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Initial experience of irreversible electroporation ablation in Brazil: a retrospective analysis

Experiência inicial de ablação por eletroporação irreversível no Brasil: uma análise retrospectiva

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ABSTRACT

Introduction: The objective of our study is to present the first Brazilian irreversible electroporation experience in the treatment of solid cancer. **Material and Methods:** A retrospective study with the first ten patients who underwent percutaneous or surgical IRE to treat solid cancer between March 2021 and May 2021. Preoperative data collection included patient demographics along with previous oncologic treatments. Operative and post-operative assessment involved number of probes, number of pulses, initial and final current and 30-days complications. **Results:** Primary tumor was locally advanced pancreatic cancer (70%), colorectal hepatic metastasis (20%), and cholangiocarcinoma (10%). All patients had previously undergone chemotherapy with stable disease in 80% and partial response in 20% before IRE. Eighty percent of the procedures was performed surgically and 20% percutaneously CT-guided. The mean procedure time of IRE was 38 minutes. Adverse events occurred in 4 patients (40%), all being grade I-II complications.

Keywords: Radiology, Interventional; Ablation techniques; Pancreatic neoplasms; Liver neoplasms.

RESUMO

Introdução: O objetivo do nosso estudo é apresentar a primeira experiência brasileira de eletroporação irreversível no tratamento de câncer sólido. **Material e Métodos:** Estudo retrospectivo com os dez primeiros pacientes submetidos à IRE percutânea ou cirúrgica para tratamento de câncer sólido entre março de 2021 e maio de 2021. A coleta de dados pré-operatórios incluiu dados demográficos dos pacientes juntamente com tratamentos oncológicos anteriores. A avaliação operatória e pós-operatória envolveu número de sondas, número de pulsos, corrente inicial e final e complicações em 30 dias. **Resultados:** Tumor primário foi câncer de pâncreas localmente avançado (70%), metástase hepática colorretal (20%) e colangiocarcinoma (10%). Todos os pacientes haviam sido submetidos à quimioterapia previamente com doença estável em 80% e resposta parcial em 20% antes da IRE. Oitenta por cento dos procedimentos foram realizados cirurgicamente e 20% guiados por TC percutânea. O tempo médio de procedimento de IRE foi de 38 minutos. Eventos adversos ocorreram em 4 pacientes (40%), todos sendo complicações grau I-II.

Descritores: Radiologia intervencionista; Técnicas de ablação; Neoplasias pancreáticas; Neoplasias hepáticas.

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INTRODUCTION

New ablative therapies have been developed in the past decades with an increasing interest in local treatment of malignant neoplasms. One of the reasons these are the high rate of unresectable tumors at the time of diagnosis, for instance, 50-70% of pancreatic cancer and 80% of colorectal liver metastasis are unsuitable for surgery, mainly because of poor clinical conditions, limited liver function or involvement of vital structures. The ablatives therapies such as radiofrequency, microwave, and cryoablation have overcome these problems by enabling smaller surgical resections and better organ function preservation, increasing the number of patients suitable for curative treatments. However, these thermal ablative technologies rely on temperature variation on the surrounding tissues, bringing some limitations concerning the size and location of the tumor. Studies demonstrate that complete ablation rate is reduced below 50% when in contact with a vessel larger than 3mm due to the heat sink effect and also when close to vital structures (i.e., central bile ducts, portal vein, and bowel loops).

Irreversible electroporation (IRE) emerges as a promising technology that achieves similar ablative treatment areas with the advantage of not using thermal effects. Instead, it uses high-voltage electrical pulses (up to 3kV/cm) that open nanopores in the cell membrane's lipid bilayer, disrupting cellular homeostasis and leading to apoptosis,[1-3] keeping the extracellular matrix unimpaired.[4,5] Due to the non-thermal ablative technology, IRE has the potential to overcome the problem of difficult tumor location faced by the other ablative methods.

Clinical applications have been increasingly expanded in cases where the neoplastic tissue is in intimate contact with heat-sensitive structures that are at high risk of morbidity and mortality, such as locally advancer pancreatic cancer (LAPC) in stage III or centrally liver neoplasms (CLM), allowing changes in the patient's oncological status and thus outcomes such as overall survival and recurrence-free time.[6-10] Another promising field of action is the association of the method with immunotherapy. Due to the mechanism of cell death by apoptosis, it has been proven that a window of tumor immune susceptibility is opened after ablative treatment, thus allowing the use of medications that strengthen the patient's immune system.[11-13]

The purpose of the present study is to present the first Brazilian IRE experience in the treatment of solid cancer.

MATERIAL AND METHODS

Patients

Clinical data from March 2021 to April 2021 of the first 10 consecutive patients who had undergone percutaneous or surgical IRE therapy were enrolled for the present analysis; there were 2 patients treated percutaneously and 8 patients treated by open surgery (Table 1). All indications were discussed in the Institution's Tumor Board with a multidisciplinary team (oncologist, interventional radiologist, and surgeon). The study was approved by the ethics committee of our hospital and the written informed consent was obtained for the procedure.

Table 1. Patient characteristics.

Patient	Age (year)	Gender	Primary tumor	Previous treatment	Procedure approach	Lesion location	Lesion size (cm)
#1	67	Male	Pancreatic cancer	FOLFIRINOX	Surgical	Pancreas	3.0
#2	89	Female	Pancreatic cancer	None	Percutaneous	Pancreas	4.7
#3	74	Male	Colorectal cancer	FOLFIRINOX + FOLFIRI	Percutaneous	Liver	Segment V (4.0cm) and Segment VI (2.5cm)
#4	60	Male	Pancreatic cancer	FOLFIRINOX	Surgical	Pancreas	3.6
#5	69	Male	Pancreatic cancer	FOLFIRINOX	Surgical	Pancreas	3.5
#6	61	Male	Cholangiocarcinoma	None	Surgical	Bile duct (Klatiskin II)	2.0
#7	55	Female	Pancreatic cancer	FOLFIRINOX	Surgical	Pancreas	2.4
#8	57	Male	Pancreatic cancer	FOLFIRINOX	Surgical	Pancreas	3.0
#9	78	Male	Pancreatic cancer	FOLFIRINOX + FOLFOX	Surgical	Pancreas	3.0
#10	43	Male	Colorectal cancer	Right colectomy + FOLFIRI + AVASTIN + RT	Percutaneous	Liver and Lymphonode	Liver 1.0cm and lymphonode 1.7cm

Abbreviations: FOLFIRINOX = 5-FU with leucovorin, oxaliplatin, and irinotecan; FOLFIRI = Irinotecan + 5-FU/folinic acid; FOLFOX = 5-FU with leucovorin and oxaliplatin; 5-FU = fluorouracil.

Definitions

Technical success was defined as the successful delivery of the planned therapy in the operation room. Procedure-related adverse event (AE) was defined as a complication occurring within 30-days of treatment, according to CTCAE version 5.0 (Common Terminology Criteria for Adverse Events).

IRE Procedure

A contrast-enhanced computed tomography (ceCT) or magnetic resonance (MRI) scan was performed before the procedure to determine the size and shape of the tumor and its proximity to surrounding structures and the required number of electrodes and their insertion position were planned based on this scan. All patients underwent general anesthesia with standard endotracheal intubation and complete muscular relaxation with heart frequency control between 65-85bpm. For open surgical patients (8/10 patients), a superior midline incision was placed, and the pancreas was exposed at the surgeon's discretion (Figure 1).

The NanoKnife (AngioDynamics, Queensbury, NY) is the only electroporation device commercially available for clinical usage. The positioning of the monopolar probes was guided exclusively by high-frequency transducer when surgically treated and CT and US-guided when performed percutaneously (Figure 2). The probes were placed precisely parallel with the inter-electrode distance probe within 1.5-2.2cm and probe exposure varying between 1.5-2.0cm, depending on the primary treated site. After probe positioning, twenty 1500-V/cm test pulses were delivered to evaluate the electrical current between probes. An initial current of 20-40A was required and manual parameter adjustment or probe replacement was made if excessive or insufficient energy was detected. Once calibrated, one ECG-synchronized cycle of 90 pulses (pulse length of 90μs; maximum voltage of 3000V) was performed. If a current change of >20% of the initial current was not achieved, a second cycle of 60 pulses with the same parameters was performed.

Follow-up

During the hospital stay, patients were closely monitored and ceCT was performed in case of abnormal clinical signs or symptoms. After discharge, patient was remotely assessed for clinical follow-up and after 4-8 weeks a ceCT or MRI was performed to evaluate late complications.

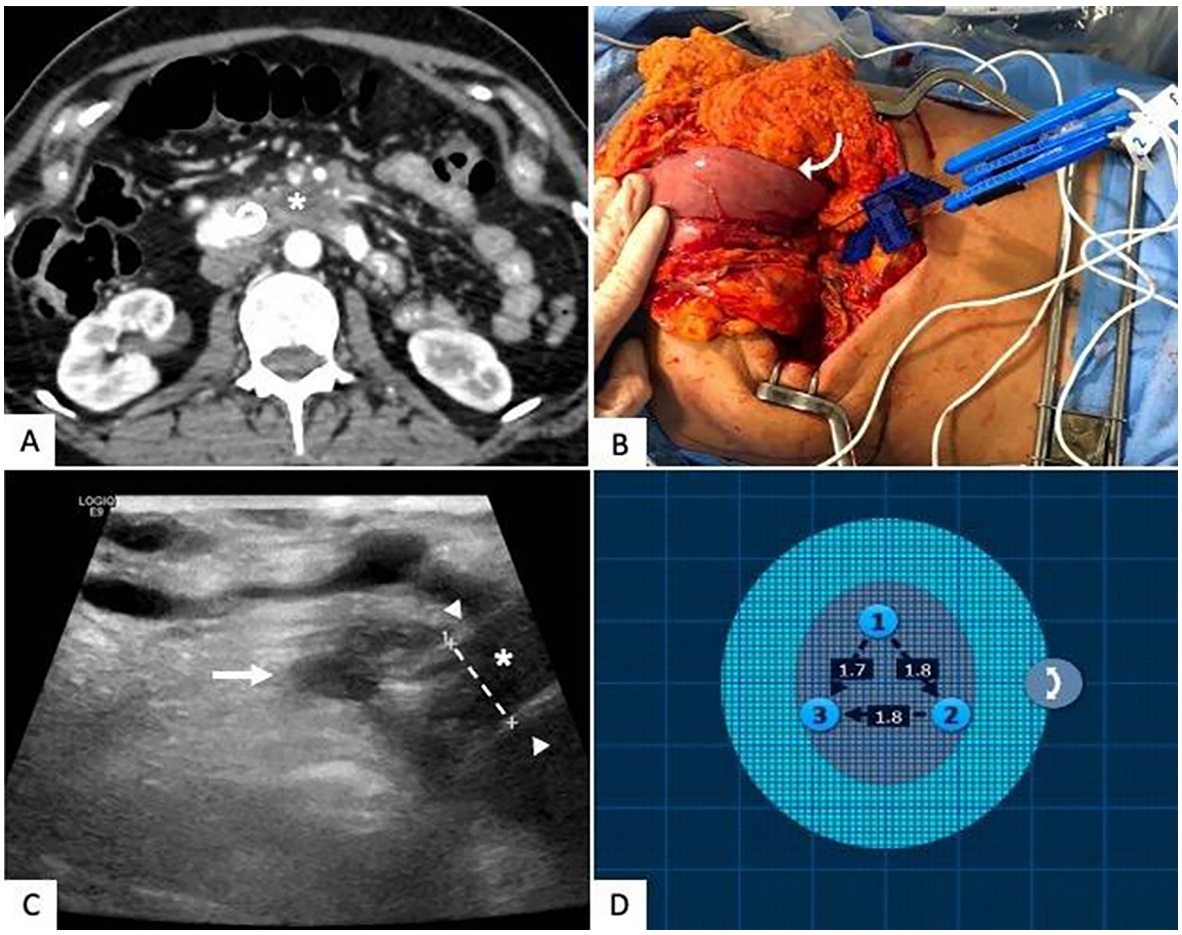

Figure 1. Surgical IRE for a borderline pancreatic neoplasm. A. Pancreatic neoplasm located in the uncinated process and in contact with mesenteric vessels (arrow); B. Surgical dissection of the pancreas with midline incision allowing probe positioning; C. Insertion of the probes were guided by ultrasound to avoid mesenteric artery (arrow) injury and to measure the inter-electrode distance (dashed line); D. Diagram of the final probe positioning with the inter-electrode distance.

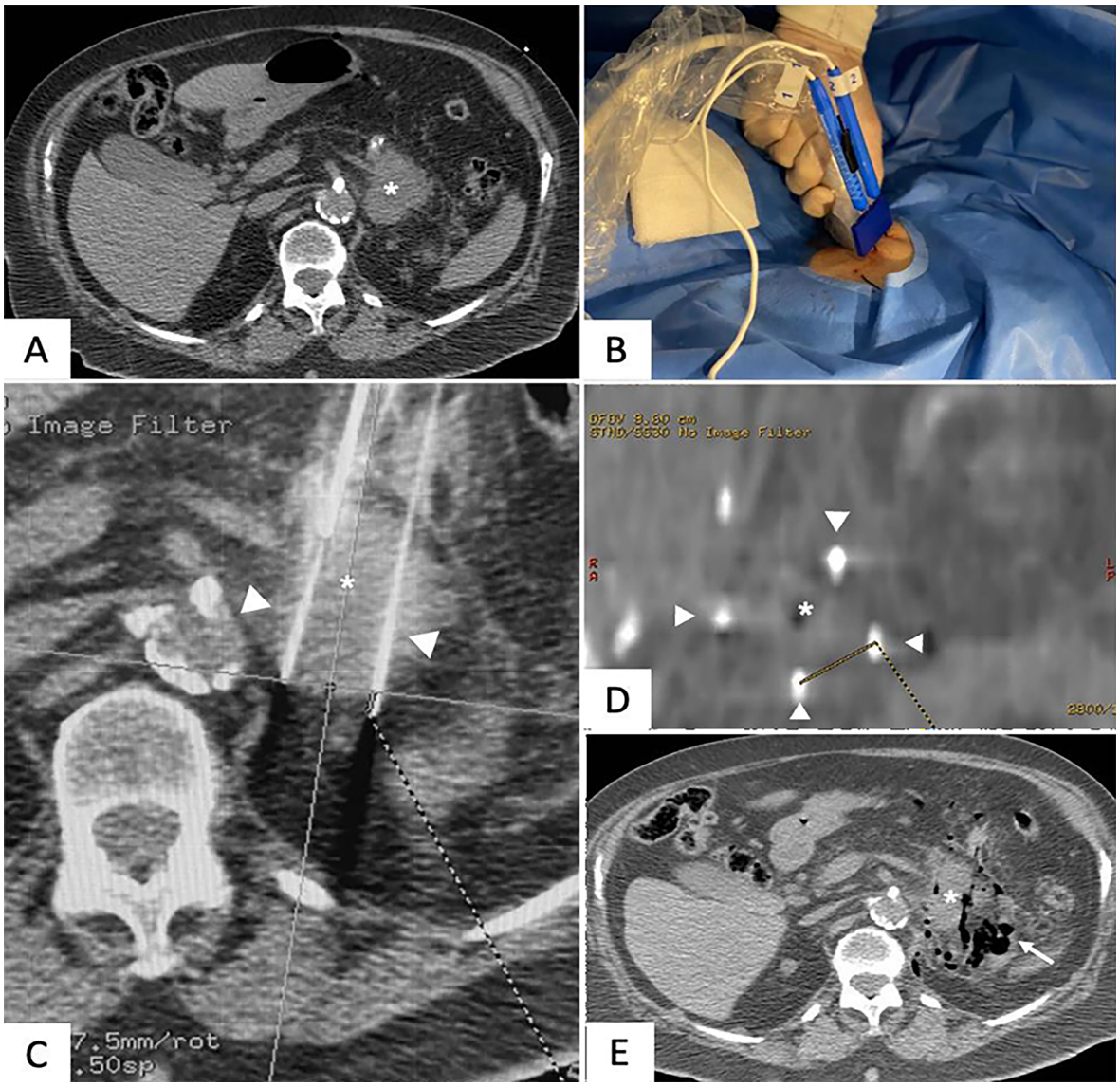

Figure 2. Percutaneous IRE of a local pancreatic recurrence. A. Pre-treatment CT showing local recurrence (asterisk); B. Percutaneous positioning of the probes; C. Probe (arrowhead) positioning confirmation within the tumor (asterisk); D. Inter-electrodes measurements (dashed line) between the probes (arrowhead); E. Immediate CT after IRE shows the lesion (asterisk) with similar aspect surrounded by gas (arrow).

RESULTS

Patient's characteristics

Baseline patient and tumor characteristics are provided in Table 1. In total, 10 patients (8 men, 2 women) underwent IRE 7 (70%) for LAPC and 3 (30%) for CLM. The median time between diagnosis and IRE was 6,5 months (range 1-30 months). Nine patients (90%) had previously undergone multiple rounds of chemotherapy and/or chemoradiation therapy and 1 (10%) had upfront surgery. In the pancreatic lesions, 3 (30%) was located in the pancreas head; 4 (40%) was located in the pancreas body or tail. The median baseline tumor diameter of the longest axis was 2,6cm (range 2-4,7cm). All of the 7 surgical patients had IRE indication due to adjacent vascular invasion (Table 2). Of these, 4 were inoperable and underwent IRE only (3 for local control and 1 for downstaging); and 3 had resection + margin accentuation.

Technical outcomes

Details of the procedures are summarized in Table 4. Technical success was achieved in all patients. The median number of electrodes used was 2,5 (range 2-4). The number of cycles per electrode was in the range of 1-6; inter-electrode distance was in the range of 1,5-2,2cm; voltage was in the range of 30.1-49.9V; and the tip exposure length was in the range of 1-1.5cm. Most patients (n=9, 90%) required 1-2 electrode pull-back techniques to treat target lesions >14mm. The mean current before and after IRE was 31.5A (range 25.1-40.3A) and 42.5A (range 30.1-49.9A). The median duration time from the start of the first cycle until the end of the last cycle was 50 minutes (04-114 minutes); percutaneous and surgical approach median time was 105 minutes and 30 minutes, respectively.

Follow-up

The median in-hospital stay after IRE was 7,3 days, 2 days (1-4) for percutaneous procedure and 10 days (3-21) for surgery. Table 4 lists procedure-related adverse events, being 3 (75%) grade 1-2 and 1 (25%) grade 3. All patients with minor complications recovered completely following conservative management.

In all 8 patients treated for LAPC, before IRE, the median serum levels of amylase and lipase were 57U/L and 25U/L, respectively. These values increased to 69U/L (average increase of 21%) and 46U/L (average increase of 84%), respectively, one day after IRE. However, these values normalized within one week after IRE and no clinical manifestation was noticed.

Table 2. Surgical IRE indication.

Patient	Primary tumor	Lesion location	IRE indication	Treatment
#1	Pancreatic cancer	Pancreas	Encasement SMV and PV	Resection + Margin accentuation
#4	Pancreatic cancer	Pancreas	Encasement SMV	Inoperable – IRE only
#5	Pancreatic cancer	Pancreas	Encasement SMV	Inoperable – IRE only
#6	Cholangiocarcinoma	Bile duct (Klatiskin II)	Abutment celiac axis	Downstaging – IRE only
#7	Pancreatic cancer	Pancreas	Encasement SMA	Resection + Margin accentuation
#8	Pancreatic cancer	Pancreas	Encasement SMV and PV; Abutment HA	Inoperable – IRE only
#9	Pancreatic cancer	Pancreas	Abutment celiac axis	Resection + Margin accentuation

Abbreviations: SMV = Superior mesenteric vein; PV = Portal vein; SMA = Superior mesenteric artery; HA = Hepatic artery; Abutment, ≤180° or ≤ 50% of the vessel circumference; encasement, ≥180° or ≥50% of the vessel circumference.

Table 3. Results summary.

	Total	Percutaneous	Surgery
Number of patients	10	3	7
Male: n (%)	8 (80%)	2 (66.6%)	6 (85.7%)
Female: n (%)	2 (20%)	1 (33.4%)	1 (14.3%)
Median age: years (range)	65.3	68.6 (43-89)	63.8 (60-78)
Primary tumor: n (%)			
Pancreas	7 (70%)	1 (25%)	6 (100%)
Colorectal (hepatic metastasis)	2 (20%)	2 (50%)	0
Colangiocarcinoma	1 (10%)	1 (25%)	0
Median tumor size: mm (range)	2.8	2.7 (1.0-4.7)	2.8 (2.0-3.5)
Median number of probes: n (range)	2,5	2,6 (2-4)	2.4 (2-3)
Median probe exposure: mm (range)	16.1	17.5 (1.5-2)	1.5 (1.5-1.5)
Median procedure time (minutes)	50	105	30
Median hospital stay: days (range)	7.3	2 (1-4)	10 (3-21)
Complications: n (%)			
Within 48 hours (NCI-CTCAE)			
Grade 1-2	1 (10%)	1 (10%)	0
Grade 3-4	0	0	0
Within 30 days (NCI-CTCAE)			
Grade 1-2	1 (10%)	0	1 (10%)
Grade 3-4	2 (20%)	0	2 (20%)

Adverse events were graded using NCI-CTCAE version 5.0. Abbreviations: IQR = Interquartile range; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 4. Adverse events.

Adverse event (NCI-CTCAE)	Grade 1-2	Grade 3	Grade 4	Treatment
Gastrointestinal				
Vomiting	0	1	0	Hospitalization with IV hydration and symptomatic medications
Abdominal fluid collection	2	0	0	Percutaneous drainage during hospitalization
Others				
Pneumothorax	1	0	0	Chest drainage during procedure.

Adverse events were graded using NCI-CTCAE version 5.0. Abbreviations: IQR = Interquartile range; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

DISCUSSION

The development of new minimally invasive technologies, such as ablative therapies for local control, is gaining an increasing role in cancer treatment. However, one of the limitations of these therapies is the thermal injury of tumor's adjacent structures. Unlike thermal ablation techniques, which induce tissue necrosis by deposition of high or low thermal energy, the electroporation phenomenon induces non-thermal tissue necrosis through high-voltage electrical pulses that determine nanopores in the cell membrane temporarily (reversible) or permanently (irreversible) in tumor cells.[5] Therefore, the extracellular matrix structures are preserved and vulnerable adjacent tissues, such as vessels, nerves, and bile ducts, should remain intact.[14]

Centrally located liver lesions can be unsuitable for resection or thermal ablation due to their proximity to the main bile ducts and portal vein. As IRE enables the preservation of these structures, it may prove particularly useful for this indication.[15] Narayanan et al. (2015)[16] investigated the effect of IRE on vessels close to the ablation zone in 101 patients. Abnormal vascular changes were seen in 7 of 158 vessels (4.4%). All changes were venous in origin, with the portal vein most affected, probably due to flow dynamics within the portal venous system. Occlusion of bile ducts has been reported after hepatic IRE, which may have been caused by thermal coagulation of the bile duct that was in direct contact with one of the needle electrodes.[17] Kingham et al. (2012)[15] treated 65 liver malignancies that were within 1cm from a major hepatic vein or portal pedicle, showing patency of all hepatic veins and pedicles on postoperative imaging, except for 1 major vessel occlusion. Therefore, to avoid damage to thermally sensitive structures, it is recommended to place the needle electrodes at least 5mm from bile ducts or large blood vessels.[18] In our 3 cases of central liver lesions, among which two were metastasis of colorectal neoplasia and the other one a cholangiocarcinoma, there was no damage to the adjacent structures with minimum distance of the probe to bile duct or major vessel >5mm.

Many studies have investigated the outcomes of percutaneous IRE under CT guidance in patients with LAPC.[16,19,20] Narayanan et al. (2017)[10] reported a median OS of 14.5 months from the date of IRE with no procedure-related deaths for percutaneous IRE, which is similar to those reported for intraoperative IRE.[21,22] Potential benefits of percutaneous IRE include a relatively short recovery time, fewer potential complications related to surgery, and better spatial guidance for needle placement. In our experience, 3 patients have successfully undergone percutaneous IRE and 7 received the surgical approach. The choice for the surgical approach was mainly because all patients had borderline surgical LAPC and IRE was planned to treat only in the region where the surgeon could not withdraw the tumor with safe margins (i.e., near the great vessel). During the probe positioning in the surgical access, the main difficult was the lack of support to maintain the probe static in the correct place, the poor ultrasound visualization of the probe while into the abdominal fat, the high flexibility of the needle turning it difficult to puncture the hard tissue of the pancreatic lesions, and the probe distribution avoiding the major vessel. As for the percutaneous approach, the access to position all needles parallel to each other proved to be quite challenging due to the costal arches and the poor visualization of the vessel anatomy in the non-enhanced CT. To overcome the latter, Timmer et al. (2020)[6] described a technique where a transarterial catheter is placed into the celiac trunk with small amount of contrast injection during probe positioning for better artery visualization. As for the laparoscopic IRE, we preferred not to use this approach once because the positioning of the probe could result in a challenging task, raising the surgical time and probably leading to higher complication rates and partial tumor ablation, mainly in the initial learning curve. As for the procedure time, the percutaneous approach was longer than surgical (median of 38min. vs. 30min.), probably because of the probe repositioning, which is more time consuming in percutaneous approach.

CT and MRI are considered the best modalities to evaluate the efficacy and possible complications after IRE.[14] A contrast-enhanced CT scan after IRE usually shows different results compared to RFA and MW due to the non-coagulative action and the consequent preservation of vital structures.[23] In our experience, the ablation zone appeared as a hypodense area with small gas bubbles, best visualized in the portal phase, as described by Rashid et al. (2018).[24] Ultrasound monitoring showed subtle hyperechogenic change with small gas formation. Several studies have demonstrated that the apparent ablation zone on CT grossly corresponds to the pathological zone of cell death.[25-27]

Several studies have reported major complications, in the range of 19%-59%,[5,21-23,28] including hemorrhage from gastrointestinal ulceration, vessel stenosis, or bile duct injury.[24,28] In the present study, there was no death within the 30-day follow-up period. In our study, the percutaneous approach had only one adverse event related to a pneumothorax due to transpulmonary access during probe positioning. Three patients in the surgical approach presented with complications, one with persistent vomiting requiring IV medication and fluid hydration; two with fluid collection in the abdominal cavity that was percutaneously drained and considered most likely to be related to the surgery. In the present study, patients treated for LAPC had transient elevation of serum amylase and lipase levels one day after IRE, returning to normal values one week after IRE. This result could be due to transient inflammation of the pancreas after inserting the electrode during the procedure.[29] No clinical significative pancreatitis was observed in our patients.

To guarantee the long-term success of IRE as an established tool for the treatment of LAPC, we must strive for continuous improvement of the technique, aiming for minimal complications and maximal attainable results. Important physical factors influencing these outcome values include the adjustable parameter settings of the IRE apparatus. These individually adjustable parameters include number, length and duration of the electrical pulses, interval between the pulses, pulse delivery protocol, interelectrode distance, voltage, number of needle electrodes, and their geometry. Hence, for optimization of IRE procedures, it is essential to elucidate the exact effect of each parameter on the ablation zone in terms of geometry and homogeneity.[6]

The current focus of several trials is the immunogenic potential of IRE, as the mechanism through which IRE operates also results in a systemic effect. Locally generated antitumor T-cell responses could eventually provide protection against tumor outgrowth of distant metastases, a process known as the "abscopal effect", which could positively affect survival.[30-34] A recent preclinical study involving immunocompetent mice with PDAC that received combined treatment with IRE and an anti-PD1 checkpoint inhibitor demonstrated significant survival benefits.[35] Furthermore, in a clinical study for unresectable LAPC, a combination of IRE and allogeneic natural killer cells achieved significant improvement in OS over IRE alone.[36,37]

The present study has some limitations. First, this study included a small number of patients and the follow-up time after IRE was relatively short. Second, there was no control group, such as patients undergoing conventional chemotherapy, to compare. Further randomized controlled studies are needed to overcome these limitations.

In conclusion, IRE is a promising treatment modality for LAPC and CLM. Although the high complication rates on this study, most of them represents minor complications with conservative treatments. Furthermore, prospective studies with control group are necessary to determine the efficacy of IRE.

AUTHORS' CONTRIBUTIONS

D.T.S: Collection and assembly of data, Conception and design, Data analysis and interpretation, Manuscript writing; D.S.O: Collection and assembly of data, Conception and design, Data analysis and interpretation; G.G.M: Collection and assembly of data; O.F.M.B: Conception and design, Data analysis and interpretation, Final approval of manuscript; A.L.V.M: Conception and design, Provision of study materials or patient; L.T.B.S: Conception and design, Data analysis and interpretation, Final approval of manuscript, Provision of study materials or patient.

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