Irreversible electroporation for the treatment of liver and pancreatic cancer

Spanish full text

Introduction: Irreversible electroporation (IRE) is a non-thermal ablative method that is based on the application of short high voltage and low frequency electric fields to create nanoscale pores, resulting in the permeabilization of the cell membrane. Due to the mostly non-thermal effect, it would allow the ablation of pancreatic and liver tumours that are localised close to major blood vessels or other sensitive's structures such as nerves or bile ducts, maintaining them intact.

Objectives: to analyse the safety, effectiveness, considerations for use, and the economic, organisational, social, ethical, or legal aspects arising in relation to the use of irreversible electroporation for the treatment of pancreatic and liver cancer.

Methods: A systematic literature search was conducted in the main medical databases, including Medline, Embase, Centre for Research and Dissemination (CRD), Web of Science up until January 2019. The selection of articles was made according to previously established inclusion/exclusion criteria. The main features and results of the studies that were included were summarised in evidence tables. A synthesis of the evidence was carried out using the GRADE system. In order to evaluate the bias risk of the studies, specific tools were used depending on the type of study. The quality of evidence was evaluated using the GRADE system. Study selection, data extraction and evaluation of evidence were performed independently by two members of the authoring team.

Results: The systematic literature search retrieved 15 observational studies that met eligibility criteria, eight for pancreatic cancer and seven for liver cancer. No randomized controlled trials were found.

One of the included studies for pancreatic cancer was a non-randomized controlled trial that included 21 patients receiving the intervention. The 32 patients of the control group received some type of non-curative surgery. The remaining seven prospective single-arm observational studies enrolled 226 patients treated with IRE. According to the only comparative study, the median overall survival of patients after IRE did not differ significantly between the treatment and the control group (10.03 versus 9.3 months; p=0.053). The median survival after IRE, ranged from 4.3 to 12 months in four of the included single-arm trials. One study accounted for a survival of 22.6 months. The median overall survival after diagnosis varied from 12.5 months to 17.5 months. Regarding safe-ty, none of the studies reported deaths during the intervention. In total, 44 out of 226 treated patients (19.5%) experienced major adverse events although at least 16 were not considered procedure related by the authors. The overall procedure related mortality (grade V adverse events) was 1.6% (4/247 patients) among all studies. The frequency of grade III or IV IRE-procedure related complications was 10.6% (range 0% - 44%).

For liver cancer, seven single arm studies were included, which enrolled 151 patients. The mean overall survival after IRE in the only study with data to calculate it was 37.92 months (95% CI 30.28, 45.57). None of the studies reported intervention specific deaths (during the intervention). The frequency of major adverse events was 8.70% (12/138), varying this frequency from 0% to 28.6% among included studies. Major adverse events were hematothorax, hemoperitoneum, hemorrhage and portal vein and bile duct stenosis.

Discussion: the quality of the evidence is very low for both indications. To date, no randomised controlled trials have been published and the only comparative trial that has been included for

pancreatic cancer has a small sample size and compares IRE with non-curative surgery without adjusting for previous or concurrent treatments such as chemotherapy. The included case series also have a small sample size, a short follow-up period and a highly selected population, which had previously undergone different types of treatment. Data to calculate survival, disease-free progression and other outcomes such as quality of life are not available in many of the trials, and this is an impediment to draw any conclusions regarding the potential of this technique to treat these tumours. This was especially notable for the liver, where most trials only reported local recurrences. Other limitations are the lack of standardized definitions regarding the success of ablation, the unclear classification of IRE-related complications, and the different and possible underreporting of some type of adverse event.

Conclusions: the evidence from the included studies is not consistent regarding the effectiveness of IRE in achieving complete ablation, nor is it sufficient to establish whether IRE would be effective in improving the overall survival of patients with pancreatic and liver cancer compared to standard treatment. For pancreatic cancer, only one low quality non-randomised trial met the eligibility criteria and it found no difference in mean overall survival despite comparing IRE with non-curative surgery. Data regarding liver tumours are even more limited, as no comparative trials have been identified and only one of the single arms studies provided long-term survival data. In addition, the survival outcome related to effectiveness should be survival from diagnosis rather than after IRE. However, only three studies provided this data, with results between 12.5-17.5 months, which would be in the range of those found in the latest chemotherapy trials. However, these data should be interpreted with caution in the absence of direct comparison.

The evidence is also insufficient to stablish whether IRE is safer, or at least as safe, as the standard treatment for both pancreatic cancer and liver cancer. In addition, the studies raise some concerns regarding the occurrence of serious adverse events when IRE is used for the treatment of these tumours.