology and radiographic correlation in six patients with HCC treated with IRE who subsequently underwent liver transplantation [14]. After IRE, five tumors showed complete pathologic necrosis without any viable carcinoma. Bile ducts within the treatment area were preserved. Only one HCC nodule showed <5% viable tumor at the periphery [14].

In our series, all IRE procedures were completed without any damage to patients under general anesthesia. No major complications were observed and only one patient showed a very small haematoma on CEUS some days after IRE. Only in the experience of Niessen, the overall complication rate was 27.5% with six major complications: one case of diffuse intraperitoneal bleeding, four liver abscesses and one partial thrombosis of the portal vein [16]. Vice versa, the majority of other studies do not report such a rate of major complications [12–15]. In our study, biliary and vascular structures did not show any damage due to the IRE application. In all patients with dilatation of intrahepatic biliary tree due to hilar HCC or biliary tumors, an increase in total bilirubin level was never observed. Thrombosis of the portal vessels was also not observed. As far as the efficacy of IRE is concerned, in our first experience, this new technique showed high efficacy in inducing radiologic necrosis of the

treated tumors. The best demonstration of IRE efficacy is the disappearance of a 7 cm NEC of the left lobe of the liver and the 4 cm gallbladder hepatic metastasis during the follow up. But, it should also be highlighted that IRE has three main limits: the very high cost, more complexity in performing the procedure and a high rate of needle tract seeding as recently reported by Distelmaier et al. (26%) [10]. This high rate of seeding is a major concern for IRE procedure and it is extremely higher than that reported for other ablative techniques. In our series, no seeding was observed, but our follow-up period was too short. The tumor seeding described after IRE is probably due to lack of track ablation at the end of the procedure, that represents the main difference from radiofrequency and microwaves. This negative adverse event, together with the very high cost of the IRE procedure, must be held in the highest consideration in clinical practice. In fact, IRE is highly expensive. The high cost induces to well evaluate the costs and real benefit for patients (often with short life expectancy) and therefore IRE should be indicated in very select patients. Nevertheless, although it is more complex with respect to RF and MWS ablation, our experience shows that the percutaneous approach is feasible and safe and US guidance in expert hands can be easily used even in the intercostal space. Maybe the so-called “hand free technique” should be used by interventional physicians and interventional radiologists, when possible, and a previous experience in percutaneous ethanol injection should be needed [17].

In conclusion, IRE is a promising ablation modality in the treatment of malignant hepatic and abdominal tumors unsuitable for resection or thermal ablation.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Informed consent The institutional review board approved the study and all patients gave their informed written consent.

References

- Narayanan G, Froud T, Suthar R, Barbary K (2013) Irreversible electroporation of hepatic malignancy. *Semin Interv Radiol* 30:67–73. <https://doi.org/10.1055/s-0033-1333655>
- Neumann E, Schaefer-Ridder M, Wang Y, Hofschneider PH (1982) Gene transfer into mouse lymphoma cells by electroporation in high electric fields. *EMBO J* 1:841–845
- Okino M, Mohri H (1987) Effects of a high-voltage electrical impulse and an anticancer drug on in vivo growing tumors. *Jpn J Cancer Res* 78:1319–1321
- Davalos RV, Mir IL, Rubinsky B (2005) Tissue ablation with irreversible electroporation. *Ann Biomed Eng* 33:223–231
- Lee EW, Chen C, Prieto VE, Dry SM, Loh CT, Kee ST (2010) Advanced hepatic ablation technique for creating complete cell death: irreversible electroporation. *Radiology* 255:426–433
- Thomson KR, Cheung W, Ellis SJ et al (2011) Investigation of the safety of irreversible electroporation in humans. *J Vasc Interv Radiol* 22:611–621
- Rubinsky B, Onik G, Mikus P (2007) Irreversible electroporation: a new ablation modality—clinical implications. *Technol Cancer Res Treat* 6:37–48
- Dollinger M et al (2015) Adverse effects of irreversible electroporation of malignant liver tumors under CT fluoroscopic guidance: a single-center experience. *Diagn Interv Radiol* 21(6):471–475. <https://doi.org/10.5152/dir.2015.14442>
- Niessen C et al (2016) Percutaneous ablation of hepatic tumors using irreversible electroporation: a prospective safety and mid-term efficacy study in 34 patients. *J Vasc Interv Radiol* 27(4):480–486. <https://doi.org/10.1016/j.jvir.2015.12.025> (Epub 2016 Feb 26)
- Distelmaier M et al (2017) Midterm safety and efficacy of irreversible electroporation of malignant liver tumors located close to major portal or hepatic veins. *Radiology* 285(3):1023–1031. <https://doi.org/10.1148/radiol.2017161561> (Epub 2017 Aug 11)
- Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 30:52–60. <https://doi.org/10.1055/s-0030-1247132>
- Lyu T, Wang X, Su Z, Shangguang J, Sun C et al (2017) Irreversible electroporation in primary and metastatic hepatic malignancies: a review. *Medicine (Baltimore)* 96:e6386. <https://doi.org/10.1097/MD.0000000000006386>
- Sugimoto K, Moriyasu F, Kobayashi Y, Saito K, Takeuchi H et al (2015) Irreversible electroporation for nonthermal tumor ablation in patients with hepatocellular carcinoma: initial clinical experience in Japan. *Jpn J Radiol* 33:424–432. <https://doi.org/10.1007/s11604-015-0442-1>
- Cheng RG, Bhattacharya R, Yeh MM, Padia SA (2015) Irreversible electroporation can effectively ablate hepatocellular carcinoma to complete pathologic necrosis. *J Vasc Interv Radiol* 26:1184–1188. <https://doi.org/10.1016/j.jvir.2015.05.014>
- Ball C, Thomson KR, Kavnoudias H (2010) Irreversible electroporation: a new challenge in “out of operating theater” anesthesia. *Anesth Analg* 110:1305–1309. <https://doi.org/10.1213/ANE.0b013e3181d27b30>
- Niessen C, Igl J, Pregler B, Beyer L, Noeva E et al (2015) Factors associated with short-term local recurrence of liver cancer after percutaneous ablation using irreversible electroporation: a prospective single-center study. *J Vasc Interv Radiol* 26:694–702. <https://doi.org/10.1016/j.jvir.2015.02.001>
- Giorgio A, Tarantino L, de Stefano G, Perrotta A, Aloisio V, del Visco L et al (2000) Ultrasound-guided percutaneous ethanol injection under general anesthesia for the treatment of hepatocellular carcinoma on cirrhosis: long-term results in 268 patients. *Eur J Ultrasound* 12:145–154

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