



Irreversible electroporation for hepatic tumors

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Irreversible electroporation (IRE) is a relatively new ablation technique for the treatment of abdominal and extra-abdominal tumors. Its working mechanism is essentially non thermal as, through the insertion of probes into the neoplasm during open laparotomy or percutaneously under ultrasound (US) or computed tomography (CT) guidance, it delivers high voltage electric pulses into the target lesion. The resultant electric field causes the formation of nanopores in the cell membrane of neoplastic cells with consequent apoptosis and cell death. The effect of IRE is limited to the cell membrane; for this reason, the adjacent extracellular matrix structures are preserved and this makes this technique a theoretically safe option for tumors located next to blood vessels, bowel loops, urethra (in the case of prostatic cancer) and major bile ducts (in the case of hepatic tumors). IRE ablation must be performed under general anesthesia, total muscle paralysis and continuous vital signs monitoring to avoid the muscle spasm related to the excitation of the motor neural end-plate, and to monitor and treat the possible cardiac arrhythmias caused by the increased cell membrane permeability [1, 2].

Since 2011, when the first clinical reports were published, several papers from both western and eastern countries have analyzed the effectiveness of IRE in the treatment of tumors of the pancreas, liver, kidney, lung, prostate and bones not amenable to surgery or thermal ablation. The effectiveness of the treatment has been shown to be generally good with an acceptable rate of complications mainly due to local injuries at the site of ablation or occurrence of post-procedural metabolic acidosis and/or electrolyte imbalance mostly in patients with impaired renal function or a large ablation area [2]. As regards the effectiveness of IRE in the treatment of

hepatic tumors, a systematic review including 129 patients showed complete necrosis of the lesions ranging between 67 and 100%, for tumors larger than 3 cm, and between 93 and 100%, for tumors smaller than 3 cm, at 3 months from IRE [3]. In a retrospective case series of IRE for hepatic tumors including 103 tumors in 71 patients [43 hepatocellular carcinoma (HCC), 42 colorectal liver metastases (CRLM), 4 cholangiocellular carcinomas (CCC), and 14 other metastases], the authors reported complete imaging response to initial treatment in 92% of patients; the size of the treated lesion was predictive of better survival as patients with tumors less than 3 cm had a nearly double average survival compared to patients with larger tumors (24.5 vs. 12.9 months) [4]. A recent prospective series of 43 primary (8 cases) or secondary (35 cases) malignant liver tumors in 29 patients who underwent CT-guided IRE of mass lesions located immediately adjacent to major hepatic veins, portal veins, or both, showed that complete ablation was achieved in 40 (93%) of the tumors with only 2 cases of late recurrence within the ablation zone [5]. Finally, in short series of patients with HCC treated with IRE before liver transplantation, most tumors appeared completely necrotic without any viable neoplastic cells and with preserved bile ducts within the treatment area [6, 7]. Another IRE-based approach to neoplastic lesions combining non-thermal effects of IRE with local application of chemotherapy and known as electrochemotherapy (ECT) should be mentioned. It is based on the application of intense and short electric pulses that make the cell membrane permeable, allowing for the penetration of chemotherapeutic agents directly into the cytosol so as to induce apoptotic cell death in the targeted neoplastic tissue [8]. ECT is an established treatment modality for skin malignancies but has been also proposed for the treatment of hepatic tumors. Indeed, an Italian group recently published preliminary experience with ECT treatment of a few cases of hilar cholangiocarcinoma [9] and portal vein thrombosis due to HCC invasion [10] reporting promising results in terms of feasibility and effectiveness.

The paper by Giorgio et al. [11] published in the present Issue of Journal of Ultrasound confirms the effectiveness of

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IRE treatment of abdominal tumors. The study is a retrospective case series and is the largest one published in Italy in this field. It includes 16 patients with 18 tumors (diameter range 1.3–7.5 cm) not amenable to surgery or thermal ablation who were treated with percutaneous IRE. Among the tumors, 16 were hepatic (6 hilar HCC, 4 CCC that were all Klatskin tumors, 6 metastases from pancreatic neuroendocrine tumor, colorectal carcinoma and gallbladder carcinoma) and 2 were large metastatic abdominal lymph nodes from HCC. Short term imaging evaluation performed at 1 month from IRE demonstrated encouraging results as complete tumor necrosis was shown in 14/16 hepatic tumors (87.5%) whereas partial necrosis was observed in both abdominal lymph nodes. During a mean follow-up period of 10 months, local tumor progression was observed in 3 tumors showing complete necrosis at short term evaluation (1 HCC, 1 Klatskin tumor, 1 colorectal metastasis). No major complications were recorded.

In conclusion, based on the available literature data, IRE is an effective technique for the treatment of abdominal tumors not amenable to surgery and candidates to laparoscopic or percutaneous ablation. In the field of hepatic tumors, the main indication appears to be the treatment of primary and metastatic lesions located next to vital structures such as major bile ducts or large vessels not amenable to thermal ablation in patients with a reasonably long tumor- and non tumor-related prediction of survival. However, compared to conventional thermal ablation procedures, IRE always requires general anesthesia and for this reason its performance is more demanding and significantly more expensive than radiofrequency or microwave ablation. Then, in an era of need for cost containment in public health, its application should be discussed in a multidisciplinary team (involving oncologists, hepatologists, surgeons, interventional radiologists and anesthesiologists) and reserved to carefully selected cases. Furthermore, the safety of the technique when used to treat hepatic tumors should be more extensively evaluated. A systematic review assessed the safety of hepatic IRE in 129 patients with 227 tumors and reported an overall complication rate of 16%; most complications were directly puncture-related but stenosis or occlusion of bile ducts or portal vessels were observed in 8 out of 129 patients (6%) [3]. Thrombosis or stenosis of portal or hepatic veins were detected in 7/101 patients (6.9%) with 129 lesions treated with IRE that were located in the liver in the large majority of cases (77.5%) [12]. In the already cited recent prospective study by Distelmaier et al. [5] have been reported worrisome rates higher than 20% of needle tract seeding of the targeted tumors and of injury of the bile ducts with consequent clinically significant cholestasis. Indeed, although

IRE effects are described to provide a non thermal method of cell death, there is evidence that pulse protocols of IRE in some cases can induce also a thermal injury to the heat susceptible structures within the ablation zone such as portal vessels or bile ducts [13]. Finally, more studies are needed including cohorts of specific patient groups and longer follow-up periods to conclusively establish that IRE is a reliable locoregional technique with results at least comparable to that achieved by the thermal ablation procedures in the treatment of primary and metastatic liver tumors [2].

Compliance with ethical standards

Conflict of interest We certify that we have not a financial or personal relationship with a third party whose interest could be positively or negatively influenced by the article's content.

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