NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of irreversible electroporation for primary liver cancer

Primary liver cancer starts in the liver, unlike secondary cancer that has spread from another part of the body. In this procedure, single-use needles are inserted into the liver. Short electrical pulses of high-voltage current are passed between the needles to create tiny holes (pores) in the cancer cells (irreversible electroporation). The aim is to kill the cancer cells without damaging the structure of the liver.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure 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 overview was prepared in March 2019.

Procedure name

- Irreversible electroporation for primary liver cancer

Specialist societies

- Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland
- British Association of Surgical Oncology (cancer surgery)
- British Society of Interventional Radiology
- Royal College of Radiology

Description of the procedure

Indications and current treatment

The most common primary liver cancers are hepatocellular carcinoma and cholangiocarcinoma.

Treatment for primary liver cancer depends on several factors, including the exact location and stage of the cancer, the patient's liver function and any patient-related comorbidities. For most patients, treatment with curative intent is not possible. The treatment options include surgical excision, chemotherapy (conventional or hepatic artery infusion), transarterial chemoembolisation, percutaneous ethanol injection, and thermal ablation techniques such as cryotherapy, radiofrequency and microwave ablation. Liver transplantation (with curative intent) may be appropriate for some patients.

The aim of irreversible electroporation (IRE) is to destroy cancerous cells by subjecting them to short pulses of high-voltage direct current. This creates multiple holes in the cell membrane, irreversibly damaging the cell's homeostasis mechanisms and leading to cell death. The key difference between IRE and thermal ablation techniques is that it does not produce extreme heat or cold. It may selectively damage cancerous cells while sparing adjacent supporting

connective tissue, for example, nearby blood vessels, bile ducts and nerves, so allowing a more targeted treatment compared with other types of treatment.

What the procedure involves

IRE for primary liver cancer is done with the patient under general anaesthesia. A neuromuscular blocking agent is used to prevent muscle spasms. Needle-like electrodes are introduced percutaneously into the tumour under imaging guidance (either CT or, less commonly, ultrasound). The distance between the electrodes is confirmed by imaging. This is to ensure that the electrodes are correctly placed parallel to each other and that enough current flow would be generated to ensure IRE. The procedure may also be done through an open surgical or laparoscopic approach, although the percutaneous route is the most common.

In each ablation cycle, pulses of high-voltage direct current are delivered in groups (of about 10) with a brief time for recharging between groups (a cycle is usually completed in less than 2 minutes). Electrodes are repositioned under imaging guidance to extend the zone of electroporation until the entire tumour and an appropriate margin have been ablated. The number of ablations is determined by the volume of the target tumour. When the ablation procedure is completed, further imaging may be done to confirm the extent of the ablation.

Outcome measures

The 'Response evaluation criteria in solid tumors' (RECIST) are used for measuring tumour response using X-ray, CT and MRI. There are 4 categories:

- complete response: disappearance of all target lesions
- partial response: 30% decrease in the sum of the longest diameter of target lesions
- progressive disease: 20% increase in the sum of the longest diameter of target lesions
- stable disease: small changes that do not meet the above criteria.

Efficacy summary

Ablation success

In a case series of 52 patients with primary or secondary liver cancer, complete ablation was reported after 75% (44/59) of procedures.[1]

In a non-randomised comparative study of 55 patients with hepatocellular carcinoma (HCC), complete ablation was reported in 100% (30/30) of patients who had IRE and 100% (25/25) of patients who had microwave ablation at 90 days.[2]

In a case series of 58 patients with HCC, 77% (58/75) of tumours were completely ablated after the first IRE session, 89% (67/75) after a second session and 92% (69/75) after a third.[3]

In a case series of 71 patients with primary or secondary liver cancer, 92% (95/103) of tumours were completely ablated at the 6-week follow up.[4]

In a case series of 20 patients with HCC, a complete response (modified [m] RECIST criteria) was seen in 92% (22/24) of tumours according to MRI and contrast-enhanced ultrasound, and 100% (24/24) according to CT. At 6 months, a complete response was reported for 92% (22/24) of tumours regardless of imaging modality.[5]

In a case series of 34 patients with primary or secondary liver cancer (65 tumours), complete ablation immediately after the procedure and at 6-week follow up was 95% (62/65). A complete response according to mRECIST criteria was reported in 87%, 74% and 62% of tumours at 3, 6 and 12 months respectively.[6]

In a case series of 14 patients with HCC, complete ablation was reported for 25% (2/8) of patients with large tumours (mean follow up: 2.8 months) and 67% (4/6) of patients with medium size tumours (mean follow up: 4.3 months).[7]

Recurrence or progression

In the case series of 52 patients, 36% of patients with HCC were progression free at 12-month follow up compared with 12% of patients with colorectal metastasis (p=0.004). The median time to progression was 8 months for tumours that were completely ablated after IRE.[1]

In the case series of 58 patients, 6-month overall local tumour progression-free survival was 87% (95% CI 77% to 93%) and 12-month overall local tumour progression-free survival was 70% (95% CI 56% to 81%).[3]

In the case series of 71 patients, local recurrence was 32% (33/103) of tumours, after a median follow up of 35.7 months.[4]

In the case series of 34 patients, local recurrence-free survival was 87%, 80% and 75% at 3, 6 and 12 months respectively. The mean time to local recurrence was 15.5 months. The median time to progressive disease (according to mRECIST criteria) was 15.6 months.[6]

In a case series of 29 patients, recurrence was reported in 39% (10/26) of patients. In 8 of these 10 patients, the recurrences were classified as needle-tract seeding. Tumour progression elsewhere in the liver was reported in 17% (5/29) of patients, between 8 weeks and 24 months after IRE.[8]

Overall survival

In the case series of 52 patients, overall survival for patients in the complete ablation group was 62% (23/37), 27% (10/37), 8% (3/37) and 0% (0/37) at 12, 24, 36 and 48 months respectively. The median survival time was 38 months.[1]

In the case series of 58 patients, 97% (56/58) of patients were alive at the end of the study (median follow up: 9 months).[3]

In the case series of 71 patients, median survival of patients with primary liver cancer was 26.8 months.[4]

Safety summary

Death

Systemic inflammatory response syndrome (SIRS) leading to death 9 days after the procedure was reported in 1 patient in the case series of 52 patients. The patient had pre-existing common bile duct stones and developed cholangitis, branch portal vein occlusion and SIRS.[1]

Death caused by liver failure was reported in 1 patient in the case series of 58 patients, 2.5 months after IRE.[3]

Haemorrhage leading to death was reported in 1 patient who had IRE in a non-randomised comparative study of 56 patients (reported in a conference abstract). The patient had a large intrahepatic haematoma with liver laceration, and subsequently had a laparotomy and liver packing because of haemodynamic instability. He died 3 weeks later.[9]

Liver failure

Liver failure (jaundice and ascites) was reported in 2 patients and transient jaundice was reported in 1 patient in the case series of 58 patients.[3]

Liver abscess

Liver abscess was reported in 6% (4/71) of patients in the case series of 71 patients.[4]

Bleeding

Intraperitoneal bleeding was reported in 1 patient in the case series of 34 patients. The bleeding stopped spontaneously but the patient needed blood transfusion and admission to the intensive care unit.[6]

Cardiac complications

Myocardial infarction was reported in 1 patient and cardiac arrhythmia in 3% (2/71) of patients in the case series of 71 patients.[4]

Atrial fibrillation was reported in 6% (3/52) of patients in the case series of 52 patients; all cases were self-limiting or medically managed.[1]

Gallbladder perforation

Gallbladder perforation with resultant bile leak and peritonitis was reported in 1 patient in the case series of 52 patients.[1]

Biliary duct dilation

Segmental dilation of the intrahepatic biliary ducts was reported in 1 patient in the case series of 20 patients. No treatment was needed.[5]

Cholestasis

Mild to moderate cholestasis was reported in 24% (5/21) of patients with target tumours adjacent to portal veins, at 2 to 6 weeks after IRE, in the case series of 29 patients.[8]

Portal vein thrombosis

Portal vein thrombosis was reported in 1 (3%) patient who had IRE and 5 (20%) patients who had microwave ablation in the non-randomised comparative study of 55 patients.[2]

Partial portal thrombosis was reported in 1 patient in the case series of 58 patients.[3]

Partial thrombosis of the portal vein was reported in 1 patient in the case series of 34 patients. The patient needed moderate anticoagulation.[6]

Pneumothorax

Pneumothorax was reported in 1 patient in the case series of 58 patients and in 3% (2/71) of patients in the case series of 71 patients.[3,4]

Haematoma

Subcapsular haematoma was reported in 1 patient in the case series of 52 patients.[1]

Haematoma was reported in 4% (3/71) of patients in the case series of 71 patients.[4]

A small subcapsular haematoma without signs of active bleeding and a small haematoma in the intercostal space (self-limiting) were each reported in 1 patient in the case series of 29 patients.[8]

A large intrahepatic haematoma was reported in 1 patient and perihepatic haematomas that could be managed without invasive procedures or blood transfusion were reported in 5% (3/56) of patients who had IRE in the non-randomised comparative study of 56 patients.[9]

Pain

Minor postoperative pain was reported in 4% (2/52) of patients in the case series of 52 patients.[1]

Pain was reported in 1 patient in the case series of 58 patients.[3]

Stomach pain was reported in 1 patient in the case series of 14 patients.[7]

Other

Asymptomatic gastric fistula, transient encephalopathy and decompensated chronic bronchitis were each reported in 1 patient in the case series of 58 patients.[3]

Peripheral arteriovenous shunt was reported in 1 patient in the case series of 20 patients. No treatment was needed.[5]

Intraoperative blood pressure up to 200/83 mmHg was reported in 1 patient with a suspected IRE ablation near the adrenal gland in the case series of 14 patients. This returned to normal after treatment with intravenous nicardipine.[7]

A small clinically asymptomatic arterioportal fistula, within the needle tract, was reported in 1 patient in the case series of 29 patients.[8]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur,

even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: cardiac arrhythmia and portal vein thrombosis. They considered that the following was a theoretical adverse event: bleeding in patients with metallic stents.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to IRE for primary liver cancer. The following databases were searched, covering the period from their start to 21 January 2019: 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 the literature 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 primary liver 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 about 350 patients who had IRE from 2 non-randomised comparative studies (1 of which was a conference abstract included for safety data only) and 7 case series.[1–9]

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

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

Study 1 Mafeld S (2019)

Details

Study type	**Case series**
Country	UK (2 centres)
Recruitment period	2013 to 2017
Study population and number	**n=52 (59 tumours; 53 treatment sessions)** Patients with primary or secondary hepatic malignancy
Age and sex	Mean 64 years (range 28 to 94); 83% (43/52) male
Patient selection criteria	All patients were discussed at a multidisciplinary tumour board, and their tumours were determined to be surgically unresectable and in a location unsuitable for thermal ablation (centrally located in proximity to major vascular structures or adjacent organs). Exclusion criteria included: presence of a cardiac pacemaker, uncontrolled cardiac arrhythmia or uncorrectable coagulopathy.
Technique	All procedures were done using the NanoKnife system. General anaesthetic with neuromuscular blockade was used. IRE electrodes were placed percutaneously using image guidance. The mean number of electrodes used was 3 (range 2 to 7), which were sited to build an ablation zone encompassing the target lesion and rim of surrounding tissue.
Follow up	**To death (median survival time 38 months)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: One patient was lost to follow up.

Study design issues: Retrospective, bi-institutional case series. The 2 outcome measures were time to progression and time to death. Patients in which these outcomes had not occurred were censored to the last time when either progression or death was recorded not have occurred. Patients were divided into 3 groups based on their tumour size. Technical success was defined as a complete response on first follow-up imaging (CT or MRI) at 4 to 8 weeks after the procedure. Tumours that were not completely ablated were subsequently managed by non-interventional treatments.

Study population issues: Tumours treated included primary hepatic malignancy (20 hepatocellular carcinoma and 3 cholangiocarcinoma) and secondary metastatic disease (28 colorectal, 1 neuroendocrine, 1 pancreatic, 1 breast, 1 gastrointestinal stromal tumour, 1 malignant thymoma). Mean tumour size diameter was 2.4 cm (range 0.7 to 5.2 cm).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 52

Complete ablation=75% (44/59) of procedures (37 patients)
Incomplete ablation=22% (13/59)

In the complete ablation group, median time to progression=8 months

At 12 months, 44% (95% CI 26 to 62%) of patients were progression free.

Time to progression by tumour size – proportion of patients who were progression free by follow-up period
<table>
<tr><th>Tumour size</th><th>n</th><th>3 months</th><th>6 months</th><th>9 months</th><th>12 months</th></tr>
<tr><td><20 mm</td><td>9</td><td>100%</td><td>89%</td><td>33%</td><td>22%</td></tr>
<tr><td>20 to 30 mm</td><td>22</td><td>91%</td><td>55%</td><td>27%</td><td>18%</td></tr>
<tr><td>>30 mm</td><td>6</td><td>100%</td><td>50%</td><td>0%</td><td>0%</td></tr>
</table>
Time to progression by pathology – proportion of patients who were progression free by follow-up period
<table>
<tr><th>Tumour type</th><th>n</th><th>3 months</th><th>6 months</th><th>9 months</th><th>12 months</th></tr>
<tr><td>Colorectal metastases</td><td>17</td><td>94%</td><td>47%</td><td>18%</td><td>12%</td></tr>
<tr><td>Hepatocellular carcinoma</td><td>11</td><td>91%</td><td>91%</td><td>45%</td><td>36%</td></tr>
</table>
p=0.004

Median survival time=38 months

Overall survival (n=37)

12 months=62% (23/37)
24 months=27% (10/37)
36 months=8% (3/37)
48 months=0% (0/37)

</td><td>
Complication rate=17% (9/52)

All complications during and after IRE

Atrial fibrillation=5.8% (3/52) (all were self-limiting or medically managed)
Minor postoperative pain=3.9% (2/52) (managed with analgesia)
Subcapsular haematoma=1.9% (1/52)
Gallbladder perforation with resultant bile leak and peritonitis=1.9% (1/52)
SIRS leading to death=1.9% (1/52) (the patient had pre-existing common bile duct stones and developed cholangitis, branch portal vein occlusion and SIRS)
Death=1.9% (1/52) (9 days after the procedure, caused by SIRS – also described above)

</td></tr>
<tr><td colspan="2">Abbreviations used: IRE, irreversible electroporation; SIRS, systemic inflammatory response syndrome</td></tr>
</table>

Study 2 Bhutiani N (2016)

Details

Study type	**Non-randomised comparative study**
Country	US
Recruitment period	2010 to 2015
Study population and number	**n=55 (30 IRE, 25 microwave ablation)** Patients with Child-Pugh (7/8) hepatocellular carcinoma
Age and sex	IRE: median age=61 years (range 51 to 75); 93% (28/30) male Microwave: median age=60 years (range 49 to 81); 92% (23/25) male
Patient selection criteria	Inclusion criteria: confirmed diagnosis of Child-Pugh B (7/8) hepatocellular carcinoma that was deemed unresectable or as a bridge to transplantation. Unresectability was determined based on tumour characteristics, baseline hepatic function, and predicted postoperative functional liver remnant. Exclusion criteria included general unfitness to have general anaesthesia, extensive extrahepatic disease, and multifocal hepatic disease not amenable to surgical ablation.
Technique	IRE: open or laparoscopic, using 19-gauge monopolar electrodes. The IRE current generator (NanoKnife, AngioDynamics, US) was synchronised to deliver electrical pulses coordinated with the patient's cardiac rhythm. Microwave ablation: open or laparoscopic. Ablation size was done to obtain at least a 1 cm margin surrounding the entire tumour.
Follow up	**6 months**
Conflict of interest/source of funding	No conflict of interest declared. One author is a paid educational consultant for AngioDynamics.

Analysis

Follow-up issues: No losses to follow up were described.

Study design issues: Prospective double arm treatment registry. The discussion section of the paper states that one of the limitations is that it is a single-institution study, but it is described as multi-institutional in the methods section. Treatment choice was based on anatomic tumour location and proximity to major vascular and biliary structures. The end points were rate of complete ablation of liver tumours (ablation success), ablation recurrence defined as recurrent disease within 1 cm from ablated sites, hepatic recurrence at nonablated sites, and morbidity and mortality associated with the procedure.

Study population issues: Pre-existing comorbidities, presence of portal hypertension, MELD scores and AFP levels were comparable between the 2 treatment groups. Most patients had at least 1 previous therapy (surgical resection, hepatic arterial therapy or liver ablation). Most tumours in the IRE group were classified as 'invaders' based on radiographic characteristics (80% in IRE group compared with 32% in the microwave group, p=0.0002). There was a statistically significantly higher proportion of tumours that were close to hepatic or portal vascular structures in the IRE group compared with the microwave ablation group (57% versus 16%, p=0.0015 and 63% versus 0%, p<0.0001 respectively). Median tumour size was 3.0 cm (range 2.0 to 3.3) in the IRE group and median tumour number 1 (range 1 to 2). In the microwave group, median tumour size was 3.2 cm (range 1.9 to 3.5) and median tumour number 1 (range 1 to 3).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **55 (30 versus 25)**

Length of stay (days; median, range)

- IRE=1 (1 to 4)
- Microwave=2 (1 to 5), p=0.05

Ablation success at 90 days

- IRE=100% (30/30)
- Microwave=100% (25/25), p=not significant

Ablation success at 180 days

- IRE=97% (29/30)
- Microwave=100% (25/25), p=0.37

Safety

Adverse events and postoperative characteristics

	IRE (n=30)	Microwave (n=25)	p
Intraoperative complications			
Arrhythmia	0	0	-
High current	2	0	0.10
30-day tolerance (median, range)			
AST (fold increase)	0 (1 to 2)	2 (1 to 4)	0.05
ALT	0 (1 to 2)	2 (1 to 4)	0.05
Total bilirubin	1 (1 to 1)	1.5 (1 to 2)	0.07
Increased ascites	5 (16%)	13 (52%)	0.02
90-day tolerance (median, range)			
AST (fold increase)	0 (1 to 2)	1 (1 to 4)	0.09
ALT	0 (1 to 2)	1 (1 to 4)	0.09
Total bilirubin	0 (0 to 1)	0 (1 to 2)	0.12
Increased ascites	2 (6%)	5 (20%)	0.05
Pleural effusion (90 day)	5 (17%)	14 (56%)	<0.01
Portal vein thrombosis (90 day)	1 (3.3%)	5 (20%)	0.03
Readmission (90 day)	4 (13%)	9 (36%)	0.03
Reasons for readmission			
Uncontrolled ascites	1 (grade II)	4 (grade III)	0.11
Dehydration	1 (grade II)	2 (grade II)	0.46
Liver failure	2 (grade II)	5 (4 grade II, 1 grade III)	0.14

There were no treatment-related deaths in either group.

Major and minor complication rates

- IRE=27%
- Microwave=76%

Abbreviations used: AFP, alpha-fetoprotein; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; IRE, irreversible electroporation; MELD, Model for End-stage Liver Disease

Study 3 Sutter O (2017)

Details

Study type	**Case series**
Country	France
Recruitment period	2012 to 2015
Study population and number	**n=58 (75 tumours)** Patients with inoperable hepatocellular carcinoma (HCC)
Age and sex	Median age 65 years (range 41 to 90); 74% (43/58) male
Patient selection criteria	Patients with cirrhosis (46 had Child-Pugh A class disease and 12 had Child-Pugh B class disease) and HCC. Therapeutic strategies for HCC were decided by an interdisciplinary liver tumour board. If the tumour load appeared sufficiently limited to expect complete response with local treatment but resection or thermal ablation were not viable options because of a high risk of major complications, IRE was chosen after elimination of specific contraindications for therapy. The proximity to large vessels, the digestive tract, diaphragm, or gallbladder was not regarded as a sufficient condition to select IRE over thermal ablation techniques if the risk of complications or incomplete ablation could be reduced by using suitable alternative strategies. IRE was chosen because of tumour location in 48 patients and because of the patient's poor general condition in 10 patients.
Technique	All procedures were done by a single operator with more than 10 years of experience of percutaneous liver tumour ablation. General anaesthesia, including muscle blockade, was used. A median of 3 electrodes (range 3 to 6) were used per procedure. A median of 120 pulses (range 30 to 480) were delivered between each combination of electrodes during the procedure. A total of 87 procedures were done, including 12 repeat sessions. Device: NanoKnife (AngioDynamics)
Follow up	**Median 9 months (range 0.3 to 31)**
Conflict of interest/source of funding	None of the authors disclosed relevant relationships related to this article.

Analysis

Follow-up issues: Patients were followed up with MRI at 1 month after the IRE procedure and every 3 months thereafter. There were no losses to follow up.

Study design issues: Retrospective single-centre case series. Primary, secondary and tertiary treatment effectiveness were assessed (defined as rates of complete ablation seen on MRI after the first or, if necessary, second or third IRE procedures, respectively). Overall local tumour progression-free survival was defined as the interval between the most recent IRE procedure and death, last follow up, the most recent follow-up visit, or the date of local tumour progression on imaging. Patients who had liver transplantation were censored from the study at the date of their transplantation.

Study population issues: The median longest tumour diameter was 24 mm (range 6 to 90). Of the 58 patients, 24 (41%) had no previous treatment. The cause of cirrhosis was alcohol in 20 patients (35%), Hepatitis C virus in 18 patients (31%), Hepatitis B virus in 5 patients (9%), non-alcoholic steatohepatitis in 11 patients (19%) and other in 4 patients (7%).

Other issues: In the same study period, 206 patients with 276 HCC tumours were treated with either microwave ablation or radiofrequency ablation at the same institution.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **58**

Effectiveness of 87 IRE procedures (75 HCC tumours)

Parameter	Complete ablation after first IRE	Complete ablation after second IRE	Complete ablation after third IRE	Local tumour progression*
Longest diameter				
<30 mm (44 nodules)	36 (81.8%)	40 (90.9%)	41 (93.2%)	7 (15.9%)
≥30 to <50 mm (17 nodules)	12 (70.6%)	16 (94.1%)	17 (100%)	2 (11.7%)
≥50 mm (3 nodules)	3 (100%)	-	-	0
Infiltration or portal invasion (11 nodules)	7 (63.6%)	8 (72.7%)	8 (72.7%)	6 (54.5%)
Total	58 (77.3%)	67 (89.3%)	69 (92.0%)	15 (20.0%)

* median follow up of 9 months, range 0.3 to 31

Failure rate=8% (6/75)

Median time to occurrence of local tumour progression=9 months (range 4 to 27)

Local tumour progression was detected in 21.7% (15/69) of tumours that appeared completely ablated. With the addition of 6 initial treatment failures, the overall local tumour progression rate was 28.0% (21/75).

6-month overall local tumour progression-free survival=87% (95% CI 77% to 93%)
12-month overall local tumour progression-free survival=70% (95% CI 56% to 81%)

At the end of the study, 96.5% (56/58) of patients were alive. The 2 deaths were related to liver failure.

Distant intrahepatic tumour progression=20.7% (12/58). No extrahepatic tumour progression was found.

Liver transplantation=6.9% (4/58) (0.25 to 11 months after the last IRE procedure); 5 patients were awaiting liver transplantation without evidence of tumour progression from 12 to 26 months.

A baseline serum alpha-fetoprotein level higher than 200 ng/ml (hazard ratio 9.94, 95% CI 2.82 to 35.06, p=0.0004) was the only factor linked with overall local tumour progression-free survival.

Safety

Complication rate=19.0% (11/58)

Complications in patients with critical tumour location (n=48)

Clavien-Dindo / Society of Interventional Radiology grade	
I/B	Pain (n=1) Transient jaundice (n=1) Asymptomatic gastric fistula (n=1)
II/C	Pneumothorax (n=1) Partial portal thrombosis (n=2) Transient encephalopathy (n=1)
IV/D	Liver failure (jaundice and ascites) (n=1)
V/F	-

Complications in patients with poor liver function or poor general condition (n=10)

Clavien-Dindo / Society of Interventional Radiology grade	
I/B	-
II/C	Decompensated chronic bronchitis (n=1)
IV/D	Liver failure (jaundice and ascites) (n=1)
V/F	Death (liver failure) (n=1) (2.5 months after IRE)

Abbreviations used: CI, confidence interval; HCC, hepatocellular carcinoma; IRE, irreversible electroporation

Study 4 Niessen C (2017)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2011 to 2015
Study population and number	**n=71 (35 with primary liver tumours); 103 tumours** Patients with primary or secondary liver tumours
Age and sex	Median age 63 years (range 32 to 84); 80% (57/71) male
Patient selection criteria	Inclusion criteria: diagnosis of an inoperable primary or secondary liver carcinoma based on biopsy or non-invasive criteria; ineligible for conventional thermal ablation because of subcapsular or central tumour location or location adjacent to a major hepatic artery or vein, a bile duct or a major portal vein branch (distance <0.5 cm); age >18 years; signed consent form. Exclusion criteria: any contraindication for general anaesthesia; cardiac pacemaker or ICD; vascular invasion, multifocal hepatic disease or extrahepatic tumour manifestation; prior or present cardiac arrhythmia, myocardial infarction, or significant heart failure, severe coagulation abnormalities.
Technique	Percutaneous IRE was done under general anaesthesia and mechanical ventilation with complete muscle relaxation. Between 2 and 6 electrodes were inserted to destroy the tumour and healthy liver tissue within a 1 cm safety margin around the tumour. Pulses were applied under constant electrocardiographic monitoring to avoid life-threatening arrhythmias. Device: NanoKnife (AngioDynamics, US).
Follow up	**Median 36 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up with MRI at 6 weeks and 3 months after the procedure and then at 3-monthly intervals for 2 years. After 2 years, MRI scans of the liver were done 2 times per year.

Study design issues: Retrospective, single-centre case series. CT and MRI were done after the procedure before the patients were discharged. The primary aim of the study was to assess survival after percutaneous IRE.

Study population issues: HCC was the most common diagnosis (44% [31/71]), followed by colorectal carcinoma (38% [27/71]), other metastases (13% [9/71]) and cholangiocellular carcinoma (6% [4/71]). Of the 31 patients with HCC, 42% were described as very early stage according to the Barcelona Clinic Liver Cancer system and 58% were described as early stage. The median tumour short-axis diameter was 1.9 cm (range 0.4 to 4.5).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **71** At the end of the study, 50.7% (36/71) patients were still alive. **Complete ablation, as documented during the 6-week follow up=92.2% (95/103) of lesions** (8 lesions needed retreatment because of incomplete ablation) **Median total survival=26.3 months** **Median survival of patients with primary liver cancer=26.8 months** **Median survival of patients with secondary liver cancer=19.9 months** Mean survival by tumour diameter • >3 cm=12.9 months (median 9.5 months) • ≤3 cm=24.5 months (median not reached), p<0.001 Median survival by number of lesions • 3 or more=12.4 months • No more than 2=32.8 months, p<0.005 **Local recurrence (after a median follow up of 35.7 months)=31.7% (33/103) of lesions** Mean survival in patients with HCC according to Child-Pugh status • Child-Pugh A=19.3 months (median not reached) • Child-Pugh B=14.5 months (median 9.7 months) • Child-Pugh C=12.7 months (median 10.4 months), p<0.05 Median survival in patients with HCC according to the Barcelona Liver Cancer Classification • Very early stage=22.3 months • Early stage=13.7 months, p<0.05	**Major complications during 83 procedures** • Liver abscess, n=4 • Myocardial infarction, n=1 **Minor complications during 83 procedures** • Pneumothorax, n=2 • Cardiac arrhythmia, n=2 • Haematoma, n=3 No minor complications needed further treatment
Abbreviations used: HCC, hepatocellular carcinoma; ICD, implantable cardioverter defibrillator	

Study 5 Granata V (2016)

Details

Study type	**Case series**
Country	Italy
Recruitment period	2012 to 2013
Study population and number	**n=20 (24 tumours)** Patients with hepatocellular carcinoma (HCC)
Age and sex	Mean 65 years (range 48 to 80); 60% (12/20) male
Patient selection criteria	Inclusion criteria: histologically proven diagnosis of HCC, surgical resection not suitable, 3 HCC nodules or less, nodule size ≤3 cm, Child-Pugh class A, Eastern Cooperative Oncology Group performance status of 0, ASA (American Society of Anesthesiologists) score of 3, prothrombin time ratio >50%, and platelet count >50x109/litre. Exclusion criteria: distant metastasis, tumour infiltration of the major liver vessels, recent (<6 months) myocardial infarction, cardiac arrhythmias, implanted pacemaker, renal failure, sepsis, poor life expectancy.
Technique	All procedures were done under general anaesthesia using a percutaneous approach. The mean number of needles per tumour was 4 (range 3 to 5). Device: NanoKnife (AngioDynamics, US).
Follow up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: All patients had MRI, CT and CEUS at 1, 3 and 6 months after the procedure. CT or MRI was done every 3 months in the first year and every 6 months thereafter.

Study design issues: Prospective, single-centre case series. The study objectives were to describe the effectiveness and safety of IRE, and to evaluate the MRI, CT and CEUS diagnostic accuracy. Tumours were classified as responders or non-responders according to the mRECIST guidelines. Complete response was defined as the disappearance of any enhancement in all target lesions, partial response as at least a 30% decrease in the sum of diameters of enhancing lesions, stationary disease as any cases that do not qualify for either partial response or progressive disease, progressive disease as the increase of at least 20% in the sum of the diameters of enhancing target lesions.

Study population issues: The mean tumour size was 2 cm (range 1 to 3). Mean number of treated lesions was 1.2 per patient. There were 20 well-differentiated HCCs, 3 moderately differentiated and 1 poorly differentiated lesion. Of the 24 tumours, 8 were classified as being located in difficult sites and 16 were regarded as being in non-difficult sites.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **20** **mRECIST at 1 month** • complete response (MRI and CEUS) = 91.7% (22/24) • partial response (MRI and CEUS) = 8.3% (2/24) • complete response (CT) = 100% (24/24) **mRECIST at 3 months** • complete response (MRI and CEUS) = 91.7% (22/24) • partial response (MRI and CEUS) = 8.3% (2/24) • complete response (CT) = 95.3% (23/24) • partial response (CT) = 4.7% (1/24) **mRECIST at 6 months** • complete response (MRI, CEUS and CT) = 91.7% (22/24) • partial response (MRI, CEUS and CT) = 8.3% (2/24) The 2 residual viable HCCs were treated with another single session of IRE achieving complete response.	There were no major complications 10% (2/20) of patients had an absent concentration of liver-specific contrast medium around the ablation zone. 2 patients developed complications: 1 peripheral arteriovenous shunt and 1 segmental dilation of the intrahepatic biliary ducts. Both these complications occurred along the needle tract. Neither needed any treatment.
Abbreviations used: IRE, irreversible electroporation; CEUS, contrast-enhanced ultrasound; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumours	

Study 6 Niessen C (2016)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2011 to 2013
Study population and number	**n=34** (65 tumours; 33 hepatocellular carcinomas [HCC], 5 cholangiocellular carcinoma, 22 colorectal cancer metastases, 5 other metastases) Patients with primary or secondary liver cancer
Age and sex	Mean 59 years; 79% (27/34)
Patient selection criteria	Inclusion criteria: diagnosis of primary or secondary liver cancer based in positive biopsy result or non-invasive criteria (1 tumour <5 cm, 3 tumours <3 cm); noncandidacy for conventional thermal ablation because of tumour location (located in proximity to bile duct, major hepatic artery or vein, or major portal vein branch or subcapsular or centrally located tumours or tumours adjacent to other organs such as gallbladder, stomach or colon); age 18 to 85 years; written informed consent. Exclusion criteria: resectable disease, defined as the possibility of completely removing all tumours and retaining a sufficient liver remnant to maintain liver function; severe coagulation disorders; presence of vascular invasion, multifocal hepatic disease, or extrahepatic spread on imaging; previous treatment of target nodule; patients who had systemic chemotherapy within 30 days of IRE treatment; severe heart failure, recent myocardial infarction, coronary artery disease, arrythmia in progress, active implantable devices, pregnancy or women of childbearing age not using contraception.
Technique	Procedures were done under general anaesthesia with mechanical ventilation and neuromuscular blocking, using a percutaneous approach. The number of electrodes ranged from 2 to 6 (mean 3). Device: NanoKnife (AngioDynamics, US)
Follow up	**Median 14 months (range 2 to 20)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up imaging was done at 24 hours, 6 weeks and 3 months after the procedure and then at 3-monthly intervals.

Study design issues: Prospective, single-centre case series. Complications were evaluated in accordance with the criteria established by the Society of Interventional Radiology and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Tumour response was evaluated as overall response and as tumour response of target lesions according to the mRECIST. Local recurrence-free survival was determined according to the Kaplan–Meier method.

Study population issues: Of the 65 tumours, 33 (51%) were HCC, 22 (34%) were metastatic colorectal cancer, 5 (8%) were cholangiocellular carcinoma and 5 (8%) were described as 'other'. The median largest diameter of the target lesions before ablation was 2.4 cm (range 0.2 to 7.1). Most patients with HCC had preserved liver function: 7 with Child-Pugh class A (47%), 6 with Child-Pugh class B (40%), and 2 with Child-Pugh class C (13%). Of the 34 patients, previous treatment included surgery (n=20), systemic therapy (n=15), radiofrequency ablation (n=7), hepatic arterial therapy (n=4), and radiation therapy (n=3).

Other issues: There may be some patient overlap with Niessen et al., 2017.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **34 (65 tumours)** **Complete ablation (immediately after the procedure and at 6-week follow up) = 95.4% (62/65)** A second treatment was needed in 12 tumours because of incomplete ablation (n=3) or early local recurrence (n=9). All tumours with incomplete ablation were colorectal liver metastases. Of the 9 tumours with early local recurrence, 7 were colorectal liver metastases, 1 was cholangiocellular carcinoma and 1 was hepatocellular carcinoma. **Local recurrence-free survival** • 3 months=87.4% • 6 months=79.8% • 12 months=74.8% Mean time to local recurrence=15.5 months Median time to progressive disease according to mRECIST criteria = 15.6 months **Complete response (according to mRECIST criteria)** • 3 months=86.6% • 6 months=74.2% • 12 months=61.9%	**Complication rate=27.5% (14/51) of procedures** **Major complications** • Intraperitoneal bleeding=2.0% (1/51) (the bleeding ceased spontaneously but needed blood transfusion and admission to the intensive care unit.) • Partial thrombosis of portal vein=2.0% (1/51) (the left branch of the portal vein abutted the tumour; the patient needed moderate anticoagulation.) • Abscess=7.8% (4/51) (All were in the ablation zone; 3 of the 4 patients had a bilioenteric anastomosis. Two patients needed CT-guided percutaneous drainage, in addition to systemic antibiotics, which were routinely given only in patients with bilioenteric anastomosis.) **Minor complications** • Haematoma=11.8% (6/51) • Pneumothorax=3.9% (2/51) (clinically inapparent, did not need treatment)
Abbreviations used: HCC, hepatocellular carcinomas; mRECIST, modified Response Evaluation Criteria in Solid Tumours	

Study 7 Zeng J (2017)

Details

Study type	**Case series**
Country	China
Recruitment period	2015 to 2016
Study population and number	**n=14** Patients with large or medium hepatocellular carcinoma (HCC)
Age and sex	Mean 53 years (range 24 to 78); 79% (11/14) male
Patient selection criteria	Inclusion criteria: histopathological diagnosis of primary liver cancer, preoperative performance status score ≤2, and not eligible for surgical resection. Exclusion criteria: could not tolerate anaesthesia through the trachea, severe coagulopathy insufficiency, severe liver and kidney function insufficiency, and cardiac pacemaker or defibrillator.
Technique	All procedures were done under general anaesthesia and muscle relaxants. Two monopolar probes were used. All pulses were delivered in the ventricular refractory period to avoid the occurrence of arrhythmias. Treatment was repeated to cover the entire target zone. Device: NanoKnife (AngioDynamics, US).
Follow up	**Mean 3 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were followed up with contrast-enhanced CT scans at 1 to 3 months and at 3-monthly intervals thereafter.

Study design issues: Prospective, single-centre case series. The study focused on the safety of IRE ablation for patients with large liver HCC whose tumours had maximum diameter greater than 5 cm. Complete ablation of the tumour was defined as an ablation region beyond the tumour, with clear boundaries and no evidence of arterial enhancement. Adverse events were recorded as per the unified standardised Society of Interventional Radiology grading system. Common procedural side effects such as pain, fever, and transient elevation of liver enzyme levels were excluded from the evaluation.

Study population issues: The tumour type was HCC in 7 patients (50%) and intrahepatic cholangiocellular carcinoma in 7 patients (50%). Most of the patients (79%) had Child-Pugh class A disease; 3 patients (21%) had Child-Pugh class B disease. Of the 14 patients, 8 had large tumours (diameter 5.1 to 11.5 cm) and 6 had medium size tumours (diameter 3.0 to 4.1 cm).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **14** **Large tumour group (n=8)** Complete ablation=25% (2/8) (mean follow up 2.8±2.1 months, median 2.5 months) **Medium tumour group (n=6)** Complete ablation=66.6% (4/6) (mean follow up 4.3±3.2 months, median 4.5 months)	**Large tumour group (n=8)** There was no treatment-related bleeding or other major adverse event during the perioperative period. 1 patient had intraoperative blood pressure up to 200/83 mmHg, with a suspected IRE ablation near the adrenal gland. This returned to normal after treatment with intravenous nicardipine. ***Minor adverse events*** • Hypokalaemia on postoperative day 1, n=3 (improved by oral or intravenous potassium) • Low blood pressure, low white blood cells and platelet function abnormalities, n=1 (improved by intravenous infusion of dopamine and phenylephrine or the same type of plasma) • Abdominal distension, n=4 • Limb oedema, n=2 **Medium tumour group (n=6)** There were no major adverse events during the perioperative period. 1 patient had intraoperative heart rate acceleration up to 140 beats/minute. ***Minor adverse events*** • Hypokalaemia, n=3 • Low serum albumin, n=3 • Low blood pressure, n=1 • Stomach pain, n=1
Abbreviations used: HCC, hepatocellular carcinomas; IRE, irreversible electroporation	

Study 8 Distelmaier M (2017)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2012 to 2015
Study population and number	**n=29 (8 primary tumours and 35 secondary tumours)** Patients with malignant liver tumours close to major portal or hepatic veins
Age and sex	Mean 63 years; 52% (15/29) male
Patient selection criteria	Hepatic tumour ablation was recommended in patients in whom surgical resection was considered impossible and who had no prognostically relevant extrahepatic tumour burden. IRE was offered for local ablation of primary or secondary liver malignancies that were not considered suitable for radiofrequency or microwave ablation because of the close proximity (<0.5 cm) to major hepatic or portal vein branches and bile duct structures. Patients were only included if they had no more than 3 malignant liver tumours, each smaller than 4 cm.
Technique	All procedures were done under general anaesthesia and muscle relaxants using a percutaneous approach. Between 2 and 5 unipolar probes were used (median 3). If there was insufficient ablation after the first probe placement, the probes were repositioned, and another pulse application was done. Device: NanoKnife (AngioDynamics, US).
Follow up	**Mean 24 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: All patients had MRI and CT within 24 hours of the procedure and MRI at 1,2,4,6,8 and 12 weeks after the procedure and every 3 months thereafter.

Study design issues: Prospective, single-centre case series with consecutive patients having percutaneous CT-guided IRE for hepatic malignancies. A diagnosis of incomplete ablation was made if the postinterventional CT or MR image showed residual tumour or if the ablation zone did not cover the target tumour with an adequate safety margin. In patients with complete ablation, MRI follow up was used to identify intrahepatic recurrence. Local recurrence was defined as the presence of recurrent tumour within or close (<0.5 cm) to the ablation zone. Regional recurrence was defined as the presence of a new tumour in the area of the intrahepatic pathway of the needle tract.

Study population issues: Of the 29 patients, 2 had HCC (4 tumours), 2 had cholangiocellular carcinoma (4 tumours) and the remaining patients had secondary tumours. All tumours were located immediately adjacent to major hepatic veins, portal vein branches or both.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **29** **Complete ablation=93.0% (40/43) of tumours; 89.7% (26/29) of patients** Recurrence=38.5% (10/26) of patients; 32.5% (13/40) of tumours (seen at 2 to 18 months after IRE) In 8 of the 10 patients, recurrence was regional (located along the needle tract of 1 or more of the IRE probes) and these recurrences were classified as needle tract seeding. In the remaining 2 patients, recurrence was located within the ablation zone (true local recurrences). 17.2% (5/29) of patients developed tumour progression elsewhere in the liver between 8 weeks and 24 months after IRE. Of these, 1 had another IRE treatment session, 2 had transarterial therapy and 2 had systemic chemotherapy.	**Vessel patency** All adjacent vessels remained perfused at follow up. There was no bleeding, thrombosis, vascular obliteration, stricture or narrowing. **Bile duct integrity** Mild to moderate cholestasis was reported in 23.8% (5/21) of patients with target tumours adjacent to portal veins at 2 to 6 weeks after IRE. **Other adverse events** 2 minor immediate complications (within 24 hours): • Small subcapsular haematoma without signs of active bleeding, n=1 • Small haematoma in the intercostal space (self-limiting), n=1 1 minor complication after 1 week: • Small clinically asymptomatic arterioportal fistula (within the needle tract), n=1 (no treatment needed)
Abbreviations used: HC, hepatocellular carcinomas; IRE, irreversible electroporation	

Study 9 Schotten S (2016) – conference abstract

Details

Study type	**Non-randomised comparative study**
Country	Not reported
Recruitment period	Not reported
Study population and number	**n=56 (24 IRE, 32 microwave ablation)** Patients with primary or secondary liver cancer
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	No details reported
Follow up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Other issues: The study is reported as a conference abstract, which includes limited information on the study design. The abstract only reports safety data.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **56** No efficacy data were reported.	**Complication rate** • IRE=20.8% (5/24) of patients; 1 was classified as major (4.2%) • Microwave ablation=6.2% (2/32) of patients; both were classified as major (6.2%) In the IRE group, all complications were related to haemorrhage. One patient had a large intrahepatic haematoma with liver laceration and subsequently had a laparotomy and liver packing because of haemodynamic instability. He died 3 weeks later. Another patient had a large intrahepatic haematoma and 3 patients had perihepatic haematomas that could be managed without invasive procedures or blood transfusion. In the microwave group, there were no haemorrhagic events. One patient had a gall bladder necrosis and had an emergency cholecystectomy. The patient died shortly after surgery. Another patient had a duodenal fistula with liver abscess; this was treated by endoscopic clipping and percutaneous abscess drainage.
Abbreviations used: IRE, irreversible electroporation	

Validity and generalisability of the studies

- There were no randomised controlled trials.
- One study included patients from the UK.[1]
- Most of the studies used a percutaneous approach. One study used a laparoscopic or open approach.[2]
- The patient populations were heterogeneous, with different types of liver tumours. Where possible, results for primary liver tumours have been presented separately.
- One study specifically included patients with larger hepatocellular carcinoma tumours.[7]
- Imaging methods used to assess ablation success and tumour recurrence or progression varied between studies.
- There is likely to be some patient overlap between the studies.

Existing assessments of this procedure

The Canadian Agency for Drugs and Technologies in Health published a rapid response report on 'Irreversible Electroporation for Tumors of the Pancreas or Liver: A Review of Clinical and Cost-Effectiveness' in February 2016.[10] The report concluded that:

'Irreversible electroporation appears to be feasible and safe for patients with tumors of the pancreas or liver. The percutaneous approach seems to result in fewer adverse events. IRE may be effective in increasing overall and progression-free survival in patients with unresectable tumors of the pancreas or liver, however, the conclusions are based on studies without a control group. Further research is needed in order to make definite conclusions.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

Related by indication

- Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma. NICE interventional procedures guidance 630 (2018). Available from http://www.nice.org.uk/guidance/IPG630

- Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. NICE interventional procedures guidance 488 (2014). Available from http://www.nice.org.uk/guidance/IPG488

- Selective internal radiation therapy for primary hepatocellular carcinoma. NICE interventional procedures guidance 460 (2013). Available from http://www.nice.org.uk/guidance/IPG460

- Ex-vivo hepatic resection and reimplantation for liver cancer. NICE interventional procedures guidance 298 (2009). Available from http://www.nice.org.uk/guidance/IPG298

- Microwave ablation of hepatocellular carcinoma. NICE interventional procedures guidance 214 (2007). Available from http://www.nice.org.uk/guidance/IPG214

- Radiofrequency-assisted liver resection. NICE interventional procedures guidance 211 (2007). Available from http://www.nice.org.uk/guidance/IPG211

- Laparoscopic liver resection. NICE interventional procedures guidance 135 (2005). Available from http://www.nice.org.uk/guidance/IPG135

Related by procedure

- Irreversible electroporation for treating pancreatic cancer. NICE interventional procedures guidance 579 (2017). Available from http://www.nice.org.uk/guidance/IPG579

- Irreversible electroporation for treating prostate cancer. NICE interventional procedures guidance 572 (2016). Available from http://www.nice.org.uk/guidance/IPG572

- Irreversible electroporation for treating liver metastases. NICE interventional procedures guidance 445 (2013). Available from http://www.nice.org.uk/guidance/IPG445

- Irreversible electroporation for treating renal cancer. NICE interventional procedures 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 procedures guidance 441 (2013). Available from http://www.nice.org.uk/guidance/IPG441

Technology appraisals

- Regorafenib for previously treated advanced hepatocellular carcinoma. NICE technology appraisal 555 (2019). Available from http://www.nice.org.uk/guidance/TA555

- Lenvatinib for untreated advanced hepatocellular carcinoma. NICE technology appraisal 551 (2018). Available from http://www.nice.org.uk/guidance/TA551

  Sorafenib for treating advanced hepatocellular carcinoma. NICE technology appraisal 474 (2017). Available from http://www.nice.org.uk/guidance/TA474

Additional information considered by IPAC

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. Two Specialist Adviser Questionnaires for irreversible electroporation for primary liver cancer were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufactures 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:

- A Clinical Trial Using Irreversible Electroporation for the Treatment of Liver Cancers (NCT02828865); Taiwan; single group assignment; n=40; estimated study completion date October 2018.

- Percutaneous Irreversible Electroporation in Unresectable Liver Cancer Close to Diaphragmatic Dome (NCT02329106); China; single group assignment; n=30; estimated study completion date January 2020.

References

1. Mafeld S, Wong JJ, Kibriya N et al. (2018) Percutaneous Irreversible Electroporation (IRE) of Hepatic Malignancy: A Bi-institutional Analysis of Safety and Outcomes. Cardiovascular & Interventional Radiology 21
2. Bhutiani N, Philips P, Scoggins C et al. (2016) Evaluation of tolerability and efficacy of irreversible electroporation (IRE) in treatment of Child-Pugh B (7/8) hepatocellular carcinoma (HCC). HPB: the official journal of the International Hepato Pancreato Biliary Association 18: 593-9
3. Sutter O, Calvo J, N'Kontchou G et al. (2017) Safety and Efficacy of Irreversible Electroporation for the Treatment of Hepatocellular Carcinoma Not Amenable to Thermal Ablation Techniques: A Retrospective Single-Center Case Series. Radiology 284: 877-86
4. Niessen C, Thumann S, Beyer L et al. (2017) Percutaneous Irreversible Electroporation: Long-term survival analysis of 71 patients with inoperable malignant hepatic tumors. Scientific reports 7: 43687
5. Granata V, de Lutio di Castelguidone E, Fusco R et al. (2016) Irreversible electroporation of hepatocellular carcinoma: preliminary report on the diagnostic accuracy of magnetic resonance, computer tomography, and contrast-enhanced ultrasound in evaluation of the ablated area. La Radiologia medica 121: 122-31
6. Niessen C, Beyer LP, Pregler B et al. (2016) Percutaneous Ablation of Hepatic Tumors Using Irreversible Electroporation: A Prospective Safety and Midterm Efficacy Study in 34 Patients. Journal of vascular and interventional radiology: JVIR 27: 480-6
7. Zeng J, Liu G, Li ZH et al. (2017) The Safety and Efficacy of Irreversible Electroporation for Large Hepatocellular Carcinoma. Technology in cancer research & treatment 16: 120-4
8. Distelmaier M, Barabasch A, Heil P et al. (2017) Midterm Safety and Efficacy of Irreversible Electroporation of Malignant Liver Tumors Located Close to Major Portal or Hepatic Veins. Radiology 285: 1023-31
9. Schotten S, Klockner R, Duber C et al. (2016) Comparison of the safety profile of IRE and MWA in the treatment of liver malignancies: Increased risk of bleeding after IRE? CardioVascular and Interventional Radiology 39: Supplement S391
10. Canadian Agency for Drugs and Technologies in Health (2016) Irreversible Electroporation for Tumors of the Pancreas or Liver: A Review of Clinical and Cost-Effectiveness. Rapid Response Report: Summary with Critical Appraisal. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/feb-2016/RC0748%20Irreversible%20Electroporation%20Final.pdf

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/01/2019	Issue 1 of 12, January 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/01/2019	Issue 1 of 12, January 2019
HTA database (CRD website)	21/01/2019	n/a
MEDLINE (Ovid)	21/01/2019	1946 to January 18, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	21/01/2019	January 18, 2019
EMBASE (Ovid)	21/01/2019	1974 to 2019 January 18

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

1 Electroporation/ (7380)
2 Electric Stimulation/ (111745)
3 (irrevers* adj4 (electropor* or electro-por* or electropermeab* or electro-permeab*)).tw. (547)
4 (electric* adj4 (field* or stimul* or pulse* or cell? or membrane* or pore?)).tw. (86228)
5 Electric Stimulation Therapy/ (19536)
6 IRE.tw. (1570)
7 Electrochemotherapy/ (552)
8 electrochemo*.tw. (568)
9 ((bipolar or unipolar) adj4 (pulse? or electrod* or mode?)).tw. (4224)
10 ablation techniques/ (2187)
11 ((tissue* or tumo?r*) adj4 ablat*).tw. (7730)
12 or/1-11 (195229)
13 exp Liver Neoplasms/ (154288)
14 ((liver or hepatic* or hepatocellular) adj4 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metastas* or lesion*)).tw. (145906)

15	(hepatoma* or cholangiocarcinoma* or hepatocarcinoma* or HCC).tw. (74079)
16	or/13-15 (217529)
17	12 and 16 (2358)
18	nanoknife.tw. (26)
19	17 or 18 (2378)
20	animals/ not humans/ (4505965)
21	19 not 20 (2007)

Appendix

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
Alnaggar M, Lin M, Mesmar A et al. (2018) Allogenic Natural Killer Cell Immunotherapy Combined with Irreversible Electroporation for Stage IV Hepatocellular Carcinoma: Survival Outcome. Cellular Physiology & Biochemistry 48: 1882-1893	Non-randomised comparative study n=40 FU=median 8 months	IRE combined with allogeneic natural killer cell immunotherapy significantly increases the median overall survival of patients with stage IV HCC.	The study focuses on the clinical effectiveness of IRE in combination with immunotherapy using allogenic natural killer cells.
Alnaggar M, Qaid AM, Chen J et al. (2018) Irreversible electroporation of malignant liver tumors: Effect on laboratory values. Oncology Letters 16: 3881-3888	Case series n=29	The findings of the present study indicate that hepatic injury caused by IRE is transient and self-limiting in patients with liver tumours.	Small case series focusing on liver function tests after IRE.
Beyer LP, Pregler B, Michalik K et al. (2017) Evaluation of a robotic system for irreversible electroporation (IRE) of malignant liver tumors: initial results. International journal of computer assisted radiology and surgery 12: 803-809	Case series n=35 (18 primary liver tumours) FU=6 weeks	Robotic assistance for IRE of liver tumours allows for faster procedure times with higher accuracy while reducing radiation dose as compared to the manual placement of IRE probes.	Small retrospective study focusing on the use of a robotic system.
Beyer LP, Pregler B, Niesen C et al. (2016) Stereotactically navigated percutaneous Irreversible Electroporation (IRE) compared to conventional IRE: a prospective trial. Peer J 4: e2277	Case series n=20 FU=6 weeks	Stereotactically navigated IRE demonstrated a significant reduction of procedure length and higher accuracy compared to conventional IRE. Stereotactic navigation has the potential to reduce radiation dose for the patient and the radiologist without increasing the risk of complications or impaired technical success compared to conventional IRE.	Small study comparing stereotactically navigated percutaneous IRE with conventional IRE.
Cannon R, Ellis S, Hayes D et al. (2013) Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. Journal of surgical oncology 107: 544-9	Case series n=44 (14 HCC) FU=12 months	Five patients had 9 adverse events, with all complications resolving within 30 days. Local recurrence-free survival at 3, 6, and 12 months was 97%, 95%, and 60%. There was a trend toward higher recurrence rates for tumours over 4 cm (HR 3.24, 95% CI: 0.59 to 17.89; p=0.178).	Small study with a mix of primary and secondary liver tumours.

Charpentier KP (2012) Irreversible electroporation for the ablation of liver tumors: are we there yet? Archives of surgery 147: 1053-61	Review	IRE is likely to fill a niche void for the ablation of small liver tumours abutting a major vascular structure and for ablation of tumours abutting a major portal pedicle where heat sink and collateral damage must be avoided for maximum efficacy and safety. Studies are still needed to define the short-term and long-term oncologic efficacy of IRE.	More recent studies are included.
Cheng RG, Bhattacharya R, Yeh MM et al. (2015) Irreversible Electroporation Can Effectively Ablate Hepatocellular Carcinoma to Complete Pathologic Necrosis. Journal of vascular and interventional radiology: JVIR 26: 1184-8	Case series n=6 FU=mean 10 months	After IRE, all tumours showed a complete response on follow-up imaging. Five tumours showed complete pathologic necrosis without any viable carcinoma, sharply demarcated from the surrounding hepatic parenchyma. Bile ducts within the treatment area were preserved. A single tumour treated with a bipolar IRE probe had <5% viable carcinoma cells at the periphery.	Small retrospective study of patients who subsequently had a liver transplant.
Cheung W, Kavnoudias H, Roberts S et al. (2013) Irreversible electroporation for unresectable hepatocellular carcinoma: initial experience and review of safety and outcomes. Technology in cancer research & treatment 12: 233-41	Case series n=11 FU=mean 18 months	Six patients had repeat treatments for local residual or recurrent disease; 2 of these also had IRE for distant intrahepatic recurrence. No serious complications were seen despite 7 lesions lying adjacent to important structures or organs. Four patients developed transient urinary retention and 7 developed transient local postprocedure pain. After IRE therapy, 13 (72%) lesions were completely ablated with 93% success for lesions <= 3cm (13/14). The local recurrence-free period was 18 +/- 4 months and the distance recurrence-free period was 14 +/- 6 months.	Larger or more recent studies are included.
Cohen EI, Field D, Lynskey G et al. (2018) Technology of irreversible electroporation and review of its clinical data on liver cancers. Expert review of medical devices 15: 99-106	Review	Continued development of IRE will lead to further advances in the management of previously untreatable liver cancers.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Dollinger M, Zeman F, Niessen C et al. (2016) Bile Duct Injury after Irreversible Electroporation of Hepatic Malignancies: Evaluation of MR Imaging Findings and Laboratory Values. Journal of vascular and interventional radiology: JVIR 27: 96-103	Case series n=24 (9 primary liver tumours) FU=mean 7 months	Subacute follow-up MRI showed 15 bile duct injuries (narrowing, n=8; dilation, n=7). At subacute follow up, 3 patients showed transient abnormalities of laboratory values. Short-term laboratory values were abnormal	Small retrospective study with a mix of primary and secondary liver tumours. Biliary duct dilation is

		in 1 patient as a result of local tumour recurrence. All bile duct injuries resolved over time.	described as a safety event in table 2.
Dollinger M, Beyer LP, Haimerl M et al. (2015) Adverse effects of irreversible electroporation of malignant liver tumors under CT fluoroscopic guidance: a single-center experience. Diagnostic and interventional radiology 21: 471-5	Case series n=56 (28 primary liver cancer) FU=median 10 months	Major complications occurred in 7% of IRE procedures (6/85), while minor complications occurred in 19% (16/85). The most frequent major complication was postablative abscess (5%, 4/85) which affected patients with bilioenteric anastomosis significantly more often than patients without this condition (43% vs. 1%, p=0.010). Bilioenteric anastomosis was additionally identified as a risk factor for major complications in general (p=0.002). Minor complications mainly consisted of haemorrhage and portal vein branch thrombosis.	More recent studies from the same centre are included.
Dollinger M, Muller-Wille R, Zeman F et al. (2015) Irreversible electroporation of malignant hepatic tumors - Alterations in venous structures at subacute follow-up and evolution at mid-term follow-up. PLoS ONE 10: e0135773	Case series n=43 (20 primary) FU=mean 6 months	At subacute follow up, vascular changes were found in 10% (19/191) of vessels, with partial portal vein thrombosis in 2, complete portal vein thrombosis in 3, and lumen narrowing in 14 of 19. At follow up of patients with subacute vessel alterations thrombosis had resolved in 2 of 5 cases; vessel narrowing had completely resolved in 8 of 14 cases, and partly resolved in 1 of 14 cases. The encasement of a vessel by ablation zone (OR=6.36, p<0.001), ablation zone being adjacent to a portal vein (OR=8.94, p<0.001), and the use of more than 3 IRE probes (OR=3.60, p=0.035) were independently associated with post-IRE vessel alterations.	Study focuses on alterations in venous structures after IRE.
Dollinger M, Jung EM, Beyer L et al. (2014) Irreversible electroporation ablation of malignant hepatic tumors: subacute and follow-up CT appearance of ablation zones. Journal of vascular and interventional radiology: JVIR 25: 1589-94	Case series n=34 (19 with primary liver cancer) FU=mean 5 months	Because normal findings on contrast-enhanced CT images after IRE ablation may be very similar to the typical characteristics of potential complications following ablation, such as liver abscesses, CT scans must be carefully analysed to distinguish normal results after intervention from complications requiring further treatment.	Study focuses on CT appearance of hepatic lesions after IRE.

Eisele RM, Chopra SS, Glanemann M et al. (2014) Risk of local failure after ultrasound guided irreversible electroporation of malignant liver tumors. Interventional medicine & applied science 6: 147-53	Case series n=14 (7 primary) FU=median 6 months	Local failure occurred in 21% of patients.	More recent or larger studies are included.
Eller A, Schmid A, Schmidt J et al. (2015) Local control of perivascular malignant liver lesions using percutaneous irreversible electroporation: initial experiences. Cardiovascular and interventional radiology 38: 152-9	Case series n=14 (3 HCC) FU=mean 388 days	71% (10/14) were successfully treated with no local recurrence to date. In 1 patient, initial tumour control was unclear and radiofrequency ablation (RFA) was done 4 weeks after IRE. Complications occurred in 29% (4/14) of patients. One procedure was terminated, and abdominal bleeding needed laparotomy. In 2 patients, a haemothorax needed intervention. In another patient, abdominal bleeding could be managed conservatively. No complications related to the bile ducts occurred.	Only 3 patients had primary liver cancer.
Figini M, Wang X, Lyu T et al. (2017) Preclinical and clinical evaluation of the liver tumor irreversible electroporation by magnetic resonance imaging. American journal of translational research 9: 580-590	Review	MRI plays an important role in the visualisation and characterisation of tumour before and after IRE in clinical and preclinical studies.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Froud T, Venkat SR, Barbery KJ et al. (2015) Liver Function Tests Following Irreversible Electroporation of Liver Tumors: Experience in 174 Procedures. Techniques in vascular and interventional radiology 18: 140-6	Case series n=124 (62 primary liver cancer) FU=14 months	IRE results in significant abnormalities in liver function test results, but in most of the cases, these are self-limiting, do not preclude treatment, and are similar to the changes seen after radiofrequency and cryoablation in the liver.	Study focuses on liver function tests after IRE.
Fruhling P, Nilsson A, Duraj F et al. (2017) Single-center nonrandomized clinical trial to assess the safety and efficacy of irreversible electroporation (IRE) ablation of liver tumors in humans: Short to mid-term results. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 43: 751-757	Case series n=30 (8 HCC) FU=6 months	At 3 months ablation success was 79%, and 66% at 6 months. A minor complication occurred in 6 patients (20%), 1 patient (3%) suffered from a major complication (bile duct dilation and stricture of the portal vein and bile duct). No mortalities occurred at 30 days.	Small case series with a mix of primary and secondary liver tumours.
Gonzalez-Beicos A, Venkat S, Songrug T et al. (2015) Irreversible Electroporation of Hepatic and Pancreatic Malignancies: Radiologic-Pathologic Correlation. Techniques in vascular and interventional radiology 18: 176-82	Case series n=12 (5 primary liver tumours)	The rate of complete response to IRE was 25% based on the histologic evaluation of the resected tumours. Although treatment-related vessel wall changes were noted in several cases in histologic findings,	Larger studies are included.

		there was no evidence of vascular luminal narrowing or obliteration in any of the specimens.	
Granata V, Fusco R, Catalano O et al. (2015) Percutaneous ablation therapy of hepatocellular carcinoma with irreversible electroporation: MRI findings. American journal of roentgenology 204: 1000-7	Case series n=20 FU=1 month	MRI detects characteristic morphologic and functional changes after IRE treatment.	A more recent study from the same centre is included.
Kingham TP, Karkar A M, D'Angelica MI et al. (2012) Ablation of perivascular hepatic malignant tumors with irreversible electroporation. Journal of the American College of Surgeons 215: 379-387	Case series n=28 (2 with HCC) FU=6 months	Overall morbidity=3% Complications included 1 intraoperative arrhythmia and 1 postoperative portal vein thrombosis (in a patient with metastatic colorectal cancer who had multiple earlier liver resections). At median follow up of 6 months there was 1 tumour with persistent disease (colorectal cancer liver metastasis) and 3 tumours recurred locally.	Most patients had liver metastases (only 2 patients had hepatocellular carcinoma). Results were not presented separately for the different indications.
Kourounis G, Paul T, Patrick M et al. (2017) Irreversible electroporation (Nanoknife treatment) in the field of hepatobiliary surgery: Current status and future perspectives. Journal of BUON: official journal of the Balkan Union of Oncology 22: 141-149	Review	IRE appears to be a promising technique in the field of hepatobiliary surgery. It emerges as an adequate method for the treatment of tumours of the pancreas and liver in cases where traditional methods are unavailable or deemed to have a high risk for complications.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Langan RC, Goldman DA, D'Angelica MI et al. (2017) Recurrence patterns following irreversible electroporation for hepatic malignancies. Journal of surgical oncology 115: 704-710	Case series n=40 (7 HCC tumours) FU=median 26 months	10 lesions in 9 patients recurred locally (13%, 95% CI: 8 to 22%). Median estimated time to local recurrence was not reached and no local recurrence occurred after 19 months. Factors statistically significantly associated with local recurrence included ablation zone size (HR 1.58; 95% CI 1.12 to 2.23; p=0.0093) and body mass index (HR 1.21 95% CI 1.10 to 1.34; p=0.0001).	Most patients had metastatic liver cancer.
Lencioni R, Crocetti L, Narayanan G (2015) Irreversible Electroporation in the Treatment of Hepatocellular Carcinoma. Techniques in vascular and interventional radiology 18: 135-9	Review	Safety is comparable with those of other ablation modalities. IRE has advantages over other ablation modalities with comparable success rates.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Li D, Kang J, Madoff DC (2014) Locally ablative therapies for primary and metastatic liver cancer.	Review	IRE is in preliminary phases of clinical validation, though its high safety profile, may expand the	No meta-analysis. All relevant studies are

Expert review of anticancer therapy 14: 931-45		role of local ablation to patients previously deemed ineligible.	included in table 2 or the appendix.
Li D, Kang J, Golas BJ et al. (2014) Minimally invasive local therapies for liver cancer. Cancer biology & medicine 11: 217-36	Review	New technologies such as IRE are currently being clinically investigated to further expand the patients eligible to safely have local ablation.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Lyu T, Wang X, Su Z et al. (2017) Irreversible electroporation in primary and metastatic hepatic malignancies. Medicine (United States) 96: e6386	Systematic review	In order to systemically test and establish its safety and efficacy for clinical applications, more studies still need to be conducted.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Narayanan G, Bhatia S, Echenique A et al. (2014) Vessel patency post irreversible electroporation. Cardiovascular and interventional radiology 37: 1523-9	Case series n=101 (35 HCC) FU=mean 10 months	Patients with tumours encasing or abutting vessels (n=50) showed 96% vessel patency rate within a 12-month period.	Includes a mix of primary and secondary tumours in different organs.
Narayanan G, Froud T, Lo K et al. (2013) Pain analysis in patients with hepatocellular carcinoma: irreversible electroporation versus radiofrequency ablation-initial observations. Cardiovascular and interventional radiology 36: 176-82	Non-randomised comparative study n=43	IRE is comparable to RFA in the amount of pain that patients experience, and the amount of pain medication self-administered. Both modalities were well tolerated by patients. Prospective, randomised trials are necessary to further evaluate these findings.	Study focuses on pain after the procedure.
Narayanan G, Froud T, Suthar R et al. (2013) Irreversible electroporation of hepatic malignancy. Seminars in interventional radiology 30: 67-73	Review	The procedure has a learning curve because multiple needle placements are needed within a prescribed distance, which can be challenging, and parallel placement of the probes may be hindered by issues such as intervening ribs. The actual timing of imaging follow up and the best modality for follow up are still being determined.	More recent studies are included.
Niessen C, Beyer LP, Haimerl M et al. (2018) Percutaneous irreversible electroporation of hepatocellular carcinoma: Contrast-enhanced ultrasound-findings during 1-year follow-up. Clinical Hemorheology & Microcirculation 17	Case series n=22 FU=12 months	CEUS showed a complete devascularisation of HCC tumours after IRE. Post-interventional peripheral enhancement returned to normal during follow up and may represent zones of reversible damage of cellular integrity through electroporation. A significant shrinkage of the ablation defects during 12 months of follow up was seen in all patients.	Larger studies from the same centre are included.

Niessen C, Beyer LP, Pregler B et al. (2016) Percutaneous Ablation of Hepatic Tumors Using Irreversible Electroporation: A Prospective Safety and Midterm Efficacy Study in 34 Patients. Journal of vascular and interventional radiology: JVIR 27: 480-6	Case series n=34 (15 HCC) FU=median 14 months	Local recurrence-free survival at 3, 6, and 12 months was 87%, 80%, and 75%. The median time to progressive disease according to mRECIST was 15.6 months. Overall complication rate was 28% with 6 major complications and 8 minor complications. Major complications included diffuse intraperitoneal bleeding (n=1), partial thrombosis of the portal vein (n=1), and liver abscesses (n=4). Minor complications were liver haematomas (n=6) and clinically inapparent pneumothoraxes (n=2).	A more recent study from the same centre is included.
Niessen C, Igl J, Pregler B et al. (2015) Factors associated with short-term local recurrence of liver cancer after percutaneous ablation using irreversible electroporation: a prospective single-center study. Journal of vascular and interventional radiology: JVIR 26: 694-702	Case series n=25 (48 primary liver tumours) FU=6 months	Because short distances to the surrounding vessels were not associated with early local recurrence, percutaneous IRE might provide an alternative treatment option for perivascular tumours. However, patients with larger tumour volumes appeared to be poor candidates for percutaneous IRE. Regarding the different types of treated lesions, patients with HCC had significantly better outcomes.	A more recent study with more patients and longer follow up from the same centre is included.
Padia SA, Johnson GE, Yeung RS et al. (2016) Irreversible Electroporation in Patients with Hepatocellular Carcinoma: Immediate versus Delayed Findings at MR Imaging. Radiology 278: 285-94	Case series n=20 FU=1 year	One month after IRE, 90% (18/20) of patients had complete response to treatment, and the remaining 2 patients (10%) had a partial response, with small foci of residual enhancing tumour that were completely surrounded by the ablation zone. After imaging done at 1 month, the mean long-axis length decreased 29% every 90 days, whereas the mean short-axis length decreased 30% to 39% every 90 days. The largest decrease in ablation size was seen between days 1 and 30 after IRE.	More recent or larger studies are included.
Philips P, Hays D, Martin RCG (2013) Irreversible electroporation ablation (IRE) of unresectable soft tissue tumors: learning curve evaluation in the first 150 patients treated. PloS one 8: e76260	Case series n=150 (13 HCC) FU=median 18 months	Over time, complex treatments of larger lesions and lesions with greater vascular involvement were done without a significant increase in adverse effects or impact on local relapse free survival. This evolution demonstrates the safety profile of IRE and speed of graduation to more complex lesions, which was greater than 5 cases by	Includes a mix of tumour types and locations.

		institution. IRE is a safe and effective alternative to conventional ablation with a demonstrable learning curve of at least 5 cases to become proficient.	
Ruarus AH, Vroomen LGPH, Puijk RS et al. (2018) Irreversible Electroporation in Hepatopancreaticobiliary Tumours. Canadian Association of Radiologists journal 69: 38-50	Review	IRE represents a promising technique about safety and local control for hepatopancreaticobiliary tumours ineligible for resection or thermal ablation because of their proximity to vital structures.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Ryan MJ, Willatt J, Majdalany BS et al. (2016) Ablation techniques for primary and metastatic liver tumors. World journal of hepatology 8: 191-9	Review	In limited studies, IRE has been shown to be safe and effective in the treatment of both HCC and metastatic disease especially near sensitive structures such as blood vessels and bile ducts, although continued research is needed to demonstrate long term efficacy.	More recent studies are included.
Scheck J, Bruners P, Schindler D et al. (2018) Comparison of Chronologic Change in the Size and Contrast-Enhancement of Ablation Zones on CT Images after Irreversible Electroporation and Radiofrequency Ablation. Korean journal of radiology 19: 560-567	Non-randomised comparative study n=19 (2 HCC)	The decrease in the lesion volume was significantly more rapid and more profound in patients who had treatment with IRE at all analysed time intervals compared with RFA.	Most patients did not have primary liver cancer.
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. Journal of vascular and interventional radiology: JVIR 25: 997-1011	Systematic review n=221 (49 HCC tumours)	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.	No meta-analysis. Includes tumours at different sites. All relevant studies are included in table 2 or the appendix.
Sugimoto K, Moriyasu F, Saito K et al. (2017) Multimodality imaging to assess immediate response following irreversible electroporation in patients with malignant hepatic tumors. Journal of medical ultrasonics 44: 247-254	Case series n=16 (13 with primary liver cancer) FU=median 11 months	CEUS was superior to contrast-enhanced CT and gadoxetic acid-enhanced MRI for the diagnosis of residual tumour in the subacute phase following IRE.	Small case series, focusing on imaging techniques.
Sugimoto K, Moriyasu F, Kobayashi Y et al. (2015) Irreversible electroporation for nonthermal tumor ablation in patients with hepatocellular carcinoma: initial clinical experience in Japan. Japanese journal of radiology 33: 424-32	Case series n=5 FU=mean 244 days	83% (5/6) of the tumours were successfully treated, with no local recurrence to date. In 1 lesion located in liver segment 1, residual tumour was diagnosed at 7 days after intervention by follow-up MRI. No serious	Larger studies are included.

		complications related to the IRE procedure were seen.	
Thomson KR, Cheung W, Ellis SJ et al. (2011) Investigation of the safety of irreversible electroporation in humans. Journal of Vascular and Interventional Radiology 22: 611–21	Case series n=38 (11 primary liver cancer) FU=3 months	In patients with primary HCC, complete target tumour ablation = 82.4% (14/17).	Larger or more recent studies are included.
Tian G, Zhao Q, Chen F et al. (2017) Ablation of hepatic malignant tumors with irreversible electroporation: A systematic review and meta-analysis of outcomes. Oncotarget 8: 5853-5860	Systematic review (9 studies; n=300)	The meta-analysis showed that comparing with the initial values, the longest diameter of the tumours was significantly decreased at the last follow-up months after IRE. Furthermore, the ALP, AST and total bilirubin levels were increased at 1 day after IRE while returned to baseline at the last follow-up month.	Meta-analysis included primary and secondary liver tumours. All relevant studies are included in table 2 or the appendix.
Vroomen LGPH, Petre EN, Cornelis FH et al. (2017) Irreversible electroporation and thermal ablation of tumors in the liver, lung, kidney and bone: What are the differences? Diagnostic and interventional imaging 98: 609-617	Review	For liver tumours, IRE should be considered in cases where thermal ablation is inapplicable because of tumour proximity to the biliary tree.	Review of radiofrequency, microwave and cryoablation as well as IRE for tumours at various sites.
Wiggermann P, Zeman F, Niessen C et al. (2012) Percutaneous irreversible electroporation (IRE) of hepatic malignant tumours: contrast-enhanced ultrasound (CEUS) findings. Clinical hemorheology and microcirculation 52: 417-27	Case series n=15	Using CEUS, a significant reduction in the microcirculation of the lesions, both centrally and marginally, could be detected following IRE.	Studies with longer follow up are included.
Wu LM, Zhang LL, Chen XH et al. (2019) Is irreversible electroporation safe and effective in the treatment of hepatobiliary and pancreatic cancers? Hepatobiliary & Pancreatic Diseases International 04	Review 14 studies on liver cancer (n=437)	2 patients (0.5%) with liver cancer died after IRE. Morbidity ranged from 7% to 35%. Most complications were mild. Complete response for hepatic tumours was reported as 57% to 97%.	No meta-analysis. All relevant studies are included in table 2 or the appendix.
Yang, Y, Qin Z, Du D et al. (2019) Safety and Short-Term Efficacy of Irreversible Electroporation and Allogenic Natural Killer Cell Immunotherapy Combination in the Treatment of Patients with Unresectable Primary Liver Cancer. Cardiovascular & Interventional Radiology 42: 48-59	RCT (IRE with or without natural killer cells) n=40	Patients who had combination therapy exhibited statistically significantly longer median progression-free survival (PFS) and overall survival (OS) than those who just had IRE (PFS 15.1 versus 10.6 months, $p<0.05$, OS 17.9 versus 23.2 months, $p<0.05$).	The study assessed the safety and short-term efficacy of IRE combined with allogenic natural killer cell immunotherapy.
Yeung ESL, Chung MWY, Wong K et al. (2014) An update on irreversible electroporation of liver tumours. Hong Kong medical journal 20: 313-6	Review	IRE is a potentially effective liver tumour ablative therapy that gives rise to only mild and transient side effects. Further studies with better patient selection criteria and longer follow up are needed to clarify its	More recent studies are included.

		role as a first-line liver tumour treatment modality.	
Zimmerman A, Grand D, Charpentier KP (2017) Irreversible electroporation of hepatocellular carcinoma: patient selection and perspectives. Journal of hepatocellular carcinoma 4: 49-58	Review	The safety of IRE for ablation of hepatocellular carcinoma (HCC) has been established. Outcome data for ablation of HCC by IRE are limited, but early results are encouraging and suggest equivalency to the outcomes obtained for thermal ablation for appropriately selected, small (<3 cm) tumours. Long term oncologic efficacy and histopathologic response data have not been published, and therefore, application of IRE for the treatment of HCC should still be viewed with caution.	No meta-analysis. All relevant studies are included in table 2 or the appendix.