

Irreversible electroporation for treating pancreatic cancer

Interventional procedures guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with

those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

This guidance replaces IPG442.

1 Recommendations

- 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating pancreatic cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
- 1.2 Further research, preferably in the form of randomised controlled trials, should assess the effect of the procedure on local tumour control, patient survival, pain control and quality of life.

2 Indications and current treatments

- 2.1 Pancreatic cancer usually causes few symptoms until the disease has reached an advanced stage, so most cases are diagnosed when curative treatment is not possible.
- 2.2 Because potentially curative surgery is rarely an option, most patients can only be offered palliative treatment to relieve their symptoms. Stenting of the bile duct and duodenum can be used to relieve obstruction caused by pancreatic cancer, and sometimes surgical bypass is needed. Other treatment options include palliative chemotherapy and radiotherapy.

3 The procedure

- 3.1 The aim of irreversible electroporation (IRE) is to destroy cancerous cells using a series of short electrical pulses using high-voltage direct current. This creates multiple holes in the cell membrane, irreversibly damaging the cells' homeostatic mechanisms and leading to cell death.
- 3.2 In pancreatic cancer, IRE is usually done to increase survival in people with locally advanced disease, or to treat resection margins to increase the success of curative surgical resection.
- 3.3 The procedure is done with the patient under general anaesthesia. A neuromuscular blocking agent is essential to prevent uncontrolled severe muscle contractions caused by the electric current. Several electrode needles (typically 3 to 5) are introduced percutaneously (or by open surgical or laparoscopic approaches), and inserted in and adjacent to the tumour using image guidance. A series of very short electrical pulses is delivered over several minutes to destroy the tumour. The electrodes may be repositioned under imaging guidance to extend the zone of electroporation until the entire tumour and an appropriate margin have been destroyed.
- 3.4 To minimise the risk of arrhythmia, cardiac synchronisation is used to time delivery of the electrical pulse within the refractory period of the heart cycle.

4 Efficacy

This section describes efficacy outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the [interventional procedure overview](#).

- 4.1 In a registry of 200 patients with locally advanced (stage III) pancreatic adenocarcinoma (LAPC) treated by irreversible electroporation (IRE; n=50 for IRE plus resection for margin enhancement and n=150 for IRE alone), the median overall survival from the date of diagnosis was 28.3 months (range 9.2 to 85.0 months) for the resection plus IRE group (n=50) and 23.2 months (range 4.9

to 76.1 months) for the IRE alone group (n=150). The median overall survival from the day of IRE treatment for the resection plus IRE group was 23.0 months (range 8.3 to 36.3 months) and for the IRE alone group was 18.0 months (range 4.9 to 55.4 months). The median overall progression-free survival for all patients was 12.4. In a case series of 50 patients with LAPC (T4 lesions) treated by IRE for primary treatment (n=29) or margin extension (n=24), the median overall survival for all patients was 12.03 months (95% confidence interval [CI] 7.71 to 23.12). For the primary treatment group it was 7.71 months (95% CI 6.03 to 12.0 months) and overall survival was not reached in the margin-extension group (p=0.01, log rank). In a case series of 21 patients with unresectable pancreatic carcinoma without metastatic disease (TNM stage III) treated by IRE, the median survival after treatment was 10.2 months compared with 9.3 months in a matched cohort (hazard ratio=0.54, p=0.053). A propensity matched case control study compared IRE plus chemotherapy or radiotherapy (n=54) with chemotherapy or radiotherapy alone (n=85). Some patients in the IRE group also had resection at the same time as the IRE procedure (19/54 patients). There are some inconsistencies between the data in the main text, the figure, and the abstract in this paper. In the text, the authors reported that local progression-free survival in the IRE group was 14.0 months compared with 6.0 months in the comparison group, p=0.01; distant progression-free survival was 15.0 months compared with 9.0 months, p=0.02; and median overall survival was 20 months compared with 11 months, p=0.03. The figure in this paper suggests median OS in the IRE group was 17 months. The survival curves for the 2 groups overlap at 20 months. The patients who had resection with simultaneous IRE (19/54) did not have statistically significantly improved survival compared with IRE alone (35/54; 23.1 months compared with 17.2 months, p=0.1).

- 4.2 In the registry of 200 patients with LAPC (TNM stage III) treated by IRE plus resection for margin enhancement (n=50) or IRE alone (n=150), recurrence (defined as persistent viable tumour assessed using dynamic imaging and compared with pre-IRE scanning or tissue diagnosis) was reported in 29% (58/200) of patients. The most common site of disease recurrence was the liver (n=34), followed by lymph nodes (n=11) and the peritoneum (n=7). Local recurrence after IRE success (defined as new low density lesions of 1 cm in the IRE region even without symptoms) was reported in 6 patients. In a case series of 50 patients with LAPC (T4 lesions) treated by IRE for primary treatment (n=29) or margin extension (n=24), overall recurrence was 58% after a median follow-up of

8.69 months (range 0.26 to 16.26 months). Distant recurrence was 47% at a median of 9.20 months (95% CI 6.66 to 16.98) and local recurrence was 11% at a median of 8.60 months (95% CI 5.51 to not reached). Neither local nor distant recurrence differed statistically significantly between the primary treatment group ($p=0.500$, log rank) and the margin-extension group ($p=0.361$, log rank). In the case series of 25 patients with LAPC treated by percutaneous computed tomographic-guided IRE, after a median follow-up of 12 months, median event-free survival after IRE was 8 months (95% CI 4 months to 12 months).

- 4.3 In a case series of 21 patients with unresectable LAPC (TNM stage III) treated by IRE, quality of life was measured at each follow-up using the Karnofsky performance scale (range 0% to 100%, with 100 representing 'completely normal' life). Quality of life declined slowly until about 8 weeks before death, when there was a sharp decline.
- 4.4 The specialist advisers listed key efficacy outcomes as overall and relapse-free patient survival, local tumour control, and tumour response (complete or partial).

5 Safety

This section describes safety outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the [interventional procedure overview](#).

- 5.1 In a systematic review of innovative ablative therapies for locally advanced pancreatic cancer (LAPC) including 141 patients (from 4 studies) treated by irreversible electroporation (IRE), overall mortality rate was 3% (3/92) in 3 studies using IRE. Two of these deaths were in patients treated by an open approach and 1 was in a patient treated by a percutaneous approach. The IRE-related mortality rate was 2% (2/87) in patients treated by an open approach. Death within 90 days (median 26 days, range 8 to 42 days) after an IRE procedure was reported in 11% (6/50) of patients in a case series of 50 patients with LAPC (T4 lesions) treated by IRE for primary treatment ($n=29$) or margin extension ($n=24$). Five of these deaths were in the primary treatment group ($n=29$) and 1 was in the margin-extension group ($n=24$).

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- 5.2 In the systematic review of 141 patients, 48% (44/92) of patients reported complications. Of these, 51% (41/81) were in patients treated by an open approach and 27% (3/11) were in patients treated by a percutaneous approach. Overall, 13% (5/38) of complications were related to an IRE procedure (open 15% [4/27]; percutaneous 9% [1/11]). Morbidity related to IRE mainly consisted of duodenal leakage (in patients with transduodenal needle placement or stent removal), pancreatic leakage, bile leakage and progression of portal vein thrombosis.
- 5.3 Pancreatic complications (including pancreatic leakage, pancreatitis and pancreatic failure) were reported in 4% (2/50) of patients in the IRE plus resection group (n=50) and none in the IRE alone group (n=150) at 90-day follow-up in a registry of 200 patients with stage 3 LAPC treated by IRE. Pancreatic fistula (treated with a stoma bag and antibiotics) in 1 patient and peripancreatic abscess (treated with percutaneous drainage and antibiotics) in 1 patient were reported in a case series of 21 patients with unresectable pancreatic cancer treated by IRE.
- 5.4 Liver complications (including ascites, biliary stricture, liver dysfunction and failure) were reported in 14% (7/50) of patients in the IRE plus resection group (n=50) and 9% (13/150) of patients in the IRE alone group (n=150) at 90-day follow-up in the registry of 200 patients. Biliary peritonitis, cholangitis and liver abscess (needing revision surgery and antibiotics) were reported in 1 patient in the case series of 21 patients. Duodenal and bile duct necrosis (needing trans-hepatic drain insertion) and haemorrhage (needing transfusion) were reported in 1 patient in the case series of 50 patients. Bile duct obstruction and biliary stent obstruction after IRE treatment were reported as the most common reasons for readmission in another case series (conference abstract) of 50 patients with LAPC treated by IRE. Bile leakage was reported in 3 patients in a case series of 48 patients with borderline resectable pancreatic cancer or LAPC treated by IRE. Liver insufficiency was reported in 4 patients in a case series of 65 patients with LAPC treated by IRE.
- 5.5 Severe complications including bowel perforation (abscess formation and perforation of the duodenum and transverse colon close to the stent) and bleeding from a pancreatic branch of the superior mesenteric artery (due to pseudo-aneurysm) leading to death were reported after IRE treatment in a case report of 1 patient with pancreatic cancer who had a metallic stent in the common

bile duct. Duodenal leakage (from transduodenal IRE needle placement) was reported in 1 patient in 1 study included in a systematic review of 74 patients with LAPC treated by IRE. Fistula and abscess in the abdominal wall (treated with drainage and antibiotics) was reported in 1 patient in the case series of 21 patients. Delayed gastric emptying (needing total parenteral nutrition and percutaneous endoscopic gastrostomy tube insertion) in 4 patients, upper gastrointestinal bleeding (needing transfusion and medical management) in 3 patients, duodenal cutaneous fistula in 1 patient and perforated gastric ulcer (needing drain placement) in 1 patient were reported in the case series of 50 patients. Ileus was reported in 5 patients in the case series of 65 patients treated with IRE. Small bowel leakage (grade 2) was reported in 1 patient in the case series of 48 patients. Other gastrointestinal complications (including anorexia, dehydration, gastritis, heartburn, nausea, vomiting) were reported in 16% (8/50) of patients in the IRE plus resection group (n=50) and 25% (38/150) of patients in the IRE alone group (n=150) at 90-day follow-up in the registry of 200 patients.

- 5.6 Vascular complications (including deep vein thrombosis, pseudo-aneurysm, hepatic arterial thrombosis, non-occlusive superior mesenteric vein/portal vein thrombosis) were reported in 8% (4/50) of patients in the IRE plus resection group (n=50) and 5% (7/150) of patients in the IRE alone group (n=150) at 90-day follow-up in the registry of 200 patients. Intraoperative haemorrhage (needing transfusion) and angiogram embolisation of the gastroduodenal artery leading to multi-organ failure was reported in 1 patient in the case series of 50 patients. Disseminated intravascular coagulopathy (leading to death 7 days after IRE because of intracranial haemorrhage) was reported in 1 patient in a case series of 8 patients with borderline resectable PC or LAPC treated by IRE. Hepatic artery graft failure was reported in 1 patient in the case series of 48 patients. Partial splenic infarction (needing no treatment) in 1 patient was reported during percutaneous IRE ablation in a case series of 15 patients with LAPC or metastatic disease treated by IRE.
- 5.7 Cardiovascular complications (including atrial fibrillation) were reported in 4% (2/50) of patients in the IRE plus resection group (n=50) at 90-day follow-up in the registry of 200 patients. Arrhythmia developed in 2 patients during IRE procedures in the case series of 8 patients.

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- 5.8 Pneumothorax (n=1) and pulmonary problems (n=3) were reported in the studies included in the systematic review of 74 patients.
- 5.9 Sepsis needing reoperation was reported in 1 patient in the case series (conference abstract) of 50 patients treated by IRE. The patient died postoperatively. Infection was reported in 6% (3/50) of patients in the IRE plus resection group (n=50) and 9% (13/150) of patients in the IRE alone group (n=150) at 90-day follow-up in the registry of 200 patients. Deep surgical site infection (needing drain placement) was reported in 3 patients in the case series of 50 patients treated by IRE.
- 5.10 In the registry of 200 patients other complications included urinary tract problems (in 7 patients), renal failure (in 1 patient), wound problems (in 6 patients), neurological changes (in 4 patients), haematological events (in 2 patients) and other adverse events (in 23 patients). The case series of 48 patients also reported complications such as hepatojejunostomy stricture (in 1 patient), pain (in 1 patient) and postoperative bleeding (in 2 patients).
- 5.11 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse events: vessel occlusion (permanent or transient and due to oedema post-IRE causing compression of an involved superior mesenteric vein). They considered that the following were theoretical adverse events: damage to major arteries or veins, gastrointestinal tract injury (for example, stomach, duodenum, small or large bowel).

6 Committee comments

- 6.1 Most of the evidence was from open or laparoscopic irreversible electroporation procedures. There is increasing use of the percutaneous approach.
- 6.2 The UK IRE registry is being developed, and NICE encourages data submission when the register becomes available.

7 Further information

- 7.1 Patient commentary was sought but none was received. However, the committee noted the views and experiences of patients (submitted during consultation) in their discussions.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

