NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of irreversible electroporation for treating pancreatic cancer

Irreversible electroporation is a procedure used to treat pancreatic cancer. Special needles are inserted into the tumour in the pancreas. Short electrical pulses of a high voltage current are then used to kill cancer cells.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in July 2016.

Procedure name

- Irreversible electroporation for treating pancreatic cancer

Specialist societies

- British Society of Interventional Radiology
- Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland
- British Society of Gastrointestinal and Abdominal Radiology.

Description

Indications and current treatment

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.

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.

What the procedure involves

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.

In pancreatic cancer, IRE is usually done to increase survival in locally advanced disease, or to treat resection margins to increase the success of curative surgical resection.

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. 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.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to irreversible electroporation for treating pancreatic cancer. The following databases were searched, covering the period from their start to March 2016: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases.

Trial registries and the internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with pancreatic cancer.
Intervention/test	Irreversible electroporation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 609 patients from 2 systematic reviews[1-2], 5 case series[3-7], 2 case reports[8-9] and 3 conference abstracts[10-12].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on irreversible electroporation for treating pancreatic cancer

Study 1 Rombouts SJE (2015)

Details

Study type	**Systematic review**
Country	The Netherlands
Study period	Search date: inception to June 2014; Databases: PubMed, Embase and the Cochrane Library; limited to English studies.
Study population and number	The review covered 1164 patients having ablative therapy, of these n=**141** patients had irreversible electroporation (IRE) for locally advanced pancreatic cancer (LAPC) (**4 studies on irreversible electroporation were included-**3 prospective case series and 1 retrospective study).
Age and sex	not reported
Patient selection criteria	Studies on ablative therapies in patients with LAPC, reporting outcomes on one or more of the following endpoints: morbidity, mortality, quality of life, and/or survival were included. Review articles, case reports, studies with less than 5 patients, studies with only combined results for stage III-IV disease or primary-recurrent disease, conference abstracts and animal studies were excluded.
Technique	Irreversible electroporation using NanoKnife: open approach in 130 patients (3 studies) and percutaneous approach in 11 patients (1 study).
Follow-up	**range 3-20 months**
Conflict of interest/source of funding	Authors declared no conflicts of interest.

Analysis

Follow-up issues: varied follow-up.

Study design issues: This systematic review included all innovative ablative techniques for locally advanced pancreatic cancer (including IRE, radiofrequency ablation, stereotactic body radiation therapy, high intensity focused ultrasound, iodine-125, iodine-125-cryodsurgery, photodynamic therapy, and microwave ablation). The systematic review was done according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Critical appraisal of studies done according to the Centre for Evidence-Based Medicine (CEBM) levels of evidence. Risk of bias was assessed using a standardised list of 10 potential risk of bias, based on the Oxford CEBM critical skills appraisal programme appraisal sheets for randomised controlled trials and observational studies. Studies were heterogeneous (different techniques, approaches, types of probes, timing, dose and number of sessions were applied) and therefore meta-analysis was not done. All studies included were non-randomised studies.

3 studies on IRE (Martin 2012, 2013, Philips 2012) were published by the same authors and might have an overlap.

Study population issues: majority of the studies defined LAPC according to the American Joint Committee on Cancer (AJCC) staging system, including stage II-III disease.

Other issues: studies with other ablative therapies for the treatment of locally advanced pancreatic cancer (radiofrequency ablation [7 studies], stereotactic body radiation therapy [16 studies], high intensity focused ultrasound [5 studies], iodine-125 [2 studies], iodine 125-cryosurgery [2 studies], photodynamic therapy [1 study] and microwave ablation [1 study]) have been excluded as they are outside the scope of this review.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **141**

	No of patients	**Number undergoing resection**	**Median survival (months)**	**Pain relief (median pain score)^**	**Quality of life**
Open approach					
Martin 2013	54	35 (19/54)*	20.2	NR	NR
Philips 2013	49	NR	NR	NR	NR
Martin 2012	27	30 (8/27)*	NR	VAS reduced from 5-3	NR
Total	130	33 (27/81)	20.2	NA	NA
Percutaneous approach					
Narayanan 2012	11+	18 (2/11)	Median OS: not reached 6 month OS:70 %	NR	NR
Total (open+ percutaneous)	141	32 (29/92)	NA	NA	NA

*patients planned for IRE appeared resectable during laparotomy and received IRE for margin attenuation followed by pancreaticoduodenectomy (PD);

+one patient with current disease after previous PD.

^ an established 10 point daily pain scale was used both preoperatively and at 90-day postoperative visit.

Safety

	No of patients	**Overall complications**	**IRE-related complication**	**Overall mortality**	**IRE-related mortality**
Open approach					
Martin 2012	54	59 (32/54)	NR	2 (1/54)	NR
Philips	49	NR	NR	NR	2 (1/49)
Martin	27	33 (9/27)	15 (4/27)	4 (1/27)	4 (1/27)
Total	130	51(41/81)	15 (4/27)	2 (2/81)	3 (2/76)
Percutaneous approach					
Narayanan	11+	27 (3/11)	9 (1/11)	9 (1/11)	0
Total (open+ percutaneous)	141	48 (44/92)	13 (5/38)	3 (3/92)	2 (2/87)

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.

Patients with metastatic disease showed no improvement and died after IRE procedure from progressive disease.

Abbreviations used: IRE, irreversible electroporation; NR, not reported; NA, not available; OS, overall survival; VAS, visual analogue scale.

Study 2 Moir J (2014)

Details

Study type	**Systematic review**
Country	UK
Study period	Search date: inception to January 2014; Databases searched: Medline, Embase, PubMed, Cochrane Library and Google scholar.
Study population and number	n=**74** patients with locally advanced pancreatic cancer (96%) and distant metastases (4%) (**4 studies on irreversible electroporation:** 2 prospective case series, 1 prospective propensity matched case control study and 1 case report). Tumour location: 60.9% in head of pancreas, 39.1% in body or tail of pancreas. Tumour size: median 3-4cm (range 1-7cm) Time from diagnosis to treatment: different between studies and ranged from 1-50 months.
Age and sex	not reported
Patient selection criteria	Studies included were any prospective or retrospective case series examining efficacy and safety of IRE, reporting details on patient selection and outcomes on survival and associated morbidity and included patients who failed to respond to chemotherapy. Conference abstracts, review articles, letters and animal studies or in vitro studies, duplicate publications were excluded.
Technique	Irreversible electroporation using NanoKnife as a salvage therapy. Open approach in 52 patients, laparoscopic approach in 2 patients (in Martin 2013), and percutaneous approach in other 3 studies (n=20). Monopolar probes were used mainly (in 49 patients) and bipolar probes in 11 patients. 1 study (Narayanan 2012) did not specify the number of monopolar probes used. In 1 study (Martin 2013), simultaneous treatments were performed in 48 patients (resections-Whipple's procedure/ partial pancreatectomy [n=19] and palliative bypass procedures –jujenostomy ([n=29]).
Follow-up	**Ranged from 3-6 months (3 months: Martin 2013, Bagla 2012; 6 months: Narayanan 2012, Mansson 2014).**
Conflict of interest/source of funding	Authors declared no conflicts of interest.

Analysis

Follow-up issues: varied follow-up.

Study design issues: Review included case series that were heterogeneous (range of approaches and simultaneous treatments were used, duration and type of chemoradiation therapies were not standardised and variable) and were considered as having a high risk of bias; primary outcome measures were survival and associated morbidity. One author independently screened and extracted data and any inconsistencies were resolved after discussion with another author. Methodological quality of studies was not reported. Statistical pooling of data was not performed because of the heterogeneity of studies.

In the prospective matched case control study included in the systematic review, patients were not randomised and the type and duration of prior chemotherapy or radiotherapy was not standardised and highly variable. 40% (19/54) of patients in the IRE group also had curative resection compared with none of the control group. The IRE group also had a total of 60 additional surgical procedures.

Study population issues: 95% of the patients had locally advanced pancreatic cancer. 1 study (Mansson 2014) did not report tumour location.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **74**

	No of patients	Survival (months)
Martin 2013	54	***prospective propensity matched case control study: IRE and CT and /or RT(n=54) vs CT and/or RT alone (n=85)^:*** local PFS: 14 vs 6 months (p=0.01) Distant PFS: 15 vs 9 months (p=0.02), median OS 17.0 vs 11 months (p=0.03)
Narayanan 2012	14	6 month OS: 70% (95% CI 35-93), significantly longer OS in localised vs metastatic group (p=0.02). Median EFS-6.7 months (95% CI 0.7-12.7)
Mansson 2014	5	6 months OS : 40% Mortality: 0 at 30 days
Bagla 2012	1	liver metastasis at 3 months, post-RFA treatment, MRI revealed no progression or recurrence

^patients who had resection with simultaneous IRE did not have significantly improved survival compared to IRE alone (23.1 months vs IRE alone 17.2 months, p=0.1).

92% (63/68) of the patients in 2 studies (Martin 2013, Narayanan 2012) received chemotherapy and/or radiotherapy.

Safety

	No of patients	Complications** % (n)
Martin 2013	54	33 (9/54) duodenal leak from IRE needle: 1 wound infection: 7 bile leak: 2 pancreatic leak: 2 DVT: 2 portal vein thrombosis/graft failure: 4 pulmonary: 3 bleeding: 3 ascites: 3 ileus: 2
Narayanan 2012	14	14 (2/14) 1 pancreatitis* 1 pneumothorax (recovered)
Mansson 2014	5	20 (1/5) subclinical pancreatitis*
Bagla 2012	1	0

*resolved with conservative management.

**it is difficult to determine the number of IRE-related complications because of the high number of simultaneous procedures (resection/bypass) performed.

Authors note that no significant bleeding occurred when IRE alone was performed.

Abbreviations used: CI, confidence interval; CT, chemotherapy; DVT, deep vein thrombosis; EFS, event free survival; IRE, irreversible electroporation; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; RFA, radiofrequency ablation.

Study 3 Martin RCG (2015)

Details

Study type	**Case series** (Soft Tissue Ablation (STAR) Registry)
Country	US
Recruitment period	2010 to 2014
Study population and number	n=**200** patients with radiographic stage III locally advanced pancreatic cancer (LAPC) Tumour location: Head 54% (108/200); Body/neck 46% (92/200) Tumour size: median 2.8 cm (range 2.5-3cm) Time from diagnosis to electroporation: range 3-32 months
Age and sex	Median 62 years; 50% (101/200) male.
Patient selection criteria	Patients with confirmed LAPC (defined at the time of diagnosis to include greater than 180 degrees encasement of either superior mesenteric artery (SMA) or coeliac artery or un-reconstructable venous involvement without any evidence of metastatic disease [lesions>1cm in size]) and not borderline resectable tumours, receiving chemotherapy, chemoradiation or both for 4-6 weeks and on restaging free of metastatic disease/progression were included for IRE treatment.
Technique	Irreversible electroporation with NanoKnife using open-supine midline incision approach. **LAPC resection and IRE (for margin enhancement): n=50,** commonly in patients with pancreatic neck/body tumours and those who had coeliac axis invasion (60%) or SMA abutment (66%). Pancreatic resection with IRE for margin accentuation was performed at surgeon's discretion only in patients with microscopic positive margins. IRE is first delivered before complete dissection. A median of 2 monopolar probes are placed under ultrasound guidance to achieve adequate margin augmentation. IRE delivery time was a maximum of 58 minutes. **LAPC with IRE alone (In Situ): n=150,** commonly with pancreatic head tumours and with long segment venous involvement (27%); these patients received IRE alone without resection. A median of 4 monopolar probes are placed and adjusted to cover the entire tumour and the involved vasculature. IRE delivery time was a median of 35 minutes and a maximum of 125 minutes. After treatment completion, imaging was performed at 12 weeks and 3 month intervals to confirm ablation success.
Follow-up	**median 29 months**
Conflict of interest/source of funding	Authors declare no conflicts of interest. Partial support of the STAR registry has come from an educational grant from Angiodynamics.

Analysis

Study design issues: large study in a small number of centres, data on patients treated with IRE were analysed from a multi-centre prospective institutional review board-approved soft tissue ablation registry. Imaging radiologists were not blinded to treatment and made the interpretation of recurrence as defined by response evaluation criteria for solid tumours (RECIST). Early postoperative scan was done to evaluate complications. There was variability in post-IRE imaging protocols between centres. Complications were graded from 1-5:grade1 required supportive care or oral medications; grade 2 required IV medication or parenteral nutrition; grade 3 required ICU admission or non-invasive procedures; grade 4 required major reoperation or involved chronic disability; grade 5 Postoperative death within 90 days of intervention.

There might be an overlap with other studies published by the same authors.

Study population issues: 50% patients had hypertension, 20% had diabetes, and a small percentage of patients had cardiac (10%) or pulmonary disease (2%) history. The degree of comorbidities was also demonstrated by a low Charleston comorbidity index (median of 4), a low frailty index (median of 2) and low short nutritional assessment (median of 2). Other operations (hepaticojejunostomy, cholecystectomy, gastrojejunostomy, coeliac plexus block) were also done in some patients in each group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **200**

Operative and ablative outcomes

	Resection and IRE (margin) (n=50)	**IRE [in situ] (n=150)**
Success of IRE delivery %	100	100
Complete ablation* %	100	99 (148/150)
Length of stay (days)	7	6

*defined as the ability to deliver planned therapy and at 3 months to have no evidence of residual tumour on imaging.

Recurrence and progression-free survival (median 29 months follow-up)**

	Time or incidence of recurrence
No of patients with recurrence % (n)	29% (58/200)^
Overall PFS (median)	12.4 months
IRE failure at 3 months (n)	3 (IRE in situ)
Local recurrence after IRE success* (n)	6
Local PFS (median)	10.7 months
Time to distant PFS (median)	16.8 months
Overall survival from date of diagnosis(median) (n=200)	**24.9 months**
IRE +resection group (n=50)	28.3 months (range 9.2-85.0)
IRE in situ only (n=150)	23.2 months (range 4.9-76.1)
Overall survival from date of IRE treatment (median)	
IRE +resection group (n=50)	23 months (range 8.3-36.3)
IRE in situ only (n=150)	18 months (range 4.9-55.4)

^The liver was the most common site of disease recurrence (n=34), followed by lymph nodes (n=11) and peritoneum (n=7).

** Recurrence defined as persistent viable tumour as defined by dynamic imaging in comparison with pre-IRE scanning or tissue diagnosis.

*development of new low density lesions of 1cm in the IRE region even in the absence of symptoms.

Safety

	Resection and IRE (margin) % (n=50)	**IRE [in situ] % (n=150)**
Adverse events	40 (20/50) 49 complications.	36 (54/150) 100 complications
Pancreatic related complications (90 days)	2 (pancreatic leak, pancreatitis)	0
Mortality (90 days)	0	2 (3/150)^

Type of complications (scored according to 5 point scale) n

	Resection and IRE (margin) % (n=50)	**IRE [in situ] % (n=150)**
Cardiovascular (includes atrial fibrillation) (grade 1)	4 (2/50)	0
Gastrointestinal (included anorexia, dehydration, gastritis, heartburn, nausea, vomiting) (grade 1-4)	16 (8/50)	25 (38/150)
Haematologic (grade 1-2)	1	1
Infection (grade 1-4)	6 (3/50)	9 (15/150)
Liver (included ascites, biliary stricture, liver dysfunction and failure) (grade 1-4)	14 (7/50)	9 (13/150)
Neuro (mental status changes) (grade 1-3)	6 (3/50)	1
Pancreatic (included pancreatic leak, pancreatitis and pancreatic failure) (grade 1-2)	4 (2/50)	0
Pulmonary (grade 1-4)	12 (6/50)	1
Renal (grade 3)	0	1
Urinary (grade 1-3)	6 (3/50)	3 (4/150)
Vascular (included DVT, pseudo-aneurysm, hepatic arterial thrombosis, nonocclusive superior mesenteric vein/portal vein thrombosis) (grade 1-5)	8 (4/50)	5 (7/150)
Wound (grade 1-4)	6 (3/50)	3 (3/150)
Other (grade 1-4)	14 (7/50)	9 (16/150)

^1 patient had duodenal ulcer and presented with gastrointestinal bleed 55 days after IRE, bleeding was from ulcerated tumour and could not be surgically corrected.

1 patient with portal vein thrombosis/SMV occlusion before IRE presented with liver failure 45 days after IRE and failed to respond to therapy.

1 patient died 50 days after IRE from pulmonary embolism.

Abbreviations used: CT, chemotherapy; DVT, deep vein thrombosis; EFS, event free survival; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; RFA, radiofrequency ablation; SMV, superior mesenteric vein.

Study 4 Martin RCG (2013)-included in Moir J 2014 systematic review

Details

Study type	**Prospective propensity matched case control study**
Country	USA
Recruitment period	2009 to 2012
Study population and number	n=**54 patients** with radiographic stage III locally advanced pancreatic cancer (LAPC) **propensity matched to 85 matched stage III patients** treated with standard therapy (defined as chemotherapy and radiation therapy alone). Tumour location: IRE group: head 65% (35/54), body/neck 35% (19/54); Standard therapy group: head 68% (58/85), body/neck 32% (27/85) Tumour size: median 2.8 cm (range 2.6 to 3.2 cm) Time from diagnosis to electroporation: median 5.1 months
Age and sex	Median 61 years; 43% (23/54) male.
Patient selection criteria	Patients with confirmed LAPC (defined as per the 7th edition of the American Joint Committee on Cancer staging system for pancreatic cancer); described as arterial encasement of either superior mesenteric artery (SMA) or coeliac artery or both and not borderline resectable tumours, receiving chemotherapy, chemoradiation or both for 4-6 weeks and on restaging free of metastatic disease/progression were included for IRE treatment.
Technique	Irreversible electroporation with NanoKnife using open-supine midline incision approach in 52 (laparoscopic in 2). **LAPC resection and IRE (for margin accentuation): n=19,** commonly in patients with pancreatic neck/body tumours. Pancreatic resection with IRE for margin accentuation was performed at surgeon's discretion only in patients with microscopic positive margins. IRE is first delivered before complete dissection. **LAPC with IRE alone (In Situ): n=35,** commonly with pancreatic head tumours and with long segment venous involvement (27%); these patients received IRE alone without resection. A median of 4 probes are placed (mainly monopolar) in a caudal to cranial fashion. IRE delivery time was a median of 16 minutes (range 2-189 minutes) 90% (49/54) patients had pre-IRE chemotherapy alone or chemoradiation therapy for a median duration 5 months. 73% (40/54) patients underwent post- IRE chemotherapy or chemoradiation. After treatment completion, imaging was performed at 2 weeks and 3 month intervals to confirm ablation success.
Follow-up	**median 29 months**
Conflict of interest/source of funding	Authors declare no conflicts of interest.

Analysis

Study design issues: patients were not randomised but were matched on a 1.5:1 basis by propensity scoring after 4 months with scores based on patient age, size of tumor, performance status, cardiac comorbidities, and pulmonary comorbidities. Comparisons were made between the matched groups in terms of patient demographics, short-term outcomes, and overall and disease-free survival. The type and duration of prior chemotherapy/radiotherapy was not standardised and highly variable. 40% (19/54) patients in the IRE group also had curative resection compared with none of the control group. IRE group also had a total of 60 additional pancreatic and other surgical procedures. Complications were graded according to a 5 point scale.

There might be an overlap with other studies published by the same authors.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **54 versus 85**

Procedure outcomes

IRE success* % (n)	98% (53/54)
Ablation success^ % (n)	94% (51/54)
Total IRE delivery time, mean (range)	16 minutes (2-189 minutes)
Total procedure time	180 minutes (40-500)
Length of stay, days (range)	7 days (1-58)

*defined as the ability to deliver at least 90 pulses at appropriate voltage

^defined as the ability to deliver the therapy and at 3 months to have no evidence of residual tumour.

Recurrence (defined as per RECIST criteria with either persistent viable tumour, persistent hypermetabolic activity)

After a median follow-up of 12 months, 48% (26/54) patients have had local recurrences.

Survival outcomes

	IRE and CT and /or RT(n=54)	**CT and/or RT alone (n=85)**	**p value**
Local PFS, months	14	6	0.01
Distant PFS, months	15	9	0.02
Median OS, months	17	11	0.03

Subgroup analysis

Patients who had resection with simultaneous IRE did not have significantly improved survival compared to IRE alone (23.1 months vs IRE alone 17.2 months, p=0.1).

Safety

Complications**

Adverse events	**IRE and CT and /or RT (n=54)**	**CT and/or RT alone (n=85)**
Death during 90 day follow-up	1	0
Duodenal leak (1 after duodenotomy and another from needle puncture sites)	2	0
Bile leak	2	0
Pancreatic leak	2	0
Ileus	2	0
Portal vein thrombosis/ graft failure	4	8
Deep vein thrombosis	2	9
Ascites	3	8
Wound infection	7	6
Pulmonary	3	9
Bleeding	3	8
Diarrhoea	3	25
Liver insufficiency	1	19
Hematologic	4	20
Dehydration/failure to thrive/nausea	8	45
Renal failure	0	8
Other	10	35

IRE group: 32 patients had 67 complications.

**it is difficult to determine the number of IRE-related complications because of the high number of simultaneous procedures (resection/bypass) performed. Authors note that no significant bleeding occurred when IRE alone was performed.

Abbreviations used: CT, chemotherapy; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; RECIST, Response Evaluation Criteria In Solid Tumors; RFA, radiofrequency ablation.

Study 5 Dunki-Jacobs EM (2014)

Details

Study type	**Case series** (registry)
Country	US
Recruitment period	2009-12
Study population and number	n=**65** patients with locally advanced pancreatic cancer (LAPC) undergoing IRE (17 with local recurrence versus 48 with no recurrence) Tumour location: head (68%), body/neck (32%) Tumour size: median 3.5 cm Time from diagnosis to electroporation: recurrence group (median 2.1 months); no recurrence group (median 6.1 months)
Age and sex	Median 66.5 years; 59% (31/50) male.
Patient selection criteria	Patients with LAPC (defined as per the American Joint Committee on Cancer staging system for pancreatic cancer-described as arterial encasement of either the coeliac axis or the superior mesenteric artery or both) were included. Patients with borderline resectable lesions were excluded.
Technique	Irreversible electroporation (IRE) with resection (to treat positive margins) or IRE alone (via NanoKnife) was done using either an open surgical technique (n=53) or a percutaneous approach (n=12) under general anaesthesia. Averages of 4 IRE probes (mainly monopolar) were placed into the central or lateral aspect of the tumour with average spacing of 1.8 cm under ultrasound guidance. CT imaging done to evaluate needle position and measure inter-probe distance. Electric pulses are delivered between the needles placed around the tumour. Pancreatic operations were performed including Whipple's procedure (n=8), pancreatectomy (n=16), hepatojejunostomy (n=12), gastrojejunostomy (n=23), partial gastrectomy (n=3), coeliac plexus block (n=10) and other procedures (n=30). Follow-up imaging done at discharge, within 2 weeks of IRE treatment and then at 3 month intervals.
Follow-up	**median 23 months**
Conflict of interest/source of funding	One author received an unrestricted education grant from Angiodynamics and all others had no conflicts of interest.

Analysis

Study design issues: prospective data from a soft tissue ablation registry was used to evaluate effectiveness of tumour ablation in terms of local failure or recurrence (LFR) and disease-free survival (DFS).

Study compared patients who had local electroporation failure or recurrence against those who did not develop recurrence after treatment. Complications up to 90 days were graded according to 5 point scale 1-5: grade1 required supportive care or oral medications; grade 2 required IV medication or parenteral nutrition; grade 3 required ICU admission or non-invasive procedures; grade 4 required major reoperation or involved chronic disability; grade 5 postoperative death within 90 days of intervention.

Local failure or electroporation failure was defined as the ability to bracket the entire tumour with needles and deliver at least 90 pulses to the target lesions and without 3 month imaging confirmation of ablation success. Local recurrence was defined as above, but with 3 month confirmation and then subsequent recurrence of the target lesion.

Study population issues: in the 2 groups compared, patients had similar characteristics in regard to location, lesion size, comorbidity index and prior chemotherapy or radiotherapy and adjuvant therapy after IRE.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **65 patients**

Operative and ablative outcomes

	Local recurrence n=17^	No recurren n=48
Success of IRE delivery, %	100	100
Local recurrence (median follow-up 12 months) n	17*	0

*7 at 3 months and 10 at 6 months.

Analysis of predictors of local recurrence after IRE treatment

	Local recurrence n=17^	No recurrence n=48	p value
Change in resistance Mean (SE)	16.2 (1.17)	28.2 (0.67)	0.02
Slope of resistance Mean (SE)	-0.16 (0.03)	-0.27 (0.02)	0.01
Local DFS Median (months)	5.5	12.6	0.03

^ At 3, 6 or 9 months after treatment.

Only change in resistance was the single factor in predicting local recurrence and failure on multivariate analysis (RR 2.5, 95% CI 1.4 to 5.6, p=0.002).

Neither mean change in tumour tissue resistance nor the slope of the resistance curve significantly predicted overall DFS.

Safety

Complications (77 adverse events were reported)

Type of complication	local recurrence n=17	Grade	no recurrence n=48	Grade
Ileus	3	2	2	2
Bile leak	0	-	2	3
Portal vein thrombosis/graft failure	2	3-4	3	2,5
Deep vein thrombosis	3	1-2	2	2
Pulmonary	4	2,3	3	2,3
Renal failure	2	1-3	0	-
Ascites	3	1-3	2	1,3
Wound infection	2	1,2	3	1-2
Dehydration/nausea	4	1-4	4	1-3
Bleeding	1	1	2	2,4
Liver insufficiency	3	2,3	1	2
Pancreatic leak	0	-	0	-
Other	16	1-4	10	1-3

Abbreviations used: CI, confidence interval; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; DFS, disease-free survival; RR, relative risk; SE, standard error.

Study 6 Kwon D (2014)

Details

Study type	**Case series** (registry)
Country	US
Recruitment period	2010-13
Study population and number	n=**48** patients with borderline resectable or locally advanced pancreatic cancer (LAPC) Tumour location: 31 in head (20 borderline and 11 locally advanced); 17 in neck/body (5 borderline and 12 locally advanced). Tumour size: median 2.7cm Time from diagnosis to electroporation: 6 months (range 4-13months)
Age and sex	Median 61 years; 54% (26/48) male.
Patient selection criteria	Patients with borderline resectable disease or locally advanced pancreatic cancer (LAPC), initial treatment with chemotherapy, chemoradiation or both as per institutions protocol for 4-6 weeks, no metastatic disease and primary tumour size not more than 3.5cm on restaging evaluation were considered as potential candidates for IRE therapy.
Technique	Patients underwent intraoperative irreversible electroporation (IRE) for margin accentuation during pancreatic resection (pancreatectomy) of either borderline resectable or LAPC at surgeon's discretion. Resection and IRE margin accentuation done only in cases where suspected positive margins (R1 resection) and IRE not performed if there was going to be residual gross disease (R2 resection). IRE was delivered before complete transection. 2-3 monopolar probes were placed under ultrasound guidance, usually after pancreatic neck has been transected but before dissection of SMV/SMA retroperitoneal tissue. In locally advanced tumours, probes were readjusted to ablate circumferential areas of the SMA or coeliac axis where an R1 resection might persist. In borderline cases, probes were placed in parallel fashion to the posterolateral aspect of the proximal 3-4 cm of the SMA. Pancreatic operations performed include pancreatoduodenectomy (58%), subtotal pancreatectomy (35%), distal pancreatectomy (4%), total pancreatectomy (4%), gastrojejunostomy (n=3), partial gastrectomy (n=3), jujenostomy tube (n=35) and coeliac axis resection (n=10).
Follow-up	**median 24 months**
Conflict of interest/source of funding	One author was a paid consultant for Angiodynamics and all others had no conflicts of interest. Partial support of the soft tissue ablation registry has come from an educational grant from Angiodynamics.

Analysis

Follow-up issues: After treatment, patients were evaluated with follow-up imaging at discharge, within 2 weeks, and every 3-4 months.

Study design issues: prospective data from a soft tissue ablation registry was used to evaluate local recurrence, margin status and survival. Borderline resectable disease was defined as one or more of the radiographic findings: tumour abutment [<180º of the circumference of the vessel] of the superior mesenteric artery [SMA] or coeliac axis; tumour abutment or encasement [>180º of the circumference of the vessel] of a short segment of the hepatic artery, short segment occlusion of the superior mesenteric vein (SMV), portal vein, or SMV-PV confluence amenable to vascular restriction and reconstruction. LAPC was defined as >1800 encasement of either SMA, coeliac artery, or both without evidence of any type of suspicious metastatic disease.

Ablation success and recurrence were defined according to response evaluation criteria in solid tumours (RECIST) criteria. Complications up to 90 days were scored based on a previously published 5 point scale graded from 1-5:grade1 required supportive care or oral medications; grade 2 required IV medication or parenteral nutrition; grade 3 required ICU admission or non-invasive procedures; grade 4 required major reoperation or involved chronic disability; grade 5 postoperative death within 90 days of intervention.

Study population issues: 69% (33/48) of patients had some form of induction therapy (chemoradiation, chemotherapy) for 4-6 weeks before resection and half of them had second-line treatment. More than half of the patients resumed both chemotherapy and /or adjuvant radiotherapy within a median time of 2.4 months.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **48 patients**

Operative and ablative outcomes

Success of IRE delivery % (n)	100
Complete ablation % (n)	100
Total procedure time (minutes, median)	180 (130-740)
IRE delivery time (minutes, median)	12 (2-90)

Recurrence and survival outcomes at 24 months follow-up

	% (n)
Overall recurrence	58 (28/48)
Liver**	25 (7/28)
Lung**	14 (4/28)
Peritoneum^	36 (10/28)
Peritoneal lymph nodes	14 (4/28)
Local retroperitoneal pancreas recurrence at the SMA or common hepatic artery*	11 (3/28)
Time to local recurrence (months)	10.7 (range 3-30)
Overall survival (median, months)	22.4 (95% CI 17.9-24.9)
Progression-free survival (median, months)	11 (95% CI 3-10)

*Local recurrence was defined as development of new, low density lesions in resection area, or near the vasculature, even in absence of symptoms.

**Distant metastasis was defined as low density lesions in liver or lungs.

^Peritoneal recurrence was defined as nodules in the peritoneum or omentum or presence of ascites.

Safety

	% (n)
Complications within 90 days	38 (18/48)
Number of adverse events	44^
Type of complications	**n**
Deaths	**0**
Haematologic (grade 1-3)	4
Ileus (grade1-2)	2
Bile leak (grade 3)	3
Portal vein thrombosis (grade 1, 3)	2
Hepatic artery graft failure (grade 2)	1
Nonocclusive SMA thrombus (grade 2)	1
Deep vein thrombosis (grade 2)	2
Pulmonary (grade 3,4)	2
Small bowel leak (grade 2)	1
Pancreatic leak	2
Renal failure (grade 3)	1
Ascites (grade 3)	2
Wound infection (grade 1,2, 3)	3
Pain (grade 1)	1
Delayed gastric emptying (grade 1)	2
Gastritis (grade 3,2)	2
Postoperative bleeding (needing reoperation, grade 4,3)	2
Hepaticojejunostomy stricture (grade 3)	1
Cardiac (grade 1)	2
Other events* (grade 1-4)	8

* Other events include urinary retention, seizure, port infection, and metal status change.

^ 5 were IRE device related complications.

Abbreviations used: CI, confidence interval; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; SMA, superior mesenteric artery.

Study 7 Kluger MD (2016)

Details

Study type	**Case series**
Country	US
Recruitment period	2012-14
Study population and number	n=**50** patients with locally advanced pancreatic cancer (LAPC) (T4 lesions) 94% (47/50) patients had adenocarcinoma Tumour location: Head, 60% (32/50); Neck/body, 40% (21/50) Tumour size: median 3.0 cm (1.7-5.0) Time from diagnosis to electroporation: median 8.4 months (range 0-25 months)
Age and sex	Median 66.5 years; 59% (31/50) male.
Patient selection criteria	Patients with pancreatic cancer, with at least 180 degree encasement of the coeliac and superior mesentery artery (T4 disease according to the American Joint Committee on Cancer) on imaging and received chemo or radiotherapy for biopsy confirmed adenocarcinoma were included. Patients with Eastern Cooperative Oncology Group (ECOG) classification of 3 or higher, atrial fibrillation, and M1 or distant N1 disease based on imaging, and those with borderline resectable disease were excluded.
Technique	Irreversible electroporation using NanoKnife. Neoadjuvant chemotherapy was received by 46 patients and radiation therapy was administered to 39 patients before IRE procedure. Patients underwent **IRE (53 procedures) for primary treatment (n=29) or margin extension (n=24)** In the margin extension group, 63% (15/24) had Whipple's procedure, 8% (2/24) had modified Appleby procedure, and 29% (7/24) had distal pancreatectomy. Venous reconstruction was needed for 52% (12/24) of the patients. 4 patients had IRE for primary control with associated procedures (2 had gastrojejunectomies and 2 underwent double-bypass operations). A median number of 4 probes were used for primary treatment and 2.5 for margin extension group.
Follow-up	**median 8.69 months (range 0.26 -16.26 months)**
Conflict of interest/source of funding	Authors declare no conflicts of interest.

Analysis

Study design issues: prospective cohort study in a single centre, primary outcomes was perioperative morbidity and mortality at 90 days (graded according to Clavien–Dindo grading system) and secondary outcomes were survival and recurrence (assessed using Kaplan-Meier methodology). Overall survival calculated from the date of IRE to last follow-up visit or death. Recurrence-free survival was calculated from the date of IRE to imaging evidence of recurrence. Recurrence was defined as radiographic appearance of a new local or distant lesion. Some patients were evaluated after chemoradiotherapy at other institutions or for local control of recurrent disease, there by affecting the regimens and number of cycles received.

Study population issues: The 2 groups were similar with regard to pre-treatment chemotherapy and radiotherapy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **50 patients (53 procedures)**

Recurrence and survival analyses

	All	**Primary treatment n=29**	**Margin extension n=24**
Median OS time	12.03 (95% CI 7.71-23.12)	7.71 (95% CI 6.03-12.0)	not reached (p=0.01, log rank)
Overall recurrence %	58%		
Distant recurrence	47% at median 9.2 months (95% CI 6.66-16.98 months)*		
Local recurrence	11% at median 8.6 months (95% CI 5.51-not reached)*		

*neither local nor distant recurrence differed significantly between the primary treatment group (p=0.50, log rank) and the margin extension group (p=0.361, log rank).

Safety

Complications (Clavien–Dindo grade 1-5) % (n)^

	All % (n)	**Primary treatment % (n=29)**	**Margin extension % (n=24)**
complications within 30 days	**52 (26/50)**		
Grade 1	10 (5/50)		
Grade 2	16 (8/50)*		
Grade 3-4 (p=0.566)	17 (9/50)	14 (4/29)	21 (5/24)
Grade 5 (p=0.397)	8 (4/50)	10 (3/29)	4 (1/24)
complications within 30-90 days	**6 (3/50)**		
Grade 1or 2	0	0	0
Grade 3-4 (p=0.341)	2 (1/50)	3 (1/29)	0
Grade 5 (p=0.190)	4 (2/50)	7 (2/29)	0
Re-admittance rates	17 (9/50)	21 (6/29)	12.5 (3/24)
Mortality within 90 days (median 26 days, range 8-42)	11 (6/50)	(5/29)	(1/24)

*One of these patients had a duodenal ulceration/perforation associated with IRE and was managed medically with an intraoperatively inserted drain.

^ 44% of these complications were directly related with IRE and mainly occurred in the primary group.

16 major complications (grade 3-5) occurred include:

Grade 5	
1 IRE	upper GI bleed (needed transfusion) and duodenal cutaneous fistula
1 IRE	intraoperative haemorrhage (needed transfusion), angiogram embolisation of gastroduodenal artery, multiorgan failure
1 IRE+Whipple	early postoperative anaemia (needed transfusion), cardiopulmonary arrest (not readmitted)
1 IRE	deep surgical site infection (drain placed),reoperation for fluid collection, stent for stenosis, intubation for respiratory failure, multiorgan failure (not readmitted)
1 IRE	duodenal bile duct necrosis, (hepatic drain insertion), haemorrhage (needed transfusion), operative re-exploration, comfort care in support of advanced directives (not readmitted
1 IRE	no details presented (admitted to another hospital)
Grade 3	
1 IRE	delayed gastric emptying (needing TPN), ascites (drain placement)
1 IRE	upper GI bleeding (needing transfusion and medical management)
1 IRE	perforated gastric ulcer (needed drain placement)- not readmitted
1 IRE	Bile duct stricture (needed stent placement)
I IRE+bypass	upper GI bleed (transfusion and medical management)
1 Whipple +IRE	delayed gastric emptying (needed TPN, PEG insertion), portal vein thrombosis (needed systemic anticoagulation)
1 Appleby +IRE	deep surgical site infection (needed drain placement)
1 distal+IRE	deep surgical site infection (needed drain placement)
1 Whipple +IRE	Delayed gastric emptying (needed PEG insertion)
1 IRE+ gastrojejunostomy	Delayed gastric emptying (needed TPN), ascites (needed drain placement)
1-Whipple +IRE	Wound dehiscence (reoperated)

Abbreviations used: CI, confidence interval; GI, gastrointestinal; IRE, irreversible electroporation; IQR, interquartile range; LAPC, locally advanced pancreatic cancer; OS, overall survival; RT, radiotherapy.

Study 8 Lambert L (2016)

Details

Study type	**Non-randomised comparative study**
Country	Czech Republic
Recruitment period	2012-14
Study population and number	n=**21** patients with unresectable pancreatic carcinoma without metastatic disease (TNM stage III) **matched cohort: n=32** Tumour location: Head, 17; body, 3; tail,1 Tumour size: mean 39±10mm (range 21-65mm) Time from diagnosis to electroporation: 9 weeks (range 2-63 weeks) Charlson Comorbidity index: mean 3 (range 2-6)
Age and sex	Mean 68.2 years; 48% (10/21) male.
Patient selection criteria	Patients with unresectable pancreatic carcinoma stage III (without metastatic disease), tumour size <6.5cm in axial plane, good performance status (Karnofsky performance status >80) were included.
Technique	Irreversible electroporation using NanoKnife (open 19, percutaneous 2) with 2 electrodes that were repositioned several times 1.5-2 cm apart to affect the whole tumour mass. Open IRE was combined with gastroenteroanastomosis (GEA), GEA and cholecystectomy, hepatojejunoanastomosis (HJA), and cholecystectomy in 4 patients. 5 patients received neoadjuvant chemotherapy and 7 patients were treated with chemotherapy after IRE. Patients were followed up at regular intervals.
Follow-up	**2 months**
Conflict of interest/source of funding	Authors declared no conflicts of interest. Study was supported by IGA NT/13263-4 and the ministry of health.

Analysis

Study design issues: prospective study in a single centre, small sample size, CT performed 1-2 months after treatment, the quality of life was assessed on a Karnofsky scale from 0 (death) to 100 (normal life) at each clinical visit. The study patients were compared with matched controls (n=32, propensity score matching based on age and size of tumour on a 1:5:1 basis) with locally advanced pancreatic carcinoma stage III, that had undergone surgery or percutaneous biopsy only with or without chemotherapy.

Study population issues: patient group was heterogeneous in terms of tumour size, location, chemotherapy received and the time from diagnosis to treatment. Only 33% of them received chemotherapy after IRE and none received surgical resection.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **21 patients**

Survival (Kaplan-Meier analysis) and quality of life

	IRE (n=21)	**Matched cohort (n=32)**	**p value**
Median survival months (n=21)	10.2	9.3	p=0.53 HR=0.54
Median survival in patients with complications (n=5), months	7.1	13.6	p=0.24 HR=2.3
Quality of life after IRE (Karnofsky performance status >70)* %	81% (range 65% to 98%)	74% (14% to 88%)	p=0.76
Disease progression (on CT imaging at 1-2 months)	38% (8/21)		

*sharp decline in quality of life occurred approximately 8 weeks before death.

CT imaging at 1-2 months showed changes in 19 patients (peripancreatic oedema=9, pancreatic necrosis=6, peripancreatic or supramesocolic inflammatory infiltrate =4, enlarged lymph nodes=4, carcinosis with ascites=4, extension of tumour to the liver =1).

Safety

Adverse events at 30 days

	IRE % (n=21)
Mortality	0
Complications*	**24 (5/21)** 1: bleeding (revision surgery) 1: peripancreatic abscess (drainage and antibiotics) 1: fistula and abscess in the abdominal wall (drainage and antibiotics) 1: pancreatic fistula (stoma bag, antibiotics) 1: biliary peritonitis, cholangitis, liver abscess (revision, antibiotics)

*the average hospital stay was prolonged in these patients from 10 to 34 days (p=0.26).

Abbreviations used: HR, hazard ratio; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.

Study 9 Mansson C (2014)

Details

Study type	**Case report**
Country	Sweden
Recruitment period	not reported
Study population and number	n=**1** patient with a 4 cm large LAPC in the pancreatic head, with a self-expanding metallic stent in the common bile duct due to a biliary obstruction.
Age and sex	72-year female.
Patient selection criteria	Patient was considered unresectable due to tumour encasement of the superior mesenteric artery and vein, and deemed unsuitable for other types of chemotherapy after she developed diarrhoea with palliative treatment (gemcitabine) and was excluded for IRE treatment due to the presence of a metallic stent.
Technique	5 months after diagnosis, patient was accepted at a private clinic and underwent irreversible electroporation (IRE) using NanoKnife in the region of pancreatic head.
Follow-up	**3 months**
Conflict of interest/source of funding	None declared/ received no specific grants from any funding agencies.

Analysis

Study design issues: this is a case report of a single patient. Patient consent was obtained to publish before her death.

Other issues: The manufacturers of this device (Angiodynamics) have stated that IRE in the vicinity of metallic parts is a contraindication but the procedure was performed in a private clinic. Authors state that 'it is not clear whether the IRE treatment alone or the presence of a metallic stent was the cause of the bowel perforation and pseudo-aneurysm formation. However, the sites of injuries are suggestive, so IRE in those with metallic stents should still be considered as an absolute contraindication and the removal of stents close to ablation zone should be mandatory until further knowledge is gained'.

Key safety findings

Safety

Number of patients analysed: **1**

Patient mortality due to the presence of a metallic stent leading to severe complications including perforation of the duodenum and transverse colon and bleeding from a branch of the superior mesenteric artery

After IRE treatment, the diarrhoea continued and after 1 month patient suffered from abdominal pain. CT revealed a small abscess but no signs of peritonitis and patient was treated with antibiotics and discharged.

8 weeks after treatment, patient had extensive diarrhoea and signs of infection. Patient was operated with a laparoscopic loop sigmoidostomy, and 2 days after surgery she went into hypovolemic shock with distended abdomen. An emergency laparotomy was performed and surgeons found no haemorrhage but an extensive well organised abscess formation behind the transverse colon and both the transverse colon and the duodenum were perforated in close vicinity to the stent. A right hemicolectomy was done and an attempt was made to suture the duodenum with several drains left in the abdomen. Due to the damage to the duodenal wall, the suture did not hold and she received both a percutaneous gastrostomy and percutaneous transhepatic drain of the common bile duct postoperatively.

17 days after the laparotomy, patient started to bleed and an angiography revealed a pseudo-aneurysm on a pancreatic branch of the superior mesenteric artery. The bleeding was treated with a coil, however, 3 days later the patient died from a further haemorrhage.

Abbreviations used: IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.

Study 10 Ierardi AM (2014)

Details

Study type	**Case report**
Country	Italy
Recruitment period	not reported
Study population and number	n=**1** patient with a large LAPC localised in the body/tail of the pancreas
Age and sex	79 year male.
Patient selection criteria	Patient presented with 3 month history of abdominal pain, 10 kg weight loss, anorexia and asthenia. CT imaging revealed a lesion in the body/tail of the pancreas obstructing the pancreatic duct. Splenic artery was patent but entirely trapped in the tumour. Patient was judged unsuitable for surgery because of vascular involvement and after failure of treating with ethanol injection IRE was given.
Technique	Patient underwent percutaneous irreversible electroporation (IRE) using NanoKnife. 5 monopolar probes were placed under ultrasound guidance at a distance of 1.8cm from each other and ablation was done in 2 sessions. CT imaging was done to evaluate needle position and inter-probe distance.
Follow-up	**1 month**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Study design issues: this is a case report of a single patient.

Other issues: Authors state that 'the cause could not be established with certainty and 'vascular lock' may be a valid hypothesis'.

Key safety findings

Safety
Number of patients analysed: **1** **Electric pulse induced 'Vascular lock' causing transient asymptomatic splenic perfusion defects** After IRE treatment, complete remission of pain was reported, with a score of 0/10. CT scan revealed there was vasoconstriction of the splenic artery associated with the presence of multiple small spleen defects that were not present on the CT scan performed before treatment. Contrast-enhanced ultrasound performed the day after did not reveal ischaemic damages of the spleen and showed normal patency of splenic artery. 1 month after treatment, CT scan showed an absence of enhancement within the ablation zone and the splenic artery remained patent and spleen was homogenous with no defects or infarcts.
Abbreviations used: IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.

Study 11 Bagla (2013)

Details

Study type	**Case series** (conference abstract)
Country	US
Recruitment period	not reported
Study population and number	n=**15** patients with locally advanced pancreatic cancer and those with metastatic disease 11 at stage 3, 4 at stage 4. **Tumour location:** body 5, neck 1, tail 3 head 6. Eastern Cooperative Oncology Group performance status: average 0.73 (range 0-3).
Age and sex	Range 49-84; 9/15 male.
Patient selection criteria	not reported
Technique	Patient underwent percutaneous irreversible electroporation (IRE) using NanoKnife (20 ablations performed). 13 of them received previous therapy (10 chemotherapy, 3 chemoradiation).
Follow-up	**12 months**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Information was only available from a conference abstract, which gave limited details of study design.

Other issues: Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.

Key safety findings

Safety
Number of patients analysed: **15** No mortalities occurred at 30 days. No arrhythmias, infection, pancreatic fistula or bowel injury occurred. Intraoperative transient hypertension occurred with all 20 treatments. One treatment was complicated by partial splenic infarction and one mesenteric haematoma; both needed no treatment.
Abbreviations used: IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.

Study 12 Hoskovec (2015)

Details

Study type	**Case series (**conference abstract)
Country	Czech Republic
Recruitment period	2012
Study population and number	n=**50** patients with locally advanced inoperable pancreatic cancer
Age and sex	not reported
Patient selection criteria	not reported
Technique	Patients underwent percutaneous irreversible electroporation (IRE) using NanoKnife during laparotomy or under CT guidance. Half of them received chemotherapy before IRE. All patients received adjuvant chemotherapy.
Follow-up	**not reported**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Information was only available from a conference abstract, which gave limited details of study design.

Other issues: Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.

Key safety findings

Safety
Number of patients analysed: **50** Complications occurred in 9 patients. Two of them were reoperated due to biliary peritonitis in one case and sepsis in the other. Two patients died in postoperative course. Bile duct obstruction or biliary stent obstruction was the most common reason for readmission.
Abbreviations used: IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.

Study 13 Yilmaz S (2013)

Details

Study type	**Case series** (conference abstract)
Country	Turkey
Recruitment period	2012
Study population and number	n=**8** patients with locally advanced inoperable pancreatic cancer All patients had invasions of the mesenteric and/or coeliac vessels and 2 patients also had oligometastases in the lung or liver.
Age and sex	range 32-72 years; 37% (3/8) male
Patient selection criteria	not reported
Technique	Patients underwent ultrasound and CT-guided IRE ablation under general anaesthesia. In all patients, 3-8 electrodes were percutaneously inserted under image guidance and up to 3000-V and 50-A current was applied to the tumour tissue. After surgery patients were observed in ICU for 2 days.
Follow-up	**not reported**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Information was only available from a conference abstract, which gave limited details of study design.

Other issues: Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.

Key safety findings

Safety
Number of patients analysed: **8** During IRE procedures, 7 patients developed hypertension, 2 developed arrhythmia, and 1 developed atrial fibrillation respectively. Follow-up CT one day after the procedure showed patient coeliac/mesenteric vessels. There was no evidence of intestinal perforation, but transient abdominal/pleural fluid was noted in 3 patients. 1 patient developed disseminated intravascular coagulopathy and died 7 days after IRE because of cranial haemorrhage.
Abbreviations used: IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.

Study 14 Scheffer HJ (2016)

Details

Study type	**Case series**
Country	
Recruitment period	2014 to 2015
Study population and number	n=**25** patients with histologically proved locally advanced pancreatic cancer The median largest tumour diameter was 4.0 cm (range, 3.3-5.0 cm).
Age and sex	Median age 61 years (range 41 to 78 years); 60% (13/12) female
Patient selection criteria	Patients with histologically proved locally advanced pancreatic cancer were included. Patients with a metallic biliary Wallstent, epilepsy, or ventricular arrhythmias were excluded.
Technique	Patients had percutaneous computed tomographic-guided IRE under general anaesthesia. In all patients, 3-8 electrodes were percutaneously inserted under image guidance and up to 3000-V and 50-A current was applied to the tumour tissue. After surgery patients were observed in ICU for 2 days.
Follow-up	**Median 12 months (range 7-16 months)**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: prospective study, Kaplan-Meier estimates were used to investigate time to local progression, event-free survival, and OS. Safety was assessed on the basis of adverse events, which were graded according to the Common Terminology Criteria for Adverse Events. Pain perception and QOL were evaluated by using specific questionnaires.

Key safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 25
Survival outcomes (median follow-up of 12 months)
<table>
<tr><td>Median event-free survival after IRE</td><td>8 months (95% confidence interval [CI]: 4 months, 12 months)</td></tr>
<tr><td>Median time to local progression after IRE</td><td>12 months (95% CI: 8 months, 16 months)</td></tr>
<tr><td>Median overall survival from IRE</td><td>11 months)95%CI: 9 months, 13 months)</td></tr>
<tr><td>Median overall survival from diagnosis</td><td>17 months (95% CI: 10 months, 24 months)</td></tr>
</table></td><td>There were 12 minor complications (grade I or II) and 11 major complications (nine grade III, two grade IV) in 10 patients.
There were no deaths within 90 days after IRE.</td></tr>
<tr><td colspan="2">Abbreviations used: IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer.</td></tr>
</table>

Efficacy

Overall survival and progression-free survival

In a registry of 200 patients with locally advanced (stage III) pancreatic adenocarcinoma (LAPC) treated by irreversible electroporation (IRE; n=50 IRE plus resection for margin enhancement and n=150 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 months[3].

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] 7.71to 23.12). For the primary treatment group it was 7.71 months (95% CI 6.03 to12.0 months) and was not reached in the margin extension group p=0.01, log rank)[7].

In a case series of 48 patients with LAPC and borderline resectable pancreatic tumours treated by pancreatectomy with margin accentuation with IRE, at a median follow-up of 24 months the median overall survival was 22.4 months (95% CI 17.9 to 24.9) and progression-free survival was 11 months (95% CI 3 to 10)[6].

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). The presence of complications reduced survival (7.1 compared with 13.6 months, hazard ratio=2.3, p=0.24)[8].

In a case series of 25 patients with locally advanced pancreatic cancer treated by percutaneous computed tomographic-guided IRE, after a median follow-up of 12 months (range 7 to 16 months), the median overall survival was 11 months from IRE (95% CI: 9 months to 13 months) and 17 months from diagnosis (95% CI: 10 months to 24 months). The median time to local progression after IRE was 12 months (95% CI: 8 months to 16 months)[14].

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 overall survival 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].

In a systematic review of 74 patients (from 4 studies) LAPC treated by IRE, at 6 months, overall survival was 40% in a study of 5 patients and 70% (95% CI35 to 93) in another study of 14 patients[2].

Disease-free survival

In a case series of 65 patients with LAPC treated by IRE, the median disease-free survival was 5.5 months in patients who had disease recurrence (n=17) compared with 12.6 months in patients with no recurrence (n=48) (p=0.03). Neither mean change in tumour tissue resistance nor the slope of the resistance curve significantly predicted overall disease-free survival[5].

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)[14].

Recurrence

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 at a median follow-up of 29 months. 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[3].

In the case series of 65 patients with LAPC treated by IRE, local recurrence was seen in 26% (17/65) of patients at 3 and 6 months after IRE. Mean change in tumour resistance during ablation (local recurrence 16.2±1.17 versus no recurrence 28.2±0.67; p=0.02) and slope of the resistance curve (-0.6±0.03 versus -0.27±0.02; p=0.01) were both significant factors in predicting local failure or recurrence on univariate analysis. Only change in resistance was the single factor in predicting local recurrence on multivariate analysis (RR 2.5, 95% CI 1.4 to 5.6, p=0.002)[5].

In the case series of 48 patients with LAPC and borderline resectable pancreatic tumours treated by pancreatectomy with margin accentuation with IRE, at a median follow-up of 24 months, 58% (28/48) developed recurrence, with majority

of them in the liver (25%[7/28]) or peritoneum (36%[10/28]). Local retroperitoneal pancreas recurrence (defined as development of new, low density lesions in resection area, or near the vasculature, even in absence of symptoms) either at the SMA or the common hepatic artery was reported in 11% (3/28) of patients. The time to local recurrence was 10.7 months (range 2-30 months)[6].

In the case series of 50 patients with T4 pancreatic cancer 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 0.26-16.26 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=0.50, log rank) and the margin extension group (p=0.361, log rank)[7].

Quality of life

In the case series of 21 patients with unresectable pancreatic carcinoma without metastatic disease (TNM stage III) treated by IRE, quality of life was measured at each follow-up using the Karnofsky scale (range 0% to 100%, with 100 representing ‘normal’ life). Quality of life declined slowly in both groups until about 8 weeks before death (when there was a sharp decline), Performance status was 81% of time after IRE compared to 74% in the control group (p=0.76) with the Karnofsky performance status of >70. Sharp decline occurred approximately 8 weeks before death[8].

Safety

Mortality

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), and was in patients treated by an open approach[1].

Death within 90 days (median 26 days, range 8-42 days) after an IRE procedure was reported in 11% (6/50) of patients in a case series of 50 patients with LAPC (T4) 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)[7].

In a registry of 200 patients with LAPC treated by IRE, 90 day mortality was reported in 2% (3/150) of patients in the IRE alone group and none in the IRE plus resection group (n=50). Deaths were caused by pulmonary embolism in 1 patient 50 days after IRE treatment; liver failure 45 days after IRE in 1 patient

with prior portal vein thrombosis/superior mesenteric vein occlusion and failed to respond to therapy; bleeding from an ulcerated tumour 55 days after IRE in 1 patient that could not be surgically corrected[3].

Morbidity

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. In all, 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[1].

Morbidity ranged from 0-33% in a systematic review of 74 patients (4 studies) treated by IRE for LAPC. Due to the high number of multiple simultaneous procedures (resections/bypass) performed it was difficult to ascertain IRE-related complications[2].

37% (74/200) of patients developed adverse events with a median grade of 2 (graded according to Clavien–Dindo grading system 1-5) after IRE treatment in the registry of 200 patients. The most common adverse event was some form of gastrointestinal problem (including anorexia, dehydration, gastritis, heartburn, nausea, vomiting)[3].

Complications within 90 days

58% (29/50) of patients developed complications within 90 days (graded according to Clavien–Dindo grading system 1-5) in the case series of 50 patients with T4 pancreatic cancer treated by IRE for primary treatment (n=29) or margin extension (n=24). 31% (16/50) of these complications were major (grade 3-5) and needed some further intervention and management[7].

38% (18/48) of patients with LAPC/borderline resectable pancreatic cancer treated by pancreatectomy with margin accentuation with IRE developed 44 complications within 90 days after IRE treatment in a case series of 48 patients. 11% (5/44) of these complications were possibly IRE-related complications[5]. 44% of these complications were directly related to IRE and mainly occurred in the primary treatment group. Grade 1 and 2 complications were reported in 5 and 8 patients at 30 days. 5 patients in each group experienced major morbidity (grade 3 or 4) within 90 days after the procedure. 5 patients in the primary group and 2 patients in the margin extension group experienced grade 5 complications. Overall 31% (9/29) were readmitted and majority were from the primary treatment group. The incidence of Clavien grade 3-5 complications did not significantly differ based on the adjustable parameters of IRE, tumour size, or primary treatment versus margin extension[6].

Pancreatic complications

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 the registry of 200 patients with stage 3 LAPC treated by IRE[3].

Pancreatitis (resolved with conservative management, n=2) and pancreatic leaks (n=2) were also reported in the studies included in the systematic review of 74 patients[2].

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[8].

Liver complications

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[3].

Biliary peritonitis, cholangitis and liver abscess were reported in 1 patient in the case series of 21 patients. Revision surgery was done and the patient was treated with antibiotics[8].

Duodenal and bile duct necrosis (needing transhepatic drain insertion) and haemorrhage (needing transfusion) were reported in 1 patient in another case series (conference abstract) of 50 patients with LAPC treated by IRE[7].

Bile duct obstruction and biliary stent obstruction after IRE treatment was reported as the most common reason for readmission in the case series (conference abstract) on 50 patients[12].

Bile leakage was reported in 3 patients in a case series of 48 patients with borderline resectable PC or LAPC treated by IRE[6].

Liver insufficiency was reported in 4 patients in the case series of 65 patients with LAPC treated by IRE[5].

Gastrointestinal complications

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[9].

Other gastrointestinal complications (including anorexia, dehydration, gastritis, heartburn, nausea, vomiting) were reported in 16% (8/50) patients in the IRE plus resection group (n=50) and 25% (38/150) patients in the IRE alone group (n=150) at 90-day follow-up in the registry of 200 patients[3].

Duodenal leakage (from transduodenal IRE needle placement) was reported in 1 patient in 1 study included in the systematic review of 74 patients with LAPC treated by IRE[2].

Fistula and abscess in the abdominal wall (treated with drainage and antibiotics) was reported in 1 patient in the case series of 21 patients[8].

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[7].

Ileus was reported in 5 patients in the case series of 65 patients treated with IRE[5].

Small bowel leakage (grade 2) was reported in 1 patient in the case series of 48 patients[6].

Vascular complications

Vascular complications (including deep vein thrombosis, pseudo-aneurysm, hepatic arterial thrombosis, nonocclusive 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[3].

Intraoperative haemorrhage (needing transfusion) and angiogram embolisation of the gastroduodenal artery leading to multiorgan failure was reported in 1 patient in the case series of 50 patients[7].

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 or LAPC treated by IRE[13].

Hepatic artery graft failure was reported in 1 patient in the case series of 48 patients treated by IRE[6].

Partial splenic infarction in 1 patient was reported during percutaneous IRE ablation in a case series of 15 patients with LAPC or metastatic disease treated by IRE. No treatment was needed[11].

Vasoconstriction of the splenic artery associated with the presence of multiple small transient asymptomatic splenic perfusion defects were seen on CT imaging after IRE treatment in a case report of 1 patient with LAPC. At 1 month follow-up, CT imaging demonstrated that the splenic artery remained patent and spleen was homogenous with no defects or infarcts[9].Anaemia (needing transfusion) was reported in 1 patient in the case series of 50 patients treated by IRE[7].

Mesenteric haematoma in 1 patient was reported during percutaneous IRE ablation in a case series of 15 patients. No treatment was needed[11].

Transient intraprocedural hypertension (attributed to the procedure) which settled during the postoperative period was reported in a case series of 15 patients [11].

Cardiac complications

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[3].

Arrhythmia developed in 2 patients during IRE procedures in a case series of 8 patients[13].

Pulmonary complications

Pneumothorax (n=1) and pulmonary problems (n=3) were reported in the studies included in the systematic review of 74 patients[2].

Infection

Sepsis needing reoperation was reported in 1 patient in a case series (conference abstract) of 50 patients treated by IRE. The patient died postoperatively[12].

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[3].

Deep surgical site infection (needing drain placement) was reported in 3 patients in the case series of 50 patients treated by IRE[7].

Other complications

The registry of 200 patients also reported other complications such as urinary tract problems (in 7 patients), renal failure (in 1), wound problems (in 6),

neurological changes (in 4), haematological events (in 2) and other adverse events (in 23)[3].

The case series of 48 patients also reported complications such as hepatojejunostomy stricture (in 1 patient), pain (in 1) and postoperative bleeding (in 2)[6].

Validity and generalisability of the studies

- There are no randomised controlled trials comparing IRE with current standard treatment. All the studies are small case series with relatively short term follow-up. There are no long-term or comparative data.
- There is some patient overlap between the studies.
- IRE has been used in locally advanced pancreatic cancer for primary control or simultaneously at the time of surgical resection of borderline resectable pancreatic tumours for margin accentuation and extension.
- Study protocols varied in terms of IRE techniques, (open or percutaneous approaches, types of probes, distance between probes and voltage), duration and chemoradiation regimens.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures
Related by indication

- Laparoscopic distal pancreatectomy. NICE interventional procedure guidance 204 (2007). Available from http://www.nice.org.uk/guidance/IPG204
- Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy. NICE interventional procedure guidance 274 (2008). Available from http://www.nice.org.uk/guidance/IPG274

- Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma. NICE interventional procedure guidance 464 (2013) Available from http://www.nice.org.uk/guidance/IPG464

Related by intervention

- Irreversible electroporation for treating pancreatic cancer. NICE interventional procedure guidance 442 (2013). Available from http://www.nice.org.uk/guidance/IPG442
- Irreversible electroporation for the treatment of liver metastases. NICE interventional procedure guidance 445 (2013). Available from http://www.nice.org.uk/guidance/IPG445
- Irreversible electroporation for the treatment of primary liver cancer. NICE interventional procedure guidance 444 (2013). Available from http://www.nice.org.uk/guidance/IPG444
- Irreversible electroporation for treating renal cancer. NICE interventional procedure guidance 443 (2013). Available from http://www.nice.org.uk/guidance/IPG443
- Irreversible electroporation for treating primary lung cancer and metastases in the lung. NICE interventional procedure guidance 441 (2013). Available from http://www.nice.org.uk/guidance/IPG441

Technology appraisals

- Guidance on the use of gemcitabine for the treatment of pancreatic cancer. NICE technology appraisal guidance 25 (2001). Available from http://www.nice.org.uk/guidance/TA25
- Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer. NICE technology appraisal guidance 360 (2015). Available from http://www.nice.org.uk/guidance/TA360

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their

individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Adviser Questionnaires for irreversible electroporation for treating pancreatic cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials

- PANFIRE - Pilot-study: Non-thermal Ablation Using Irreversible Electroporation (IRE) to Treat Locally Advanced Pancreatic Carcinoma - a Phase I Clinical Trial (NCT01939665); single group assignment; The Netherlands; n=40; primary outcome: safety, tumour response; estimated completion date: October 2016; status: currently recruiting.
- Evaluation of the Short and Intermediate Term Outcomes of Ablation of Locally Advanced Unresectable Pancreatic Cancer Using the NanoKnife Irreversible Electroporation (IRE) System - A Prospective Study (NCT02041936); single group assignment; USA; n=12; primary outcome: safety, pain, quality of life; estimated completion date: February 2018; status: currently recruiting.
- AHPBA Pancreatic Irreversible Electroporation (IRE) Registry for Pancreatic Cancer (NCT02674100) observational patient registry, cohort study; USA; n=1000; primary outcome: safety, patient selection, overall survival; estimated completion date: January 2030; status: currently recruiting.
- Phase I Study of FOLFIRINOX Electrochemotherapy in the Treatment of Pancreatic Adenocarcinoma (NCT02592395); phase I study; single group

assignment; n=24; USA; primary outcome: dose limiting toxicity; estimated completion date: October 2017; status: currently recruiting.

- Implementation of Electroporation - NanoKnife as Treatment for Advanced Pancreatic Cancer. (NCT02079623); single group assignment; n=25; Denmark; primary outcome: tumor response; completion date: 2015; status: enrolling by invitation only.
- IRE: Anti-Tumor Immunity Induced by IRE of Unresectable Pancreatic Cancer (NCT0234835); single group assignment; n=20; China; primary outcome: tumor response; estimated study completion date: January 2020; status: currently recruiting.
- Irreversible Electroporation for treatment of unresectable, locally advanced pancreatic cancer in the Leiden University Medical Center: a phase I/II study - IRE-pancreas LUMC (NTR4049); single group assignment; The Netherlands; n=15; primary outcome: safety; Recruitment status : pending.
- The assessment of efficacy and safety of Irreversible Electroporation(IRE) to treat unresectable locally advanced pancreatic cancer (JPRN-UMIN000016423); single arm non-randomised; n=6; Japan; Status: open public recruiting.

Register:

- The soft tissue ablation registry (STAR), in USA collects data on patients treated by IRE for liver, pancreas, lung, prostate and kidney tumours, as well as other soft tissue tumours. Three studies included in the overview analysed data from this registry[3-5].

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13. Yilmaz S, Ozdogan M, Kaymakci F et al. (2013) Value of irreversible electroporation in patients with inoperable pancreatic carcinoma: Experience in 8 patients. *CardioVascular and Interventional Radiology* 36: S336-.

14. Scheffer HJ, Vroomen, LG et al (2016). Ablation of Locally Advanced Pancreatic Cancer with Percutaneous Irreversible Electroporation: Results of the Phase I/II PANFIRE Study. Radiology 152835.

Appendix A: Additional papers on irreversible electroporation for treating pancreatic cancer

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Al EM, Wolfgang CL, Weiss MJ (2015) Stage III pancreatic cancer and the role of irreversible electroporation. [Review]. BMJ 350: h521-.	Review Data from 5 clinical studies were reviewed. All non-randomised prospective case series.	AEs include thrombus of the portal vein, duodenal leaks, spontaneous pneumothorax, and pancreatitis. One systematic review of194 patients cited a 19% complication rate with pancreas surgeries. 8 deaths reported: 3 patients died from metastatic growth (non-pancreatic), 1 died from thrombus of the portal vein, and 4 from unmentioned causes. In one study involving 54 patients, IRE was associated with an increase in local PFS (14-vs 6 months; *P* = 0.01), distant PFS (15-vs 9 months; *P* = 0.02), and OS (20 vs 13 months; *P* = 0.03).	Review Studies in this review are included in systematic reviews included in table 2.
Akinwande O, Ahmad SS, Van MT et al. (2015) **CT** Findings of Patients Treated with Irreversible Electroporation for Locally Advanced Pancreatic Cancer. Journal of Oncology Print 2015: 680319-.	Case series (registry) n=5 patients with LAPC treated with IRE in situ and had CT imaging before and after ablation were reviewed.	Following IRE, the postablation bed is larger than the original ablated tumour. This ablation zone may get smaller in size (due to decreased edema and hyperemia) and remains stable provided there is no recurrence. In cases of recurrent disease there is increased size of the ablation bed, mass effect, and new or worsening vascular encasement or occlusion.	CT imaging findings to assess post-ablation changes.
Bagla S, Papadouris D (2012). Percutaneous irreversible electroporation of surgically unresectable pancreatic cancer: a case report. J Vasc Interv Radiol. 23(1):142-5.	Case report n=1 A 78-year-old man with surgically unresectable stage III pancreatic adenocarcinoma was treated with IRE. Follow-Up: 3 months	Percutaneous IRE shows promise as a feasible and potentially safe method for local tumour control in patients with surgically unresectable disease.	Included in systematic review (Moir J 2014).

Bates BJ, Hellan M, Kauffman S et al. (2015) Irreversible electroporation of malignant lesions: An institution experience. Journal of Solid Tumors 5 (2): 11-17.	Case series (retrospective) n=27 patients underwent IRE during 16 laparotomies and 12 CT-guided percutaneous procedures. Anatomic locations: 9 liver, 7 pancreas, 7 pelvis, 2 retroperitoneal, 1 lung, 1 chest wall, and 1 mesentery. Different lesion types and lesion size ranged from 1 to 6cm. Follow-up: median 12.5 months.	30-day mortality was 0%. Complications included muscle weakness, gastric outlet obstruction, intragastric hematoma, pancreatic fistula, small bowel obstruction, and urinary retention. 1 patient experienced obstructive jaundice and portal vein thrombosis. 8 patients developed recurrence. IRE is safe and feasible in a variety of situations.	variety of anatomical locations, outcomes not reported separately for each location.
Belfiore MP, Ronza FM, Romano F et al. (2015) Percutaneous CT-guided irreversible electroporation followed by chemotherapy as a novel neoadjuvant protocol in locally advanced pancreatic cancer: Our preliminary experience. International Journal Of Surgery 21: Suppl-9, S34-39.	Case series n=20 patients with locally advanced pancreatic cancer (LAPC) CT-guided percutaneous IRE followed by chemotherapy bi weekly. Follow-up: mean 9 months	No major complications occurred. 2 patients died 3 and 4 months after IRE because of progressive disease. In the remaining 18 patients 6-month imaging follow-up showed a mean lesions volumetric decrease percentage of 42.89% (95% Confidence Interval: 34.90-54.88%). 3 patients underwent R0 resection. At last follow-up (mean follow-up 9 months; range 6-14), imaging showed no disease progression or post-surgical relapse in all 18 cases. The mean estimated survival was 12,950 months (95% CI: 11,570-14,332).	Larger studies included in table 2 Neoadjuvant treatment.
Gonzalez-Beicos A, Venkat S, Songrug T et al. (2015) Irreversible Electroporation of Hepatic and Pancreatic Malignancies: Radiologic-Pathologic Correlation. Techniques in Vascular & Interventional Radiology 18 (3): 176-182.	Case series n=12 tumours-3 pancreatic, 5 primary liver tumour and 4 metastatic liver tumours treated with IRE.	Complete response to IRE was 25% based on the histologic evaluation. Treatment-related vessel wall changes were noted in several cases in histologic findings, but there was no evidence of vascular luminal narrowing or obliteration. The imaging response to IRE before surgical resection usually resulted in underestimation of disease burden when compared with the histologic response.	Mix of hepatic and pancreatic tumours assessed.

Gajjar S, Yechieli R et al (2016). Outcomes Associated With a Combination of Radiation Therapy and Irreversible Electroporation for Pancreatic Cancer. International Journal of Radiation Oncology Biology Physics 96 (2S) E206.	Combined IRE and radiotherapy		No abstract
Jourabchi N, Beroukhim K, Tafti BA et al. (2014) Irreversible electroporation (NanoKnife) in cancer treatment. Gastrointestinal Intervention 3 (1): 8-18.	General review on IRE		Review of preclinical data and preliminary clinical data for a variety of tumours
Kambakamba P, Bonvini JM et al (2016). Intraoperative adverse events during irreversible electroporation-a call for caution. American Journal of Surgery 212 (4) 715-721.	Case series n=43 patients with hepato-pancreato-biliary and retroperitoneal malignancies. IRE for tumour ablation	Adverse events (n = 20, 47%) were primarily cardiac (90%, n = 18), including blood pressure elevation (77%, n = 14/18) and arrhythmia (16%, n = 7/43). All but 1 was managed medically, 1 patient with arrhythmia required termination of ablation. Bleeding and problems with the equipment occurred in 1 patient each. Multivariable analysis revealed previous cardiovascular disease and needle placement close to the celiac trunk associated with increased likelihood for cardiac events.	Mix of hepato-pancreato-biliary and retroperitoneal malignancies.
Lu DS, Kee ST, Lee EW (2013) Irreversible electroporation: ready for prime time?. [Review]. Techniques in Vascular & Interventional Radiology 16 (4): 277-286	General review on IRE		Review of preclinical data and preliminary clinical data for a variety of tumours
Mansson C, Bergenfeldt M, Brahmstaedt R et al. (2014) Safety and preliminary efficacy of ultrasound-guided percutaneous irreversible electroporation for treatment of localized pancreatic cancer. Anticancer Research 34 (1): 289-293.	Case series n=5 with LPC unsuitable for surgery, chemotherapy, or non-resectable after standard oncological treatment, were treated with percutaneous CT-guided IRE. Follow-up: 6 months	No serious treatment-related adverse events were observed. There was no 30-day mortality. 1 patient had laparotomy and had a R0 pancreaticoduodenectomy with portal vein resection. 6 months after the treatment, 2 patients had no signs of recurrence on computed tomography or contrast-enhanced ultrasound.	Included in systematic review (Moir 2014).

Mansson, C. et al (2016). Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy European Journal of Surgical Oncology , Feb 10. pii: S0748-7983(16)00094-9. doi: 10.1016/j.ejso.2016.01.024. [Epub ahead of print]	Case series n=24 patients with biopsy proven LAPC and who had received chemo- and/or radiochemotherapy with no metastases were included and treated with IRE. Follow-up: 17.9 months	The median overall survival from diagnosis of LAPC was 17.9 months; this included 7.0 months after IRE. Median time from IRE was 6.1 months to local progression and 2.7 months to observation of metastases. Local control was observed in 9 patients. IRE-related complications were observed in 11 patients, 3 of which were serious complications. There was no IRE-related mortality.	Larger studies included in table 2.
Martin RC, McFarland K, Ellis S et al (2013). Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. Annals of Surgical Oncology 20: Suppl-9. S443-449.	propensity matched study n=54 patients with locally advanced pancreatic cancer treated with IRE (open approach in 52 and laparoscopic in 2) 85 matched stage 3 patients treated with standard therapy (chemotherapy and radiotherapy) Follow-up: 4 months	54 patients had IRE successfully. Patients had pre or post-IRE chemotherapy or chemoradiation. The 90 day mortality in the IRE patients was 1 (2 %). In a comparison of IRE patients to standard therapy, we have seen an improvement in local progression-free survival (14 vs. 6 months, p = 0.01), distant progression-free survival (15 vs. 9 months, p = 0.02), and overall survival (20 vs. 13 months, p = 0.03).	Included in systematic review (Moir 2014).
Martin RC, McFarland K, Ellis S, Velanovich V (2012). Irreversible electroporation therapy in the management of locally advanced pancreatic adenocarcinoma. J Am Coll Surg. 215(3):361-9.	Case series n=27 patients undergoing IRE for LAPC. Follow-up:90 days	8 patients had margin accentuation with IRE in combination with left-sided resection (n=4) or pancreatic head resection (n=4). 19 patients had in situ IRE. There was 100% ablation success.1 patient died within 90-days and 4 IRE-related complications (duodenotomy leak [n=2] and portal vein thrombosis [n=2]) were reported.	Included in systematic review (Rombouts SJE 2014)

Martin RC, Philips P et al (2014). Irreversible electroporation of unresectable soft tissue tumors with vascular invasion: effective palliation. BMC Cancer, 14:540.	Case series n=107 patients from 7 institutions with tumours that had vascular invasion (locally advanced cancer) treated with IRE (liver 42, pancreas 37, other 28). Median number of lesions 2; mean tumour size of 3 cm.	40% (43/107) patients had 84 complications, including temporary renal failure, wound infection, bile leak, and pneumonia. No significant vascular complications were seen, and of the high-grade complications, bleeding (2), biliary complications (3) and deep vein thrombosis (DVT)/pulmonary embolism (PE) (3) were the most common. Complications were more likely with pancreatic lesions *(P* = 0.0001) and open surgery *(P* = 0.001). Local recurrence-free survival (LRFS) was 12.7 months with a median follow-up of 26 months. The tumour target size was inversely associated with recurrence- free survival (b = 0). 81, 95% CI: 1.6 to 4.7, *P* = 0.02) but this did not have a significant impact on overall survival.	Tumours in different regions assessed and outcomes not reported separately.
Martin RC (2015) Use of irreversible electroporation in unresectable pancreatic cancer. Hepatobiliary Surgery & Nutrition 4 (3): 211-215.	IRE	IRE has been used in locally advanced (stage III) pancreatic cancer. Recent studies have demonstrated the safety and palliation with encouraging improvement in overall survival. Its inherent limitation still remains tissue heterogeneity and the unique settings based on tumour histology and prior induction therapy.	General review on method and clinical use.
Martin RC (2015) Irreversible electroporation of locally advanced pancreatic neck/body adenocarcinoma. Journal of Gastrointestinal Oncology 6 (3): 329-335.	Patients with locally advanced pancreatic adenocarcinoma of the body/neck who had IRE	The technique of open IRE of the pancreatic neck/body with bracketing of the coeliac axis and superior mesenteric artery with continuous intraoperative ultrasound imaging and consideration of intraoperative navigational system is described. IRE is feasible for appropriate patients with locally advanced unresectable pancreatic cancer.	General article on technique and management.

Martin RC (2013) Irreversible electroporation of locally advanced pancreatic head adenocarcinoma. Journal of Gastrointestinal Surgery 17 (10): 1850-1856.	Patients with locally advanced pancreatic adenocarcinoma of the head who had IRE	The technique of open irreversible electroporation with continuous intraoperative ultrasound imaging and consideration of intraoperative navigational system is described.	General article on technique and management.
Martin RC (2016). An update on the role of irreversible electroporation in locally advanced pancreatic adenocarcinoma. HPB 18 (10) 791-792.			General update
Martin RC, Durham AN et al (2016). Irreversible electroporation in locally advanced pancreatic cancer: A call for standardization of energy delivery. J.Surg Oncol.	Review	This article provides a set of technical recommendations for the use of IRE in the treatment of locally advanced pancreatic cancer.	General review
Narayanan G, Hosein PJ, Arora G et al (2012) Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. Journal of Vascular & Interventional Radiology 23 (12): 1613-1621.	Case series n=14 patients with unresectable pancreatic cancer (15 procedures) 3 had metastatic disease and 11 had LAPC. Treated with percutaneous CT-guided IRE. Follow-up:14 months.	24-hour postprocedural scans demonstrated patent vasculature in the treatment zone in all patients. 2 patients had surgery 4 and 5 months after IRE. Both remain disease-free after 11 and 14 months. Complications included spontaneous pneumothorax during anaesthesia (n = 1) and pancreatitis (n = 1), and both recovered completely. There were no deaths related to the procedure. 3 patients with metastatic disease at IRE died from progression of their disease.	Included in systematic review (Moir 2014).

Narayanan G et al 2016. Percutaneous image-guided irreversible electroporation for the treatment of unresectable, locally advanced pancreatic adenocarcinoma. Journal of Vascular and Interventional Radiology. Article in press, published online: December 16 2016	Retrospective case series N=50 patients with biopsy-proven, unresectable LAPC, who received percutaneous computed tomography (CT)-guided IRE. All patients had prior chemotherapy and radiation therapy.	There was no treatment-related death and no 30-day mortality. Serious adverse events occurred in 10 (20%) of 50 patients and included abdominal pain (n=7), pancreatitis (n=1), sepsis (n=1), and gastric leak (n=1). Median OS was 27.0 months (95% confidence interval [CI], 22.7-32.5 months) from the time of diagnosis and 14.2 months (95% CI, 9.7-16.2 months) from the time of IRE. Patients with tumors ≤3 cm (n=24) had significantly longer median OS than those with tumors >3 cm (n=26): 33.8 vs 22.7 months from the time of diagnosis (p=0.002) and 16.2 vs 9.9 months from the time of IRE (p=0.031). Tumor size was confirmed as the only independent predictor of OS at multivariate analysis.	Efficacy data and adverse events have already reported in the overview.
Paiella S, Butturini G, Salvia R et al. (2014) Results of a phase I study for the evaluation of the feasibility and safety of irreversible electroporation (IRE) in patients with locally advanced pancreatic cancer. HPB 16: 637-638.	Case series n=10 patients with unresectable pancreatic adenocarcinoma not responsive to standard treatments treated with IRE open approach. Median tumour size of 30 mm.	All patients were treated successfully. 3 patients had early progression of disease: 1 patient developed pulmonary metastases 30 days post-IRE, and 2 patients had liver metastases 60 days after the procedure. Registered an OS of 7.5 months (range: 2.9–15.9). Two procedure-related complications were reported in 1 patient (10%): a pancreatic abscess with a pancreoduodenal fistula.	Larger studies included in table 2.

Philips P, Hays D, Martin RC (2013) Irreversible electroporation ablation (IRE) of unresectable soft tissue tumors: learning curve evaluation in the first 150 patients treated. PLoS ONE [Electronic Resource] 8 (11): e76260-.	Case series n=150 patients with liver (39.5%), pancreatic (35.5%) and other lesions treated with IRE.	Outcomes were analysed chronologically. Patients had similar complication and high-grade complication rates (p=0.24). Attributable morbidity rate was 13.3% (total 29.3%) and high-grade complications were seen in 4.19% (total 12.6%). Pancreatic lesions (p=0.001) and laparotomy (p=0.001) were associated with complications. Complex treatments of larger lesions with greater vascular involvement were performed without increase in adverse effects or impact on local relapse free survival.	Included in systematic review (Rombouts SJE 2014).
Papamichail M, Ali A et al (2016). Irreversible electroporation for the treatment of pancreatic neuroendocrine tumors. Korean Journal of Hepatobiliarypancreatic Surgery 20 (3) 116-120.	Case series n=3 patients with small (<2 cm) pancreatic neuroendocrine tumors were treated with percutaneous irreversible electroporation.	There were no adverse effects during the procedure. Mean hospital stay was 2.6 days. All patients remained disease free on 12-19 months follow up. One patient developed recurrent pancreatitis with pseudocyst formation.	Larger studies with longer follow-up included in table 2.

Scheffer HJ, Melenhorst MC, Vogel JA et al. (2015) Percutaneous irreversible electroporation of locally advanced pancreatic carcinoma using the dorsal approach: a case report. Cardiovascular & Interventional Radiology 38 (3): 760-765.	Case report n=1 patient with a 5 cm stage III pancreatic tumour who was treated with IRE	The ventral approach for electrode placement was considered dangerous due to vicinity of the tumour to collateral vessels and duodenum, so dorsal approach was chosen. Under CT guidance, 6 electrodes were advanced in the tumour, approaching paravertebrally alongside the aorta and inferior vena cava. Ablation was performed without complications.	Larger studies with longer follow-up included in table 2.

Scheffer HJ, Nielsen K, de Jong MC et al. (2014) Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. [Review]. *Journal of Vascular & Interventional Radiology* 25 (7): 997-1011.	Systematic review.	In 16 studies, 221 patients had 325 tumours treated in liver (n = 129), pancreas (n = 69), kidney (n = 14), lung (n = 6), lesser pelvis (n = 1), and lymph node (n = 2). No major adverse events during IRE were reported. IRE caused only minor complications in the liver; however, 3 major complications were reported in the pancreas (bile leak [n = 2], portal vein thrombosis [n = 1]). Complete response at 3 months was 67%-100% for hepatic tumours (93%-100% for tumours of3 cm). Pancreatic IRE combined with surgery led to prolonged survival compared with control patients (20 months vs 13 months) and significant pain reduction. In cases where other techniques are unsuitable, IRE is a promising modality for the ablation of tumours near bile ducts and blood vessels. This articles gives an extensive overview of the available evidence, which is limited in terms of quality and quantity. With the limitations of the evidence in mind, IRE of central liver tumours seems relatively safe without major complications, whereas complications after pancreatic IRE appear more severe. The available limited results for tumour control are generally good. Overall, the future of IRE for difficult-to-reach tumours appears promising.	Studies included in this review on pancreatic cancer are already included in the 2 systematic reviews included in table 2.
Schulz B, Ou J, Van Meter T and Martin RC (2016). Early nontumorous CT findings after irreversible electroporation of locally advanced pancreatic cancer. Abdominal Radiology 41 (11) 2142-2149.	Retrospective review of patients having IRE for locally advanced pancreatic adenocarcinoma n=36 nontumourous CT imaging findings 30	Nontumorous abnormalities identified in the peri-electroporation bed on Computed Tomography (CT) during the early postoperative period (within 30 days) were characterized and classified into categories. Our results indicate that	CT findings already reported in table 2 studies.

	days after IRE were reviewed.	the most common nontumorous findings in the peri-electroporation bed were vascular, followed by changes involving the gastrointestinal tract, peritoneal cavity, and, infrequently, the biliary tree. Interpretation of CT imaging of the postoperative peri-electroporation bed is challenging. This review of CT findings allows the radiologist to recognize and anticipate significant nontumorous findings in the peri-electroporation bed during early follow-up after IRE.	
Stillstrom D, Nilsson H et al (2016). A new technique for minimally invasive irreversible electroporation of tumors in the head and body of the pancreas. Surgical Endoscopy and Other Interventional Techniques 1-4 (article in press).	Irreversible electroporation of pancreatic tumors through computer-assisted navigation of needles and laparoscopy.	Description of a minimally invasive approach to irreversible electroporation of pancreatic tumors using computer-assisted navigation, laparoscopy and laparoscopic ultrasound to correctly guide electrodes into the tissue.	Procedure description only.

Trueba-Arguinarena et al (2015). Pancreatic adenocarcinoma treated with irreversible electroporation Case report. Medicine 94 (26):e946.	Case report n=1 A 66-year-old male patient with locally advanced pancreatic adenocarcinoma was treated with IRE.	At 12-month follow-up, the patient is disease free. Complications included significant pain requiring morphine for 1 week; fluid and edema in the wall of the ascending colon (managed with diuretics); hematemesis in 1 (needed transfusion and was related to the placement of 6 transgastric needles).	Larger studies included in table 2.
Villamarín BB, Atienza MG (2014) Irreversible electroporation in pancreatic and liver cancer (Structured abstract). Health Technology Assessment Database (1)	HTA report IRE in the treatment of pancreatic cancer and metastatic primary liver cancer compared to other ablation procedures and the standard treatment.	Evidence on this technique's effectiveness and safety is based on a small number of observational studies, some with methodological limitations and possible biases that might affect the results. Heterogeneity when it comes to establishing and defining outcome variables, in patient populations and in the approach to IRE, renders inter-study comparison of results difficult. What this means is that no conclusions can be drawn as to whether IRE is more effective and safer than other ablation techniques or the standard treatment, until such a time as there are results yielded by studies having a good methodological design and a long-term follow-up.	Main report in non-English-language. Studies included in the review are included in the systematic reviews included in table 2.
Wichtowski M, Nowazyk P et al (2016). Irreversible electroporation in the treatment of locally advanced pancreas and liver metastases of colorectal carcinoma. Contemp Oncol (Pozn). 2016;20 (1):39-44.	Case series n=3 (2 patients with locally advanced pancreatic cancer and 1 with colorectal metastasis) treated with IRE.	At 7 month follow-up, 1005 local control was achieved without progression. In LAPC patients a significant reduction of pain was noted. No direct complication related to the procedure noted.	Larger studies included in table 2.
Young SJ (2015). Irreversible electroporation and the pancreas: what we know and where are we going?. World Journal of Gastrointestinal Surgery. 27; 7(8):138-144.	Review on IRE and the pancreas.	IRE showed significant promise during preclinical trials and has moved on to clinical testing. There are only a few studies which look at the applications of IRE within humans in pancreatic adenocarcinoma.	Reviews principles, techniques and clinical data on IRE.

Appendix B: Related NICE guidance for irreversible electroporation for treating pancreatic cancer

Guidance	Recommendations
Interventional procedures	**Laparoscopic distal pancreatectomy. NICE interventional procedure guidance 204 (2007).** 1.1 Current evidence on the safety and efficacy of laparoscopic distal pancreatectomy appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Laparoscopic distal pancreatectomy should only be performed in centres specialising in pancreatic surgery and with appropriate expertise in advanced laparoscopic techniques, and in the context of a multidisciplinary team, which should usually include a pancreatic surgeon, a gastroenterologist, an endocrinologist and a pathologist.
	Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy. NICE interventional procedure guidance 274 (2008). 1.1 The current evidence on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy shows some short term efficacy, although most patients require insulin therapy in the long term. The reported complications result mainly from the major surgery involved in pancreatectomy (rather than from the islet cell transplantation). The procedure may be used with normal arrangements for clinical governance in units with facilities for islet cell isolation (see also section 2.5.1). 1.2 During consent, clinicians should ensure that patients understand that they may require insulin therapy in the long term. They should provide them with clear written information. In addition, the use of the NICE's information for patients ('Understanding NICE guidance') is recommended. 1.3 Patient selection for this procedure should involve a multidisciplinary team with experience in the management of benign complex chronic pancreatic disease. The procedure should be carried out by surgeons with experience in complex pancreatic surgery and clinicians with experience in islet cell isolation and transplantation. 1.4 Further audit and research should address the long-term efficacy of the procedure, quality of life, insulin independence and the management of patients' diabetes (see section 3.1).

	Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma. NICE interventional procedure guidance 464 (2013) 1.1 Current evidence on the safety and efficacy of endoscopic bipolar radiofrequency ablation for treating biliary obstructions caused by cholangiocarcinoma or pancreatic adenocarcinoma is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. 1.2 Further research, in the form of comparative or observational studies, should document details of patient selection and should report all adverse events. Outcomes should include survival, quality of life, biliary patency and the need for further procedures. 1.3 Clinicians should consider entering patients with pancreatic adenocarcinoma into the EndoHPB 1001 trial.
	Irreversible electroporation for treating pancreatic cancer. NICE interventional procedure guidance 442 (2013). 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. In particular, studies should report the effect of the procedure on local tumour control and patient survival.
	Irreversible electroporation for the treatment of liver metastases. NICE interventional procedure guidance 445 (2013). 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating liver metastases is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival
	Irreversible electroporation for the treatment of primary liver cancer. NICE interventional procedure guidance 444 (2013). 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating primary liver cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival.

	Irreversible electroporation for treating renal cancer. NICE interventional procedure guidance 443 (2013). 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating renal cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival.
	Irreversible electroporation for treating primary lung cancer and metastases in the lung. NICE interventional procedure guidance 441 (2013). 1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating primary lung cancer and metastases in the lung is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumour control and patient survival.
Technology appraisals	**Guidance on the use of gemcitabine for the treatment of pancreatic cancer. NICE technology appraisal guidance 25 (2001).** 1.1 Gemcitabine may be considered as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of 50 or more, where first line chemotherapy is to be used. 1.2 Gemcitabine is not recommended for patients who are suitable for potentially curative surgery, or patients with a Karnofsky (see Appendix D) score of less than 50. 1.3 There is insufficient evidence to support the use of gemcitabine as a second line treatment in patients with pancreatic adenocarcinoma.
	Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer. NICE technology appraisal guidance 360 (2015). 1.1 Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine is not recommended within its marketing authorisation for adults with previously untreated metastatic adenocarcinoma of the pancreas. 1.2 People whose treatment with paclitaxel as albumin-bound nanoparticles, in combination with gemcitabine, was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Appendix C: Literature search for irreversible electroporation for treating pancreatic cancer

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/10/2016	Issue 10 of 12, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/10/2016	Issue 9 of 12, September 2016
HTA database (Cochrane Library)	21/10/2016	Issue 3 of 4, July 2016
MEDLINE (Ovid)	21/10/2016	1946 to October week 2 2016
MEDLINE In-Process (Ovid)	21/10/2016	October 20, 2016
EMBASE (Ovid)	21/10/2016	1974 to 2016 week 42
CINAHL (NLH Search 2.0)	21/10/2016	N/A
PubMed	21/10/2016	N/A
JournalTOCS	21/10/2016	N/A

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Electroporation/
2 Electric Stimulation/
3 exp Nanotechnology/
4 nanoknife.tw
5 (irrevers* adj4 (electropor* or electro-por* or electropermeab* or electro-permeab*)).tw.
6 ((electric* or electro*) adj4 (field* or stimul* or pulse* or cell? or membrane* or pore? or burst* or needle*)).tw.
7 Electric Stimulation Therapy/
8 IRE.tw.
9 LEDC.tw.
10 low* energ* direct* current*.tw.
11 Electrochemotherapy/
12 electrochemo*.tw.
13 Ablation Techniques/
14 ((tissue* or tumor* or tumour*) adj4 ablat*).tw. (6383)
15 ((bipolar* or unipolar*) adj4 (puls? or electrod* or mode? or needle*)).tw.
16 or/1-15
17 pancreas/
18 exp Pancreatic Neoplasms/

19 ((pancrea* or neuroendocrin* or ductal*) adj4 (adenoma*or Neoplasm* or Cancer* or Metastas* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcoma*)).tw.
20 ((islet cell or islet-cell or island cell) adj4 (adenoma* or Neoplasm* or Cancer* or Metastas* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcoma*)).tw.
21 Adenoma, Islet Cell/
22 Islet Cell Carcinoma/
23 Somatostatinoma/
24 somatostatinoma*.tw.
25 nesidioblastoma*.tw.
26 or/17-25
27 16 and 26
28 animals/ not humans/
29 27 not 28
30 limit 29 to ed=20120927-20160331
31 30 and 29