

Review

Systematic review of irreversible electroporation in the treatment of advanced pancreatic cancer



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Abstract

Background: Irreversible electroporation (IRE) is a novel procedure to combat pancreatic cancer, whereby high voltage pulses are delivered, resulting in cell death. This represents an ideal alternative to other thermal treatment modalities, as there is no overriding heat effect, therefore reducing the risk of injury to vessels and ducts.

Methods: Multiple databases were searched to January 2014. Primary outcome measures were survival and associated morbidity. 41 articles were initially identified; of these 4 studies met the inclusion criteria, yielding 74 patients in total.

Results: 94.5% of patients had locally advanced tumours, the remainder had metastatic disease. Treated tumour size ranged from 1 to 7 cm. IRE approach included open (70.3%), laparoscopic (2.7%) and percutaneous (27%); ultrasound-guided 30%, CT-guided 70%) Morbidity ranged from 0 to 33%; due to the high number of simultaneous procedures performed (resection/bypass) it was difficult to ascertain IRE-related complications. However no significant bleeding occurred when IRE-alone was performed. Survival statistics suggest a prognostic benefit. Reported survival included: 6 month survival of 40% ($n = 5$) and 70% ($n = 14$); PFS and OS 14 and 20 months respectively ($n = 54$). Results of most interest showed a significant survival benefit in matched IRE vs non-IRE groups (PFS 14 vs 6 mths; $p = 0.01$, OS 20 vs 11 mths; $p = 0.03$).

Conclusion: Initial evidence suggests IRE incurs a prognostic benefit with minimal morbidity. More high quality research is required to determine the role IRE may play in the multi-modal management of pancreatic cancers.

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Keywords: Irreversible electroporation; Pancreatic cancer

Introduction

Pancreatic cancer remains one of the most challenging malignancies to treat due to its late presentation, aggressive nature and resistance to most currently available treatments. As a result prognosis is dismal, with 1 and 5 year survival rates being 18% and 3.5% respectively. It represents the fifth most common cause of cancer death in the UK, with approximately 8000 cases per year.¹ The location of the pancreas means patients are often asymptomatic until the disease presents at an advanced stage, at which point curative resection is not possible due to either distant metastases or involvement of local vascular structures, such as the

portal vein, coeliac trunk and superior mesenteric vessels.² At presentation only 20% of patients are suitable for surgery.³

In the palliative setting combination chemotherapy regimens have been developed to improve survival. This includes the FOLFIRINOX/gemcitabine combination which demonstrated marginally improved survival,⁴ and more recently the promising phase 3 study of Abraxane (nab-paclitaxel) plus gemcitabine demonstrating significantly improved OS, PFS and response rate.⁵ Patients can also receive adjuvant chemotherapy post-resection to combat the risk of recurrence. However despite many well-designed RCT's describing aggressive chemotherapy (ESPAC)⁶ and/or radiotherapy⁷ combined with surgical resection, survival rates have remained relatively unchanged with postoperative 5 year survival of 10–20%.

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Neoadjuvant chemotherapy for borderline resectable locally advanced tumours also has a role, with evidence suggesting this can offer the potential for cure by inducing resectability in 30–40%.⁸

An alternative method of providing symptomatic relief, survival benefit, and potentially downsizing tumours to facilitate resection involves a number of ablative techniques. This includes radiofrequency ablation (RFA) and microwave ablation (MWA). These modalities demonstrate promising results, however due to the highly vascular nature of the pancreas, inadvertent thermal injury to adjacent vessels can result in significant bleeding. Furthermore thermal injury to the pancreatic and bile duct can result in fistulae or bile leaks respectively.

Irreversible electroporation (IRE) is a relatively novel procedure which represents a potentially ideal solution for the ablative treatment of pancreatic tumours as no thermal tissue damage occurs, thus avoiding vessel or duct injury.⁹ This technique involves the delivery of a high voltage current through electrodes placed into the tumour, either under radiological guidance, via laparoscopy or by an open surgical approach. This method results in the creation of pores in the phospholipid bilayer, and the cell membrane damage disrupts intra-cellular homeostasis, ultimately causing apoptotic cell death, whilst sparing surrounding structures such as vessels, ducts (biliary and pancreatic) and connective tissue.^{9–11} This review concentrates on current evidence regarding the clinical applicability of IRE in the management of pancreatic tumours, examining efficacy, safety and survival.

Methods

Search strategy

Multiple databases were searched up to January 27th 2014, including Medline, Embase, Pubmed, Cochrane library and Google Scholar. Search terms based on MeSH key words included pancreatic cancer/carcinoma/neoplasm and irreversible electroporation. The literature was searched and data extracted independently by the first author (JM), and any inconsistencies discussed with a second author (SW).

Criteria for inclusion/exclusion

Studies included were any retrospective or prospective case series or reports. The main aim of this review is to examine the safety and efficacy of IRE, therefore the types of outcome measurements concentrated on survival and associated morbidity. Studies were also included to observe details regarding patient selection and the IRE procedure itself. Given the above criteria a number of conference abstracts were excluded; however given the paucity of evidence on the subject, these will be discussed briefly in a later section of this review. Other reasons for exclusion included; animal or *in vitro* studies; studies not representing

primary research (review article or letter to editor etc.); and any studies representing duplication of publications by the same institution.

Results

The search strategy initially yielded 33 citations. After review of titles and abstracts 27 studies were excluded with reasons as documented in Fig. 1. Two studies were excluded after full text review, leaving a total of 4 included studies.

Study characteristics

Table 1 demonstrates basic characteristics of the treatment groups.^{12–15} Of the 4 studies included, 3 were case series and 1 was a case report, amounting to a total of 74 patients who underwent IRE. Most studies treated patients with locally advanced disease (96%), however there were instances of IRE being performed in those with distant metastases (4%); it is notable that these patients all failed to respond to chemotherapy, therefore IRE was being used as a “salvage” therapy. Mansson et al. did not disclose tumour location; however of the remaining studies 60.9% were in the head of pancreas, and 39.1% in the body or tail. The sizes of tumours treated were similar, with median sizes of 3–4 cm diameter; the smallest and largest tumour treated was 1 cm and 7 cm respectively.

IRE procedure details

Table 2 details information regarding the timing and technique of the procedure. The time from diagnosis to IRE was significantly different when comparing the two larger studies ranging from 1 to 50 months. Martin et al. are the only authors to utilise IRE whilst simultaneously performing surgery. In another 19 patients, during initial exploratory surgery the degree of arterial encasement was much less severe than anticipated, so much so that resection

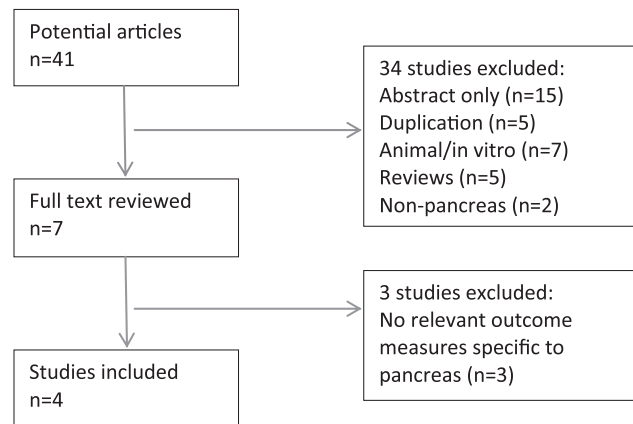


Figure 1. Flowchart demonstrating search strategy process.

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