Role of Irreversible Electroporation in Solid Abdominal Tumors Management

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Abstract:

Background: Irreversible electroporation (IRE) is a new non thermal ablation modality with promise for revolutionizing the treatment for solid local tumors specially to overcome the disadvantages of other ablation maneuvers in nonsurgical cases. The study aimed to evaluate the role of irreversible electroporation as a new promising minimally invasive technique for ablation of solid abdominal tumors.

Methods: 25 patients were included with unrespectable solid abdominal tumors (15 pancreatic, 7 hepatic and 3 LNs), the masses size measures about 4 cm, which are applicable for percutaneous needle insertion and associated with oligo or no metastatic lesion however patients with cardiac arrhythmias or pacemaker, patients unfit for general anesthesia, multiple metastatic lesions, patients with renal impairment and patient with metallic stent were excluded. Full radiological follow up was done as well.

Results: There was significant reduction in level of tumor markers in pancreatic tumors after IRE in comparison to baseline level o as well as tumor size during different periods of follow up. The same was detected for hepatic focal lesions regard its size however metastasis was reported. While variable response was detected in LN ablation.

Conclusion: The Irreversible electroporation is a promising less invasive technique for ablation of local solid tumors especially in pancreatic tumors.

Keywords: Irreversible electroporation (IRE), ablation, pancreatic tumors, hepatic focal lesions, metastatic LN, NHL.

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Background:

Irreversible electroporation (IRE) is a new non thermal modality for ablation with promise for revolutionizing the treatment of solid local tumors [1–5]. There was growing demand for alternative and less invasive modalities for treatment of localized solid tumors, we have seen the development and investigation of multiple modalities for tissue ablation, including radiofrequency ablation (RFA), microwave ablation, and cryo- ablation. Although these modalities were efficient, they have some disadvantages due to their reliance on thermal energy for creating cell death [1-4].

IRE is novel in that it does not use thermal energy, but it uses electrical energy to produce focused cell death and spare the normal extracellular matrix, nearby vessels, and structures, and allow rapid normal tissue regrowth [1- 10].

Unlike the other thermal ablation modalities, IRE does not require significant consideration for dissipation of thermal energy, or heat sink, and has less complications relating to damage of normal soft tissue, this eliminates a major cause of treatment failure [2,3,5,10,11]. IRE has shorter treatment time than the thermal ablation modalities, in minute ranges, and may allow for treatment of considerably larger lesions than thermal ablation modalities [7,12]

IRE has been investigated and utilized for only the past few years; however, its potential use for cancer ablation has been receiving growing attention leading to a considerable number of studies on its safety and efficacy. IRE showed effective cell death in normal tissue, cancer cell cultures, in vivo animal studies, and human clinical studies [13-27]

Patients and Methods:

The study design: was ethically approved at Assiut university (ethical approval number: 04- 2023- 200659), clinical trial number: NCT03169439 and performed at South Egypt cancer institute, Assiut university, during the period from January 2018 to November 2021. The 25 patients who involved in the study were precisely selected by our multidisciplinary team according to our following inclusion such as the unrespectable solid abdominal tumors 15 of them with pancreatic cancer, 7 of them with hepatic focal lesions and 3 with nodal lesions, the mean age of the enrolled patients was 57 ± 12.08 years with range between 29 to 80 years. The average size was about 4 cm, applicable for percutaneous needle insertion and associated with oligo or no metastatic lesion. The exclusion criteria include patients with cardiac arrhythmias, pacemaker, unfit for general anesthesia, multiple metastatic lesions, renal impairment and patients with metallic stent.

Pre-ablation radiological workup: it was crucial step in treatment plan to ensure of the targeted lesion response. Patients were evaluated pre-procedure by: Ultrasonography as a primary imaging modality for the patient to detect its site, size and relations. Multidetector Ct: to assess the adjacent vital structure such as blood vessel, biliary channel, gall bladder, as a metastatic work up to exclude presence of multiple metastatic lesions and to evaluate contrast enhancement. Magnetic resonance imaging (MRI): This is very helpful; it was mainly done in pancreatic cancer patients for more information about the lesion such as the diffusion weighted image (DWI) and the ADC in evaluation if there is any change in it after the intervention. Intravenous gadolinium injection was done to detect the enhancement too. (Fig. 1)

Pretreatment patient evaluation and preparation: informative medical history must be taken carefully of any present illness, detailed patient complaints especially the pain which was the main complaint in most of the patients.

Laboratory evaluation: including complete blood picture, renal and liver function tests, coagulation profile including the INR, platelet count, prothrombin time and concentration and tumor marker such as CA19-9.

Pre-procedure cardiac assessment: to evaluate any type of arrhythmias by electrocardiography (ECG) and echocardiography. Pre-anesthesia fitness assessment to evaluate the patient's eligibility for general anesthesia. Pre-procedure chemotherapy three cycles were given by specialist.

The treatment procedure: General anesthesia was performed for all cases. All anesthesia procedures and medications were performed by anesthesia specialists, all patients monitored for vital signs with continuous pulse oximeter and ECG and automatic blood pressure monitoring and take muscle relaxant. Ablation procedure: In our study we employed Nanoknief Angio-Dynamics 603 Queensbury Ave., Queensbury, NY 12804 in south Egypt cancer institute. (Fig. 2). [20,28].

All patients either with pancreatic, hepatic or nodal tumors underwent the same procedure techniques. However, it differs from one another in the number of needles used based on the size of the tumor. The IRE ablation is done in three steps which are; Needle approach planning: at first, US was initially done followed by CT in order to accurately confirm the best approach for the lesion. After accurate detection of the position and the entry point to the targeted lesion, a needle was inserted trans-cutaneous to intra-abdominal, it introduced gradually in the planned approach for the lesion, then the Nanoknief needle inserted to reach the lesion with selected CT levels at each time we introduce the needle, (Fig. 3) to ensure that we are in the correct safe approach line till the needle`s tip touch the lesion and reach it`s posterior margin with distance between each needle up to six needles and the other about 2 cm.[20,28]. Planning algorithm: after the needles insertion the Nanoknief machine has its own planning algorithm system, we insert the distance between each needle and the other after calculation by CT at the workstation. The generator can deliver between 100 to 3000 V of energy in 90 pulses, with pulse length about 70 ms, with the electrodes are 15 cm in length and 16-19 gauge in diameter, with active tip about 2-3 cm [28]. The generator connected by ECG so the ablation would be synchronized all the time and stops itself automatically if there is any abnormality in it [14,20,28,29] Adjustment of the parameters: the procedure started by giving test pulses 10 in numbers with ranging voltage from 1080 to 2400 V of energy and pulse length 70 ms, to achieve current about 40 which was our average. So, we needed adjustment of the voltage sometimes to give us the average current for energy delivery [30]. (Fig. 4)

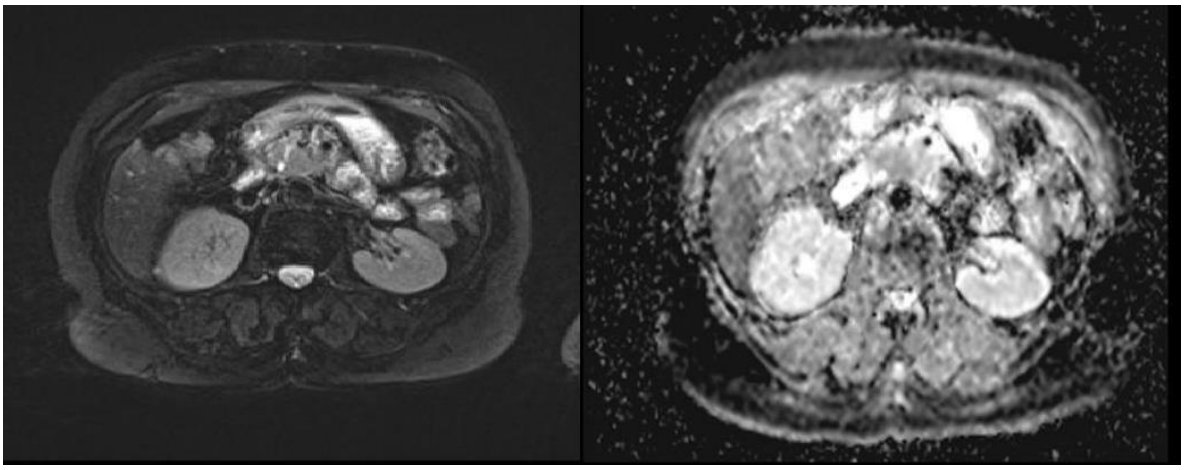
After termination of ablation immediate CT with contrast was done to exclude any residual and any immediate complications, then the probes are removed slowly. (Fig. 5)

Post ablation care: All patients were observed for 4-6 hours in the post anesthesia care unite for any immediate post procedural and anesthesia complications, most of patients complained from post ablation pain, symptomatic treatment was done by IV analgesics, anti-inflammatory and antibiotic to avoid any post ablation infection. Most of the patients are discharged from the hospital in two to four days.

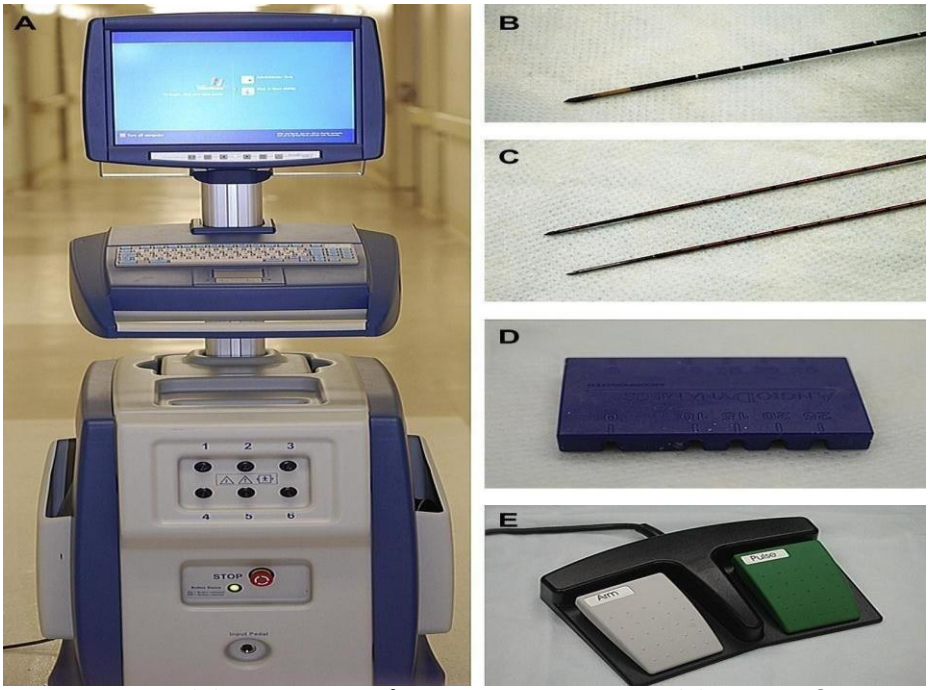
Post procedure follow up: the treated patients were scheduled for follow up after 3 months, 6 months and1year interval. Radiological follow up by CT in all

cases and MRI was done in the patients with pancreatic cancer with contrast injection in all cases to evaluate the effectiveness of the ablation and exclude any recurrence or new lesions [31]. (Fig. 6) Then patients fulfilled their treatment protocols at the medical oncology department. Five patients with pancreatic tumor and one patient with nodal lesion died, most of them died after 12 months of follow up. The reason of death was due to causes other than the procedure itself and no cases was excluded from the study.

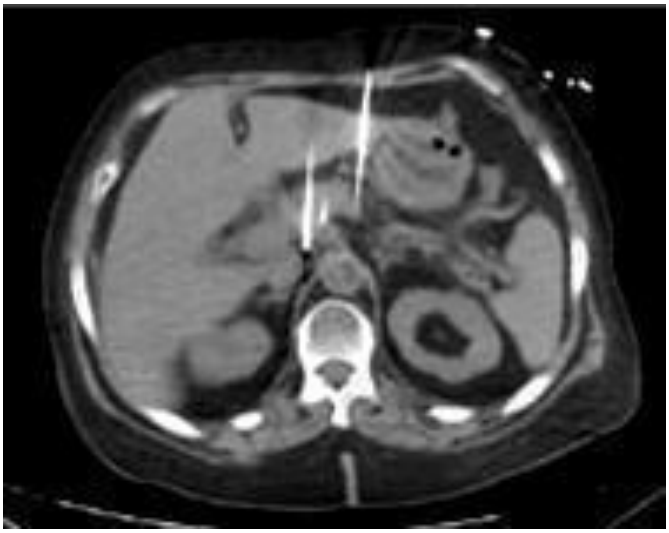
Statistical analysis Data was collected and analyzed those using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD or median (range) while nominal data was expressed in form of frequency (percentage). Follow up data was compared to the baseline (size of tumor, ADC value, and CA19-9) by Wilcoxon test. Level of confidence was kept at 95% and hence, P value was considered significant if < 0.055.



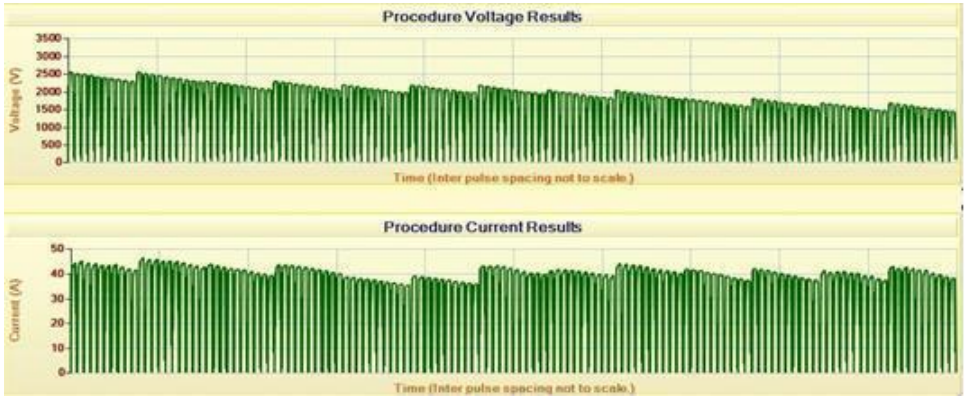
(Fig. 1) pancreatic cancer patient, pre-ablation MR. DWI MRI axial section shows mass in the bodyencasing vessels, STIR axial section of the mass.



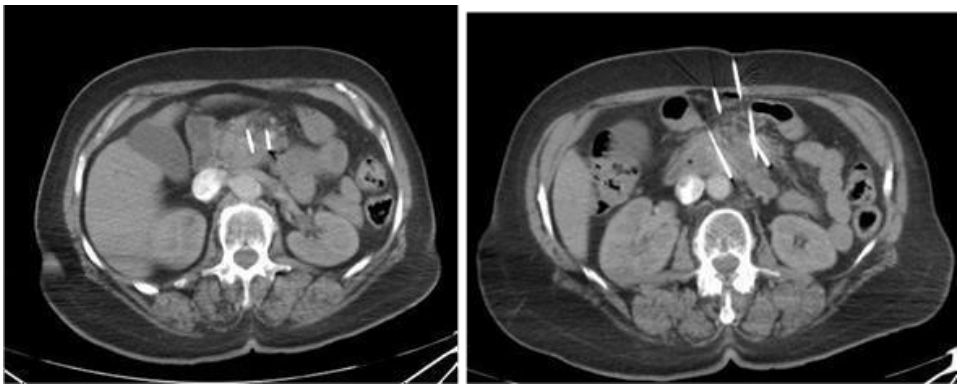
(Fig. 2) Current IRE system. (A) IRE generator from AngioDynamics Inc. (B) 16G Bipolar IRE probe. (C)19G monopolar IRE probes. (D) Monopolar IRE probe spacer. (E) IRE generator pedal. IRE, irreversible electroporation (20.28).



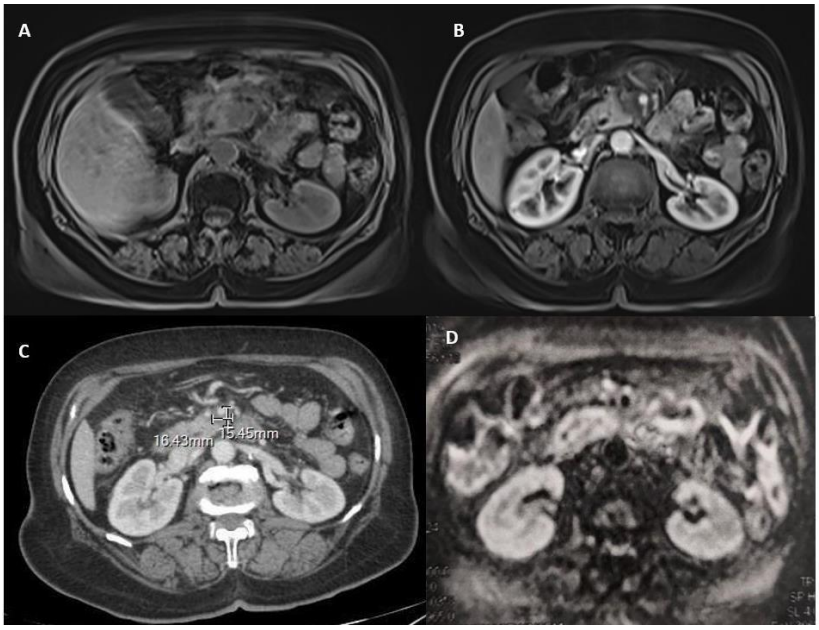
(Fig. 3) Axial image of non-contrast MDCT show probes inserted into the lesion.



(Fig. 4) Procedure voltage/current graph.



(Fig. 5) Axial images of contrast enhanced MDCT, done after termination of the procedure.



(Fig. 6) A&B; Axial MRI 3 months post ablation, T1 & T1 post contrast, show no residual enhancement, with significant reduction in the size, C; 6 months axial CT portovenous phase shows reduction in the size of the mass. D; MRI 12 months post ablation, axial ADC show scarring at the site of the lesion.

Results and Discussion:

The mean age of all enrolled patients was 57.12 ± 12.08 years with a range between 29 and 80 years. Thirteen (52%) patients were males, and 12 (48%) patients were females. Fifteen (60%), and 7 (28%) patients had pancreatic and hepatic lesions, respectively. Three patients had metastatic lymph node; from pancreatic cancer, non-Hodgkin lymphoma, and colonic cancer.

Pancreatic head, uncinate process, body and pancreatic tail lesion present 8 (32%), 5 (20%), 1 (4%) and 1 (4%)

patient, respectively. Hepatic lesions present in segment IV, V, VI, VII, and VIII in 1 (4%), 1 (4%), 1 (4%), 1 (4%), and 3 (12%) patients, respectively. (Table .1) Characteristics of pancreatic lesions before and after Irreversible electroporation:

Mean duration of IRE among those patients with pancreatic cancer was 110.27 ± 25.96 minutes with a range between 75 and 150 minutes. The median number of used needles was three needles with a range between three and six needles.

There was significant reduction in level of CA19-9 after IRE in comparison to baseline level of CA19-9 (69.42 ± 23.28 vs. 245.64 ± 22.31 (u/l); P < 0.001) but ADC insignificantly increased after IRE (1.37 ± 0.29 vs. 0.84± 0.12 (10-3 mm2/s); P= 0.57). (Fig.7)

As regard size of the tumor, it was noticed that size of the pancreatic lesion was significantly decreased during different period of follow up at 3- months after IRE (3.05 ± 0.58 cm), 6- months after IRE (2.48 ± 0.68 cm) and 12- months after IRE (2.01 ± 0.91 cm) in comparison to baseline size of the lesion (3.64 ± 0.41 cm) show the characteristics of pancreatic lesions before and after IRE. (Fig. 8)

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. IRE: irreversible electroporation; ADC: apparent diffusion co-efficient (Fig.7) Immediate complications and long term follow up in patients with pancreatic cancer: Abdominal pain was the most frequent immediate complication (60%) while vomiting occurred in three patients (20%). Each arrhythmia, hematoma, fever, and redness occurred in one patient. Only one patient did not record any immediate complications.

As regards long-term follow up; one patient developed ascites, 3 (20%) patients developed pulmonary nodules and another three (20%) patients had hepatic 6 metastasis. Five (33.3%) patients were deteriorated and died.

Characteristics of hepatic lesions before and after IRE:

Mean duration of IRE among enrolled patients with hepatic lesions was 45 ± 9.12 minutes with a range between 30 and 60 minutes. The median number of needles was three needles with a range between two and four needles. All patients developed abdominal pain after the procedure while two (28.6%) patients had chest pain.

Two patients developed new hepatic focal lesions and another one patient developed pulmonary nodule on long- term follow up.

As regard size of the tumor, it was noticed that size of hepatic lesion was significantly decreased during different period of follow up at 3- months after IRE (2.12 ± 0.25 cm), 6- months after IRE (1.64 ± 0.47 cm)

and 12- months after IRE (1.10 ± 0.42 cm) in comparison to baseline size of the lesion (2.37 ± 0.47 cm). (Table.2) (Fig. 8)

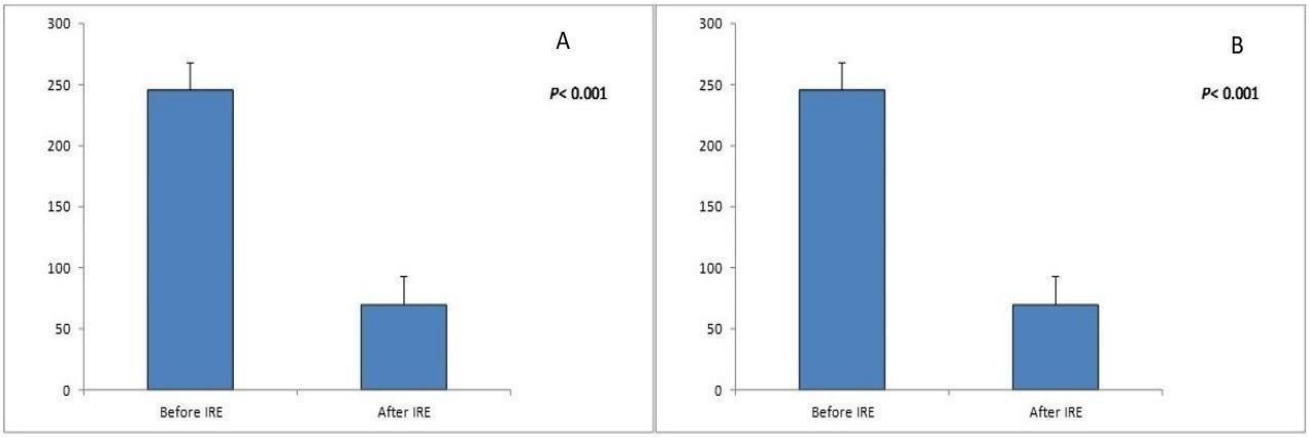
(Table 1): Patients characteristics

	N= 25
Age (years)	57.12 ± 12.08
Range	29-80
Sex	
Male	13 (52%)
Female	12 (48%)
Site of the lesion	
Pancreatic lesion	15 (60%)
Head	8 (32%)
Uncinate process	5 (20%)
Body	1 (4%)
Tail	1 (4%)
Hepatic lesion	7 (28%)
Segment IV	1 (4%)
Segment V	1 (4%)
Segment VI	1 (4%)
Segment VII	1 (4%)
Segment VIII	3 (12%)
Lymphadenopathy	3 (12%)
Aortocaval LNs	1 (4%)
Paraaortic LNs	1 (4%)
Porta hepatis LNs	1 (4%)

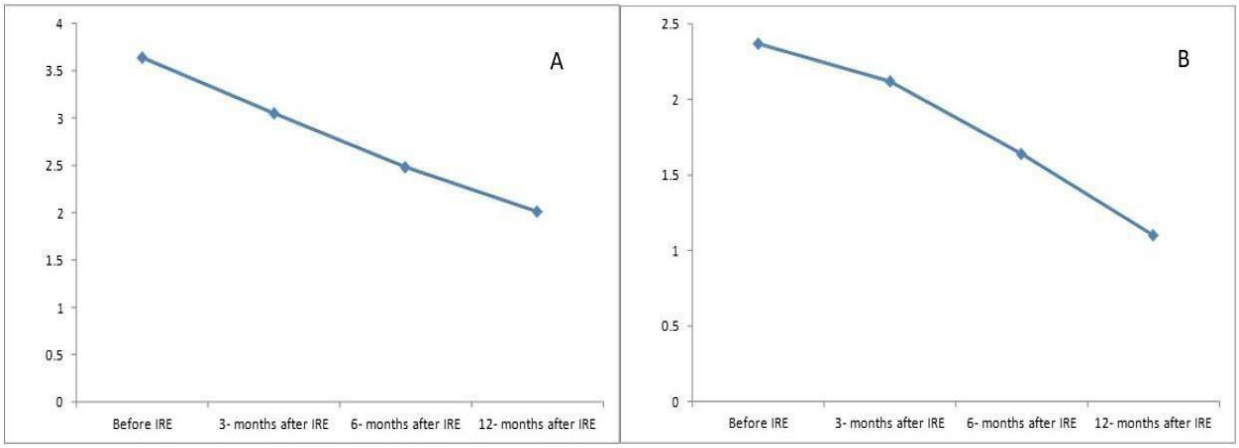
Data expressed as frequency (percentage), mean (SD). LN: lymph node

(Table 2): Characteristics of hepatic lesions before and after IRE

	N= 7
Size of the tumor (cm) before IRE	2.37 ± 0.47
3- months after IRE	2.12 ± 0.25
6- months after IRE	1.64 ± 0.47
12- months after IRE	1.10 ± 0.42
P value	< 0.001
Number of needles	3 (2-4)
Duration of IRE (minute)	45 ± 9.12
Range	30-60



(Fig.7) A; Mean CA19-9 before and after IRE among patients with pancreatic cancer. B; mean ADC before and after IRE among patients with pancreatic cancer Characteristics of pancreatic lesions beforeand after IRE. Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05.IRE: irreversible electroporation; ADC: apparent diffusion co-efficient.



(Fig. 8) A; Mean size of pancreatic lesion at baseline and after IRE. B; Mean size of hepatic lesion at baselineand after IRE.

Characteristics of patients with malignant abdominal LNs after IRE:

The current study enrolled three patients with malignant abdominal LNs as following;

- One patient had porta hepatis LN secondary metastasis from pancreatic cancer. Its size was 2 cm before IRE but at 3 months, 6 months and 12 months after IRE; it was 2 cm, 1.5 cm and 1.2 cm, respectively. The patient reported epigastric pain after IRE but after one year he died secondary to extensive hepatic infiltration.
- Another patient had para-aortic LN secondary metastasis from colonic cancer. Its size was 3 cm before IRE but at 3 months, 6 months and 12 months after IRE; it was 2.5 cm, 2.2 cm and 1.6 cm, respectively. The patient reported no epigastric pain after IRE.
- The last patient had aortocaval LN secondary to non-Hodgkin lymphoma. Its size was 4cm before IRE but at 3 months, and 6 months after IRE; it was 3 cm, and 2.7 cm. patients refuse to do follow up imaging at 12 months after IRE. The patient reported epigastric pain, sweating and vomiting after IRE.

Discussion: In the past 20 years, multiple modalities for the treatment of focal liver and pancreatic tumors were developed. Among hepato-biliary surgeons, IRE is of special interest because it is a non-thermal ablation modality which allows it to be implemented in anatomical regions which were previously considered inaccessible. More specifically, IRE is a modality of ablation which can be used in the treatment of tumors located near vital structures such as bile ducts and blood vessels which aren't eligible for surgical excision or thermal ablation. [32:34] The irreversible electroporation ablation technique is a new, non-thermal method for ablation of parenchymal organ tumors.

The area of IRE ablation close to blood vessels does not suffer from the heat sink effect and thus the cells in the vicinity of the vessels undergo ablation equally with the rest of the ablated part of the tissue; and IRE ablation retains functionality of the blood vessels, bile ducts, urinary tract and nerves which are found in the ablation area. [35]

In our study 25 patients underwent percutaneous IRE, mean age of all enrolled patients was 57.12 ± 12.08 years with range between 29 and 80 years. Thirteen (52%) patients were males, and 12 (48%) patients were females. Fifteen (60%) and seven (28%) patients had pancreatic and hepatic lesions, respectively. Three (14%) patients had metastatic lymph nodes; from pancreatic cancer, non-Hodgkin lymphoma, and colonic cancer.

Pancreatic cancer patients, it is nearly like Martin et al, who had only 10 patients in their study.

The procedure was performed under general anesthesia with standard hemodynamic monitoring to prevent arrhythmia induced by IRE the patients were secured with a synchronizer connected to a 5-lead ECG whose purpose was to synchronize the delivered electrical pulses with the diastole phase in the refractory period.

The electrodes of AngioDynamics Queensberry, NY were introduced subcutaneously guided by ultrasonography aided by CT to ensure correct distance and depth of the needles in the lesion and that was done in most of the previous studies done using the Nanokneif.

The mean duration of IRE among those patients with pancreatic cancer was 110.27 ± 25.96 minutes with a range between 75 and 150 minutes (about 2 and a half hours). The median number of used needles was three needles with a range between three and six needles. The median energy varied from 1400 to 2900 V, giving 90 pulses in each patient with pulse length 70 ms. That was stated also in other studies. [31]

In locally advanced pancreatic cancer, in IRE it's difficult-to-measure the response of the tumor endpoint.

However, tumor size alone does not fully encompass tumor response and may thus lead to inaccurate conclusions. So, the preferable evaluation method is to combine the tumor response and ablation size together with functional information such as change of the enhancement, development of vascular or biliary stenosis or occlusions and tumor marker CA 19-9 levels. [36,37].

The patients in our study with locally advanced pancreatic cancer underwent percutaneous IRE, with masses had variable size ranging from 3.64± 0.41cm pre ablation and post ablation follow up done after three, six and twelve months it became 3.05± 0.58 cm, 2.48 ± 0.68 cm and 2.01 ± 0.91 cm respectively, with high significant reduction in the size ($p < 0.001$).

Scheffer et al. and Narayanan et al and more recently, Ruarus et al. in their PANFIRE-II trial, confirm that tumor size correlates with the overall survival. [38:40]

Also, the CA19-9 (carbohydrate antigen) was significantly reduced comparing the pre ablation value average about 245.64 ± 22.31 U/mL and post ablation was about 69.42 ± 23.28 U/mL, ($p < 0.001$). This was also noted in a previous study by Mateusz et al. patients with pancreatic cancer, the CA19-9 level after the procedure by three months the level decreased to less than 80 U/ml and remained at a similar value in subsequent analyses. [41]

In our study the patients with pancreatic lesion who underwent imaging by MRI pre ablation, was 11 cases and they show diffusion restriction with low ADC value in the range 0.84 ± 0.12 x10-3mm2/s. And post ablation follows up done only to 10 patients. We noticed that there was an increase in the ADC value in spite of an insignificant difference found comparing the pre ablation to post ablation MRI ($p=0.59$), this owing to the small sample size. Another study found no significant differences in ADC after IRE by 1 to 6 months. [41] The observed discrepancies could be explained by the different extent and timing of the multiple mechanisms involved in the response to IRE treatment. [42]

The most frequent immediate post ablation complication was the pain, and it was subjective in about 12 patients who were controlled with intravenous analgesics, vomiting was the second one seen in three of them which was controlled with antiemetic. One of them had retro gastric small hematomas that was resolved in three days with post ablation follow up and anti-inflammatory medications, and another one developed transient ischemic attack and arrhythmia and referred to ICU unite, the patient was controlled and discharged after two days from the ICU, one of them developed fever together with rash and redness. Only one has no significant immediate post ablation complications. The average post ablation hospital stay was 2±2 days.

Other studies stated that the expected median hospitals stay of up to 3-4 days, including days of treatment. Pain is reported as moderate 1 day post treatment. [43]. In the long-term 12-month follow-up, we reported 3 patients who developed 9 metastatic hepatic focal lesions, 3 patients developed pulmonary metastatic lesions, and one of them also developed ascites. Thus, the overall long-term morbidity is 46.7%. No long-term complication could be detected in the three (20%). While 5 of them died during the follow-up. Three deaths were due to advanced metastatic disease, one from severe pneumonia, and one with no definite cause of death.

Recently, a systematic review for IRE of pancreatic lesions by Ruarus et al. provides an overview of the morbidity and mortality rates. [44] The average cumulative morbidity for surgical and percutaneous IRE was 36% vs 24%, respectively [45]. The most frequent adverse events include GI-related complaints including pain, diarrhea, nausea, vomiting, and loss of appetite, and delayed gastric emptying. The most severe complications include vascular occlusion, hemorrhage, severe pancreatitis, and death. [45]. Also, Philips et al.'s study included 59 patients with a morbidity rate of about 46% [46] and Martin et al.'s study included 27 patients with a 33% morbidity rate [47,48].

The present study included 7 patients with liver tumors, 4 of them had colorectal liver metastatic lesions (CRLM), two with hepatocellular (HCC) and one of them was metastatic from pancreatic cancer. The lesion size reduced significantly on a 12-month follow-up post IRE from baseline 2.37±0.47 to 1.1±0.42 cm ($p<0.001$).

Some lesions show early degeneration inside and no residual enhancement in post-procedure contrast-enhanced multi-detector CT study.

The systematic review with patients that had hepatocellular carcinoma, colorectal liver metastases, or other liver tumors, [49] The number of included patients in these studies ranged from 5 to 52. [50]

All the patients received 90 pulses with voltage vary from 1400 to 2900 with pulse length 70 and using 2-4 probes. Comparing the technical parameters to the other study by Cannon et al. and his coworkers, they used about four probes (range 3–6). The number of pulses per lesion was 180 (range 90–270) and the median energy deposited per lesion was 2600 V (range 2300–3000 V). [51]

Kalra et al. defined the complete tumor ablation when CT is done after 4 weeks and shows no arterial hyper vascularity or washout in the portal venous or delayed phase. Residual disease or incomplete ablation was defined as the presence of a tumor adjacent to the site of ablation on CT during the initial 1- month follow-up. Recurrent disease was diagnosed in subsequent follow-up CT scan that showed tumor was identified at or adjacent to the ablation site (local recurrence) or away from the ablation site (distant recurrence), which wasn't present at the initial 1-month CT. [51]

In the current study, the long-term follow-up showed 2 patients who developed new hepatic focal lesions nearby and away from the original lesion during the follow up indicating tumor recurrence (local and distant). Another one developed pulmonary nodule. The long-term complication was about 42.9%. Four of the patients didn’t show any long-term complications (failure).

Kalra et al. showed tumor ablation was complete in all patients after 1- month follow-up. Five patients show local recurrence (24%). [51] That study stated the effectiveness of IRE as a method for ablation of small HCCs.

However, it requires more prospective studies with a larger sample size and randomized control trials to establish the safety and efficacy of IRE for the ablation of HCC. [51]

Lastly in the current study, IRE was done for three selected patients with malignant featuring lymph nodes, which were encasing blood vessels and did not respond to chemotherapy and or radiotherapy.

One patient had a recurrent porta hepatis lymph node that was metastatic from pancreatic cancer after surgery. It was resistant to chemotherapy. It was measuring about 2 cm before IRE and on 3,6 and 12-month follow-up its size reduced to about 2, 1.5, and 1.2 cm respectively. We used two probes and median energy delivered about 2250 and pulse length was 70.

The patient developed epigastric pain as immediate post procedure complications and on long-term follow-up, the patient developed metastatic hepatic focal lesions (hepatic infiltration).

Another patient with non-Hodgkin lymphoma had residual un-resect able retro-caval lymph node. It was resistant to chemotherapy, and it measured about 3 cm pre ablation and post-ablation 3- and 6-months follow-up, the size was about 3 and 2.5 cm. This patient refused the 12-month follow-up. We used 5 probes with an average pulse length of 70 and median energy range from 1600 to 2960 with a total of 90 pulses.

The patient had severe epigastric pain and vomiting as an immediate complication and both serum amylase and lipase were raised indicating pancreatitis, so shifted on nothing per oral with strong antibiotics and anti-inflammatory medications. The patient improved after 2 days with no pain and the value of the enzyme was reduced. Then the patient was discharged from the hospital after 5 days' post-ablation.

The main limitation of the study was the limited sample size due to the high cost of each maneuver which is still the main obstacle for the IRE. Also due to the exclusion criteria so many patients were unfit for this ablative modality.

Conclusion:

The Irreversible electroporation is a promising less invasive technique for ablation of local solid tumors. It has the advantage of being non thermal so not affected by heat sink effect of hypervascular tumors and tumors near major vessels, causing apoptotic non necrotic cellular death and sparing the surrounding normal structure so it can be used more safely than any type of ablation.

List of abbreviations:

ADC Apparent diffusion coefficient
CA Cancer antigen
CT Computed tomography
DWI Diffusion weighted image
ECG Electrocardiography
GI Gastro-intestinal
HCC Hepatocellular carcinoma

Competing interests:

The authors declare that they have no competing interests. There is no interpretation of interest data or any financial competing interests.

Authors contributions:

JW collected the cases and prepared all investigations and manuscript writing. AM contributed to the idea of the research and collecting cases. MH and EH participate in main maneuver and practical work. GS and DMF help in results, statistics and manuscript writing. All authors read and approved the final manuscript out.

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