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EDITORIAL

Irreversible electroporation for metastatic pancreatic carcinoma with liver metastasis: What does the evidence say

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Abstract

Irreversible electroporation is a promising non-thermal ablation method that has been shown to increase overall survival in locally advanced pancreatic cancer in some studies. However, higher quality studies with proper controls and randomization are required to establish its superiority when added with neoadjuvant chemotherapy over the current management of choice, which is chemotherapy alone. Further studies are required before establishment of any survival benefit in metastatic pancreatic carcinoma, and such evidence is lacking at present.

Key Words: Irreversible electroporation; Locally advanced pancreatic carcinoma; Metastatic pancreatic carcinoma; Advanced pancreatic carcinoma; Chemotherapy

Core Tip: Irreversible electroporation (IRE) is a non-thermal ablation technique that may increase survival for locally advanced pancreatic carcinoma when combined with chemotherapy. However, its efficacy in metastatic pancreatic carcinoma with liver metastasis is not yet established. Further high-quality studies with proper controls and randomization are needed. IRE can preserve neighboring structures and avoid the heat-sink effect, but it requires careful patient selection and has potential complications. The procedure is typically performed under general anesthesia and has several contraindications. While IRE may offer a new frontier in treating pancreatic cancer, its role in metastatic disease requires more research to confirm its benefits.

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INTRODUCTION

We read with great interest the article by Yang *et al*[1] describing a 66-year-old female patient with liver metastasis who underwent synchronous irreversible electroporation (IRE) ablation of the liver and pancreatic lesions by percutaneous route combined with gemcitabine arterial infusion chemotherapy and oral tegafur for four cycles. The patient developed metastatic (stage IV) locally advanced pancreatic cancer (PanCa).

Chemoradiation combines chemotherapy and radiotherapy to destroy cancer cells. While chemotherapy involves the use of cytotoxic drugs to target cancer cells at different stages of the cell cycle, radiotherapy uses high energy rays to destroy cancer cells. Chemotherapy can lead to stable disease or even tumor regression in some cases, leading to downstaging to resectable disease by cytotoxic effect. Chemotherapy can cause a multitude of side effects including common ones like fatigue, hair loss, weight loss, gastrointestinal issues like nausea, vomiting, and diarrhea to more severe side effect such as neutropenia leading to various infections and septicemia.

Yang *et al*[1] reported a complete response at 12 months after IRE (RECIST 1.1) as the pancreatic tumor completely disappeared on the whole abdomen contrast enhanced CT. There was also marked shrinkage of the liver mass. Furthermore, there were no serious side effects while receiving medication. The study concluded that treating metastatic PanCa with IRE in conjunction with gemcitabine and tegafur, an oral fluoropyrimidine derivative, might be a good alternative with manageable side effects.

Metastatic pancreatic adenocarcinoma is very aggressive, and the 5-year survival is 3%. The last stage of PanCa is metastatic pancreatic adenocarcinoma. Although an interesting prospect arises from this exciting case report regarding treatment of a grim condition like metastatic PanCa, some discussions are required regarding more generalized reproducibility of such results. Patients with PanCa are evaluated for diagnosis, staging, and prognosis for surgical fitness. Laboratory tests such as serum carbohydrate antigen 19-9 and imaging techniques like high resolution triphasic contrast enhanced CT are used to aid diagnosis. Definitive diagnosis with preoperative biopsy is not always necessary, but when required endoscopic ultrasound guided fine-needle aspiration is the preferred choice. Diagnostic laparoscopy may also be required. To this aim we shall review the evidence from prior large scale studies regarding application of IRE in PanCa.

ELECTROPORATION

Electroporation is a phenomenon characterized by a temporary increase in membrane permeability and is induced by exposing cells to high-voltage electric pulses. Initially electroporation is reversible. However, when cells are exposed to a certain threshold of electric field strengths and durations, the increased membrane permeability disrupts cellular homeostasis and culminates in cell death. This phenomenon is termed IRE. IRE is a non-thermal physical ablation technique that disrupts the tumor cell membrane using brief, high-frequency, and repeated high-voltage pulses directed at the tumor cells. IRE is an investigative new local ablation method being explored for treatment of locally advanced nonresectable pancreas cancers or as "margin accentuation" to treat grossly positive margins[2-4].

High voltage bursts of direct current electrical energy modify the existing transmembrane potential of cells. Pulsed electrical fields of 2000 V/cm induce either direct membrane rupture or secondary effects due to excessive transmembrane movement of intracellular electrolytes and adenosine triphosphate, resulting in the disruption of cellular homeostasis and ultimately cell death *via* both apoptosis and necrosis[5]. Electrical pulses are sent through two or more needle electrodes, resulting in electrical fields between the electrode pairs. Needles are precisely inserted in and around the tumor, including a tumor-free margin (5 mm), with the goal of achieving complete tumor ablation. Furthermore, some new evidence suggests that IRE can promote immunomodulation by substantial antigen release and T cell activation[6-8].

There are two distinct advantages of IRE over other ablation methods. First, neighboring structures such as large blood vessels, bile ducts, and bowel wall are preserved. This is particularly useful in cases of unresectable PanCa that are closely related to these, especially major blood vessels. Thus, IRE is mainly used for locally advanced PanCa. Locally advanced PanCa has multiple classifications but fundamentally refers to nonmetastatic PanCa where first surgical resection is deemed unbeneficial due to significant vascular involvement with a consequent elevated risk of incomplete resection.

Evaluation is performed by radiological investigations preoperatively. At diagnosis, over half of the patients have systemic metastasis, and another one-third have locally advanced disease precluding immediate surgery. Advanced PanCa is not curable. Palliation is the mainstay of treatment. Chemoradiation can be used in locally advanced PanCa as neoadjuvant therapy before surgery in borderline resectable cases. Five to six weeks of intensity modulated radiation therapy given along with low dose chemotherapy commonly oral capecitabine can be used for this purpose. Neoadjuvant chemotherapy is used prior to surgery with the specific objective of downsizing the tumor to make it surgically resectable. Adjuvant chemotherapy on the other hand is given after surgery to eliminate any remnant tumor cells following surgery. The proposed mechanism of this preservation is the sparing of extracellular matrix of connective tissue, which allows regeneration of cholangiocytes/endothelial cells that may be affected[9].

The other advantage is the absence of the heat-sink effect, which reduces the efficacy of thermal ablation methods. The heat-sink effect is the phenomenon where heat is dissipated due to the presence of large blood vessels in the vicinity of the target area (as in head of pancreas) leading to an inadequate local effect.

IRE is performed under general endotracheal anesthesia with muscle relaxation as the electrical pulses cause generalized muscular contractions. An Accusync equine chorionic gonadotrophin equipment is utilized to avert pulse-induced arrhythmias by synchronizing pulse delivery with the refractory period of the heart. Due to the considerable strain on the heart, a prior consultation with a cardiologist is required. Many cardiac-related illnesses such as cardiac arrhythmias, congestive heart failure New York Heart Association class 4, acute coronary artery disease *etc*. are considered absolute or relative contraindications to this procedure[9]. For tumors close to the common bile duct, biliary protection with nonmetallic stents is recommended as post IRE swelling can cause obstruction to bile flow. Also, patients with a partially occluded portal vein prior to IRE should undergo portal vein stenting. Finally, the presence of metal stents within the ablation zone has been a subject of varied discourse concerning safety and efficacy. However, robust evidence is lacking.

A systematic review by Ruarus *et al*[10] provided an overview of various reported complications, most of which were minor. The most common adverse effects were gastrointestinal in nature, including discomfort, diarrhea, nausea, vomiting, anorexia, and delayed gastric emptying. The most serious effects were hemorrhage, vascular occlusion, acute pancreatitis, and mortality. The average cumulative morbidity for surgical and percutaneous IRE was 36% compared to 24%, with an average peri-procedural death rate of 2% *vs* 0%, respectively. A similar overall low mortality rate of 2% was reported by Ansari *et al*[3] in their systematic review.

We reviewed the various studies on IRE and found that most studies were conducted in locally advanced PanCa and not metastatic PanCa. Advanced PanCa refers to locally advanced PanCa, and metastatic PanCa. usually involves stage III and IV PanCas. The first organ involved upon metastasis is usually the liver. Although findings varied, a trend towards an increase in recurrence-free survival and overall survival in patients treated with IRE (surgical or CT-guided percutaneous approach) along with chemotherapy/concurrent radiation in comparison to patients receiving only chemotherapy/chemoradiation was observed. Median survival for untreated advanced PanCa is about 3 months. However, none of these studies were randomized clinical trials, and the studies lacked an appropriate control group (historical control has been used for comparison).

Martin *et al*[11] in 2015 conducted the largest study with 200 patients treated with IRE during laparotomy, 50 of whom also underwent pancreatic resection. They determined that the judicious incorporation of IRE in suitably chosen patients with locally advanced PanCa, in conjunction with chemotherapy or chemoradiation, yielded a median overall survival of approximately 24 months, virtually doubling the survival rate associated with the most effective contemporary chemotherapy and chemoradiation. For this study, they used three points for eligibility of treatment: (1) Tumors to be less than 5 cm; (2) Tumor should not progress after induction chemotherapy; and (3) Patient must have adequate performance status to be able to tolerate general endotracheal anesthesia[12-16]. Although promising results were obtained in this study, many other smaller studies did not show such drastic improvement in survival.

A systematic review of all studies on IRE use in human PanCa with a minimum of 10 patients was published by Ansari *et al*[3] in 2017 and showed that median overall survival varied widely between 7-23 months among all the studies. It is interesting to note that all of these studies with at least 10 patients were conducted in patients with locally advanced PanCa (stage III), and none were conducted on metastatic PanCa (stage IV disease)[17-20].

Belfiore *et al*[9] compared IRE use in hepatic secondary lesions (metastases) and more traditional thermal ablation methods like radiofrequency ablation. They concluded that it is more costly and potentially more hazardous than the conventional ablation technique, owing to its necessity for general anesthesia, and should be reserved for the treatment of metastatic lesions near critical structures such as major bile ducts or large vessels.

CONCLUSION

Although the use of IRE opens up an interesting frontier in treating cases of locally advanced PanCa, further large-scale studies with appropriate controls and randomized control trials are needed before it can be adopted outside of research purposes. Prospective studies with significant sample sizes (we could not find any study with a sample size more than 10) are lacking for stage IV (metastatic) PanCa being treated with IRE. Therefore, evidence regarding improvement in overall survival in these patients is not available. Radiofrequency ablation remains the preferred ablation method for liver metastasis due to its relative safety and similar efficacy compared to IRE, except when metastasis is in close proximity to large vessels or bile ducts.

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FOOTNOTES

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