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Irreversible Electroporation for Locally Advanced Pancreatic Cancer: A Ray of Hope in a Difficult Problem

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Abstract

Irreversible Electroporation (IRE) is a recent tool of tumor ablation techniques added to the management of Locally Advanced Pancreatic Cancer (LAPC). As opposed to the thermal ablative techniques, IRE induces cancer cell death by the delivery of high-voltage electrical pulses. The electrical energy disrupts the cellular membrane causes loss of cellular homeostasis and respects the surrounding structures such as bile ducts, bowel well and large vessels. All this makes IRE attractive. This review discusses several practical and technical issues, indications, patients selection and clinical results.

Keywords: Irreversible Electroporation (IRE); Locally Advanced Pancreatic Cancer (LAPC); Pancreatic Ductal Adenocarcinoma (PDAC).

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is one of the most aggressive tumor types and is expected to become the leading cause of cancer-related deaths by 2030 [1,2]. The overall 5 year survival rates estimated between 8 to 10% [3].

Of the patients with PDAC about 30-40% encompasses non-metastatic Locally Advanced Pancreatic Cancer (LAPC).

LAPC is broadly defined by its encasement of the superior mesenteric artery or celiac axis or encasement of mesenteric-portal axis without possibility of reconstruction after resection [4,5].

For patients with LACP, treatment options, include stereotactic body radiotherapy, chemotherapy, chemo radiation and so forth.

Overall systemic chemotherapy delivers poor median overall survival of 16-22 months [6-8].

Therefore, different approaches to treat LAPC are required.

Ablation techniques present a promising method for the local treatment of LAPC [9-12].

The most well know methods re RFA, microwave ablation and cvyoablation and recently a primarily non-thermal method known as Irreversible Electroporation (IRE). The most important difference between IRE to thermal ablation method is that IRE employs electrical energy in the form of high-voltage electrical pulses that after the existing tumor cellular transmembrane potential [13].

This effect lead to loss cellular home ostasis which it results in tumor cells death through both apoptosis and necrosis [14]. The two main advantages of IRE are:

First with the use of non-thermal electrical energy protects the surrounding structures of large vessels, bile ducts and intestine [15].

Second the thermal ablations (RFA, microwaves) potentially incomplete by the ''heat-sink effect'' resulting incomplete ablation; on the other hand IRE obviates this phenomenon due to the non-thermal use of energy.

One interesting observation compares IRE vs RFA is that IRE stimulates a T cell activation with the establishment of anticancer systemic immune response to destroy the malignant tumor cells remands from the inside out [16,17].

The aim of this review is to present the issues of IRE for LAPC and discuss future prospective combines IRE with systemic or locally chemotherapy or immunotherapy.

Patients selection and evaluation

IRE for LAPC is currently used as a cytoreductive surgery for patients that lack signs of distant metastatic disease. This procedure is considered high risk due to anatomical reasons of surrounded structures [18]. Hence patient selection for IRE is crucial and essential, must be reviewed by multidisciplinary tumor board, stage III LAPC, without diabetes without history of cardiac arrhythmias, or implanted cardiac pacemaker epilepsy or congestive heart failure [19,20].

Anesthetic review and management during IRE differs from standard anesthesia due to the increased risk of cardiac arrhythmias and severe muscle contractions [21].

Complete preoperative imaging with CT, MRI angiography are essential and bowel preparation and nasogastric tube placement is necessary [22,23].

Outcome of IRE for LAPC

Most of the current trial to evaluate the benefits of IRE therapy in LAPC is retrospective studies [24].

The survival results are varied with a median overall survival ranges from 10 to 30 months [25-26].

The most important factor which must considered as standard of care is the use of neo-adjuvant systemic chemotherapy before IRE. Despite this, Alette et al. [27] recommend at least four cycles of FOLFIRINOX before IRE. The ongoing LAP-PIE clinical trial aims to perform a randomized comparison of combination treatment FOLFIRINOX+IRE versus FOLFIRINOX alone [28].

In Table 1 overview overall survival from 2017 until now.

Table 1: Irreversible electroporation for locally advanced pancreatic cancer. survival rates (median in months).

Authors	Year	Approach	Median O.S. (months)
Scheffer et al. [35]	2017	Percutaneous	11
Belfiore et al. [36]	2017	Percutaneous	14
Narayanan et al. [37]	2017	Percutaneous	14.2
Vogel et al. [38]	2017	Open	16
Spiliotis et al. [12]	2018	Open	16.7
Sugimoto et al. [39]	2018	Open/ Percutaneous	17.5
Leen et al. [40]	2018	Percutaneous	27
Ruarus et al. [41]	2018	Percutaneous	17

Complications

Several studies examing cumulative morbidity and mortality rates of IRE. The morbidity range from 24% to 36% and the average peri-procedure mortality rate of 0% to 2% respectively [29,30].

The most severe complications are, vessel thrombosis, bleeding or acute pancreatitis GI-related complaints are pain, diarrhea, vomiting or nausea and delayed gastric emptying.

Recent data from a meta-analysis that evaluate morbidity and mortality for treating LAPC showed that major complication rates were approximately 17% [31].

Table 2 summarized the IRE complications.

Table 2: IRE's complications.

- Pancreatitis
- Biliary obstruction
- Portal vein thrombosis
- Bleeding
- Intestinal Perforations
- Fistula formation
- Abscess formation
- Post-procedural pneumonia

Clinical response of IRE-follow-up

Tumor response remains a difficult-to-measure endpoint; tumor size alone does not fully encompass tumor response, because initially an increase in tumor volume can be detected due to reactive edema, with a progressive decrease thereafter [32]. For this reason, a preferable method of evaluation of tumor response is the combination of tumor size after 2 months together with functional parameters such as tumor marker CA 19-9 Level and alterations in development of vascular and biliary imaging [33].

Martin et al. [34] recommended a triple-phased CT in the plain, arterial and venous phases within 1 month to assess the patency of local structures.

Conclusion

IRE offers in well selected LAPC patients an alternative efficacious treatment when combined with neo-adjuvant and post IRE systemic chemotherapy. Several retrospective trials and case studies have been confirmed overall survival benefit compared to systemic chemotherapy alone.

Furthermore electro chemotherapy or electro immunotherapy using the synergy between IRE and the other two options represents a new challenge for LAPC and opens a ray of hope in the future management of pancreatic cancer.

Declarations

Conflicts of interest: Not applicable.

Sources of support for the work: Not applicable.

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