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Irreversible electroporation for stage III locally advanced pancreatic cancer: Single-center experience

John Spiliotis^{1,2,*}, Theodoros Metaxas¹, Dimitrios Farmakis¹, Dimitrios Karachalios¹, Mairi Gianniri¹, Alexandros Tefas³, Pinelopi Stefanopoulou³ and Georgios Dadoudis³

¹ Department of Surgical Oncology, Interbalkan Medical Center, Thessaloniki, Greece.

² Department of Surgery, Metaxa Cancer Hospital, Pireaus, Greece.

³ ICU, European Interbalkan Medical Center, Thessaloniki, Greece.

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Abstract

Introduction: Irreversible Electroporation (IRE) is a non-thermal ablation technique with promising results for treating locally advanced pancreatic cancer (LAPC). This study was conducted to evaluate safety and efficacy of IRE in the management of LAPC.

Methods: This was a retrospective single center study of ten patients with radiographic and biopsy proven stage III pancreatic head or body cancer that received open IRE with intraoperative ultrasound imaging. Perioperative complications at 90 days, tumor volume measurements, local recurrence and survival were recorded.

Results: 20 patients, with a median age of 62, underwent IRE for locally advanced pancreatic head cancer (n=11) and body cancer (n=9). All patients were treated successfully with an open IRE approach. Nine patients experienced grade II (Clavien-Dindo) procedure related complications. There were no grade 3 to 5 complications. Median follow up was 30 months. Tumor volume decrease at 6 months imaging follow up was found in 70% of patients (n=14). Local disease progression was observed in two patients, and there was evidence of metastatic disease in 7 patients. 8 patients died with a mean of 15, 2 months and 12 patients are still alive with a mean of 17,3 months. Median overall survival was 16,5 months.

Conclusion: Our initial experience with IRE showed encouraging results regarding safety, feasibility and efficacy in patients with locally advanced pancreatic head or body cancer. Further investigation is needed.

Keywords: Irreversible Electroporation (IRE); Locally advanced pancreatic cancer (LAPC); Pancreatic adenocarcinoma; Palliative procedure

1. Introduction

Pancreatic adenocarcinoma remains a devastating disease with a 5-year survival rate not exceeding 6% [1]. It is a highly lethal malignancy due to the obstacles that have been imposed concerning its early detection. 50% of patients with advanced pancreatic cancer have a metastatic disease and an additional 25% to 35% patient at that stage with borderline respectable PC or with locally advanced unresectable PC. Lack of sensitive biomarkers as well as the multiplicative biology and the inscrutable architecture of the tumor make it more difficult to approach and develop an

* Corresponding author: Dr John Spiliotis
Department of Surgical Oncology, Interbalkan Medical Center, Thessaloniki, Greece.

effective therapeutic method so as to improve disease outcome. That is why, there has been an urgent need for technological evolution regarding unresectable cases.

New ablation techniques for LAPC, which remain unresectable even after neoadjuvant chemo (radio) therapy due to their spread to vital structures, such as IRE (Irreversible electroporation) use electrodes which deliver high-voltage electricity directly to the tumor, under radiological control [2]. Therefore, a phenomenon called apoptosis is induced due to nanopores that are created irreversibly in the cell membrane. It is very important to notice that it influences only the cells inside the non-thermal ablation area of the tumor [3, 4]. Thus, it has been proved that IRE is safe for vascular and ductal structures and in addition to that, it does not harm supporting connective tissue. This fact makes this method suitable for the treatment of LAPC.

In our retrospective analysis, we size up the safety, feasibility and efficacy of IRE as an integrative therapy in the management of patients with LAPC.

2. Methods

This was a retrospective, single center study from August 2015 to December August 2020 with locally advanced pancreatic cancers that were treated with Irreversible Electroporation. The study was approved by an institutional board review.

Patients were staged according to the NCCN staging system with a computed tomography scan (CT) either with an angiography protocol either with a Magnetic Resonance Angiogram (MRA) [5]. All patients included in the study were biopsy proven and had at least a greater than 180° degrees SMA or celiac artery encasement, or an unreconstructable SMV or portal vein occlusion with no evidence of any distant metastasis. Tumor volume was calculated using an ellipsoid volume formula ($V=4/3\pi abc$) by measuring all axes in imaging. All patients were reviewed in a multidisciplinary conference and were confirmed to have LAPC. After treatment with chemotherapy as proposed by the NCCN guidelines, patients were restaged and reevaluated [6, 7]. Patients that were still found to have Locally Advanced Pancreatic Cancer were proposed to be treated with Irreversible Electroporation.

IRE was performed with an open technique, using the Nanoknife IRE device in all patients. After general anesthesia and use of neuromuscular blocking agents (NMBA), a midline incision was made. After thorough investigation, no signs of metastatic disease were found, then the omental foramen was exposed by opening the gastrocolic ligament. Finally, the IRE probes were placed under direct Ultrasound guidance.

After treatment with IRE, an early imaging was performed to identify early postoperative complications. Chemotherapy was started early post operatively in consensus by oncologist and all patients were evaluated with computerized tomography every month. Tumor volume was measured and recorded with the help of imaging. Complications were recorded at 90 days and were classified with the Clavien-Dindo classification at surgical complications.

3. Results

In this study, 20 patients (12 men and 8 women) with locally advanced pancreatic cancer were included. Median age was 62 years (range: 48-73). Clinical demographics of the patients are shown in Table 1. All patients were treated for biopsy proven adenocarcinomas, 12 of them had a pancreatic head lesion, 6 had a pancreatic body lesion and 2 a tail lesion. Mean baseline tumor volume at the time of the IRE procedure was 9.42 cm³ (range: 2.13-25.09). Near all patients had prior chemotherapy (90%). None had chemoradiotherapy and one was treated straight with IRE refusing any neoadjuvant type of therapy.

The median time from initial diagnosis to treatment with IRE 4, 7 months (range: 1-6,5m). In all patients, IRE treatment was successfully completed with no intraoperative complications. Median procedure time was 89, 8 min (range: 45-128 min). In most patients 4 needles were needed, 5 in three and 6 in another patient. The median length of stay was 7, 2 days (range: 4-13).

There was no IRE related mortality. Five patients experienced grade 2 complications (Clavien-Dindo Classification). Two patients developed postoperative paralytic ileus and were treated conservatively. One patient experienced pneumonia and one urinary tract infection, both were treated with antibiotics. Only three patients presented a pancreatic related complication, pancreatitis. Serum amylase was restored in 72h. After IRE, 14 patients received chemotherapy, approximately 14 days after treatment.

Two patients died 6 months after the IRE treatment due to liver failure, although tumor volume decrease was observed at 3-month imaging follow up. 12 patients are still alive at that moment.

Median overall survival from diagnosis was 28, 5 months. And the median overall survival after IRE's procedure was 17 months.

4. Discussion

Irreversible electroporation, a relatively new tumor ablation technique that induces cell membrane porosity through high voltage pulses which leads to cells apoptosis. To date, a number of studies have been reported to demonstrate the use of irreversible electroporation in locally advanced pancreatic cancer [8]. There are currently reports for the open technique, the percutaneous and the laparoscopic approach [9, 10, 11, 12]. IRE has also been tested in increasing surgical resection margins in borderline pancreatic cancer with as shown by Kluger and Marsanic [14, 15].

In this study, we report a 50% complication rate, but most were grade 2 complications and there was no mortality in our patients. Morbidity rates ranged from 26-37% in Martin et. al and Kluger et. al reports, two of the biggest reports on IRE in locally advanced pancreatic cancer [14, 16].

Belfiore demonstrated a benefit for patients followed by chemotherapy, increasing median overall survival rate and quality-of-life of LAPC-diagnosed patients when compared to patients treated with chemotherapy alone [17]. Belfiore's patients also experienced a 40.3% mean percentage decrease volume 6 months after IRE [17]. In our study, we demonstrated a mean volume decrease of 48.25% [95% CI, 37.25-59.25].

There were limitations to this study. First and foremost, the most significant lime is the total number of patients that was low. To that end, the results retrieved on the overall survival in this study may not be assumed to the larger patient population. Although, it is our first attempt to enroll a study concerning the application of irreversible electroporation in locally advanced pancreatic cancer cases, we can report that overall response to the surgical procedure was satisfying. Given that there is only one reported death out of ten patients that were included in the study, this, in turn, leads to an increase in overall survival.

Irreversible electroporation is bringing new hopes in the treatment and management of LAPC. The majority of studies on efficacy and safety of this method are based on nonrandomized series but have shown that IRE is encouraging in terms of overall patient survival [18].

Nonetheless, it is an expensive technique with risks of complications. Hence, it needs to be ratified in large, randomized, prospective series.

Table 1 Patient demographic characteristics

Number of patients: n=20	
Median age, year	62 (range: 48-73)
Male/Female	12/8
Body Mass Index (BMI)	26.7 (range: 18.6-42.1)
Medical history, n (%)	
Cardiovascular	12/20
Pulmonary	5 (25%)
Gastrointestinal	5 (25%)
Metabolic	5 (25%)
Karnofsky performance status	77.5 (range: 50-100)

Table 2 Tumor and patient oncological characteristics

Number of patients: n=20	
Tumor location	
Head	11
Body	9
Median tumor volume prior to IRE, cm ³	9.42 (range: 2.13-25.09)
Prior chemotherapy, n (%)	11 (55)
Gemcitabine	8
GemOx	6
Post-IRE chemotherapy, n (%)	18/20 (90%)
Post-IRE radiotherapy, n (%)	4/20 (20%)

Table 3 Operative characteristics of patients

Number of patients: n=20	
Median time from diagnosis to IRE, months	4.7 (range: 1-6.5)
Number of IRE probes, n	4.3 (range: 4-6)
Total procedure time, min	89.8 (range: 45-128)
Length of stay, days	7.2 (range: 4-13)
Complications, n (%)	11 (55)
Paralytic ileus	4
Pneumonia	2
Urinary tract infection	1
Pancreatitis	3

Table 4 Outcome data per patient

	Sex	Age	Tumor location	Survival after IRE (m)	Follow up
1	M	57	H	26	D
2	M	61	H	14	A
3	F	64	H	14	A
4	M	62	H	29	A
5	F	48	H	16	A
6	F	54	B	8	A
7	M	62	H	12	D
8	M	66	B	6	A
9	F	73	B	6	D
10	M	70	H	12	A

11	M	69	T	31	D
12	M	48	T	22	D
13	F	52	B	37	A
14	M	64	B	12	D
15	F	50	H	18	A
16	F	48	H	22	A
17	M	71	H	16	D
18	M	67	B	20	A
19	F	64	H	12	A
20	M	58	H	19	D

M=Male, H=Head, m=months, A=Alive, F=Femal, B=Body, D=Dead, T=Tale

5. Conclusion

The locally advance pancreatic cancer remain a 40% of new diagnose cases. The corner stone of the treatment remains the systemic chemotherapy in order to down staging the disease. IRE remains on alternative procedure to eliminate the tumor burden and achieved a prolongs to O.S.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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