Irreversible Elektroporation (IRE) bei Bauchspeicheldrüsen- und Leberkrebs

EUnetHTA-Report

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Ludwig Boltzmann Institut
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Wien, Juli 2019

Zusammenfassung

Einleitung: Beschreibung der Technologie und der Vergleichstherapien

minimalinvasives, nicht-thermisches Gewebeablationsverfahren

Die Irreversible Elektroporation (IRE) ist ein nicht-thermisches ablatives Verfahren, bei dem kurze, aber starke elektrische Felder mittels präzise platzierter Nadeln und mit vom Computer gesteuerte Potentialdifferenzen zwischen diesen Nadeln erzeugt werden. Durch Ablation der Zellen mittels IRE sterben die Zellen einen apoptotischen Zelltod. Aufgrund des meist nicht-thermischen Effekts wird erwartet, dass die IRE zu weniger Schäden an angrenzenden Strukturen führt als andere thermische Ablationsansätze (Radiofrequenzablation [RFA], Mikrowellenablation [MWA] und Kryoablation). So können Pankreas- und Lebertumore, die in der Nähe von großen Blutgefäßen oder anderen empfindlichen Strukturen wie Nerven und Gallenweg lokalisiert sind, ohne sie zu schädigen, entfernt werden.

IRE kann perkutan, laparoskopisch oder im Rahmen einer offenen Operation eingesetzt werden

IRE kann perkutan, laparoskopisch oder im Rahmen einer offenen Operation (Laparotomie) durchgeführt werden. In allen Fällen werden mehrere Elektroden um den Zieltumor gelegt, wobei manchmal auch eine Sonde in der Mitte platziert werden kann. Die Sonde wird unter Bildführung mittels Ultraschall (US) oder Computertomographie (CT) geführt. Der/die PatientIn benötigt eine Vollnarkose mit tiefer Sedierung und vollständiger Muskelentspannung, mit Herzsynchronisation während der Abgabe des Hochspannungsstroms.

CE-Kennzeichnung und FDA-Zulassung

Das einzige kommerziell erhältliche IRE-Gerät ist das NanoKnife System® (AngioDynamics®). Dieses System hat das Zeichen Conformité Européenne (CE) für Zellmembran-Elektroporation und die Zulassung der US Food and Drug Administration (FDA) für die Weichgewebeablation. Die Zulassungen beziehen sich nicht auf spezifische Therapie oder Behandlung bestimmter Krankheiten.

Zielgruppe und Komparatoren bei Bauchspeicheldrüsenkrebs und Leberkrebs

Pts mit inoperablem, lokal fortgeschrittenem Pankreaskrebs

Die Zielgruppe für IRE bei Bauchspeicheldrüsenkrebs sind PatientInnen mit inoperablen, lokal fortgeschrittenen Pankreastumoren. Die Standardtherapie für diese PatientInnen ist Chemotherapie mit oder ohne Strahlentherapie (Chemoradiotherapie [CRT]). Die Strahlentherapie (RT) wird typischerweise auch als palliative Option angeboten, da sie Schmerzen reduziert, aber keine positiven Auswirkungen auf das Überleben nachgewiesen wurden.

Pts mit inoperablem primärem oder sekundärem Leberkrebs

Die Zielgruppe für IRE bei Leberkrebs sind PatientInnen mit inoperablem primärem oder sekundärem Leberkrebs, die eine Kontraindikation zur Thermoablation haben. Zu den häufigsten Behandlungsmöglichkeiten gehören die transarterielle Chemoembolisation (TACE), Multikinase-Inhibitoren wie Sorafenib und Levatinib sowie die palliative und symptomatische Therapie. Typischerweise wird TACE für PatientInnen mit Erkrankungen im mittleren Stadium angeboten, die die Leberfunktion erhalten haben, während Sorafenib als Standard der systemischen Erstlinientherapie für PatientInnen in fortgeschrittenem Stadium und erhaltener Leberfunktion angesehen werden kann. PatientInnen, die an der Erkrankung im Endstadium leiden und nicht für eine Transplantation in Frage kommen, kommen möglicherweise nur für eine unterstützende symptomatische Behandlung in Frage. Die Anwendung von Strahlentherapie wurde auch in verschiedenen Stadien von Leberkrebs berichtet und wird speziell zur Schmerzlinderung bei PatientInnen mit Knochenmetastasen empfohlen.

Gesundheitsproblem: Bauchspeicheldrüsenkrebs und Leberkrebs

Bauchspeicheldrüsenkrebs ist eine der tödlichsten Krebsarten, mit mehr als 458.918 neuen Fällen (2018), die weltweit geschätzt wurden. Der Krebs schreitet schnell voran und wird oft erst im fortgeschrittenen Stadium diagnostiziert. Es wird geschätzt, dass zum Zeitpunkt der Diagnose etwa 40% der Fälle mit lokal fortgeschrittenem Bauchspeicheldrüsenkrebs (LAPC) und weitere 40% mit Metastasierung diagnostiziert werden.

Bauchspeicheldrüsenkrebs:
40% LAPC, weitere 40% metastasiert bei Diagnose

Die Zielpopulation in dieser Bewertung umfasst PatientInnen, bei denen eine nicht metastasierte, aber inoperable Erkrankung aufgrund der Beteiligung des Zöliakie-Stammes oder der oberen mesenterialen Arterie diagnostiziert wurde, die nach den Richtlinien des National Comprehensive Cancer Network (NCCN) als LAPC oder nach den Kriterien des American Joint Committee on Cancer (AJCC) als Stufe III eingestuft werden. Wiederkehrende Erkrankungen werden ebenfalls berücksichtigt.

gemäß NCCN oder AJCC Einstufung:

LAPC, auch Rezidive

Leberkrebs ist weltweit die zweithäufigste Todesursache durch Krebs. 2015 wurden 850.000 neue Fälle diagnostiziert und 810.000 Todesfälle gezählt. Das Hepatozelluläre Karzinom (HCC) ist die häufigste Form von Leberkrebs und macht 90% aller primären Krebsarten der Leber aus. Neben primären Lebertumoren - in den meisten Fällen geht dem Auftreten von primärem Leberkrebs eine Leberzirrhose voraus - sind Metastasen bei PatientInnen mit extrahepatischer Neoplasie - oft ein kolorektales Adenokarzinom - eine häufige Ursache für die Erkrankung.

Leberkrebs:
HCC am häufigsten (90%)

Primärtumor oder Metastasierung anderer Tumore

Die Zielpopulation in dieser Bewertung umfasst PatientInnen mit inoperablem (primärem oder sekundärem) Leberkrebs mit einer Kontraindikation für die thermische Ablation (wegen des Risikos von Kollateralschäden an Gallen, Gefäß- oder anderen Strukturen durch Wärmeeinwirkung).

Kontraindikation für thermische Ablation

Methoden

Im September 2018 wurde eine systematische Literaturrecherche in verschiedenen Datenbanken durchgeführt: Centre for Research and Dissemination (CRD) Database, Cochrane Library (Wiley), Embase (OVID), Medline (PubMed), Web of Science (Web of Knowledge) und Scopus (Stand Januar 2019), gefolgt von einer manuellen Suche in der Referenzliste von relevanten Studien. In Guideline Datenbanken wurden relevante Leitlinien zur aktuelle Nutzung der Technologie IRE gesucht: Guidelines International Network [GIN]-Datenbank, Trip-Datenbank, PubMed Central [PMC], CMA Infobase und Google Scholar. Laufende klinische Studien und Forschungsprojekte wurden über Clinicaltrials.gov, das EU Clinical Registry und die International Clinical Trials Registry Platform (ICTRP) gefunden.

systematische Literatursuche in 6 Datenbanken

Leitliniensuche in 5 Datenbanken

laufende Studien in 3 Registern

Der einzige zum Zeitpunkt der Suche identifizierte Hersteller (AngioDynamics®) wurde kontaktiert und gebeten, die Kurzfassung der Submissionsdatei auszufüllen und zu bestätigen, dass es sich bei dem Produkt um eine CE-gekennzeichnete Technologie handelt und dass es sich um das einzige Produkt des Unternehmens handelt, das für diese Bewertung relevant ist.

Hersteller kontaktiert

Das Autorenteam screente die Titel und Abstracts nach vordefinierten Kriterien, überprüfte die Volltexte der potenziell relevanten Artikel und schloss letztendlich auf Grundlage von Scoping-Fragen die relevanten Studien ein. Für die Bereiche klinische Wirksamkeit und Sicherheit wurden die Daten von

Abstractscreening, Auswahl der Studien

zwei AutorInnen unabhängig voneinander extrahiert und vom Ko-Autor auf Konsistenz und Genauigkeit überprüft. Diskrepanzen zwischen den AutorInnen wurden durch Diskussion und Konsultation mit dem Ko-Autor bis zur Einigung gelöst.

RoB-Bewertungen:
IHE
ROBINS-I

Das Risiko einer Verzerrung auf Studienebene wurde anhand der 20-Kriterien-Checkliste des Institute of Health Economics (IHE) für einarmige Studien (Fallserien) und des Risk of Bias in Nonrandomised Studies of Interventions (ROBINS-I) für nicht-randomisierte kontrollierte Studien (Non-RCTs) bewertet. Für die technischen Merkmale der Technologie wurde kein Qualitätsbewertungsinstrument verwendet, obwohl die Informationen durch Vergleich und Gegenüberstellung von Informationen aus verschiedenen Quellen (Hersteller, Bibliographien, offizielle Webseiten und allgemeine Internetrecherchen) validiert wurden. Danach wurden die Informationen zusammengefasst.

QoE: GRADE

Die Qualität der Evidenz wurde nach dem GRADE-System (Grading of Recommendations, Assessment, Development and Evaluation) bewertet und zusammengefasst. Eine Metaanalyse war methodisch nicht möglich, da die Studien sehr unterschiedlich sind, unter anderem in Bezug auf Populationsmerkmale, Tumorgröße, Behandlungen vor, während und nach der IRE und Dauer der Nachbeobachtung. Dementsprechend wurde eine narrative Synthese der Daten mit Hilfe von deskriptiven Statistiken durchgeführt.

Patienteninvolvierung

Zwei einzelne PatientInnen waren an der Bewertung beteiligt. Die PatientInnen wurden durch die Abteilung für Patienten-/Bürgerpflegedienste (Servicio de Atención ao Ciudadán e ao paciente) des Galizischen Gesundheitswesens (SERGAS) identifiziert. PatientInnen mit Bauchspeicheldrüsen- oder Leberkrebs, die mit anderen Methoden behandelt wurden (da sie Erfahrungen mit der Krankheit und mit Behandlungsverfahren im Allgemeinen hatten) waren dazu eingeladen.

Ergebnisse

Verfügbare Evidenz

Wirksamkeit

15 Beobachtungsstudien

8 Studien PankreasCa:
247 Pts mit IRE

Die systematische Literaturrecherche identifizierte 15 Beobachtungsstudien, die die Auswahlkriterien erfüllten, acht für Bauchspeicheldrüsenkrebs und sieben für Leberkrebs. Es wurden keine RCTs gefunden. Eine der Studien, die für Bauchspeicheldrüsenkrebs durchgeführt wurde, war ein (zweiarmiger) non-RCT, an dem 21 PatientInnen teilnahmen, die die Intervention IRE erhielten, mit einem medianen Follow-up von 8 Monaten. Die 32 PatienInnten in der Kontrollgruppe erhielten eine Form von nicht-kurativem chirurgischem Eingriff (nur Laparotomie, nicht-radikuläre Resektion, Bypassoperation, Cholezystektomie oder perkutane Biopsie). Die restlichen sieben prospektiven einarmigen Beobachtungsstudien umfassten 226 PatientInnen, die mit IRE behandelt wurden. Sechs von ihnen hatten eine mediane Nachbeobachtung von ≤12 Monaten. Die längste Nachbeobachtungszeit betrug 28 Monate.

7 Studien LeberCa:
151 Pts mit IRE

Für Leberkrebs wurden sieben prospektive einarmige Studien mit 151 PatientInnen identifiziert: es wurden 220 mit IRE behandelten Läsionen behandelt. Die durchschnittliche Nachbeobachtungszeit betrug ≤18 Monate in fünf dieser Studien und das Maximum betrug 24 Monate.

Sicherheit

Bei Bauchspeicheldrüsenkrebs unterscheiden sich die eingeschlossenen Studien nicht von jenen zur Wirksamkeit; bei Leberkrebs wurde eine Studie nicht eingeschlossen, da keine Sicherheitsergebnisse gemeldet wurden.

Klinische Wirksamkeit

Bauchspeicheldrüsenkrebs

in der Vergleichsgruppe: kein Unterschied (OS und QoL)

Tumor bleibt unverändert

Laut der einzigen Vergleichsstudie (non-RCT) unterschied sich das mediane Gesamtüberleben (OS) für PatientInnen nach IRE nicht signifikant zwischen Behandlungs- und Kontrollgruppe (10,03 versus 9,3 Monate; p = 0,053). Die Lebensqualität (QoL) nach IRE verringerte sich langsam, ohne aber statistisch signifikante Unterschiede zwischen den Gruppen zu zeigen. Nach der Definition des "Erfolgs des Verfahrens" im PICO (vgl. Hauptbericht) würden alle mit IRE behandelten PatientInnen als erfolglos behandelt definiert werden (die Größe des Tumors hat sich nach IRE nicht verändert).

in den einarmigen Studien

sehr unterschiedliche Überlebenszeiten

Das mediane Überleben nach IRE basierend auf Kaplan-Meier-Schätzungen lag in vier der einarmigen Studien zwischen 4,3 und 12 Monaten. Eine Studie berichtete von einem Überleben von 22,6 Monaten. Das Überleben nach 3 Monaten betrug ≥90% in vier einarmigen Studien mit verfügbaren Daten. Nach 6 Monaten lag die Überlebensrate zwischen 50% (95% Konfidenzintervall[CI] 18.36, 75.32) und 100% (CI nicht angegeben). Nach 12 Monaten lag die Überlebensrate zwischen 20% (95% CI 3.09, 47.47) und 90% (95% CI 65.60, 97.40). Die einzigen beiden Studien, die über 12 Monate hinaus berichteten, hatten Überlebensraten von 13,6% (95% CI 2.33, 34.71) nach 18 Monaten und 37% nach 24 Monaten.

OS ab Zeitpunkt der Diagnose: einheitlichere Ergebnisse

12 Monate: 60-79%
18 Monate: 50%
24 Monate: 14-30%

Nur drei Studien lieferten Daten zur Berechnung des OS ab dem Zeitpunkt der Diagnose. Der Median des OS in diesen Studien variierte zwischen 12,5 Monaten und 17,5 Monaten. Die Überlebensrate nach 3 und 6 Monaten in den beiden Studien, für die diese Berechnung möglich war, betrug 100%. Die jeweiligen Raten betrugen 60% (95% CI 25.27, 82.72) und 79.2% (95% CI 56.98, 90.75) nach 12 Monaten, 50% (95% CI 29.10, 67.76) und 50% (95% CI 18.36, 75.32) nach 18 Monaten und 13.9% (95% CI 3.54, 31.14) und 30% (95% CI 7.11, 57.79) nach 24 Monaten.

PFS nach IRE: 3,2-15,4 Monate
QoL: ging zurück

Die drei Studien, die über das progressionsfreie Überleben (PFS) nach IRE berichteten, zeigten ein Median OS zwischen 3,2 Monaten und 15,4 Monaten. Die QoL wurde nur in zwei der einarmigen Studien berücksichtigt: in beiden Studien ging die QoL zurück.

Leberkrebs

Gesamtüberleben: 38 Monate
OS ab Zeitpunkt der Diagnose, QoL: nicht berichtet

Das mittlere Gesamtüberleben nach IRE wurde nur aus einer Studie berichtet und betrug 37,9 Monate (95% CI 30.28, 45.57). OS nach dem Zeitpunkt der Diagnose oder PFS wurde in den Leberkrebsstudien nicht berichtet. Der mediane TTP war nur in einer Studie verfügbar, d.h. 15,6 Monate. Laut dieser Studie betrug die mittlere Zeit bis zum lokalen Wiederauftreten 15,5 Monate. Das lokale rezidiv-freie Überleben nach 3 Monaten betrug 87,4% (CI nicht berichtet), 79,8% nach 6 Monaten und 74,8% nach 12 Monaten. Keine der Studien berichtete über QoL.

Sicherheit

Bauchspeicheldrüsenkrebs

Keine der Studien berichtete über interventionsbedingte Todesfälle (während der Intervention). Insgesamt erlebten 44 von 226 behandelten Patienten (19,5%) schwere Nebenwirkungen (AEs), obwohl mindestens 16 als nicht verfahrensbezogen eingestuft wurden. Die gesamte verfahrensbezogene Mortalität (Grad V) betrug in allen Studien 1,6% (4/247 Patienten). Die Todesursachen waren Blutungen, Duodenal- und Gallengangsnekrosen sowie Pfortaderthrombosen. Die Häufigkeit von Komplikationen im Zusammenhang mit dem IRE-Verfahren des Grades III oder IV in den Studien, die relevante Daten lieferten, betrug 10,6% (Bereich 0-44%). Die Häufigkeit kleinerer (Grad I-II) Komplikationen in den Studien, die relevante Daten lieferten, betrug 32,7% (74/226). Die meisten der kleinen AEs waren gastrointestinale Probleme, Infektionen und andere wie Blutungen und Thrombosen.

SAE: 44/226 (19,5%) SAE

Grad 5 SAE: 4/247 (1,6%), Grades 3-4 (verfahrensbedingt): 10,6%
Grad 1-2: 32,7%

Leberkrebs

Keine der Studien berichtete über interventionsspezifische Todesfälle. Die Häufigkeit der wichtigsten AEs betrug 8,7% (12/138; Bereich 0-28,6%). Keine berichtete über eine verfahrensbedingte Mortalität. Zu den wichtigsten AEs gehörten Hämothorax, Hämoperitoneum, Blutungen und Verengungen der Portalvene oder des Gallengangs. Die häufigsten kleinen AEs waren Schmerzen, Hämatome und Cholestasen. Arteriovenöse Shunts, unter anderem Pneumothorax und Fistel, wurden ebenfalls berichtet.

AEs: 8,7%

In einer Studie wurde von Nadel-Trakt-Seedings berichtet, wobei 30,8% (8/26) der Patienten ein regionales Rezidiv im Nadelkanal aufwiesen (bei Tumor: 11/40).

Nadel-Trakt-Seedings

Organisatorische Aspekte

IRE benötigt Fachleute, die bereits Erfahrungen mit der Technik gesammelt haben. Es liegen keine Informationen über die Kosten im Zusammenhang mit der Anschaffung und Einrichtung von IRE-Geräten vor, aber da IRE Anästhesie und radiologische und/oder chirurgische Operationsgeräte erfordert, gelten sie als ressourcenaufwändiger als andere ablative Methoden.

ressourcenaufwändiger als andere ablative Methoden

Zukünftige Evidenz: laufende Studien

Eine Suche nach laufenden Studien ergab 22 Studien im Bereich Bauchspeicheldrüsenkrebs, von denen die meisten aber einarmige Studien sind (Stadium: Rekrutierung). Eine der Studien ist ein Patientenregister. Für Leberkrebs wurden 16 Studien gefunden (mindestens acht: Rekrutierung), die meisten davon sind einarmige Studien und einige sind auch bereits abgeschlossen: Es wurden keine entsprechenden Veröffentlichung gefunden.

PankreasCa laufend: 22 Studien, meist einarmig

LeberCa laufend: 16 Studien, meist einarmig

Tabelle 1: Zusammenfassung der Ergebnisse für IRE: Bauchspeicheldrüsenkrebs

Erfolg des Verfahrens	0	NA	Nicht abschätzbar	53 (1)	Sehr niedrig[1234]	Die Größe des Tumors hat sich nach der IRE in der Interventionsgruppe nicht verändert.
Gesamtüberleben	10.03 Monate	9.3 Monate	HR = 0.54 (p = 0.053)	53 (1)	Sehr niedrig[1256]	Das Gesamtüberleben war für IRE höher (aber nicht signifikant).
Gesamtüberleben nach 3 Monaten	90,48% (67.00, 97.53)	NA	Nicht abschätzbar	53 (1)	Sehr niedrig[1234]	
Gesamtüberleben nach 6 Monaten	75.00% (49.81, 88.80)	NA	Nicht abschätzbar	53 (1)	Sehr niedrig[1234]	
Gesamtüberleben nach 12 Monaten	47.62% (24.37, 67.71)	NA	Nicht abschätzbar	53 (1)	Sehr niedrig[1234]	
Gesamtüberleben nach 18 Monaten	13.61% (2.33, 34.71)	NA	Nicht abschätzbar	53 (1)	Sehr niedrig[1234]	
Gesamtüberleben nach 24 Monaten	--	--	--	--	--	Nicht berichtetes Ergebnis
Krebsspezifisches Überleben	--	--	--	--	--	Nicht berichtetes Ergebnis
Krankheitsfreies Überleben	--	--	--	--	--	Nicht berichtetes Ergebnis
Progressionsfreies Überleben	--	--	--	--	--	Nicht berichtetes Ergebnis
Zeit bis zum Wiederauftreten	--	--	--	--	--	Nicht berichtetes Ergebnis
Zeit bis zur Progression	--	--	--	--	--	Nicht berichtetes Ergebnis
Zeit bis zum lokalen Wiederauftreten	--	--	--	--	--	Nicht berichtetes Ergebnis

1 Das Risiko einer Verzerrung für diesen bestimmten Endpunkt wurde als sehr ernst eingestuft, aufgrund fehlender Randomisierung, weil die Patienten adjuvante Therapien erhielten, Informationen über die Patientenauswahl, Follow-up fehlten und Daten aus der Kontrolle unvollständig waren.

2 Inkonsistenzen können nicht bewertet werden, da es nur eine Studie gibt.

3 Die Indirektheit wurde mangels Vergleichsdaten als sehr schwerwiegend eingestuft.

4 Die Ungenauigkeit wurde aufgrund des geringen Stichprobenumfangs als sehr schwerwiegend eingestuft und Unterschiede zwischen den Gruppen lassen sich nicht abschätzen.

5 Die Indirektheit wurde als sehr schwerwiegend eingestuft, da es wichtige Fragen der Anwendbarkeit im Zusammenhang mit der Intervention (neoadjuvantes CHEMO und/oder CHEMO nach IRE) und dem Komparator (wenige Informationen über zusätzliche Behandlungen und Vorbehandlungen) gibt.

6 Die Ungenauigkeit war aufgrund des geringen Stichprobenumfangs sehr gravierend, kein 95% CI verfügbar, p =0,053.

Gesundheitsbezogene Lebensqualität	KPS ≥70 81% der Zeit nach IRE (IQR 65–98)	KPS ≥70 74% der Zeit nach IRE (IQR 14-88)	Nicht abschätzbar (p = 0.076)		Sehr niedrig[1254]	
Schmerzen	--	--	--	--	--	Nicht berichtetes Ergebnis

Tabelle 2: Zusammenfassung der Ergebnisse für IRE: Bauchspeicheldrüsenkrebs

Ergebnis		**Erwartete absolute Effekte (95% CI)**		**Relativer Effekt (95% CI)**	**Anzahl der Teilnehmer (Studien)**	**Qualität**	**Anmerkungen**
		Risiko mit IRE	**Risiko mit Komparator**				
Sicherheit							
Interventionsspezifische Mortalität	Vergleichend	0	NA	Nicht abschätzbar	53 (1)	Sehr niedrig[1234]	Keine interventionsspezifische Mortalität
	Einzelarm	0/226 (0%)		-	226 (7)	Sehr niedrig[78910]	Keine interventionsspezifische Mortalität
Schwere- AEs	Vergleichend	-	NA	-	-	-	Ergebnis nicht berichtet; AE nicht bewertet
	Einzelarm	44/26 (19.5%)		-	226 (7)	Sehr niedrig [7910]11	

7 Das Risiko einer Verzerrung wurde als sehr ernst eingestuft, da es nur einarmige Studien gibt, die Patienten verschiedene adjuvante Therapien erhielten, es mehrere Verzerrungen und mangelnde Informationen über die Patientenauswahl und -nachsorge gibt und die Daten unvollständig sind.

8 Die Inkonsistenz für diesen bestimmten Endpunkt wurde als nicht schwerwiegend eingestuft, da keine Todesfälle aufgetreten sind.

9 Die Indirektheit wurde wegen des Fehlens einer Kontrollgruppe und wichtiger Fragen der Übertragbarkeit im Zusammenhang mit der Intervention in den meisten Studien aufgrund unterschiedlicher Behandlungsstrategien und adjuvanter Behandlungen als sehr ernst eingestuft.

10 Die Ungenauigkeit wurde als sehr schwerwiegend eingestuft, da der Stichprobenumfang gering ist und der Effekt nicht abgeschätzt werden kann.

11 Inkonsistenz wurde als sehr schwerwiegend (sehr variabel) eingestuft.

Abkürzungen: AE = Nebenwirkung; CHEMO = Chemotherapie; HR = Hazard Ratio; IQR = Interquartilbereich; IRE = irreversible Elektroporation; KPS = Karnofsky Leistungsstatus; NA = nicht verfügbar; QoL = Lebensqualität.

Geringfügige AEs	Vergleichend	-	NA	-	-	-	Ergebnis nicht berichtet; AEs nicht bewertet
	Einzelarm	74/226 (32,7%)		-	226 (7)	Sehr niedrig[7119 10]	

Tabelle 3: Zusammenfassung der Ergebnisse für IRE: Leberkrebs

Ergebnis	**Erwartete absolute Effekte (95% CI)** Risiko mit IRE	**Relativer Effekt (95% CI)**	**Anzahl der Teilnehmer (Studien)**	**Qualität**	**Anmerkungen**
Wirksamkeit					keine Vergleichsstudien
Sicherheit					
Intervetions-spezifische Mortalität (Einzelarm)	0/138 (0%)	--	138 (6)	Sehr niedrig[1213141516]	
Schwere-AEs (Einzelarm)	12/138 (8.7%)	--	138 (6)	Sehr niedrig[13417]	
Geringfügige AEs (Einzelarm)	41/124 (33.1%)	--	124 (5)	Sehr niedrig[1534]	

12 Das Risiko einer Verzerrung wurde als sehr ernst eingestuft, da es nur einarmige Studien gibt und die Patienten verschiedene adjuvante Therapien erhielten, es gibt mehrere Verzerrungen und es mangelt an Informationen über den Patienten bzgl. Auswahl und Nachbereitung und es gibt unvollständige Daten.

2Die Inkonsistenz für diesen bestimmten Endpunkt wurde als nicht schwerwiegend eingestuft, da keine Todesfälle aufgetreten sind.

3 Die Indirektheit wurde als sehr schwerwiegend eingestuft, da es keine Kontrollgruppe gab und wichtige Aspekte der Anwendbarkeit im Zusammenhang mit der Intervention in den meisten Studien wegen der Unterschiede in den Behandlungsstrategien und den adjuvanten Behandlungen fehlten.

4 Die Ungenauigkeit wurde als sehr schwerwiegend eingestuft, da der Stichprobenumfang gering ist und der Effekt nicht abgeschätzt werden kann.

5 Inkonsistenz wurde als sehr schwerwiegend (sehr variabel) eingestuft.

Abkürzungen: AE = unerwünschtes Ereignis, CI = Konfidenzintervall; IRE = irreversible Elektroporation.

Diskussion

Die Evidenz aus den eingeschlossenen Studien ist nicht konsistent hinsichtlich der Wirksamkeit von IRE bei der Erreichung einer vollständigen Ablation, und in vielen der Studien fehlen Informationen über den Erfolg dieser. Einige AutorInnen verweisen auf die Schwierigkeit, den ablativen Erfolg und das lokale Rezidiv mit herkömmlichen bildgebenden Verfahren zu beurteilen und führen die unterschiedlichen Ergebnisse auf die Merkmale der abgetragenen Tumore, frühere Behandlungen oder darauf zurück, wie das chirurgische oder IRE-Verfahren geplant und durchgeführt wurde.

wenig konsistente Ergebnisse

Erklärung: Schwierigkeit, den ablativen Erfolg zu beurteilen

Die verfügbare Evidenz reicht nicht aus, um festzustellen, ob IRE die OS für PatientInnen mit Bauchspeicheldrüsen- oder Leberkrebs im Vergleich zur Standardversorgung wirksam verbessern würde. Für LAPC erfüllte nur eine qualitativ minderwertige, nicht-randomisierte Studie die Auswahlkriterien, und diese Studie ergab keinen Unterschied im mittleren OS, obwohl sie IRE mit nicht-kurativer Chirurgie verglich (10,03 Monate gegenüber 9,3 Monate; $p = 0,053$).

verfügbare Evidenz reicht nicht aus

Die prospektiven einarmigen Beobachtungsstudien zu LAPC lieferten nur wenige relevante Ergebnisdaten. Das relevante Ergebnis, Überleben ab dem Zeitpunkt der Diagnose, wurde nur selten berichtet. Für die drei Studien, die über dieses Ergebnis berichten, lag OS zwischen 12,5 und 17,5 Monaten, was dem Überleben in anderen Studien entspricht. Es können aber keine Annahmen getroffen werden, da die Studien nicht vergleichbar sind. Es sei darauf hingewiesen, dass die in die Studien einbezogenen PatientInnen vor oder gleichzeitig mit IRE mit verschiedenen Chemotherapien und/oder Chemoradiotherapien behandelt wurden, und es ist nicht bekannt, wie diese zum Überleben beigetragen haben könnten.

wenige relevante Ergebnisdaten

Ergebnisse vergleichbar mit Ergebnissen aus Studien zu Chemo/ Radiotherapien

Die Daten zu Lebertumoren sind noch geringer, da keine Vergleichsstudien identifiziert wurden und nur eine der einarmigen Studien Langzeitüberlebensdaten lieferte.

Es ist bemerkenswert, dass, obwohl es eines der wichtigsten Ziele im Management von lokal fortgeschrittenen Krebsarten ist, nur wenige Studien über QoL berichten. Die Ergebnisse der vorliegenden Studien, einschließlich des non-RCTs, unterstützen die Annahme, dass IRE keine signifikanten Verbesserungen in Bezug auf den Versorgungsstandard bringt. Im Gegenteil, es wurde ein Rückgang der QoL berichtet und eine Studie berichtete sogar von einem Anstieg der Schmerzen.

erstaunlich ist, dass wenig QoL Daten berichtet werden

ev. sogar Rückgang der QoL ?

Insgesamt ist die Sicherheit von IRE ein Problem. Obwohl keine interventionsbedingte Mortalität berichtet wurde, litten 1,6% der in LAPC-Studien rekrutierten PatientInnen an IRE-bezogenen AEs, die in den nächsten 30-90 Tagen zum Tod (Grad V) führten. Die Häufigkeit anderer schwerer IRE-bezogener Komplikationen war in mehreren der Studien ebenfalls relativ hoch. Allerdings war die Berichterstattung über AEs auch unter den untersuchten Studien sehr heterogen. Es wurden verschiedene Skalen für die Einstufung von AEs verwendet, es gibt keinen klaren Konsens über die Klassifizierung von IRE-bezogenen Komplikationen und Komplikationen wurden in den Studien unterschiedlich gezählt.

sehr heterogene Berichterstattung (und Messung) von Komplikationen

interventionsbedingte Mortalität: 1,6%

Eine wichtige Einschränkung des vorliegenden systematischen Reviews besteht darin, dass es unmöglich ist, eine vergleichende Analyse durchzuführen, da keine vergleichenden Informationen vorliegen. Es besteht derzeit eine große Unsicherheit darüber, wie sich IRE im Vergleich zur Behandlung ohne IRE verhält und wie Unterschiede zwischen den Untergruppen die Ergebnisse beeinflussen könnten. Es wurde beobachtet, dass die Gesamthäufigkeit von IRE-bedingten schweren AEs in den Pankreasstudien, die perkutane IRE im Vergleich zur offenen Chirurgie verwendeten, höher war, obwohl, wie bereits

keine vergleichenden Studien: große Unsicherheit

mehr Komplikationen bei perkutaner IRE als bei offener Chirurgie IRE

erwähnt, diese wenigen Studien im Hinblick auf andere Störfaktoren nicht vergleichbar sind. Dennoch könnte es wichtig sein, darauf hinzuweisen, dass einige AutorInnen berichteten, dass der perkutane Ansatz wegen abschreckender Komplikationen aufgegeben wurde.

geringe Qualität der Evidenz:

Mangel an Vergleichen
Häufig nicht berichtete Endpunkte
Fehlen standardisierter Definitionen
unklare Klassifizierung von Komplikationen

Im Allgemeinen ist die Qualität der Evidenz für beide Indikationen sehr gering. Bis heute gibt es keine veröffentlichten RCTs und die einzige vergleichende LAPC-Studie, die aufgenommen wurde, ist eine kleine Studie, die IRE mit nicht-kurativer Chirurgie (Laparotomie, nicht-radikale Resektion, Biopsie) vergleicht und frühere oder gleichzeitige Behandlungen nicht berücksichtigt. Die einarmigen Studien, die zur Feststellung der Ergebnisse zur Wirksamkeit und Sicherheit durchgeführt wurden, sind aufgrund ihrer geringen Größe, der kurzen Nachbeobachtungszeit und der stark ausgewählten Populationen, die verschiedene Arten von Behandlungen erhalten hatten, stark eingeschränkt. Daten, die die Berechnung von OS, PFS und anderen kritischen Ergebnisse wie QoL ermöglichen, fehlten ebenfalls in vielen der Studien. Dies stellt ein wesentliches Hindernis dar, um Rückschlüsse auf das Potenzial von IRE zur Behandlung dieser Tumore zu ziehen. Dies war insbesondere bei Leberkrebs der Fall, bei dem die meisten Studien nur über ein lokales Rezidiv während der Nachbeobachtung berichteten. Zu den weiteren wichtigen Mängeln gehören das Fehlen standardisierter Definitionen des Erfolgs, die unklare Klassifizierung von IRE-bezogenen Komplikationen und die unterschiedliche und mögliche Unterberichterstattung einiger Arten von AE.

zweifelhafte Übertragbarkeit der Ergebnisse:

Behandlungs-algorithmus
Begleittherapien

Auch die Übertragbarkeit der Ergebnisse ist sehr zweifelhaft. Wir beobachteten, dass die Anwendung von IRE innerhalb des Behandlungsalgorithmus in allen Studien inkonsistent war, was zu Unsicherheiten bei der Anwendung dieser Technik in der Praxis führte. Während einige Studien IRE auf PatientInnen beschränkten, die nicht auf eine Standardbehandlung ansprachen, wendeten andere diese Technik nur dann an, wenn die PatientInnen ungünstige Überlebenschancen hatten oder wenn die Krankheit nach der vorherigen Chemotherapie-Behandlung nicht voranschritt. Das Behandlungsprotokoll variierte ebenfalls erheblich; einige Studien boten Chemotherapie vor IRE und andere Chemoradiotherapie oder Induktion Chemotherapie und Chemoradiotherapie vor IRE an, während einige Chemotherapie nach IRE verwendeten. Unterschiede wurden auch in Bezug auf die Anzahl der Ablationssitzungen, die bildgebenden Verfahren und die IRE-Technik festgestellt.

prospektive Vergleichsstudien sind notwendig

Es ist von wesentlicher Bedeutung, dass angemessen konzipierte prospektive Vergleichsstudien durchgeführt werden, um die vergleichende Wirksamkeit und Sicherheit des IRE zu ermitteln. Im Idealfall handelt es sich um randomisierte Studien, die auch eine Bewertung ermöglichen, ob zusätzliche Vorteile in Bezug auf Sicherheit, Überlebensmessungen, QoL und Schmerz beobachtet werden.

Conclusio

Bauchspeicheldrüsenkrebs

Es liegt keine ausreichende Evidenz vor, um festzustellen, ob IRE bei der Behandlung von inoperablem LAPC wirksamer oder mindestens so wirksam ist wie der konventionelle Standard der Versorgung (Chemotherapie, Chemoradiotherapie oder Palliativtherapie). Es gibt keine ausreichenden Beweise, um festzustellen, ob IRE bei der Behandlung von inoperablem LAPC sicherer oder mindestens so sicher ist wie der konventionelle Standard der Versorgung (Chemotherapie, Chemoradiotherapie oder Palliativtherapie).

keine ausreichende Evidenz:

wirksamer oder gleich wirksam
sicherer oder gleich sicher

Die vorliegenden Erkenntnisse lassen Zweifel an der Wirksamkeit von IRE für die vollständige Ablation von inoperablem LAPC aufkommen. Die vorliegenden Erkenntnisse lassen Zweifel an der Wirksamkeit von IRE als einzige lokale Behandlung von LAPC aufkommen. Derzeit ist unklar, ob IRE mit Chemotherapie kombiniert werden muss und wenn ja, welche Therapien optimal sind. Es gibt Unsicherheiten bezüglich des Auftretens schwerer AEs, wenn IRE zur Behandlung von inoperablem LAPC eingesetzt wird.

im Gegenteil: Zweifel

ev. Unterlegenheit bei Wirksamkeit und Sicherheit ?

Leberkrebs

Es fehlen Daten, um festzustellen, ob IRE bei der Behandlung von PatientInnen mit primärem oder sekundärem, inoperablem Leberkrebs, der nicht für die thermische Ablation geeignet ist, effektiver oder mindestens so effektiv ist wie der konventionelle Standard der Versorgung (TACE, Sorafenib oder Palliativtherapie). Es fehlen Belege dafür, ob IRE sicherer oder mindestens so sicher ist wie der konventionelle Versorgungsstandard (TACE, Sorafenib oder Palliativtherapie) für die Behandlung von PatientInnen mit primärem oder sekundärem inoperablem Leberkrebs, der nicht für die thermische Ablation geeignet ist.

keine Daten:

wirksamer oder gleich wirksam
sicherer oder gleich sicher

Die vorliegenden Erkenntnisse lassen Zweifel an der Wirksamkeit von IRE für die vollständige Ablation von primären oder sekundären inoperablen Lebertumoren aufkommen, die für die thermische Ablation nicht geeignet sind. Die vorliegenden Erkenntnisse lassen Zweifel an der Wirksamkeit von IRE als alleinige primäre lokale Behandlung von primären oder sekundären Lebertumoren aufkommen, die nicht für die thermische Ablation geeignet sind.

im Gegenteil: Zweifel

ev. Unterlegenheit bei Wirksamkeit und Sicherheit ?

Bei der Anwendung von IRE zur Behandlung von Lebertumoren, die nicht für die thermische Ablation geeignet sind, gibt es Unsicherheiten hinsichtlich des Auftretens von schweren AEs.

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

IRREVERSIBLE ELECTROPORATION FOR THE TREATMENT OF LIVER AND PANCREATIC CANCER

Project ID: OTCA15

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Disclaimer

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Two Spanish patients with the disease were involved in the assessment. Details of their involvement are provided in the assessment.

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Conflict of interest

All authors, dedicated reviewers and external experts involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form.

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LIST OF ABBREVIATIONS

AE	Adverse event
AJCC	American Joint Committee on Cancer
BCLC	Barcelona Clinic for Liver Cancer
CE	Conformité Européenne
CHEMO	Chemotherapy
CI	Confidence interval
CRD	Centre for Research and Dissemination
CRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUR	Current use of the technology
DATECAN	Definition for the Assessment of Time-to-event Endpoints in CANcer trials
DOICU	Declaration of interest and confidentiality undertaking of interest
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFF	Clinical effectiveness
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol – five dimensions
ESMO	European Society for Medical Oncology
ESRC	Economic and Social Research Council
ETH	Ethical
EUnetHTA	European Network for Health Technology Assessment
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FOLFIRINOX	Fluorouracil, leucovorin, irinotecan and oxaliplatin
GEPAC	*Grupo Español de Pacientes con Cáncer* (Spanish Group of Patients with Cancer)
GIN	Guidelines International Network
GMDN	Global Medical Device Nomenclature
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IHE	Institute of Health Economics
IRE	Irreversible electroporation
IQR	Interquartile range

KPS	Karnofsky performance status
LAPC	Locally advanced pancreatic cancer
LEG	Legal
LR	Liver resection
LT	Liver transplantation
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MRI	Magnetic resonance imaging
MWA	Microwave ablation
NA	Not available
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORG	Organisational
OS	Overall survival
pANin	Preinvasive pancreatic intraepithelial neoplasia
PET	Positron emission tomography
PICO	P: patient, problem or population; I: intervention; C: comparison, control or comparator; O: outcome
PFS	Progression-free survival
PMC	PubMed Central
QoL	Quality of life
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RFA	Radiofrequency ablation
RFID	Radiofrequency identification
ROBINS-I	Risk of Bias in Nonrandomised Studies of Interventions
RT	Radiotherapy
SAF	Safety
SD	Standard deviation
SEOM	Spanish Society of Medical Oncology
SIR	Society of Interventional Radiology
SOC	Social
TACE	Transarterial chemoembolisation
TEC	Description and current use of the technology
TTP	Time to progression
UPN	Universal product number
US	Ultrasound
WW	Watchful waiting

SUMMARY OF THE RELATIVE EFFECTIVENESS OF IRREVERSIBLE ELECTROPORATION

Scope

The scope can be found here: Scope.

Introduction

Description of technology and comparators

Irreversible electroporation (IRE) is a nonthermal ablative method involving the application of short high-voltage and low-frequency electric fields to create nanoscale pores in tissue, resulting in permeabilisation of cell membranes. This permeabilisation can become irreversible when the magnitude, duration and number of the electrical fields applied are above a certain threshold [1] (B0001). Because of the mostly nonthermal effect, it is alleged that IRE leads to less damage to adjacent structures in comparison to other thermal ablative approaches (radiofrequency ablation [RFA], microwave ablation [MWA] and cryoablation). This allows ablation of pancreatic and liver tumours that are localised close to major blood vessels or other sensitive structures such as nerves and the bile duct without causing them damage.

IRE can be performed percutaneously, laparoscopically or as part of open surgery (laparotomy) [2]. In all cases, the procedure involves placing multiple electrodes around the target tumour, although sometimes a probe can also be placed in the centre of the nodule. The probe is directed under image guidance via ultrasound (US) or computed tomography (CT). The patient requires general anaesthesia with deep sedation and complete muscle relaxation, with cardiac synchronisation during delivery of the high-voltage current (B0001, B0009).

The only commercialised IRE device is the NanoKnife System® (AngioDynamics®). This system has the Conformité Européenne (CE) mark for cell membrane electroporation and US Food and Drug Administration (FDA) approval for soft tissue ablation. It has not received clearance for therapy or treatment of any specific disease or condition (B0003, A0020).

Comparators in pancreatic cancer

The intended population for IRE is patients diagnosed with unresectable locally advanced pancreatic tumours. The standard-of-care therapy for these patients is chemotherapy (CHEMO), with or without radiation therapy (chemoradiotherapy [CRT]). Radiotherapy (RT) is also typically offered as a palliative option as it reduces pain, but positive effects on survival have not been demonstrated (B0001).

Comparators in liver cancer

The intended population for IRE consists of patients with unresectable primary or secondary liver cancer who have a contraindication to thermal ablation. The most common treatment options include transarterial chemoembolisation (TACE), multikinase inhibitors such as sorafenib and levatinib, and palliative and symptomatic therapy. Typically, TACE is offered to patients with intermediate-stage disease who have preserved liver function, while sorafenib can be considered the standard first-line systemic therapy for patients with more advanced cancers and preserved liver function. Patients who have end-stage disease and are not candidates for a transplant might only be eligible for supportive palliative care and symptomatic treatment. The use of external beam RT has also been reported in different stages of liver cancer, and is specifically recommended for alleviating pain in patients with bone metastases (B0001).

Health problem

Pancreatic cancer

Cancer of the pancreas is one of the most lethal cancer types, with more than 458,918 new cases estimated in 2018 worldwide [3] (A0002). The cancer progresses rapidly and is often diagnosed when it is at an advanced stage (A0004). It is estimated that at the time of diagnosis, approximately 40% of cases are diagnosed with locally advanced pancreatic cancer (LAPC) and another 40% with metastatic disease [4] (A0023).

The target population in this assessment includes patients diagnosed with nonmetastasised but unresectable disease due to involvement of the coeliac trunk or superior mesenteric artery, classified as LAPC according to the National Comprehensive Cancer Network (NCCN) guidelines or as stage III by the American Joint Committee on Cancer (AJCC) criteria. Recurrent disease will also be considered (A0007).

Liver cancer

Liver cancer is the second most frequent cause of death from cancer worldwide [5].There were 850,000 new cases diagnosed in 2015 and 810,000 deaths [6]. Estimates for Europe in 2018 showed a 5-year prevalence of 8.7% [3].

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for 90% off all primary cancers of the liver. A more frequent cause of liver tumours besides primary liver tumours is metastases in patients with extrahepatic neoplasia, which is often a colorectal adenocarcinoma [7] (A0002). Some authors have reported hepatic metastases in as many as 40–50% of adult patients with extrahepatic primary tumours [8] (A0023). In most cases, the onset of primary liver cancer is preceded by cirrhosis of the liver (A0004).

The target population in this assessment includes patients diagnosed with unresectable (primary or secondary) liver cancer with a contraindication for thermal ablation (because of the risk of collateral damage to biliary, vascular or other structures due to the effect of heat) (A0007).

Methods

A systematic literature search was carried out on 26 September 2018 (and updated in January 2019) using the Centre for Research and Dissemination (CRD), Cochrane Library (Wiley), Embase (OVID), Medline (PubMed), Web of Science (Web of Knowledge) and Scopus. A manual search of the reference list of relevant studies was also undertaken to recover published studies that might have been missed by the search. Detailed tables on the search strategy are included in Appendix 1.

Guideline repositories were used to identify relevant guidelines for the current use of the technology (CUR) domain (Guidelines International Network [GIN] database, Trip database, PubMed Central [PMC], CMA Infobase and Google Scholar). Ongoing clinical trials and research projects were found through Clinicaltrials.gov, the EU Clinical Registry and the International Clinical Trials Registry Platform (ICTRP).

The only manufacturer identified at the time of the search (AngioDynamics®) was also contacted by the EUnetHTA Joint Action 3 WP4 Project Manager and asked to fill in the short version of the submission file and to confirm that the product is a CE marked technology and that it is the only product produced by the company that is relevant for this assessment.

The authoring team independently screened the titles and abstracts according to the predefined inclusion criteria. The full text of potentially relevant articles was read, and studies were included or excluded on the basis of scoping questions. For the clinical effectiveness (EFF) and safety (SAF) domains, data were extracted independently by two authors and double-checked regarding consistency and accuracy by the co-author. Discrepancies between authors in relation to data were resolved through discussion and consultation with the co-author until agreement was reached.

The risk of bias at the study level was assessed using the Institute of Health Economics (IHE) 20-Criteria Checklist [9] for single-arm studies (case series) and Risk of Bias in Nonrandomised Studies of Interventions (ROBINS-I) for nonrandomised controlled trials (non-RCTs) [10]. No quality assessment tool was used for the technical characteristics of the technology (TEC) and CUR domains, although information was validated by comparing and contrasting information from multiple sources (manufacturers, bibliography searches, official web pages and general Internet searches). Information was synthesised in a descriptive manner.

The quality of the body of evidence was assessed and synthesised according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. A meta-analysis or pooling of data was not methodologically possible because of the great variability between trials in terms of population characteristics, tumour size, treatments before, concomitant with and after IRE and length of follow-up, among other parameters. Accordingly, a narrative synthesis of the data is reported using descriptive statistics to summarise quantitative measures.

Two individual patients were involved in the assessment. Individual patients were identified through the Department of Patient/Citizen Care Services (*Servicio de Atención ao Ciudadán e ao paciente*) of the Galician Health Service (*SERGAS*). Participation was opened to patients with pancreatic or liver cancer who have undergone treatment with other ablative methods (as experiences with the disease and ablative methods will generally be shared).

Results

Available evidence

Effectiveness

The systematic literature search identified 15 observational studies that met the eligibility criteria, eight for pancreatic cancer and seven for liver cancer. No RCTs were found. One of the studies included for pancreatic cancer was a non-RCT that included 21 patients receiving the intervention, with median follow-up of 8.19 months [11]. The 32 patients in the control group received some type of noncurative surgery (laparotomy, nonradical resection, bypass surgery, cholecystectomy or percutaneous biopsy only). The remaining seven prospective single-arm observational studies enrolled 226 patients treated with IRE. Six of these had median follow-up of ≤12 months. The longest follow-up was 28.1 months.

For liver cancer, seven prospective single-arm trials were included involving 151 patients with 220 IRE-treated lesions. The mean follow-up was ≤18 months in five of these studies and the maximum recorded was 24 months.

Summary-of-findings tables (GRADE approach) are presented in Tables 1 and 2. For the EFF domain, only comparative trial data are included.

Safety

For pancreatic cancer, articles included in the SAF domain do not differ from those for the EFF domain. For liver cancer, one study [12] was not included as safety outcomes were not reported.

Clinical effectiveness

Pancreatic cancer

According to the only comparative study [11], the median overall survival (OS) for patients after IRE did not differ significantly between the treatment and control group (10.03 versus 9.3 months; $p = 0.053$) (D0001). The quality of life (QoL) after IRE declined slowly, without statistically significant differences between groups (D0013). According to the definition of “success of the procedure” in the PICO (P: patient, problem or population; I: intervention; C: comparison, control or comparator; O:

outcome) question, all patients treated with IRE would be defined as unsuccessfully treated (the size of the tumour did not change after IRE).

The median survival after IRE based on Kaplan-Meier estimations ranged from 4.3 to 12 months in four of the single-arm trials [13–16]. One study reported survival of 22.6 months [17]. The survival at 3 months was ≥90% in the four single-arm studies [14,15,17,18] with data available (D0001). At 6 months, the survival rate ranged from 50% (95% confidence interval [CI] 18.36, 75.32) [15] to 100% (CI not provided) [17]. At 12 months the survival rate ranged from 20% (95% CI 3.09, 47.47) [15] to 90% (95% CI 65.60, 97.40) [17,18]. The only two studies reporting beyond 12 months had survival rates of 13.6% (95% CI 2.33, 34.71) at 18 months [11] and 37% at 24 months [17].

Only three studies provided data to calculate OS from the time of diagnosis [14–16]. The median OS in these studies varied from 12.5 months to 17.5 months. The survival rate at 3 and 6 months in the two studies for which this calculation was possible [14,15] was 100%. The respective rates were 60% (95% CI 25.27, 82.72) and 79.2% (95% CI 56.98, 90.75) at 12 months, 50% (95% CI 29.10, 67.76) and 50% (95% CI 18.36, 75.32) at 18 months, and 13.9% (95% CI 3.54, 31.14) and 30% (95% CI 7.11, 57.79) at 24 months.

The three studies that reported on progression-free survival (PFS) after IRE showed median OS between 3.2 months and 15.4 months [14,16,17] (D0001).

Of the seven single-arm studies, only one provided information regarding the actual success of the procedure (according to the PICO definition for this assessment), which was 96% [19]. One study reported time to progression (TTP) [14], which was 3.3 months (95% CI 2.30, 6.38). The median time to local recurrence varied from 6.8 months to 12 months [13,14,16] (D0006).

QoL was only considered in two of the single-arm studies. In the study by Scheffer et al. [16] some QoL items declined after IRE. QoL also declined in the study by Paiella et al. [15]: the median pre-operative QoL score of 58.3 declines to 37.5 at 2 weeks and 33.33 at 3 months after IRE (D0013).

Liver cancer

The mean OS after IRE was only available from one study [20], which was 37.9 months (95% CI 30.28, 45.57). OS from the time of diagnosis or PFS was not reported in the liver cancer studies (D0001).

The outcome “success of the procedure” according to the PICO question was not available in any of the studies, although incomplete definitions of success were provided in five studies [21–25]. The median TTP was only available in one study [25], which was 15.6 months. According to this study, the mean time to local recurrence was 15.5 months. Local recurrence-free survival at 3 months was 87.4% (CI not reported), 79.8% at 6 months and 74.8% at 12 months (D0006).

None of the studies reported QoL. However, two provided information on postprocedural pain as a complication (D0013).

Safety

Pancreatic cancer

None of the studies reported intervention-specific deaths (during the intervention). In total, 44 out of 226 treated patients (19.5%) experienced major adverse events (AEs) although at least 16 were not considered procedure-related by the authors. The overall procedure-related mortality (grade V AE) was 1.6% (4/247 patients) among all studies. The causes of death were haemorrhage, duodenal and bile duct necrosis and portal vein thrombosis. The frequency of grade III or IV IRE procedure-related complications in the studies that provided relevant data was 10.6% (range 0–44%). For patients who underwent IRE for primary control, the frequency was 5.6% (6/107) for open surgery (>90% of cases) and 20.3% (14/69) for the percutaneous approach (C0008).

The frequency of minor (grade I–II) complications in the studies that provided relevant data was 32.7% (74/226). The frequency of procedure-related AE was 13.1% (14/107) among open surgery

cases and 31.9% (22/69) among percutaneous IRE cases. Most of the minor AEs were gastrointestinal problems, infection and others such as bleeding and thrombosis (C0008).

Liver cancer

None of the studies reported intervention-specific deaths. The overall frequency of major AEs was 8.7% (12/138; range 0–28.6%). None reported procedure-related mortality. Major AEs included haemothorax, haemoperitoneum, bleeding and stricture of the portal vein or bile duct. The most common minor AEs were pain, haematomas and cholestasis. Arteriovenous shunts, pneumothorax and fistula, among others, were also reported (C0008).

Needle-tract seeding was reported in one study [22], with 30.8% (8/26) of patients experiencing regional recurrence in the needle tract (by tumour: 11/40). Granata et al. [24] reported that two minor AEs occurred along the needle tract (C0008).

Organisational aspects

IRE requires professionals who have acquired previous experience with the technique [26] (G0003). No information exists regarding costs related to IRE equipment acquisition and set up (G0006), but given that IRE requires anaesthesia and radiological and/or surgical operating equipment, it is deemed costlier in terms of resources than other ablative methods [5] (G0007).

Upcoming evidence

A search for ongoing studies identified 22 trials in the pancreatic cancer setting, most of which are single-arm trials that are still recruiting patients. One of the studies is a patient registry. For liver cancer, 16 trials were found, of which at least eight are still recruiting. Most of these are single-arm trials and some are finished, but no publication was found.

Table 1. Summary-of-findings table for IRE: Pancreatic cancer

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with IRE	Risk with comparator				
Effectiveness (comparative trials)						
Success of the procedure	0	NA	Not estimable	53 (1)	Very low[1,2,3,4]	The size of the tumour did not change after IRE in the intervention group
Overall survival	10.03 months	9.3 months	HR = 0.54 (p = 0.053)	53 (1)	Very low[1,2,5,6]	Overall survival was higher (but not significantly) for IRE
Overall survival at 3 months	90.48% (67.00, 97.53)	NA	Not estimable	53 (1)	Very low[1,2,3,4]	
Overall survival at 6 months	75.00% (49.81, 88.80)	NA	Not estimable	53 (1)	Very low[1,2,3,4]	
Overall survival at 12 months	47.62% (24.37, 67.71)	NA	Not estimable	53 (1)	Very low[1,2,3,4]	
Overall survival at 18 months	13.61% (2.33, 34.71)	NA	Not estimable	53 (1)	Very low[1,2,3,4]	
Overall survival at 24 months	--	--	--	--	--	Outcome not reported
Cancer-specific survival	--	--	--	--	--	Outcome not reported
Disease-free survival	--	--	--	--	--	Outcome not reported
Progression-free survival	--	--	--	--	--	Outcome not reported
Time to recurrence	--	--	--	--	--	Outcome not reported
Time to progression	--	--	--	--	--	Outcome not reported
Time to local recurrence	--	--	--	--	--	Outcome not reported
Health-related quality of life	KPS ≥70 81% of the time after IRE (IQR 65–98)	KPS ≥70 74% of the time after IRE (IQR 14-88)	Not estimable (*p* = 0.076)	53 (1)	Very low[1,2,5,4]	
Pain	--	--	--	--	--	Outcome not reported

Outcome		Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
		Risk with IRE	Risk with comparator				
Safety							
Intervention-specific mortality	Comparative	0	NA	Not estimable	53 (1)	Very low[1,2,3,4]	No intervention-specific mortality
	Single arm	0/226 (0%)		–	226 (7)	Very low[7,8,9,10]	No intervention-specific mortality
Major AEs	Comparative	–	NA	–	--	--	Outcome not reported; AE not graded
	Single arm	44/226 (19.5%)		–	226 (7)	Very low[7,11,9,10]	
Minor AEs	Comparative	–	NA	–	--	--	Outcome not reported; AEs not graded
	Single arm	74/226 (32.7%)		–	226 (7)	Very low[7,11,9,10]	

[1] The risk of bias for this particular endpoint was categorised as very serious because of the lack of randomisation, patients received adjuvant therapies, lack of information on patient selection, follow-up and incomplete data from the control.
[2] Inconsistency cannot be assessed because there is only one study.
[3] Indirectness was categorised as very serious owing to the lack of comparative data.
[4] Imprecision was categorised as very serious owing to the small sample size and differences between groups cannot be estimated.
[5] Indirectness was categorised as very serious because there are important applicability issues related to the intervention (neoadjuvant CHEMO and/or CHEMO after IRE) and comparator (few information regarding additional treatments and pretreatments).
[6] Imprecision was very serious due to small sample size, no 95% CI available, $p = 0.053$.
[7] The risk of bias was categorised as very serious because there are only single-arm studies, patients received different adjuvant therapies, there are several biases and a lack of information on patient selection and follow-up and there are incomplete data.
[8] Inconsistency for this particular endpoint was categorised as not serious because no deaths occurred.
[9] Indirectness was categorised as very serious because of the lack of control group and important applicability issues related to the intervention in most studies owing to differences in treatment strategies and adjuvant treatments.
[10] Imprecision was categorised as very serious because the sample size is small and the effect cannot be estimated.
[11] Inconsistency was categorised as very serious (highly variable).
Abbreviations: AE = adverse event; CHEMO = chemotherapy; HR = hazard ratio; IQR = interquartile range; IRE = irreversible electroporation; KPS = Karnofsky performance status; NA = not available; QoL = quality of life.

Table 2. Summary-of-findings table for IRE: Liver cancer

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with IRE				
Effectiveness					**No comparative trials**
Safety					
Intervention specific mortality (single arm)	0/138 (0%)	–	138 (6)	Very low[1,2,3,4]	
Major AEs (single arm)	12/138 (8.7%)	–	138 (6)	Very low[1,5,3,4]	
Minor AEs (single arm)	41/124 (33.1%)	–	124 (5)	Very low[1,5,3,4]	

[1] The risk of bias was categorised as very serious because there are only single-arm studies, patients received different adjuvant therapies, there are several biases and a lack of information on patient selection and follow-up and there are incomplete data.
[2] Inconsistency for this particular endpoint was categorised as not serious because no deaths occurred.
[3] Indirectness was categorised as very serious owing to the lack of a control group and important applicability issues related to the intervention in most studies because of differences in treatment strategies and adjuvant treatments.
[4] Imprecision was categorised as very serious because the sample size is small and the effect cannot be estimated.
[5] Inconsistency was categorised as very serious (highly variable).
Abbreviations: AE = adverse event, CI = confidence interval; IRE = irreversible electroporation.

Discussion

Evidence from the studies included is not consistent regarding the effectiveness of IRE in achieving complete ablation, and information regarding success is lacking in many of the studies. Some authors refer to the difficulty in assessing ablative success and local recurrence using conventional imaging modalities [19,20,24], and attribute the different results to characteristics of the tumours ablated, prior treatments or to how the surgical or IRE procedure was planned and performed [17].

The evidence available is insufficient to establish if IRE would be effective in improving OS for patients with pancreatic or liver cancer when compared to the standard of care. For LAPC, only one low-quality nonrandomised trial [11] met the eligibility criteria and this trial found no difference in mean OS, despite comparing IRE to noncurative surgery (10.03 months versus 9.3 months; $p = 0.053$).

The prospective single-arm observational trials on LAPC provided few relevant outcome data. The critical effectiveness-related survival outcome would be OS from the time of diagnosis. For the three studies reporting on this outcome, OS ranged from 12.5 to 17.5 months, which is in the OS range found in the latest CHEMO trials [27], but no assumptions can be made given that the studies lack comparability. It should be noted that the patients included in the trials were treated with different CHEMO and/or CRT regimens before or concurrent with IRE, and it is not known how these might have contributed to OS or control rates.

Data regarding liver tumours are even more limited, as no comparative trials have been identified and only one of the single-arm studies provided long-term survival data [20].

It is noteworthy that despite being one of the most relevant goals in the management of locally advanced cancers, few studies report on QoL. The results from these studies, including the one non-RCT [11], do not support significant improvements with respect to standard of care. On the contrary, they found a decrease in QoL [15,16] and one study reported increases in pain scores [16].

Overall, the safety of IRE is a concern. Although no intervention-specific mortality was reported, 1.6% of the patients recruited in LAPC studies suffered from IRE-related AEs that led to death (grade V) during the next 30–90 days. The frequency of other severe IRE-related complications was also relatively high in several of the trials [13,16,25]. However, the reporting of AEs was also very heterogeneous among the studies included. Different scales for grading AEs were used, there is no clear consensus regarding the classification of IRE-related complication and complications were counted differently among studies.

An important limitation of the present systematic review is that it is the impossible to carry out a comparative analysis to assess how the tumour location and size and the approach could affect SAF outcomes. There is currently great uncertainty regarding how IRE compares to treatment without IRE and how differences between subgroups could influence results. We observed that the overall frequency of IRE-related severe AEs was higher in the pancreatic studies that used percutaneous IRE in comparison to open surgery, although as already noted, these few studies are not comparable in terms of other confounding factors. Nonetheless, it might be important to note that some authors reported that the percutaneous approach was abandoned because of discouraging complications [11].

In general, the quality of the evidence is very low for both indications. To date, there are no published RCTs and the only comparative LAPC trial that was included is a small propensity-matched trial that compares IRE to noncurative surgery (laparotomy, nonradical resection, biopsy) and does not take into account previous or concurrent treatments [11]. The single-arm trials included to ascertain EFF or SAF outcomes are greatly limited by their small size, short follow-up period and highly selected populations that had received different types of treatments. Data allowing calculating OS, PFS and other critical measures of EFF such as QoL were also missing in many of the trials. This constitutes an important impediment to drawing any conclusions regarding the potential of IRE for treating these tumours. This was especially noticeable for liver cancer, for which most trials only reported on local recurrence during follow-up. Among other important shortcomings are the lack of standardised definitions regarding success, the unclear classification of IRE-related complications and different and possible underreporting of some types of AE.

The applicability of the EFF and SAF results is also very doubtful. We observed that application of IRE within the treatment algorithm was inconsistent across studies, raising uncertainties regarding the use of this technique in real practice. For example, while some studies restricted IRE to patients unresponsive to standard treatment [15], others only applied this technique when patients had favourable survival characteristics [14] or when the disease did not progress after previous CHEMO treatment [17]. The treatment protocol also varied substantially; some studies offered CHEMO before IRE and others CRT or induction CHEMO and CRT before IRE, while several used CHEMO after IRE. Differences were also noted regarding the number of ablative sessions, the imaging modalities and IRE technique, with no formal consensus regarding the considerations that should be taken into account to identify tumours for which IRE might be more beneficial.

It is essential that appropriately designed prospective comparative trials are carried out to determine the comparative effectiveness and safety of IRE. Ideally, these would be randomised trials that would also allow evaluation of whether additional benefits are observed in terms of safety, survival measures, QoL and pain.

Conclusion

Pancreatic cancer

There is insufficient evidence to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (CHEMO, CRT or palliative therapy) for the treatment of unresectable LAPC.

There is insufficient evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (CHEMO, CRT or palliative therapy) for the treatment of unresectable LAPC.

The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of unresectable LAPC.

The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for LAPC. Currently, it is unclear whether IRE needs to be combined with CHEMO and, if so, which regimens are optimal.

There are uncertainties regarding the occurrence of severe AEs when IRE is used for the treatment of unresectable LAPC.

Liver cancer

There is a lack of data to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (TACE, sorafenib or palliative therapy) for the treatment of patients with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.

There is a lack of evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (TACE, sorafenib or palliative therapy) for the treatment of patients with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.

The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of primary or secondary unresectable liver tumours that are not suitable for thermal ablation.

The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for primary or secondary liver tumours that are not suitable for thermal ablation.

There are uncertainties regarding the occurrence of severe AEs when IRE is used for the treatment of liver tumours that are not suitable for thermal ablation.

1 SCOPE

Description	Project scope
Population	**The diseases of interest are:** • Pancreatic neoplasm. MeSH terms: C04.588.274.761, C04.588.322.475, C06.301.761, C06.689.667, C19.344.421; malignant neoplasm of pancreas International Classification of Diseases (ICD)-10: C25 • Liver neoplasms. MeSH terms: C04.588.274.623, C06.301.623, C06.552.697; malignant neoplasm of liver ICD-10: C22; malignant neoplasm metastasis in liver ICD-10: C78-7 **The target populations are:** • Patients with histologically proven unresectable LAPC/stage III. The following subgroups will be considered: ◊ Patients who have already received CHEMO and/or RT after which the tumour did not progress ◊ Patients who have already received CHEMO and/or RT after which the tumour becomes resectable; IRE is applied for margin accentuation ◊ Patients who have not received CHEMO or RT • Patients with unresectable primary or secondary liver cancer and a contraindication for thermal ablation The following subgroups will be considered: ◊ Patients with primary liver cancer ◊ Patients with secondary liver cancer, differentiated by origin/histology *The intended use of the technology is as an ablative treatment.* **Rationale:** The population was defined according to: • European guidelines (European Society for Medical Oncology [ESMO] clinical practice guideline for the diagnosis, treatment and follow-up of cancer of the pancreas [27]; European Association for the Study of the Liver [EASL] clinical practice guideline on management of hepatocellular carcinoma [5]). • American guidelines: NCCN clinical practice guidelines in oncology on pancreatic adenocarcinoma and hepatobiliary cancers [28,29] • AJCC cancer staging manual for pancreas and hepatobiliary cancers [30]
Intervention	• Tumour resection by IRE using the NanoKnife System, with the following subanalyses considered, depending on the approach: percutaneous, laparoscopic or open surgery • MeSH: Electroporation E05.200.500.454, E05.242.448, E05.301.500 • Manufacturers: ◊ NanoKnife (Company: AngioDynamics, USA)
Comparison	• **Pancreatic cancer** – *Standard of care therapy:* ◊ CHEMO ◊ RT ◊ CRT ◊ Palliative care ◊ No treatment (watchful waiting) • **Liver cancer** – *Standard of care therapy:* ◊ Chemoembolisation ◊ Kinase inhibitor: sorafenib or others ◊ RT ◊ Palliative care ◊ No treatment (watchful waiting)

Description	Project scope
	Rationale: Standard therapy was established according to: • European guidelines: ESMO clinical practice guideline on the diagnosis, treatment and follow-up for cancer of the pancreas [27]; EASL clinical practice guidelines on the management of hepatocellular carcinoma [5,31] • NICE guideline on pancreatic cancer in adults: diagnosis and management [32] • American Society of Clinical Oncology clinical practice guideline on locally advanced, unresectable pancreatic cancer 2016 [33] • EUnetHTA guideline on comparators and comparisons: criteria for the choice of the most appropriate comparator(s) [34]
Outcomes	**EFF-related:** • Success of the procedure (defined as the ability to complete the IRE procedure as planned and the absence of any residual tumour on imaging) • OS (at 3, 6, 12, 18 and 24 months) • Cancer-specific survival • Disease-free survival • PFS • Time to recurrence • Time to progression: radiological progression via CT scan or magnetic resonance imaging (MRI) at 6 weeks and 3, 6, 12, 18 and 24 months • Time to local recurrence: local radiological progression at 6 weeks and 3, 6, 12, 18 and 24 months • Health-related QoL (measured via European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaires [QLQs] C30 andPAN26, Functional Assessment of Cancer Therapy hepatic [FACT-Hep], EuroQol – five dimensions [EQ-5D] or other questionnaires at baseline and at 6 weeks and 3, 6 and 12 months after IRE) • Pain **SAF-related:** • Procedure-related complications (e.g., needle-tract seeding) • Adverse events: type, graded using the Common Terminology Criteria for Adverse Events (CTCAE), Dindo-Clavien classification, Society of Interventional Radiology (SIR) grading system or others • Intervention-specific mortality **Rationale:** The outcomes were chosen on the basis of the following guides: • Design and endpoints of clinical trials in hepatocellular carcinoma [35] • Guidelines for time-to-event and endpoint definitions in trial for pancreatic cancer: Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) [36]. • EUnetHTA guidelines on endpoints used in relative effectiveness assessments: clinical endpoints, safety and health-related QoL and utility measures [37–39]
Study design	**EFF:** RCTs, prospective non-RCTs and single-arm prospective studies with at least ten patients **SAF:** RCTs, prospective non-RCT and single-arm prospective studies with at least ten patients

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment team

Description of the distribution of responsibilities and the workload between authors and co-authors:

Avalia-t, as author:

- Developed the first draft of the EUnetHTA project plan and amended the project plan following comments from the co-author, dedicated reviewers and external experts.
- Performed the literature search and study selection.
- Conducted the assessment (data extraction, analysis, risk-of-bias assessment of the references selected, synthesis and interpretation of findings).
- Checked assessment elements; filled in the checklist regarding potential ethical (ETH), organisational (ORG), social (SOC) and legal (LEG) aspects of the HTA Core Model® for Rapid Relative Effectiveness Assessment (REA).
- Sent the first draft to the dedicated reviewers, compiled feedback, answered comments and made changes according to the reviewers' comments.
- Sent the second draft to the external experts, compiled feedback provided as answers to the reviewers and was responsible for making the corresponding changes.
- Sent the second draft to the manufacturer for fact checking, compiled feedback and made changes.
- Prepared the final assessment and wrote a final summary of the assessment.

LBI, as co-author:

- Collaborated in the development of the EUnetHTA project plan.
- Collaborated in the literature selection.
- Checked and approved all the steps (e.g., data extraction, assessment of the risk of bias and the quality of the body-of-evidence assessment) and provided methodological support.
- Reviewed the first and second draft assessments, proposed amendments where necessary (performed additional manual searches when needed) and provided written feedback.
- Collaborated on elaboration of the conclusions, which were discussed and agreed on.

VASPVT, NIPN and SNHTA as dedicated reviewers:

- Reviewed and discussed the EUnetHTA project plan (scoping meeting).
- Reviewed and provided comments on the first draft assessment.
- Guaranteed quality assurance.
- Reviewed and agreed on the conclusions.

2.2 Source of assessment elements

Assessment elements for the TEC, health problem, CUR, EFF and SAF domains were selected according to the HTA Core Model Application for Rapid REAs (4.2). The checklist for potential ETH, ORG, patient, SOC and LEG aspects was used to ascertain if these domains were relevant for assessment. For the purpose of the report, critical issues were defined in accordance with the ORG aspects of the HTA Core Model Application for Medical and Surgical Interventions (3.0).

General questions referring to selected issues were translated into actual research questions (answerable questions). Some research questions were grouped and answered together: the questions were listed below each other and the answer was provided subsequently.

2.3 Search

A systematic literature search was carried out on 26 September 2018 (and updated in January 2019) to identify primary studies fulfilling the inclusion criteria to address the EFF and SAF domain elements. Search terms related to IRE and NanoKnife were used in combination with terms related to liver and pancreatic cancer. The bibliographic research was restricted to studies written in English, Spanish, Portuguese, French or Italian. No time restrictions were applied. Detailed tables on the search strategy are included in Appendix 1.

Information retrieval was carried out in accordance with EUnetHTA guidelines [40,41]. The following sources of information were used in the search:

- CRD
- Cochrane Library (Wiley)
- Embase (OVID)
- Medline (PubMed)
- Web of Science (Web of Knowledge)
- Scopus

A manual search of the reference list in relevant articles was also undertaken to recover published studies that might have been missed by the search. In addition, the following clinical trial databases were searched to identify ongoing studies:

- Clinicaltrials.gov
- ICTRP
- EU Clinical Registry

Guideline repositories were used to identify relevant guidelines for the CUR domain (GIN database, Trip database, PMC, CMA Infobase and Google Scholar). In addition, we searched the GLOBOCAN database for estimates of incidence and mortality for pancreatic and liver cancer and carried out a general Internet search to identify other possible publications relevant to symptoms, the natural course of the diseases and other issues.

Information for the TEC domain came mainly from the previous systematic literature search and the manufacturer's EUnetHTA submission file, although we also carried out a general Internet search and reviewed the manufacturer's website pages to compare data.

The only manufacturer identified at the time of the search (AngioDynamics) was contacted by the EUnetHTA Joint Action 3 WP4 Project Manager. The short version of the submission file was sent to the manufacturer on 16 October 2018. They were encouraged to complete sections 1, 2, 3 and 4. The submission file was received on 14 November 2018. The manufacturer also answered the following points:

- Confirmation that the product is a CE marked technology and that it is the only product produced by the company that is relevant for this assessment.
- If they were aware of any other CE marked products that would be relevant for this assessment.
- To send the instructions for use and the CE certification document for the product.
- To send unpublished but nonconfidential (studies, etc.) data on the product. This ensured that no key information was missed.

2.4 Study selection

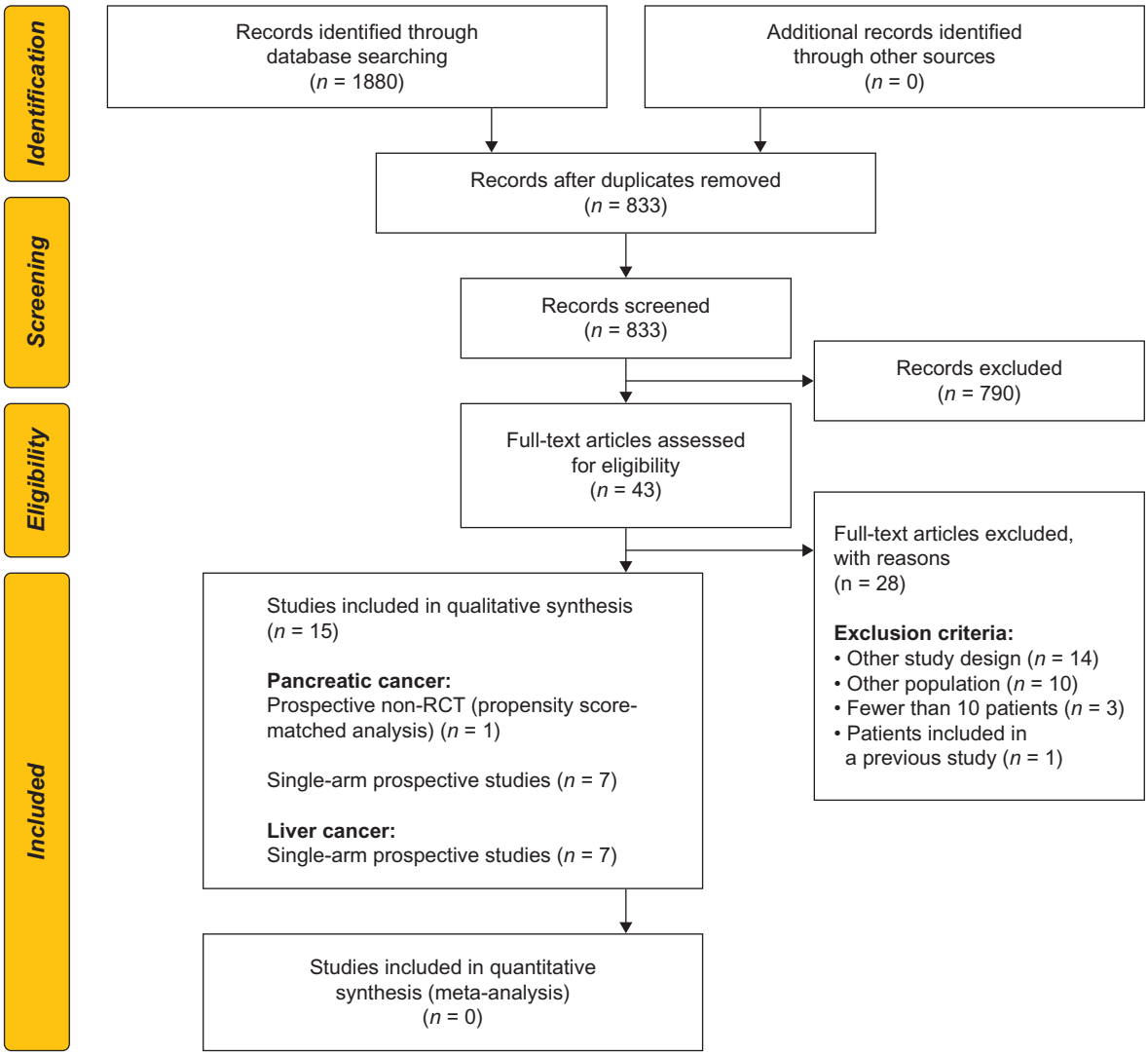

Figure 1: Flow chart for study inclusion

A total of 1880 abstracts were retrieved via the bibliographic search. After removing duplicates, 833 abstracts remained for screening. The authoring team independently screened the titles and abstracts according to the predefined inclusion criteria specified in the Scope. The following publication types were excluded: case reports, letters, congress presentations and editorials. A total of 43 articles were selected for full-text examination. When the same institution had published sequential studies, the study with the largest number of cases was chosen to avoid overlap. Disagreements were resolved via consensus.

Twenty-eight articles were excluded for the following reasons: 14 studies had another study design (13 retrospective analyses and 1 letter to the editor), ten papers had a study population that differed from the predefined PICO question, three studies had fewer than ten patients and one study had duplicated patients (Figure 1).

2.5 Data extraction and analyses

Data were extracted independently by the two authors and double-checked regarding consistency and accuracy by the co-author. A predefined data extraction form was used for this purpose (Tables A2, A3 and A4 in Appendix 1). Discrepancies between authors in relation to data were resolved through discussion and consultation with the co-author until agreement was reached. The main investigators

for two of the trials [15,20] were contacted in relation to data discrepancies. Inconsistencies were resolved in only one of these two cases [20].

For each individual study, the following information was recorded:

- Study characteristics (author, centre, funding, conflicts of interest, trial registration number, study design, data collection period, inclusion and exclusion criteria)
- Population characteristics (number of participants, age, gender, clinical stage, tumour type and location, tumour size, treatments before the intervention, simultaneous treatments and treatments after the intervention)
- Intervention and control characteristics (device, approach, imaging guidance, IRE intention, comparator, hospital stay and length of follow-up)
- Outcomes:
  - ◊ EFF endpoints: success of the procedure, OS (after diagnosis and after IRE), cancer-specific survival, disease-free survival, PFS, time to recurrence, time to progression, time to local recurrence, health-related QoL and pain
  - ◊ SAF endpoints: procedure-related complications, AEs and intervention-specific mortality

A meta-analysis or pooling of data was not methodologically possible owing to the great variability between trials in terms of population characteristics, tumour size, treatments before, concomitant with and after IRE and length of follow-up, among other parameters. Accordingly, a narrative data synthesis using descriptive statistics to summarise quantitative measures is reported.

The proposed subanalyses by approach (open surgery, laparoscopy or percutaneous) or the treatment received (CHEMO and/or RT) or by intention for IRE (ablation or margin accentuation) were not possible for any of the questions because of the lack of direct comparative data and the impossibility of aggregate analysis given the great variability among the studies included.

Continuous variables are presented either as the mean with standard deviation (SD) and/or the median with the interquartile range (IQR) or range. Categorical variables are reported as frequencies or percentages. Whenever possible, data reported for different measures were transformed into a common statistical or descriptive format.

For cases in which the authors did not report survival outcomes but did provide individual data, Kaplan-Meier analysis was performed for each study as part of the assessment [14,15,18,20]. In five cases [11,13,16,17,19], additional data were requested from investigators to estimate survival outcomes. This information was only obtained for two of the trials [11,17]. In calculating survival and recurrence/progression rates, only successfully treated patients were considered.

AEs were categorised as grade I, II, III, IV or V classes 1, 2, 3 and 4 according to the CTCAE, Dindo-Clavien classification, SIR or other grading system. Grades III, IV and IV correspond to major AEs and grades II and I to minor AEs. When AEs or complications were not graded, they were recorded in tables as “other adverse events/complications”. Whenever possible, the number of patients who experienced AEs was provided. IRE-related and non–IRE-related AEs were recorded. When the article did not provide this information, AE were classified as IRE-related.

Data were grouped and tabulated in accordance with guidance on narrative synthesis from the UK Economic and Social Research Council (ESRC) [42] and the Cochrane Consumers and Communication Review Group guidelines on data synthesis and analysis [43].

2.6 Quality rating

Quality assessment of studies included for the EFF and the SAF domains was carried out in accordance with EUnetHTA guidelines [41]. Risk of bias at the study level was assessed using the IHE 20-Criteria Checklist [9] for single-arm studies (case series) and ROBINS-I for non-RCTs [10].

The quality of the body of evidence was assessed using GRADE. The author team performed the risk-of-bias assessment and the GRADE assessment independently. Disagreements were resolved via consensus.

No quality assessment tool was used for the TEC and CUR domains, although information was validated by comparing and contrasting information from multiple sources (manufacturers, bibliography searches, official web pages and general Internet searches). Information was synthesised in a descriptive manner.

Multiple sources were also used to validate individual, possibly biased, sources of information for the assessment of ORG issues. A descriptive analysis was performed.

2.7 Patient involvement

The current assessment involved a patient representative recruited via a patient organisation, as well as two individual patients. The Spanish Group of Patients with Cancer (GEPAC; *Grupo Español de Pacientes con Cáncer*) was contacted to involve a patient representative during the scoping phase. The president and founder of GEPAC acted as the patient representative and was responsible for reviewing the preliminary PICO question and the draft project plan.

Individual patients were identified through the Department of Patient/Citizen Care Services (*Servicio de Atención ao Ciudadán e ao paciente*) of the Galician Health Service (*SERGAS*). They were responsible for preliminary contact with a hepatobiliary surgery clinician who arranged meetings with patients. As IRE is not performed in our setting, participation was open to patients with pancreatic or liver cancer who had undergone treatment with other ablative methods, as experiences with the disease and ablative methods will generally be shared. Two semi-structured interviews were conducted with two patients who had suffered from liver cancer and had undergone MWA. The clinician considered that interviewing LAPC patients would not be possible given their poor health status. The schedule of questions for the interview was based on the non-medicine template of the Health Technology Assessment International patient group [44], with questions related to key topics selected and redefined according to the intervention. Questions that were asked in the interview are shown in Appendix 1. The 1-hour face-to-face meeting was conducted by the main author after receiving appropriate training. The meeting was held in Santiago de Compostela Hospital and was recorded and transcribed. Patient-relevant endpoints were extracted by one author (from Avalia-t) and checked by a second author (from Avalia-t). No formal data analysis method was used given the simple structure of the interview. No ethical approval was needed. Patients were asked to sign an informed consent form. Relevant results were incorporated in the assessment element domains as appropriate.

2.8 Description of the evidence used

Pancreatic cancer

Evidence for the EFF and SAF domains for pancreatic cancer comes from one prospective non-RCT (propensity score-matched analysis) and seven prospective single-arm trials. Table 3 summarises the main characteristics of the studies included.

Table 3. Main characteristics of studies included for pancreatic cancer

Author and year	Study type	Number of IRE patients	Intervention(s)	Main endpoints	Included in EFF and/or SAF domain
Huang 2018 [17]	Prospective single-arm study	70	Open IRE and laparoscopic IRE	Success of the procedure, OS, PFS, complications	EFF and SAF
Scheffer 2017 [16]	Prospective single-arm study	25	Percutaneous IRE	OS, PFS, time to local progression, pain, QoL, complications	EFF and SAF
Mansson 2016 [14]	Prospective single-arm study	24	Percutaneous IRE	OS, time to local recurrence, complications	EFF and SAF
Lambert 2016 [11]	Prospective non-RCT (propensity score matched analysis)	21	Percutaneous and open IRE	OS, QoL, complications	EFF and SAF
Kluger 2016 [13]	Prospective single-arm study	50	NR	OS, time to local recurrence, complications	EFF and SAF
Paiella 2015 [15]	Prospective single-arm study	10	Open IRE	OS, QoL, complications	EFF and SAF
Belfiore 2015 [18]	Prospective single-arm study	20	Percutaneous IRE	OS, complications	EFF and SAF
Martin 2012 [19]	Prospective single-arm study	27	Open and percutaneous IRE	Success of the procedure, complications	EFF and SAF

Abbreviations: EFF = effectiveness; IRE = irreversible electroporation; NR = not reported; OS = overall survival; QoL = quality of life; PFS = progression-free survival; RCT = randomised controlled trial; SAF = safety.
Sources: [11,13–19].

According to GRADE, the quality of evidence was very low for EFF and SAF outcomes (Tables A10 and A11 in Appendix 1), as most of the evidence is from highly biased, small, single-arm trials with serious issues regarding inconsistency and indirectness (Table A8 in Appendix 1). The only comparative trial that was included for LAPC is a small propensity-matched trial that compares IRE to non-curative surgery [11]. As shown in Table A7 (Appendix 1) the risk of bias for this trial was classified as critical because of the high potential for confounding arising from the unclear patient selection and the possible imbalance between the intervention and control groups in terms of adjuvant treatments and co-interventions.

Liver cancer

Evidence for the EFF and SAF domains for liver cancer comes from seven prospective single-arm trials (Table 4).

Table 4. Main characteristics of studies included for liver cancer

Author and year	Study type	Number of IRE patients	Intervention(s)	Main endpoints	Included in EFF and/or SAF domain
Fruhling 2017 [20]	Prospective single-arm study	30	Percutaneous IRE	Local recurrence, complications	EFF and SAF
Distelmaier 2017 [22]	Prospective single-arm study	29	Percutaneous IRE	Success of the procedure, local recurrence, complications	EFF and SAF
Niessen 2016 [25]	Prospective single-arm study	34	Percutaneous IRE	Success of the procedure, time to local recurrence, complications	EFF and SAF
Granata 2016 [24]	Prospective single-arm study	20	Percutaneous IRE	Success of the procedure, complications	EFF and SAF
Eller 2015 [23]	Prospective single-arm study	14	Percutaneous IRE	Local recurrence, complications	EFF and SAF
Eisele 2014 [12]	Prospective single-arm study	13	Percutaneous, laparoscopic and open IRE	Success of the procedure, local recurrence	EFF
Cheung 2013 [21]	Prospective single-arm study	11	Percutaneous IRE	Success of the procedure, local recurrence, complications	EFF and SAF

Abbreviations: EFF = effectiveness; IRE = irreversible electroporation; SAF = safety.
Sources: [12,20–25].

According to GRADE, the quality of evidence for liver cancer was also very low for EFF and SAF outcomes (Table A12 in Appendix 1) as the evidence comes from seven small, single-arm trials that show a critical risk of bias and serious concerns regarding inconsistency and indirectness. The patient selection criteria are unclear in most of the studies, and many studies lack information regarding co-interventions and follow-up losses (Table A9 in Appendix 1).

2.9 Deviations from project plan

With regard to efficacy outcomes, PFS was added.

With regard to the standard of care in liver cancer, CHEMO was deleted.

With regard to the LAPC population, “primary or recurrent” was deleted to avoid confusion. This change does not affect the study population.

Two external experts failed to provide comments.

The patient representative from GEPAC reviewed the PICO question but failed to provide comments on the project plan.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is irreversible electroporation (IRE) ablation [with a percutaneous, laparoscopic or open surgical approach]?
B0002	What is the claimed benefit of IRE in relation to the comparators?
B0003	What is the phase of development and implementation of IRE?
B0004	Who administers IRE? In what context and level of care is IRE provided?
B0008	What kind of special premises are needed to use IRE?
B0009	What equipment and supplies are needed to use IRE?
A0020	For what indications has IRE received marketing authorisation or a CE mark?
A0021	What is the reimbursement status for IRE?

3.2 Results

Features of the technology and comparators

[B0001] What is irreversible electroporation (IRE) ablation [with a percutaneous, laparoscopic or open surgical approach]?

IRE is a nonthermal ablative method involving application of short high-voltage and low-frequency electric fields to create nanoscale pores in tissue, resulting in permeabilisation of cell membranes. The permeabilisation can become irreversible when the magnitude, duration and number of the electrical fields applied are above a certain threshold [1]. While the mechanism of cell death caused by IRE is not exactly known, it is believed that it is due in part to the formation of permanent pores (nanopores), as this permeabilisation can lead to disruption of homeostasis and consequently induction of apoptosis.

It is alleged that IRE causes less damage to adjacent structures than other thermal ablative approaches (RFA, MWA and cryoablation). Thus, IRE would allow ablation of tumours that are localised close to major blood vessels or other sensitive structures such as nerves and the bile duct, maintaining them intact. However, while it is not a thermal-based ablation technique, IRE can create thermal energy [45], and this thermal effect can also contribute in a lesser way to induction of cell death due to necrosis [46]. It is also believed that IRE avoids one of the limitations of other techniques that can lead to incomplete ablation: loss of heat (in RFA or MWA) or cold (in cryoablation) through the blood flow, which is known as the “heat sink effect”.

IRE can be performed percutaneously, laparoscopically or via open surgery [2]. In all cases, the procedure involves placing multiple electrodes around the target lesion, although sometimes a probe can also be placed in the centre of the nodule. The probe number and placement configuration can depend on the location, size and shape of the target, commonly varying from two to six per lesion in the studies included. The probe is directed under image guidance via US or CT. The patient requires general anaesthesia with deep sedation and complete muscle relaxation, with cardiac synchronisation during delivery of the high-voltage current.

According to the literature, the percutaneous approach appears to be the preferred method given the potentially fewer complications. However, the laparoscopic and open surgery approaches could have the advantages of allowing visualisation and determination of the extent of the tumour, and allow additional resections and procedures to be carried out if required [12,19]. For pancreatic cancer,

these approaches also have the advantage of allowing the needles to be positioned parallel to the mesenteric vessels, which is the preferred strategy for mesenteric involvement [47]. The decision regarding the best approach is commonly taken by a multidisciplinary team (surgeons, radiologists, oncologists and gastroenterologist) on the basis of CT measurements before the procedure, but further investigations are recommended to differentiate the patients who might be best treated by each approach [2]. For example, it has been shown that some comorbidities such as gastric varices could be a contraindication for ablation using the percutaneous approach [48].

Marketed products

The only commercialised IRE device is the NanoKnife System (AngioDynamics, Qeensbury, NY, USA). This system has a CE mark for cell membrane electroporation and FDA approval for soft-tissue ablation. It has not received clearance for therapy or treatment of any specific disease or condition.

One of the components of the NanoKnife System is the NanoKnife generator (Figure 2): a reusable, nonsterile low-energy direct current generator consisting of an LCD display, a console keyboard, a power unit and cord and a double footswitch. The unit includes software that generates a two-dimensional representation of the ablation zone (according to the company EUnetHTA submission file) [26].

Figure 2. NanoKnife generator

1, LCD display; 2, console keyboard; 3, power unit and cord; 4, double footswitch

Single-use electrodes are connected to the generator. The NanoKnife System has six probes outputs, so users can connect up to six NanoKnife electrode probes at one time; however, only one pair of NanoKnife electrode probes can be operated at a time.

The probes are 15 cm or 25 cm in length and 19 gauge in diameter and are covered in a retractable insulation sheath, which allows adjustment of the active tip length. The probe components are labelled in Figure 3.

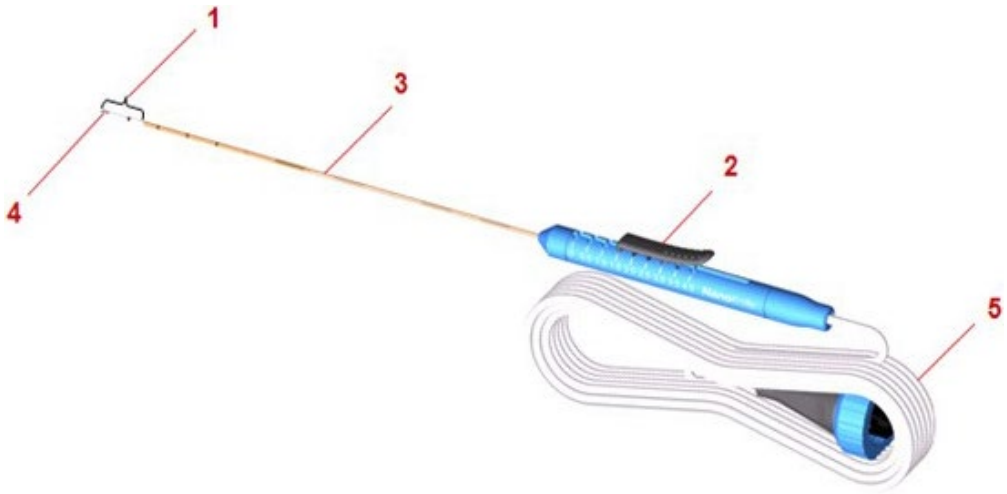

Figure 3. NanoKnife electrode probe components

1, Active electrode, with length adjustable in 0.5-cm increments from 0 cm to 4 cm; 2, thumb slide; 3, insulation sleeve; 4, 19-gauge needle with depth markers and an echogenic needle tip; 5, 10-foot connection cable

There are two types of probe: an activation probe (blue in colour; Figure 4) and the standard single-electrode probe (white in colour; Figure 5). The blue single-electrode activation probe is required to activate the generator, which will allow other standard single-electrode probes to function with it. Only one single-electrode activation probe is required to activate the generator, but a minimum of two probes (blue and white) are required to execute a procedure. Depending on the size of the soft tissue area to be ablated, a maximum of six probes can be used in a procedure.

Figure 4. NanoKnife single-electrode activation probe

Figure 5. NanoKnife single-electrode standard probe

The generator can deliver between 100 V and 3000 V of energy in 90–100 pulses, with a maximum pulse length of 100 ms [49]. Table 5 outlines the main features of the intervention.

Table 5. Features of the intervention

	Technology
Name	NanoKnife System
Manufacturer	AngioDynamics, 603 Queensbury Avenue Queensbury, NY 12804, USA
Reference codes	**Device Description** — **Product Code (UPN or catalogue #)** NanoKnife generator — 20300101 (v 2.2) H787203003010 (v 3) IRE probe spacer — H787204003015 NanoKnife single-electrode probe, RFID activation, 15 cm — H787204001030 NanoKnife single-electrode probe, 15 cm — H787204001040 NanoKnife single-electrode probe, RFID activation, 25 cm — H787204001050 NanoKnife single-electrode probe, 25 cm — H787204001060
Class/GMDN code	• Council Directive 93/42/EEC concerning medical devices: class II b • FDA classification: class II • GMDN: irreversible electroporation system
Mechanism of action	The device applies high-voltage direct current to pairs of electrodes that are inserted into the body, bracketing the target tissue to be ablated. The electric field acts as a physical stimulus, inducing holes in cell membranes and resulting in loss of homeostasis and subsequent cell death. The mechanism that causes permanent cell damage is referred to as irreversible electroporation.
Mode of administration	Percutaneous, laparoscopic or laparotomy (open surgical) approaches

Abbreviations: FDA = Food and Drug Administration; GMDN = Global Medical Device Nomenclature; IRE = irreversible electroporation; RFID = radiofrequency identification; UPN = universal product number.
Source: [26].

Comparators in pancreatic cancer: What is the standard-of-care therapy?

The intended population for IRE is patients diagnosed with unresectable locally advanced pancreatic tumours. Despite the great advances in molecular approaches, outcomes for this population are very poor. The standard-of-care therapy for these patients, and thus the main comparator for our analysis, is CHEMO with or without RT (CRT). While the appropriate treatment has to be determined individually on the basis of performance status, gemcitabine has been the standard treatment for many years. The effectiveness of other chemotherapies, such as FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin), is still being studied. RT is also typically offered as a palliative option to reduce pain. Other palliative measures might also be required to relieve symptoms such as severe pain. Complications such as biliary and/or duodenal obstruction may also need to be resolved, in addition to nutritional support [50].

For some patients who have completed or stopped CHEMO because of severe AEs, a waiting period can be advised, known as watchful waiting (WW). WW consists of closely watching but not giving treatment unless symptoms appear or change. WW is intended to minimise treatment-related toxicity and can also be adopted when the risks of treatment are greater than the possible benefits. WW is more frequent for cancers that grow slowly or for cystic lesions of the pancreas [51].

Comparators in liver cancer: What is the standard-of-care therapy?

The intended population for IRE includes patients with unresectable primary or secondary liver cancer who have a contraindication for thermal ablation. There are currently multiple treatment options for these patients, but none is highly effective. The most common treatments, and thus possible comparators, are TACE, multikinase inhibitors such as sorafenib and levatinib, palliative therapy and symptomatic therapy.

Typically, TACE is offered to patients with intermediate-stage disease and preserved liver function, while sorafenib can be considered the standard first-line systemic therapy for patients with more advanced cancers and preserved liver function. As in pancreatic cancer, a WW period can be advised. Patients who have end-stage disease and are not candidates for a transplant might only be eligible for supportive palliative care and symptomatic treatment. The use of external beam RT has also been reported in different stages of liver cancer, and is specifically recommended to alleviate pain in patients with bone metastases.

[B0002] What is the claimed benefit of IRE in relation to the comparators?

Owing to its mostly nonthermal effect, IRE allows ablation of tumours localised close to major blood vessels or other sensitive structures. These tumours are considered unresectable [46] given the potential for damage to critical structures and the prognosis with existing treatments is very poor. Another possible advantage of IRE could be its potential for avoiding the serious toxic side effects related to the systemic treatments commonly used for advanced pancreatic and hepatic tumours (CHEMO, multikinase inhibitors, TACE and other systemic therapies). While most of the common toxicities include mild to moderate AEs, such as nausea, vomiting, diarrhoea, fatigue, loss of appetite and anaemia, some might lead to life-threatening events. In the case of sorafenib, cardiovascular events, arterial thromboembolic events, haemorrhage complications and renal toxicity could be fatal [52].

[B0003] What is the phase of development and implementation of IRE?

The technology underlying IRE, electroporation, has been in use since the 1960s [53]. It was initially used to introduce macromolecules, such as anticancer drugs, into the cell membrane, and the subsequent cell death was considered a side effect. However, in 2005 Davalos demonstrated the usefulness of IRE as an ablative method, ablating liver tissue without thermal effects. The first human experience with IRE was described in 2011 by Pech [54], who assessed IRE in renal cell carcinoma.

The only commercial system is the NanoKnife System, which has been available on the market since 2006. The system received FDA 510K clearance for surgical ablation of soft tissue in 2006 [55] and a CE mark for cell membrane electroporation in 2010. According to company information [26], the NanoKnife System is currently marketed in 38 countries and territories, including Austria, Belgium, Denmark, England, France, Germany, Italy and Spain. Since 2017, it seems to be used in more than 135 unique hospitals or cancer centres in the USA (>5450 procedures). No data on its implementation in Europe were found, apart from the fact that NanoKnife procedures are reimbursed in Germany for these two cancers.

Since its approval, IRE has been used in tumours in different locations, such as liver, lung, pancreas, kidney and prostate [56]. There are currently several ongoing trials of IRE in additional tumours.

[B0004] Who administers IRE? In what context and level of care is IRE provided?

IRE is intended to be used in a tertiary care centre, either within an interventional radiology suite or in an operating room, depending on the guidance method required (open or laparoscopic placement versus imaging-guided percutaneous placement). The decision regarding eligibility for IRE should be taken by a multidisciplinary disease management team that should include surgical oncologists, medical oncologists, radiation oncologists, anaesthesiologists, interventional radiologists, gastroenterologists and pathologists [26].

Users of the NanoKnife System will include surgeons and interventional radiologists. Nurses, radiology technicians, clinical specialists (depending on hospital guidelines) and other general clinical staff assist with the procedure. Primary and extended users may operate the user interface to control the NanoKnife generator and associated peripherals, including physical procedure set-up (which may include manoeuvring equipment and devices, connecting electrodes, placing electrocardiogram [ECG] connections, connecting to the power supply, etc.), establishing procedure protocols, monitoring procedure progress and stopping procedures under the supervision and direction of the primary treating physician.

The team should have previous experience with ablative techniques and a minimum of previous procedures with IRE is recommended [26]. For ablation of the pancreas, a physician with extensive

thermal ablation experience is required (minimum of 50 cases of RFA, MWA or cryoablation in the liver, lung or kidney), as well as a minimum of five IRE procedures on solid organs that have greater degrees of tolerance, such as the liver and kidney [19].

[B0008] What kind of special premises are needed to use IRE?

[B0009] What equipment and supplies are needed to use IRE?

Before the procedure, the size and form of the tumour must be assessed to determine the number of probes that are needed, usually via CT or US. These imaging modalities are also used to guide the insertion of IRE electrodes (to ensure appropriate treatment planning and that electrodes are parallel to each other, otherwise incomplete ablation may occur). After the procedure, imaging techniques are also used to evaluate the extent of the ablated area, commonly using CT, US or MRI [49]. In some cases, functional positron emission tomography (PET) is used.

IRE is intended to be used with standard anaesthetic, radiological and surgical operating equipment. It is performed under general anaesthesia and it is important to administer a neuromuscular blocking agent because uncontrolled muscle contractions could occur. To reduce the risk of inducing cardiac arrhythmias, an ECG synchronisation device should be coupled to the IRE system [57] to ensure that pulses are delivered during the refractory cardiac period to prevent dysrhythmias [58]. Besides, it is recommended to connect the patient to an external defibrillator to intervene in case of ventricular arrhythmias.

The length of hospital stay will depend on the patient's general condition and the approach that has been used. A laparotomy approach (open surgery) usually requires a longer hospital stay, while a percutaneous approach should lead to a shorter stay. Globally, it has been reported that some patients return home the same day or the following morning, while in other studies the stay is longer than 2 weeks.

[A0020] For what indications has IRE received marketing authorisation or a CE mark?

The NanoKnife System has received a CE mark for cell membrane electroporation but has not been approved for the treatment of any specific disease or condition. In the USA, it has received FDA approval for surgical ablation of soft tissue and in early 2018 the NanoKnife System received expedited access pathway designation for the treatment of stage III pancreatic cancer. The expedited access pathway is designed to accelerate the approval process for medical devices to treat conditions for which no alternatives are available.

The IRE system has been used to treat various organs, including liver, pancreas, prostate, kidney, lung, pelvis and lymph nodes, with different levels of evidence available for each organ. With regard to the pancreas and liver, most patients are offered NanoKnife IRE for local ablation of primary or secondary tumours that are not resectable or suitable for thermal ablation because of proximity (<0.5 cm) to major hepatic or portal vein branches or bile duct structures [59].

Contraindications for the technique are as follows [26,47]:

- Ablation of lesions in the thoracic area in the presence of implanted cardiac pacemakers or defibrillators
- Ablation of lesions in the vicinity of implanted electronic devices or implanted devices with metal parts
- Ablation of lesions of the eyes, including the eyelids
- A patient history of epilepsy or cardiac arrhythmia
- Recent history of myocardial infarction

[A0021] What is the reimbursement status of IRE?

To the best of our knowledge, IRE reimbursement for pancreas and liver cancer is only available in Germany. Detailed information on the reimbursement status/recommendations for IRE is included in Table A15 in Appendix 2.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is pancreatic cancer? What is liver cancer (primary or secondary)?
A0004	What is the natural course of the pancreatic cancer? What is the natural course of the liver cancer (primary or secondary)?
A0005	What are the symptoms and the burden of disease for patients with pancreatic cancer? What are the symptoms and the burden of disease for patients with liver cancer (primary or secondary)?
A0024	How is pancreatic cancer currently diagnosed according to published guidelines and in practice? How is liver cancer (primary or secondary) currently diagnosed according to published guidelines and in practice?
A0025	How is pancreatic cancer currently managed according to published guidelines and in practice? How is liver cancer (primary or secondary) currently managed according to published guidelines and in practice?
A0007	What is unresectable locally advanced pancreatic cancer (LAPC)? What is unresectable liver cancer (primary or secondary) for which thermal ablation is contraindicated?
A0023	How many patients belong to the unresecatble LAPC) group? How many patients belong to the unresectable liver cancer (primary or secondary) contraindicated for thermal ablation group?
A0011	How much is IRE utilised?

4.2 Results

Overview of the disease or health condition

[A0002] What is pancreatic cancer?

Cancer of the pancreas is one the most lethal cancer types, with more than 330,000 new cases diagnosed in 2012 and approximately the same number of deaths worldwide [60]. For 2018, the estimated incidence increased to 458,918 new cases [3]. In Europe, pancreatic cancer is the fourth most fatal cancer among both men and women [61].

Pancreatic cancer may arise in the exocrine or endocrine parenchyma, but the exocrine parenchyma is the most common site. Most often, these tumours begin to develop in the pancreatic ducts, so they are called ductal adenocarcinomas [27]. The head of the pancreas is the most common location of tumours. Male sex and age 60–80 years are two risk factors for pancreatic cancer.

What is liver cancer (primary or secondary)?

Liver cancer is the second most frequent cause of death from cancer worldwide [5].There were 850,000 new cases diagnosed in 2015 and 810,000 deaths [6]. Estimations for Europe in 2018 showed a 5-year prevalence of 8.7% [3].

HCC is the most common type of liver cancer, accounting for 90% off all cancers of the liver. This type of cancer begins in hepatocytes. The incidence of HCC increases progressively with age and is higher among males. However, HCC incidence varies by geographic areas, and is highest in Asian and African countries and moderate in Europe and Latin America. This difference is because of variation in the prevalence of associated risk factors [62]. A much less common cancer is intrahepatic cholangiocarcinoma, which begins in intrahepatic bile ducts [63]. Apart from primary hepatic cancer, a more frequent cause of liver tumours besides primary tumours is metastases in patients with extrahepatic neoplasia, which is often a colorectal adenocarcinoma [7]. Metastases from breast and lung cancer are also common [64].

[A0004] What is the natural course of the pancreatic cancer?

Most pancreatic cancers are caused by mutations that occur sporadically, and only 10% of cases are associated with hereditary syndromes. Most pancreatic cancers originate in the ductal epithelium and grow through different grades of preinvasive pancreatic intraepithelial neoplasia (pANin) to fully invasive cancer [65]. This histological progression is accompanied by consecutive genetic mutations. There are four major driver genes for pancreatic cancer: *KRAS*, *CDKN2A*, *TP53* and *SMAD4* [66]. From a genetic perspective, pancreatic cancer is a complex and heterogeneous disease [65] and approximately 63 mutations are estimated to be involved [67].

Pancreatic cancer progresses rapidly and is often diagnosed when it is at an advanced stage. In contrast to other types of cancer, the prognosis has not improved in recent years. The overall 5-year survival is approximately 5% (65). Therefore, in most cases therapeutic measures will be focused on relieving symptoms and prolonging survival as much as possible.

What is the natural course of the liver cancer (primary or secondary)?

In most cases, the onset of primary liver cancer is preceded by cirrhosis of the liver [5]. The liver tissue slowly changes to the detriment of normal hepatocytes, and becomes fibrous and scarred [68]. Among the most common risk factors are viral hepatitis (B or C), chronic alcohol intake and other metabolic diseases such as haemochromatosis, α_1-antitrypsin deficiency and nonalcoholic fatty liver disease [5].

Approximately one-third of cirrhotic patients will develop HCC [5]. The prognosis for this type of tumour depends on the degree of liver dysfunction and the tumour extent. In many cases, when symptoms appear the cancer is already at an advanced stage. If the diagnosis is made at an early state, the estimated 5-year survival is approximately 28% [69].

The natural course of secondary liver cancer depends on the origin of the neoplasm.

Effects of the disease or health condition

[A0005] What are the symptoms and the burden of disease for patients with pancreatic cancer?

In the early stages of pancreatic cancer there are usually no symptoms to raise suspicion of the disease. Symptoms usually appear when the cancer is already at an advanced stage and there are metastases in distant organs. The symptoms depend on the area of the pancreas in which the tumour is located as well as the stage of the disease [65].

Obstructive cholestasis due to compression of the common bile duct is common in cancers located in the head of the pancreas. Tumours located in the body and tail of the pancreas do not have a specific symptomatology, which normally leads to later diagnosis. Some of the most common symptoms are weight loss, jaundice, abdominal pain, bloating, floating stools, dyspepsia, nausea, vomiting, pruritus, lethargy and in some cases pancreatitis [27]. Recent-onset non-insulin-dependent diabetes is also relatively common [70–72].

What are the symptoms and the burden of disease for patients with liver cancer (primary or secondary)?

In liver cancer, symptoms commonly appear when the cancer is at an advanced stage. Some of the frequent symptoms are loss of appetite, weight loss, nausea or vomiting, pain in the abdomen and jaundice, among others [73].

In cirrhotic patients, a liver tumour may be suspected if the symptomatology gets worse, although the cancer is commonly diagnosed during radiological and serological surveillance testing.

Current clinical management of the disease or health condition

[A0024] How is pancreatic cancer currently diagnosed according to published guidelines and in practice?

When a pancreatic tumour is suspected, diagnostic imaging tests should be performed to provide information about the size of the tumour and the disease burden. Serum biomarkers CA 19-9 and CEA lack sensitivity as single tests for diagnosing malignancy [27,32,50,74]. CT is considered the imaging technique of choice for diagnosis and staging [27,32,74]. A CT scan can confirm the presence of a pancreatic tumour and guide the surgical approach, as it identifies the location of the tumour in relation to the mesenteric artery, celiac axis, superior mesenteric vein and portal vein [65].

Endoscopic US can also be used to provide complementary information [27,32,50]. This technique has the advantage of allowing biopsy of pancreatic tissue and lymph nodes to check for distant metastasis [27], which is indicated when there is high suspicion of pancreatic cancer but CT imaging is inconclusive, or when cytological or histological pancreatic samples are required. The NICE guideline also proposes offering fluorodeoxyglucose PET/CT when the diagnosis is not clear [32]. Less commonly, clinicians may sometimes find it necessary to perform MRI or magnetic resonance cholangiopancreatography, for example in cases of allergy to CT contrast medium or for patients with cystic lesions [27,29,32]. Endoscopic retrograde cholangiopancreatography could be useful in evaluating biliary anatomy but has on added diagnostic value over CT or MRI [27].

How is liver cancer (primary or secondary) currently diagnosed according to published guidelines and in practice?

Liver cancer diagnosis is based on imaging tests [5]. Patients with chronic liver disease should be entered into screening programs and undergo US every 6 months. When a nodule larger than 1 cm is found, additional contrast-enhanced tests (mainly CT or MRI) should be performed to confirm the existence of the tumour. Further confirmation using other invasive tests is not required because of the typical hallmarks of HCC: a combination of hypervascularity in the late arterial phase and washout on portal venous and/or delayed phases, which reflects the vascular derangement that occurs during hepatocarcinogenesis. In cases of doubt, a biopsy should be performed [5]. For any mass found that is <1 cm, the patient should be followed up every 4 months during the first year and then every 6 months.

Nodules found in noncirrhotic patients should be confirmed by liver biopsy (as the presence of the hallmarks may not be HCC-specific). Noncirrhotic patients are usually diagnosed at a more advanced disease stage as they are not included in screening programs.

[A0025] How is pancreatic cancer currently managed according to published guidelines and in practice?

Clinical staging

Staging of pancreatic cancer is the first step in deciding on the best treatment option. The AJCC TNM system is often used for pancreatic cancer staging [75]. Three categories are considered in this classification: the size and location of the primary tumour (T), the adjacent lymph nodes (N) and the presence or absence of metastasis (M). In pancreatic cancer, the local extent, which may involve surrounding vessels, is taken into account. Using this classification, stages I, II, III and IV can be identified. The TNM classification nomenclature is presented in Table 6.

Table 6. TNM staging of pancreatic tumours

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1 T2	Tumour limited to the pancreas, ≤2 cm in diameter Tumour limited to the pancreas, >2 cm in diameter
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node(s) metastasis
N1	Regional lymph node(s) metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T1-3 N1 M0
Stage III	T4 any N M0
Stage IV	Any T any N M1

Source: AJCC cancer staging manual [75].

The AJCC staging system is used to assess the clinical prognosis and generate patient survival data according to the disease stage. However, the NCCN consensus guidelines [29] define a staging system for treatment purposes that is based on whether the tumour is considered operable or not (depending on tumour location within the pancreas and arterial or venous involvement). According to this system, based on the American Hepato-Pancreatico-Biliary Association consensus report, a tumour is considered resectable if it can be completely removed with negative margins. The categories are as follows:

- Resectable (localised disease, includes stages I and II)
- Unresectable:
  - ◊ Borderline resectable: tumour abutment or <180° contact around the circumference of the superior mesenteric artery or coeliac arteries, or a short segment of hepatic artery or the superior mesenteric vein, pulmonary vein or confluence of these veins
  - ◊ Locally advanced (stage III): tumour encasement of >180° of the circumference of the superior mesenteric artery or coeliac arteries, any unreconstructable venous involvement
  - ◊ Metastatic (stage IV)

Resectability as defined according to the NCCN guidelines is presented in Table 7.

Table 7. Definition of resectability according to NCCN guidelines

Resectability status	Arterial	Venous
Resectable	No arterial contact (CA, SMA or CHA)	No tumour contact with the SMV or PV or <180° contact without vein contour irregularity
Borderline resectable	Pancreatic head/uncinated process • Solid tumour with CHA without extension coeliac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumour contact with the SMA <180 • Presence of variant arterial anatomy (e.g. accessory right hepatic artery) and the presence and degree of tumour contact should be noted if present as if may affect surgical planning Pancreatic body/tail • Solid tumour contact with the CA of 180° • Solid tumour contact with the CA of 180° without involvement of the aorta and with an intact and uninvolved gastroduodenal artery (some prefer these criteria to be in the unresectable category)	• Solid tumour contact with the SMV or PV or >180° contact without vein contour irregularity or thrombosis of the vein, but with suitable vessels proximal and distal to the site of involvement to allow safe and compete resection and vein reconstruction • Solid tumour contact with the IVC
Unresectable	Distant metastases • Pancreatic head/uncinated process • Solid tumour contact with SMA of >180° • Solid tumour contact with CA of >180° • Solid tumour contact with the first jejunal SMA branch Body and tail • Solid tumour contact with SMA and CA • Solid tumour contact with CA and aorta	Pancreatic head/uncinated process • Unreconstructable SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) • Contact with the most proximal draining jejunal branch into SMV Body and tail • Unreconstructable SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

Abbreviations: CA = coeliac axis; CHA = common hepatic artery; IVC = inferior vena cava; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric vein.
Source: National Comprehensive Cancer Network guidelines [29].

Treatment of pancreatic cancer

Treatment of pancreatic cancer should be managed by a multidisciplinary team that includes surgeons, medical and radiation oncologists, radiologists, gastroenterologists, nutritionists, pain specialists and palliative care specialists. There are different possibilities according to the disease stage, the tumour location, whether main vascular structures and/or nerves are affected and the general health status of the patient.

Open surgery is the standard of care and the only curative option for pancreatic cancer [27,32].

Surgical candidates can be divided into patients with clearly resectable cancer at diagnosis and patients with borderline resectable cancer. Existing guidelines recommend that patients with resectable disease should be treated with immediate surgery followed by adjuvant therapy to decrease the risk of metastasis [27,29,32,50]. The ESMO and Spanish Society of Medical Oncology (SEOM) guidelines recommend adjuvant treatment with either with F-fluorouracil/folinic acid or gemcitabine [27,50]. The NICE guideline recommends gemcitabine plus capecitabine, and gemcitabine for those who are not

able to tolerate a combined treatment. Most guidelines agree that CRT should be considered only in the clinical trial setting, as controversial results have been obtained in previous studies [27,32,50].

While it is considered that surgery should not be the initial approach for patients with borderline resectable cancer, there is no clear consensus regarding the use of neoadjuvant CHEMO outside of clinical trials [27,29,32,50,74]. According to the ESMO guideline, the best option for patients not included in a trial appears to be CHEMO (gemcitabine or FOLFORINOX) followed by CRT before surgery.

Regardless of treatment, survival for patients with nonresectable cancer or LAPC is low, at <1 year in older studies and approximately 15–16 months in recent trials [27]. According to existing European guidelines, the preferred treatment for advanced cases is CHEMO [27,32,50,74]. The ESMO, SEOM and Belgian Health Care Knowledge Centre guidelines recommend gemcitabine as monotherapy [27,50,74]. According to SEOM, FOLFIRINOX or gemcitabine/albumin-bound paclitaxel could be a valid alternative, while NICE recommends combination CHEMO, with gemcitabine for those who cannot tolerate this treatment. SEOM also recommends CRT for selected patients after stabilisation of the CHEMO response or induction consolidation. The only radiosensitiser recommended is capecitabine [27,32]. American guidelines [33,76] also recommend combination regimens and propose that CRT/stereotactic body RT may be offered as an alternative when there is a response or stable disease after 6 months of induction therapy. In all cases, these treatments should be accompanied by the recommended strategies for relief of pain and symptom burden, which might include palliative RT, as well as other medication.

Ablative techniques such as IRE and other thermal techniques are not considered standard of care for patients with pancreatic tumours.

Pain control or relief from biliary and/or duodenal obstruction is frequently needed in LAPC and metastatic cancer. CHEMO is only recommended when the patient's performance status is good enough. In general, gemcitabine is considered as the first option, and can be combined with other chemotherapies, depending on the patient's performance status.

A summary of treatments in pancreatic cancer according to stage is presented in Figure 6.

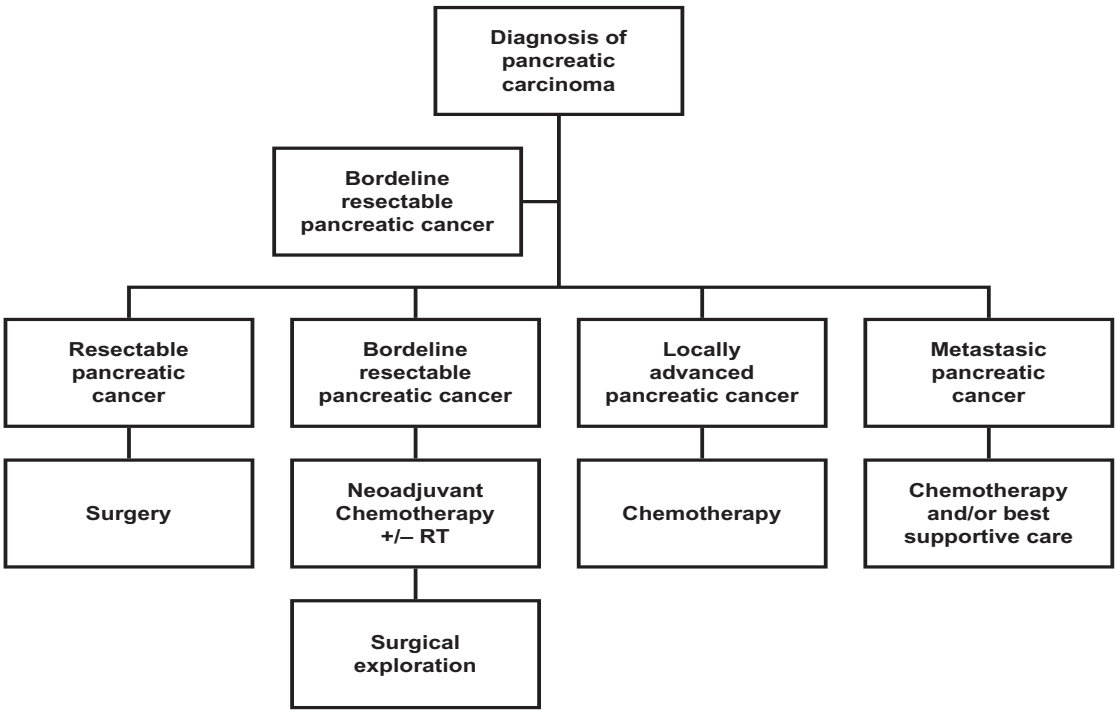

Figure 6. Treatment of pancreatic cancer

Abbreviations: RT = radiotherapy.
Source: Adapted from ESMO guidelines [27].

How is liver cancer (primary or secondary) currently managed according to published guidelines and in practice?

Once the presence of a liver neoplasm has been confirmed, the disease extent should be investigated and the prognosis evaluated to define the best management strategy. To this end, different staging systems have been developed. One of these is the TNM, which is the standard staging system in oncology. According to this classification there are four main T stages (T1–T4) with subcategories as shown in Table 8.

Table 8. TNM staging of liver cancer

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Solitary tumour without vascular invasion
T2	Solitary tumour with vascular invasion or multiple tumours (none >5 cm)
T3a	Multiple tumours >5 cm
T3b	Single tumour or multiple tumours of any size involving a major branch of the portal vein or hepatic vein
T4	Tumour(s) with direct invasion of adjacent organs other than the gallbladder or perforation of the visceral peritoneum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage IIIA	T3a N0 M0
Stage IIIB	T3b N0 M0
Stage IIIC	T4 N0 M0
Stage IVA	Any T N1 M0
Stage IVB	Any T N1 M1

Source: AJCC cancer staging manual (75).

The TNM classification, which is widely used for other types of cancer, has several limitations for HCCs [77,78]. First, pathological information is required to classify patients and this is not always available. Second, the TNM system does not allow classification according to liver functional status or health status or evaluation of a patient's prognosis. European guidelines recommend that staging should include assessment of tumour extent, as well as liver function, portal pressure and clinical performance status [5,31].

The EASL and ESMO guidelines, as well as many other guidelines of national HCC associations (Spain, Italy), endorse the Barcelona Clinic Liver Cancer (BCLC) [79] classification for HCC staging. This classification has been externally validated and has the advantage of being a dynamic system that allows the entry of new treatments shown to improve patient survival. The BCLC classification considers tumour status, liver function and health performance status, along with treatment-dependent variables. Liver function is assessed via the Child-Pugh class, which takes into account ascites, encephalopathy, serum albumin, bilirubin and prothrombin time; each parameter is scored from 1 to 3, with 3 indicating the most severe damage. Three categories are then defined (A, B or C) according to the total score. Health performance status is assessed using the Eastern Cooperative Oncology Group (ECOG) scheme, which has five categories according to the patient's ability to care for themselves, daily activity and physical ability [80].

The BCLC classification has five stages (0, A, B, C and D) with therapeutic options recommended for each (Figure 7).

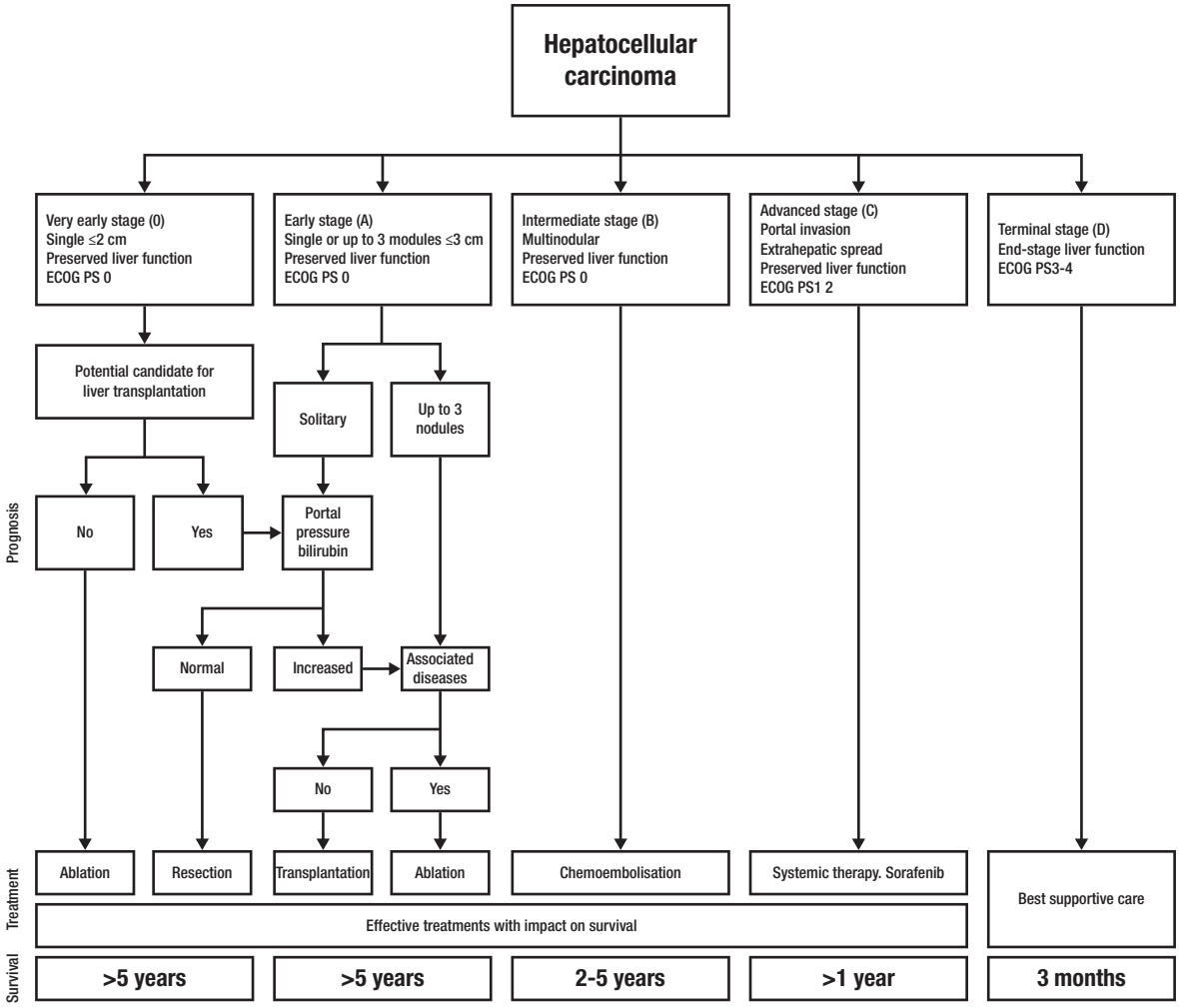

Figure 7. BCLC classification of liver cancer

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.
Source: BCLC classification [79].

Treatment of hepatocarcinoma cancers

HCC patients should be treated by multidisciplinary teams that include hepatologists, radiologists, surgeons, pathologists and oncologists. In general, the treatment choice for HCC depends on the degree of hepatic involvement, the size and distribution of the tumour, the vascular involvement and the general health status of the patient.

According to current guidelines [5,28,31,81–85], liver resection (LR) represents the treatment of choice for small early-stage tumours in noncirrhotic patients and in cirrhotic patients with single nodules with preserved liver function and no evidence of portal hypertension (Child Pugh A–B; BCLC stage 0 and A). There is no proof of any additional benefit with neoadjuvant or adjuvant systemic therapies.

Liver transplantation (LT) is recommended for early-stage disease in noncirrhotic and cirrhotic patients who meet the Milan criteria (solitary lesion of <5 cm or 2–3 nodules <3 cm, without vascular invasion or extrahepatic dissemination) [5,31,81–85].

Among ablative techniques, RFA is considered the first-line treatment for patients with a contra-indicated to LR or LT because of associated disease. RFA can also constitute an alternative to surgery for noncirrhotic patients with very early-stage disease (solitary nodules <2 cm) [5,31,81–85]. While awaiting LT, patients could also be offered resection, local ablation or TACE. The estimated 5-year survival for patients treated with LR, LT or RFA is 70–90% for those diagnosed with very early-stage disease (BCLC 0) and 50–70% for those presenting with early-stage disease (BCLC A) [31]. Although there is no consensus on extending the criteria for surgery, several guidelines propose that the suitability for LR or LT should also be assessed for patients with intermediate-stage tumours that can be downgraded to meet the corresponding criteria, given that surgery is the only curative option [5,83,84]. Selected patients with larger or multinodular tumours or advanced compensated liver failure can also be treated with RFA, but the response rate for these tumours is much lower. According to the Dutch guideline, RFA can be also be used for larger tumours provided the Child Pugh score is <8 [81]. The EASL guideline states that IRE can be considered as a novel form of ablation that is currently not recommended over thermal ablation techniques as it requires general anaesthesia and deep muscular blockage, making it more demanding and costly. Other ablative treatments under investigation are laser ablation and cryoablation [5].

Currently, TACE is the first-line treatment for cirrhotic patients with intermediate-stage tumours that do not meet the Milan criteria [5,81–85] or those with asymptomatic multinodular tumours without macroscopic vascular invasion or extrahepatic spread (BCCL B). TACE involves infusion of a cytotoxic agent, followed by arterial occlusion with embolising agents, most often Gelfoam particles. Although TACE is the only potential strategy with clinical benefits, the median patient survival is just approximately 20 months [5,31]. Side effects include those due to the chemoembolisation agent used, commonly doxorubicin, in addition to those due to the intra-arterial procedure, which can include pain, fever, hepatic decompensation and in rare case infarction of organs other than the liver [5,84].Serious complications can occur in 3–5% of patients treated [84]. Some studies seem to have shown that doxorubicin-eluting beads might result in fewer systemic side effects and some guidelines recommend these over conventional TACE [81]. Although there are multiple ongoing trials assessing other locoregional treatments such as transcatheter arterial radioembolisation and external RT, these are not recommended in most guidelines given the lack of comparative evidence.

Although it is acknowledged that there is currently no effective treatment for advanced-stage cancer (BCCL C), sorafenib is commonly recommended for patients with compensated cirrhotic disease and good performance status [5,31,81–85]. An Italian position paper recommends sorafenib only for patients who are not candidates for surgery or locoregional treatments (ablation, TACE) or when TACE has failed [83]. A randomised trial has shown that sorafenib can increase median survival from approximately 8 to 10 months. Best supportive care is recommended for patients with heavily impaired liver function or poor performance status (BCLC C) and for patients who experience progression or are intolerant to sorafenib. For example, patients who might have bone metastases might benefit from palliative RT. CHEMO is currently not recommended.

Target population

[A0007] What is unresectable locally advanced pancreatic cancer (LAPC)?

Regarding pancreatic cancer, the target population in this assessment is:

- Patients diagnosed with nonmetastatic but unresectable disease due to involvement of the coeliac trunk or superior mesenteric artery, classified as LAPC according to the NCCN guidelines or as stage III according to the AJCC criteria. Recurrent cancers will also be considered.

The following subgroups will be considered:

◊ Patients who have already received CHEMO and/or RT and the tumour does not progress

◊ Patients who have already received CHEMO and/or RT and the tumour becomes resectable; IRE is applied for margin accentuation

◊ Patients who have not received CHEMO or RT

What is unresectable liver cancer (primary or secondary) for which thermal ablation is contraindicated?

Regarding liver cancer, the target population in this assessment is:

- Patients diagnosed with unresectable (primary or secondary) liver cancer for which thermal ablation is contraindicated because of the risk of collateral damage to biliary, vascular or structures due to the effect of heat.

  The following subgroups will be considered:

  ◊ Patients with primary liver cancer

  ◊ Patients with secondary liver cancer, differentiated by origin/histology

[A0023] How many patients belong to the unresectable LAPC?

The global incidence of pancreatic cancer is increasing, with more than 330,000 new cases diagnosed in 2012 [60]. For 2018, the estimated incidence was 458,918 new cases [3], and 18.8 new cases per 100,000 individuals in Europe, with the highest incidence in Western Europe [86].

Estimating exactly how many patients have LAPC and could therefore benefit from IRE is not easy. It is estimated that at the time of diagnosis, approximately 40% of patients have metastatic disease and another 40% have LAPC (stage III) [4]. According to these data, we could estimate that more than 180,000 cases of LAPC would be diagnosed each year worldwide. According to a systematic review, approximately one-third of patients who are diagnosed with LAPC may show resectable disease after neoadjuvant therapy [87].

How many patients belong to the unresectable liver cancer (primary or secondary) contraindicated for thermal ablation group?

The incidence of primary liver cancer is increasing. In 2012, there were 782,000 new cases worldwide [60]. The estimated incidence for 2018 in Europe is 12.4 new cases per 100,000 individuals, with the highest estimates for Southern and Western Europe [86]. Secondary liver tumours are even more frequent than primary liver cancer but the incidence is unknown. Some authors have reported hepatic metastases in as many as 40–50% of adult patients with extrahepatic primary tumours [8].

[A0011] How much is IRE utilised?

According to the manufacturer, more than 135 unique hospitals or cancer centres have performed NanoKnife procedures in the USA since 2017. The NanoKnife System has been used in >5450 procedures since being introduced to the US market in 2007.

No information regarding the extent of IRE utilisation in the European Union was found.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of IRE on mortality?
D0005	How does IRE affect the symptoms and findings (severity, frequency) of pancreatic cancer? How does IRE affect the symptoms and findings (severity, frequency) of liver cancer (primary or secondary)?
D0006	How does IRE affect the progression (or recurrence) of pancreatic cancer? How does IRE affect the progression (or recurrence) of liver cancer (primary or secondary)?
D0011	What is the effect of IRE on patients' body functions?
D0012	How does IRE affect general health-related quality of life?
D0013	What is the effect of IRE on disease-specific quality of life?
D0017	Were patients satisfied with the technology?

5.2 Results

The critical outcomes for evaluating effectiveness were OS, cancer-specific survival, disease-free survival, PFS, time to progression, time to recurrence, time to local recurrence, QoL and pain, as these reflect the main endpoints of the treatment.

Pancreatic cancer

Included studies

The systematic literature search was restricted to randomised and nonrandomised clinical trials and prospective observational studies. A total of eight studies met our eligibility criteria. No RCTs were found. One of the studies included was a non-RCT trial (propensity score matched) [11]. The rest of the studies were considered to have a prospective single-arm design, although the information provided was uncertain in three cases [14,17,19]. Characteristics of the studies included and the results are presented in Tables A2 and A3 in Appendix 1.

The studies included were published between 2012 and 2018 and originated from the Czech Republic (*n* = 1), Netherlands (*n* = 1), Sweden (*n* = 1), USA (*n* = 2), Italy (*n* = 2) and East Asia countries (Taiwan, Singapore, Korea and China). All but two [17,19] described single-centre experiences. Safety/procedural complications or feasibility were reported as the main objective in five of these studies [11,13,15–17]. Efficacy outcomes included control of disease, local progression, event-free survival, PFS, OS and alleviation of pain.

Patient characteristics

Overall, the studies included provided results for 247 IRE-treated patients. The study sample size studies ranged from 10 to 70 patients.

The non-RCT [11] included 21 patients with AJCC stage III disease who were treated with IRE. These patients were compared with 32 patients who underwent some type of noncurative surgery, including exploratory laparotomy, non-radical resection, bypass surgery, cholecystectomy or percutaneous biopsy only. All of the patients had a good performance status (Karnofsky performance status [KPS] ≥80). The mean age of subjects was 68 years in the IRE group and 65.2 years in the control group (p = 0.22). Females accounted for 52.4% of the IRE group and 31.3% of the control group (p = 0.10).

In both groups, most of the tumours were adenocarcinomas (76% vs 69%) located in the head of the pancreas (81% vs 75%). All tumours were ≤6.5 cm. In the IRE group, neoadjuvant CHEMO was given to 23.8% of the patients and 33.3% received CHEMO after IRE. Some patients from the control group received CHEMO (percentage not reported). The median follow-up for patients was 8.19 months (range 1.25–26.8).

The seven prospective single-arm observational studies enrolled 226 patients treated with IRE. The median age ranged between 61 and 70 years (Huang et al. [17] did not report age information). All of the patients were estimated to have biopsy/histologically confirmed LAPC defined according to the NCCN or AJCC TNM system. With the exception of Kluger et al. [13], studies included only patients with unresectable disease before CHEMO/CRT. The majority suffered from adenocarcinomas located in the head of the pancreas. Tumour size ranged from ≤3 cm to 6.5 cm. Patients with severe disease and those who were completely disabled were commonly excluded [11,13,14,16]. Mansson et al. [14] restricted inclusion to individuals with expected survival of ≥3 months. In the study by Martin et al. [19] all patients had advanced pain previous to IRE.

Most of the patients received CHEMO and/or CRT before IRE, and CHEMO was also offered to some of the subjects after IRE in several trials [11,14,15,17,18] using different treatment regimens and schemes. In two of the studies, patients who experienced downstaging received surgery [13,18]. In the study by Huang et al. [17], only patients who did not experience disease progression after CHEMO were included. Scheffer et al. [16] excluded subjects who could be successfully downstaged to resectable tumour and Paiella et al. [15] considered only those who did not respond to standard treatments.

Two of the studies declared a conflict of interest [16,19].

Procedure

IRE was performed using the NanoKnife System in all cases. The approach was open surgery in four of the trials (≥90% of patients) [11,15,17,19] and percutaneous in three studies [14,16,18]; information was lacking in one study [13]. Overall, open surgery was used in 120 procedures (48.6%), a percutaneous approach in 72 (29.1%) and a laparoscopic approach in five (2.0%). Image guidance was carried out using US in four studies and CT in two.

In most cases, IRE was performed with an ablative intent using CT or US guidance. In two studies, IRE was offered for either margin accentuation or primary control [13,19]. Kluger et al. [13] treated three patients with a second IRE procedure. The number of needles used for IRE varied from two to six (mean 3–4). The median procedure duration in the studies that mainly used open surgery varied from 79 to 165 minutes [11,15,17,19]. The duration for the percutaneous approach was not reported, except for two patients included in the study by Lambert et al. (26 minutes) [11].

In three of the studies, additional procedures were also performed at the time of IRE, including gastrojejunostomy, double bypass, cholecystectomy, gastroenteroanastomosis and hepaticojejunostomy [11,13,19].

Follow-up

Seven of the eight studies had median follow-up of ≤12 months. The longest follow-up was 28.1 months [17] and the shortest was 3 months [19].

Liver cancer

Studies included

The systematic search was restricted to randomised and nonrandomised clinical trials and prospective observational studies. No RCTs were found. A total of seven prospective single-arm studies met our eligibility criteria. The characteristics of the studies included and the results are presented in Table A3 in Appendix 1. The trials were single-centre experiences in Sweden (*n* = 1), Germany (*n* = 4), Italy (*n* = 1) and Australia (*n* = 1). The studies were published between 2013 and 2017. Six trials reported on EFF and SAF outcomes and one on only EFF outcomes.

Patient characteristics

The seven studies enrolled 151 patients with 220 IRE-treated lesions. The study sample size varied from 11 to 34 patients (mean 20.57 ± 8.84). The mean age of patients ranged from 59.4 to 70 years. Females represented 30% of the population. All of the patients treated had unresectable liver tumours not suitable for thermal ablation (RFA, MWA or cryoablation) because they were located near major hepatic or portal vessels, bile duct structures or peripheral important structures. All of the patients had fewer than three malignant lesions, which were commonly ≤3 cm. Two studies restricted inclusion to primary HCC tumours [21,24]; the rest included primary and secondary tumours, mainly colorectal liver metastases. Another two restricted inclusion to patients with good performance status [20,24]. All of the patients included in the two studies that treated only primary tumours had chronic liver disease of Child-Pugh class A [24] and Child-Pugh classes A and B [21]. Apart from Niessen et al. [25], who included patients with Child-Pugh class A, B and C disease, none of the studies provided information regarding liver function. Tumour stage for primary HCC was only provided in one study (stage A, BCLC classification) [24].

Four studies [12,20,23,25] reported that patients had received several treatments before IRE, including surgical treatments, systematic therapy, RFA/MWA, brachytherapy, RT and TACE, among others.

Only Cheung et al. [21] declared a potential conflict of interest: the research equipment was received from AngioDynamics.

Procedure

The NanoKnife System was used in all cases. In six of the seven studies, IRE was performed via a percutaneous approach. Overall, the percutaneous approach was used in 145 patients (96%), the laparoscopic approach in four (2.6%) and open surgery in two (1.3%).

In all studies, IRE was used with an ablative intent and CT or US was used for imaging guidance. The number of needles used varied from two to six. The mean duration reported for percutaneous procedures varied from 1 to 5 hours. Eisele et al. [12] reported a mean procedure time of 4 hours for an open approach and 2.58 hours for a laparoscopic approach.

Follow-up

The mean follow-up was <18 months in four studies [12,23–25]. The shortest follow-up was in the study by Granata et al. [24] at 6 months. The longest follow-up times were in the studies by Fruhling et al. [20] (median 22.3 months, range 2.5–55.6) and Distelmaier et al. [22] (mean 24 ± 7 months).

Table 9. Evidence used in effectiveness domain in pancreatic cancer (comparative studies)

Author, year, country, study characteristics	Tumour stage	Number of patients	Median FU, mo (range)	Adjuvant treatments	Irreversible electroporation approach	Success of the procedure	Overall survival (95% CI)	Progression Free Survival (95% CI)	Time to Recurrence (95% CI)		Health-related quality of life and pain
									Progression	Local recurrence	
Lambert, 2016, Czech Republic [11] Prospective non-RCT (propensity score-matched analysis) 2012–2014	Stage III LAPC	21	8.19 (1.25–26.84)[1]	CHEMO before IRE: 23.8% (*n* = 5) CHEMO after IRE: 33.3% (*n* = 7)	Open surgery: 90.5% (*n* = 19) Percutaneous: 9.5% (*n* = 2)	– *(tumour size did not change after IRE)*	Median 10.03 mo (5.26, 15.39)[1] • 3 mo: 90.48 (67.00, 97.53)[1] • 6 mo: 75.00 (49.81, 88.80)[1] • 12 mo: 47.62 (24.37, 67.71)[1] • 18 mo: 13.61 (2.33, 34.71)[1]	--	-- *[P: 42.1% (not FU reported)]*	--	KPS ≥70 81% of the time after IRE (IQR 65–98)
	Matched cohort: stage III LAPC	32	--	Patients who had undergone some type of surgery or percutaneous biopsy only, with or without CHEMO	NA	NA	Median 9.3 mo HR: 0.54 (*p* = 0.053)	--	--	--	KPS ≥70 74% of the time after surgery (IQR 14–88) *p* = 0.076

Outcomes refer to the time from IRE to the event of interest. When they refer to the time after diagnosis, this is indicated in the text.

[1] Calculated using individual data provided by the author.

Abbreviations: CHEMO = chemotherapy; CI = confidence interval; FU = follow-up; HR = hazard ratio; IQR = interquartile range; IRE = irreversible electroporation; KPS = Karnofsky performance status; LAPC = locally advanced pancreatic cancer; mo = months; NA = not applicable; P = progression; RCT = randomised controlled trial.

Source: [11].

Table 10. Evidence used in effectiveness domain in pancreatic cancer (single-arm studies)

Author, year, country, study characteristics	Tumour stage	Number of patients	FU	Adjuvant treatments	IRE approach	Success of the procedure	Overall survival (95% CI)	Progression Free Survival (95% CI)	Time to Recurrence (95% CI)		Health-related quality of life and pain
									Progression	Local recurrence	
Huang, 2018, China [17] Prospective multicentre single-arm study 2012–2015	Stage III LAPC (AJCC)	70	Median 28.1 mo	CHEMO/CRT before and after IRE: 100% (*n* = 70)	Open surgery: 92.9% (*n* = 65) Laparoscopic: 7.1% (*n* = 5)	– *[complete ablation 100% (90 d after IRE)]*[1]	Median 22.6 mo (19.60–25.60, range 6.6–52.3)[2] • 3 mo: 100% • 6 mo: 100% • 12 mo: 90% • 24 mo: 37%	Median 15.4 mo (range 5.3–52.3)	– *[DP: 34.2% (median FU 28.1 m)]*	– *[LR: 8.6% (median FU 28.1 m)]*	–
Scheffer, 2017, Netherlands [16] Prospective single-arm study 2014–2015	LAPC (NCCN)	25	Median 12 mo (IQR 7–16)	CHEMO before IRE:100% (*n* = 25)	Percutaneous: 100% (*n* = 25)	– *[IRE procedure 100% successful]*	After IRE: median 11 mo (9–13) After diagnosis: 17 mo (10–24)	After IRE: median 8 mo (4–12) After diagnosis: 15 mo (10–20)	–	Median 12 m (8, 16)	EORTC QLQ-C30 and PAN26 • 6 w:reduced appetite (p = 0.048) • 3 mo: diminished general functioning (p = 0.040) • 6 mo: diminished general functioning (p = 0.028) • 6 mo: increased feeling of weak arms and/or legs (p = 0.031) and indigestion problems (p = 0.007) Pain • 1 d: median 2 (range 0–5) • 6 w: impact of pain on gait (p = .016), normal work (p = 039), and daily activities (p = 0.023) • 6 mo: pain increased and more difficult to treat with analgesics (p = 0.039)

Author, year, country, study characteristics	Tumour stage	Number of patients	FU	Adjuvant treatments	IRE approach	Success of the procedure	Overall survival (95% CI)	Progression Free Survival (95% CI)	Time to Recurrence (95% CI)		Health-related quality of life and pain
									Progression	Local recurrence	
Mansson, 2016, Sweden [14] Prospective single-arm study Data collection period not reported	LAPC (equivalent to NCCN)	24	Median 6.96 mo (range 1.12–18.75)	CHEMO + CRT before IRE: 29.2% (*n* = 7) RT alone before IRE: 12.5% (*n* = 3) CHEMO alone before IRE: 8.3% (*n* = 14) CHEMO after IRE: 58.3% (*n* = 14)	Percutaneous: 100% (*n* = 24)	–	Median 8.95 mo (6.79–11.11)[3] • 3 mo: 95.83% (73.92, 99.40) • 6 mo: 58.33% (36.45, 74.99) • 12 mo: 29.55% (12.45, 48.99) After diagnosis: 17.5 mo (13.18–21.83)	Median 3.19 mo (2.14–6.18)[3] • 3 mo: 58.33% (36.45, 74.99) • 6 mo: 33.33% (15.90, 1.87)	TTP: median 3.32 mo (2.30–6.38)[3]	Median 6.81 mo (4.87–8.78) [3] *[LR: 58.3%]*	–
Kluger, 2016, USA [13] Prospective single-arm study October 2012 onwards	LAPC (NCCN)	Ablation									
		--			--	--	Median 7.71 mo (6.03–12.0)	--	--		--
		Margin accentuation									
		--			--	--	--	--	--		--
		Total									
		50	Median 8.69 mo (IQR: 0.26-16.26)	CHEMO before IRE: 92% (*n* = 46) RT before IRE: 78% (*n* = 39)	--	--	Median 12.03 mo (7.71–23.12)	--	– *[P: 58% (FU 8.69 mo)]*	Median 8.6 mo (5.51–not reached) *[LR: 11% (FU 8.69 mo)]*	--

Author, year, country, study characteristics	Tumour stage	Number of patients	FU	Adjuvant treatments	IRE approach	Success of the procedure	Overall survival (95% CI)	Progression Free Survival (95% CI)	Time to Recurrence (95% CI)		Health-related quality of life and pain
									Progression	Local recurrence	
Paiella, 2015, Italy [15] Prospective single-arm study June 2011–December 2011	LAPC (equivalent to NCCN)	10	Median 7.6 mo	CHEMO before IRE: 100% (*n* = 10) RT before IRE: 40% (*n* = 4) CHEMO after IRE: 30% (*n* = 3)	Open surgery: 100% (*n* = 10)	– *[IRE procedure 100% successful]*	Median 4.3 m (2.9–10.1) [mean 7.5 mo (24.95–10.03)][3] • 3 mo: 90% (47.30, 98.53) • 6 mo: 50% (18.36, 75.32) • 12 mo: 20% (3.09, 47.47) After diagnosis: median 12.5 mo (8.5–24.1) [mean 16.79 mo (12.40–21.18)][3]	–	–	–	EORTC QLQ c30/ PAN26: Preoperatively: 58.3 • 2 w: 37.5 • 3 mo: 33.5 KPS: Baseline: 100 • 30 d: 80 • 60 d: 77.5 • 90 d: 70 Pain (VAS): Baseline: 0.5 • 30 d: 3 • 60 d: 4 • 90 d: 1
Belfiore, 2015, Italy [18] Prospective single-arm study April 2013–June 2014	LAPC (NCCN)	20	Mean 8.55 mo (range 3–14)[3]	100% CHEMO after IRE (*n* = 20)	Percutaneous: 100% (*n* = 20)	– *[IRE procedure 100% successful]*	Mean 12.95 mo (11.57–14.33) • 3 m: 95% (69.5, 99.3)[3] • 6 mo: 90% (65.6, 97.4)[3] • 12 mo: 90% (65.6, 97.4)[3]	–	– *[P 10% (FU 8.55 mo)]*	– *[LR 10% (FU 6 mo)]*	–
Martin, 2012, USA [19] Prospective single-arm study December 2009–March 2011	Stage III LAPC (AJCC)	27	90 d	CHEMO and/or RT before IRE: 85% (*n* = 23)	Open surgery: 96.3% (*n* = 26) Percutaneous: 3.7% (*n* = 1)	96.3% (90-d after IRE) [1 patient died][4]	– *[after FU of 90 d: 100%]*	–	–	–	Pain before IRE: 5 points (range 3–9)

Outcomes refer to the time from IRE to the event of interest. When they refer to the time after diagnosis, this is indicated in the text.

[1] Success of the procedure defined as "complete ablation", with no residual contrast-enhanced tumour on dynamic imaging after 3 months.

[2] Data provided by the author.

[3] Calculated using individual data provided in the article.

[4] Success of the procedure defined as the ability to deliver the planned therapy in the operative room and no evidence of residual tumour at 3 months.

Abbreviations: AJCC = American Joint Committee on Cancer; CHEMO = chemotherapy; CI = confidence interval; CRT = chemoradiotherapy; d = days; DP = distant progression; FU = follow-up; EORTCQLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; IQR = interquartile range; IRE = irreversible electroporation; KPS = Karnofsky performance score; LAPC = locally advanced pancreatic cancer; LR = local recurrence; mo = months; NCCN = National Comprehensive Cancer Network; P = progression; PFS = progression-free survival; RT = radiotherapy; TTP = time to progression; VAS = visual analogue scale; w = weeks.

Sources: [13–19].

Table 11. Evidence used in effectiveness domain in liver cancer

Author, year, country, study characteristics	Tumour stage	Number of patients	FU	Tumour type	IRE approach	Success of the procedure (95% CI)	Overall survival (95% CI)	PFS (95% CI)	Time to Recurrence (95% CI)		Health-related quality of life and pain
									Progression	Local recurrence	
Fruhling, 2017, Sweden [20] Prospective single-arm study September 2011–September 2014	–	30	Median 22.3 mo (range 2.5–55.6)	• PT: HCC (21.1%, *n* = 8) • ST: CRLM (60.5%, *n* = 23), other (18.4%, *n* = 7)	Percutaneous 100% (*n* = 30)	–	[Mean 37.92 mo (30.28–45.57)][1] • 3 mo: 96.67% (78.61, 99.52)[1] • 6 mo: 96.67% (78.61, 99.52)[1] • 12 mo: 89.76% (71.51, 96.58)[1] • 18 mo: 69.05% (48.93, 82.54)[1] • 24 mo: 65.21% (44.92, 79.58)[1]	–	–	– *% LR:* 3 m / 6 m All tumours 21.1% / 34.2% CRLM 26.1% / 47.8% HCC 0% / 0% Other 28.6% / 28.6%	–
Distelmaier, 2017, Germany [22] Prospective single-arm study February 2012–June 2015	–	29	Mean 24 mo (SD 7)	29 pts, 43 Ts: • PT: HCC (2 pts, 4 Ts) • ST: breast (4 pts, 4 Ts), colorectal (13 pts, 21 Ts), cholangiocellular (2 pts, 4 Ts), pancreas (2 pts, 2 Ts), melanoma (1 pt, 1 T), mesothelioma (1 pt, 1 T), oesophageal (2 pts, 2 Ts), renal (1 pt, 3 Ts), gastrointestinal stroma (1 pt, 1 T)	Percutaneous 100% (*n* = 29)	– *[90% (79, 98) by pt at 1 d after IRE; 93% (85, 100) by T]* [2]	–	–	– *[DP 17.2% at mean FU of 24 mo]*	– *LR + RR by pt: 10/26 (38% (95% CI 20, 59) at mean FU of 24 mo)* *LR by pt: 7.7% (2/26)* *RR by pt: 30.8% (8/26)* *[seeding along the needle tract]*	–
Niessen, 2016, Germany [25] Prospective single-arm study December 2011–June 2013	–	34	Median 13.9 mo (range 1.8–19.5)	34 pts, 65 Ts: • PT: HCC: 15 pts, 33 Ts • ST: colorectal (12 pts, 22 Ts), cholangiocellular (4 pts, 5 Ts), testicular (1 pt, 2 Ts), neuroendocrine (2 pts, 3 Ts)	Percutaneous 100% (*n* = 34)	– [95.4% by T 6 w after IRE] [3]	–	–	TTP: median 15.6 mo	By T: mean 15.5 mo LR-free survival: • 3 mo: 87.4% • 6 mo: 79.8% • 12 mo: 74.8%	–
Granata, 2016, Italy [24] Prospective single-arm study January 2012–July 2013	Stage A (BCLC classification)	20	6 mo	24 PTs: well-differentiated HCC (83.3%), moderately differentiated nodule (12.5%), poorly differentiated lesion (4.17%)	Percutaneous 100% (*n* = 20)	– *[91.7% by T 1 mo after IRE]*[4]	– *[100% after 6 mo of FU]*	–	–	–	–

Author, year, country, study characteristics	Tumour stage	Number of patients	FU	Tumour type	IRE approach	Success of the procedure (95% CI)	Overall survival (95% CI)	PFS (95% CI)	Time to Recurrence (95% CI)		Health-related quality of life and pain
									Progression	Local recurrence	
Eller, 2015, Germany [23] Prospective single-arm study Data collection period not reported	–	14	Mean 388 d (SD 160; range 120–594) [among 10 patients without LR]	14 pts, 18 Ts: • PT (21.4%): HCC • ST (78.6%), neuroendocrine (1/14), squamous cell (1/14), colorectal (9/14)	Percutaneous 100% (*n* = 14)	– [86% 1 d after IRE] [5]	–	–	– *[P 50% at mean FU of 388 d]*	– *[LR 17% at mean FU of 388 d]*	–
Eisele, 2014, Germany [12] Prospective single-arm study Data collection period not reported	–	13	Median 8 mo (range 3–12)	14 Ts: • PT: HCC (5 pts, 5 Ts, 35.7%), intrahepatic recurrent cholangiocarcinoma (2 pts, 2 Ts, 14.3%) • ST: colorectal liver metastases (6 pts, 7 Ts, 42.9%)	Percutaneous 53.8% (*n* = 7) Laparoscopic 30.8% (*n* = 4) Open surgery 15.4% (*n* = 2)	– *[76.9%]* [6] Percutaneous 57.1%, laparoscopic 100%, open surgery 100%	100% (100% at 3 mo, 60 and 12 mo)	–	– *[P 20% at mean FU of 8 mo]*	–	–
Cheung, 2013, Australia [21] Prospective single-arm study November 2008–December 2009	–	11	Mean 18 mo (SD 4; range 14–24)	18 T: HCC (100%)	Percutaneous 100% (154 procedures)	– *[54.5% (1st and 2nd IRE) after 6 mo* [7]*; 72% by T]*	–	–	– *[mean time to DP 14 mo (SD 6)]*	– *[LR 0% at mean FU of 18 m]*	-

Outcomes refer to the time from IRE to the event of interest. When they refer to the time after diagnosis, this is indicated in the text.

[1] Calculated using individual data provided in the article.

[2] Successful ablation defined as no residual tumour and the ablation zone covered the target tumour with an adequate safety margin.

[3] Technical success defined as successful delivery of all planned pulses to the target volume as calculated by the IRE generator and complete tumour coverage (assessed via computed tomography or magnetic resonance imaging 6 weeks after ablation).

[4] Defined as a "complete response": disappearance of any enhancement in all target lesions.

[5] Defined as total inclusion in the devascularised area in the initial postinterventional computed tomography scan performed the first day after IRE.

[6] No definition provided.

[7] No residual tumour or recurrence at or directly adjacent to the treated location following up to two IRE ablations.

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; CRLM = colorectal liver metastases; d = day; DP = distant progression; FU = follow-up; HCC = hepatocellular carcinoma; IRE = irreversible electroporation; LR = local recurrence; mo = months; pt = patient; P = progression; PFS = progression free survival; PT = primary tumour; RR = regional recurrence; SD = standard deviation; ST = secondary tumour; T = tumour; TTP = time to progression; w = weeks.

Sources: [12,20–25].

Mortality

[D0001] What is the expected beneficial effect of IRE on mortality?

Pancreatic cancer

Overall survival

- *Overall survival after IRE*

The comparative trial [11] reported median survival of 10.03 months (95% CI 5.26, 15.39) in the IRE group and 9.3 months in the control group; the difference between the groups was not significant (hazard ratio 0.54, $p = 0.053$). The survival probability calculated from data provided by the authors was 90.5% (95% CI 67.00, 97.53) at 3 months, 75% (95% CI 49.81, 88.80) at 6 months, 47.6% (95% CI 24.37, 67.71) at 12 months and 13.6% (95% CI 2.33, 34.71) at 18 months. These data were not available for the control group.

The median survival after IRE according to Kaplan-Meier estimation ranged from 4.3 to 12 months in four of the single-arm trials [13–16]. One study provided only the mean survival, which was 12.95 months [18]. One study reported survival of 22.6 months [17]. In this trial, survival was significantly longer for patients treated with TS-1 CHEMO (28.7 months) than for those who received gemcitabine (13.2 months). There was no information for one study [19]. Median survival was significantly higher in the margin extension group than in the primary treatment group ($p = 0.01$; data not provided) in one of the studies [13].

OS at specified time points after IRE (3, 6, 12 and 24) was not reported in individual studies but could be calculated from data given in the publication or provided by the contact author. The OS at 3 months was available from four studies [14,15,17,18] and ranged from 90% to 100%. The OS ranged from 50% (95% CI 18.36, 75.32) [15] to 100% (CI not provided) [17] at 6 months and from 20% (95% CI 3.09, 47.47) [15] to 90% [17,18] at 12 months. In the only study reporting beyond 12 months, OS was 37% at 24 months [17].

- *Overall survival from the time of diagnosis*

The median OS from the time of diagnosis could only be obtained in three studies [14–16] and varied from 12.5 to 17.5 months. Survival at 3 and 6 months was 100% in two of these studies [14,15]. At 12 months it was 60% (95% CI 25.27, 82.72) and 79.17% (95% CI 56.98, 90.75). At 18 months, it was 50% (95% CI 29.10, 67.76; 18.36, 75.32) and at 24 months, 13.89% (95% CI 3.54, 31.14) and 30% (95% CI 7.11, 57.79).

Cancer-specific survival

Cancer-specific survival was not reported.

Disease-free survival

Disease-free survival was not reported.

Progression-free survival

In the three studies that reported PFS after IRE (defined as the time from intervention to either radiological progression or death) the median PFS was 15.4 months (95% CI 10, 20) [17], 8 months (95% CI 4, 12) [16] and 3.19 months (95% CI 2.14, 6.18) [14]. Kaplan Meier analysis of the individual data for the last study gave PFS of 58.33% (95% CI 36.45, 74.99) at 3 months and 33.33% (95% CI 15.90, 51.87) at 6 months. In the only study reporting PFS after diagnosis, median PFS was 15 months (95% CI 10, 20) [16].

Liver cancer

Overall survival after IRE

The mean OS after IRE in the only study with data available for calculation [20] was 37.92 months (95% CI 30.28, 45.57). OS was 96.67% (95% CI 78.61, 99.52) at 3 months, 96.67% (95% CI 78.61, 99.52) at 6 months, 89.76% (95% CI 71.51, 96.58) at 12 months, 69.05% (95% CI 48.93, 82.54) at 18 months and 65.21% (95% CI 44.92, 79.58) at 24 months.

Overall survival after diagnosis

No data were available for calculating OS after diagnosis.

Cancer-specific survival

Cancer-specific survival was not reported.

Progression-free survival

PFS was not reported in the liver cancer studies.

Morbidity

[D0005] How does IRE affect the symptoms and findings (severity, frequency) of pancreatic cancer? How does IRE affect the symptoms and findings (severity, frequency) of liver cancer (primary or secondary)?

Evidence is lacking regarding the effect on symptoms and findings.

[D0006] How does IRE affect the progression (or recurrence) of pancreatic cancer? How does IRE affect the progression (or recurrence) of liver cancer (primary or secondary)?

Pancreatic cancer

Success of the procedure

Success of the procedure as defined in the PICO question was the ability to complete the IRE procedure as planned and the absence of any residual tumour. According to this definition, for all patients treated with IRE in the only comparative study [11] the treatment would be defined as unsuccessful. The authors explained that the size of the tumour did not change after IRE (39 ± 10 mm vs 39 ± 14 mm; $p = 0.65$). Only in five patients did the tumour decrease in size by >10 mm.

One of the single-arm trials reported success as defined by the PICO question [19], which was 96.3%. This study defined ablation success as the ability to deliver the planned therapy in the operative room and no residual tumour at 3 months. Another study partly defined success [17]; the authors assessed complete ablation of the tumour at 90 days after IRE, defined as no residual contrast-enhanced tumour on dynamic imaging, which was reported as 100%. Three studies assessed only the technical success of the procedure [15,16,18].

Time to progression after IRE

Time to progression (local recurrence + distant progression) was only available in one study [14], reported as 3.32 months (95% CI 2.30, 6.38).

Time to local recurrence after IRE

The median time to local recurrence was 12 months (95% CI 8, 16) in the study by Scheffer et al. [16], 6.81 months (95% CI 4.87, 8.78) in the study by Mansson et al. [14] and 8.6 months (95% CI 5.51, not reached) in the study by Kluger et al. [13].

Liver cancer

The outcome "success of the procedure", as considered in the PICO question was not available in any of the studies, although incomplete definitions of success were provided in five studies [21–25], with assessments carried out at different time points. One study [22] assessed success the day after IRE and reported that complete ablation, defined as no residual tumour and complete tumour coverage with an adequate safety margin, was achieved in 90% of the subjects (93% by tumour). Another study [21] reported an ablation success per tumour of 72%, considering cases that showed no residual or recurrent disease at or directly adjacent to the ablation site after two treatments and at least 6 months of follow-up; the per-patient rate of success was 54.5%. Granata et al. [24] observed a complete response in 91.7% of patients at 1 month according to the metastatic Response Evaluation Criteria in Solid Tumours scheme (disappearance of any enhancement in all target lesions). Niessen et al. [25] assessed successful delivery of all planned pulses to the target volume as calculated by the IRE generator and complete tumour coverage (via CT and/MRI performed 6 weeks after ablation), reported as 95.4%. Eller et al. [23] reported the technical success of the procedure as 86% (defined as total inclusion in the devascularised area in the initial postinterventional CT performed the first day after IRE). In the study by Eisele et al. [12] ablation success of 76.9% was reported but no definition was provided. Fruhling et al. [20] did not provide results.

Time to progression after IRE

The time to progression was available only in one study [25], which included patients undergoing percutaneous IRE, for whom the median time to progression was 15.6 months. Two studies provided the percentage of patients who experienced progression during follow-up. In the first study [23], 50% of patients experienced progression after mean follow-up of 12.8 months. In the second study [12], progression was observed in 20% of patients after median follow-up of 8 months.

Time to local recurrence after IRE

The mean time to local recurrence (15.5 months) was only available in one study [25]. Local recurrence–free survival at 3 months was 87.4% (no CI reported), 79.8% at 6 months and 74.8% at 12 months. While not providing the time to local recurrence, one study [20] reported that 21% of the patients had a local recurrence at 3 months and 34.2% at 6 months, with corresponding colorectal cancer liver metastasis rates of 26.1% and 47.8%. There were no local recurrences at either time point for HCC (p = 0.084, colorectal cancer liver metastases vs HCC).

Another study [23] reported that 17% of patients experienced a local recurrence after mean follow-up of 12.8 months. Distelmaier et al. [22] observed a local recurrence rate of 7.7% after mean follow-up of 24 months, with regional recurrences in 30.8% of patients due to needle-tract seeding. Cheung et al. [21] did not observe any local recurrence during the mean 18 months of follow-up.

[D0011] What is the effect of IRE on patients' body functions?

No evidence was found to answer this research question.

Health-related QoL

[D0012] How does IRE affect general health-related quality of life?

[D0013] What is the effect of IRE on disease-specific quality of life?

Pancreatic cancer

The study with a comparator group [11] analysed functional status in terms of KPS using a scale from 0 (death) to 100 (normal life) at each clinical visit. The results showed that functional status after IRE slowly declined. KPS was ≥70 81% (IQR 65–98%) of the time after IRE, compared to 74% (IQR 14–88%) of the time after surgery in the control group; the difference was not statistically significant. A sharp decline occurred approximately 8 weeks before death in the IRE group (no data available for the control group).

In the study by Scheffer et al. [16], patients completed two QoL questionnaires (QLQ-C30 and QLQ-PAN26) and a pain registration form (with a visual analogue score ranging from 0 to 10) at each visit. The questionnaire response was 100% before IRE but varied after IRE: 80% of patients completed the questionnaires 6 weeks after IRE, 88% at 3 months and 85% at 6 months. Compared with baseline, patients had reduced appetite at 6 weeks (p = 0.048) and diminished general functioning at 3 months (p = 0.04) and 6 months (p = 0.028). At 6 months they also had an increased feeling of weak arms and/or legs (p = 0.031) and indigestion problems (p = 0.007). Patients reported moderate pain after IRE, with a median visual analogue scale score of 2 (range 0–5). Compared with baseline, 23% of the pain items deteriorated after 6 weeks: impact of pain in gait (p = 0.016), normal work (p = 0.039) and daily activities (p = 0.023). After 6 months, the pain was more difficult to treat with analgesics (p = 0.039). The rest of the items did not change significantly.

Only one more study provided QoL data [15] and used the Italian versions of QLQ-C30 and QLQ-PAN26. Performance status was evaluated using the Karnofsky score. According to the questionnaires, the median QoL score was 58.3 preoperatively, and declined to 37.5 at 2 weeks and 33.33 at 3 months after IRE. The median baseline KPS recorded was 100 and was 80, 77.5 and 70 at 30, 60 and 90 days after IRE, respectively.

Liver cancer

None of the studies reported QoL, although two provided information on postprocedural pain as a complication.

Satisfaction

[D0017] Were patients satisfied with the technology?

No evidence was identified to answer this research question.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is IRE?
C0002	Are the harms related to dosage or frequency of applying IRE?
C0004	How does the frequency or severity of harms change over the time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of IRE?
B0010	What kind of data/records and/or registry is needed to monitor the use of IRE?

6.2 Results

The critical outcomes used to evaluate the evidence were intervention-specific mortality and major AEs. Minor AEs were considered to be important.

Studies included

Pancreatic cancer

The study inclusion criteria for assessing SAF did not differ from those used for assessing EFF and the same articles were included for both domains. The characteristics of the studies included and the results are described in the previous section and presented in Tables A2 and A3 in Appendix 1.

AEs were reported and graded in all of the studies included, except the non-RCT [11]. The Clavien-Dindo grading system was used in three studies [13,14,17] and CTCAE in two studies [15,16]. Two of the trials did not report on the grading system used [18,19]. Another two reported exclusively on the number of events and did not provide the number of events per patient [15,16].

Three studies recorded AEs at 90 days [13,16,19] and one reported AEs at 30 days [14]. The timing was not available in four studies [11,15,17,18]. Classification of IRE-related complications was missing [11,16–18] or unclear [13–15,19] in the studies included.

Liver cancer

The study inclusion criteria for assessing SAF did not differ from those used for assessing EFF. All but one of the studies were included, as AEs were not reported in one study [12]. Characteristics of the studies and the results are described in the previous section and presented in Table A4 in Appendix 1.

All of the liver cancer studies provided AEs per patient graded according to severity, although two did not provide information regarding the grading system [21,24]. The SIR grading system was used in three studies [20,22,25] and the CTCAE in one study [23]. One study [20] reported immediate and periprocedural (within 30 days) AE. Another study also classified the complications according to time of occurrence (immediate, periprocedural or delayed) [22]. The rest did not provide this information. The classification of IRE related or no IRE related complications was missing in most of the studies [20,22,23,25].

Patient safety

[C0008] How safe is IRE?

Pancreatic cancer

Intervention-specific mortality

None of the studies reported intervention-specific deaths (during the intervention).

Major adverse events

Among seven studies grading AEs, all but one [18] reported some type of major AEs (grade III, IV or V). In total, 44 out of 226 patients (19.47%) experienced major AEs, although at least 16 were not considered procedure-related by the authors. In some cases, the same patient experienced several AEs.

The overall procedure-related mortality was 1.62% (4/247 patients) among all the studies. Kluger et al. [13] reported that six of the 50 patients enrolled (12%) died within 90 days after the procedure (median 26 days, range 8–42); five of these deaths occurred in the primary treatment group (17.3%) and one in the margin extension group (4.2%). They considered that only three of the six deaths were procedure-related. The causes of death were cardiopulmonary arrest, duodenal and bile duct necrosis, multisystem organ failure caused by placement of a vena cava stent for symptomatic stenosis and an angiogram embolisation of the gastroduodenal artery, portal vein thrombosis and intraperitoneal haemorrhage. One cause of death was not reported. The study did not specify whether these interventions were performed via open surgery or a percutaneous approach. In the study by Martin et al. [19], one of the 27 patients (3.7%) treated with IRE (open surgery 90.5%; percutaneous approach 9.5%) died due to progression of a portal vein thrombosis. It is unknown if this patient was in the open surgery or percutaneous group.

The mean frequency of grade III or IV IRE procedure-related complications for the studies that provided relevant data was 10.62% (range 0–44%). The frequency was 5.61% (6/107) for patients undergoing IRE mainly for primary control via open surgery (>90% of cases) and 20.29% (14/69) for those undergoing percutaneous IRE. The overall frequency of AEs in the open surgery group, including other non-IRE related 30-90 day severe AEs was 12.15% (13/107). Kluger et al. [13] found no significant difference in the incidence of severe AEs based on tumour location (head, 31%; body, 15%; $p = 0.49$), tumour size (≤3 cm, 26%; >3 cm, 21%; $p = 0.53$), approach (caudad–cephalad, 23%; anterioposterior, 26%; $p = 0.81$) or when IRE was used as a primary treatment versus for margin extension (24% vs 25%; $p = 0.59$).

The procedure-related complications recorded in the open surgery studies were pseudoaneurysm bleeding ($n = 1$), duodenal leaks ($n = 2$), pancreatic and internal fistula ($n = 2$) and intraabdominal abscess ($n = 2$). The most common severe AEs found for the percutaneous group were biliary obstruction ($n = 3$) and pancreatitis ($n = 3$). Others included cholangitis and biloma ($n = 1$), mesenteric vein thrombosis ($n = 1$), mesenteric artery stenosis ($n = 1$), bleeding from an ulcer ($n = 1$), haematemesis due to a duodenal wall ulcer ($n = 1$) and gastrointestinal AEs (vomiting, loss of appetite). Kluger et al. [13] (no approach reported) described three cases of delayed gastric emptying and three deep surgery infections, among others. The comparative trial [11] did not grade the procedure-related complications but reported that the percutaneous approach was abandoned after two cases given the high rate of complications (biliary peritonitis, cholangitis, liver abscesses and pancreatic fistula). The frequency of complications in the open surgery group was 15.8%.

Minor adverse events

In total, 74 of 226 patients (32.74%) experienced minor AEs, including those related and unrelated to IRE. The overall frequency of minor AEs was 24.30% (26/107) for the open surgery group and 50.7% (35/69) for the percutaneous group.

Overall, the frequency of minor (grades I and II) IRE procedure-related complications among the studies that provided relevant data was 21.7% (49/226). One study [16] counted all complications separately and complications such as pneumonia, nausea and vomiting were considered

procedure-related .The percentage of minor complications in the studies varied from 0% to 48%. The frequency was 13% (14/107) in the open surgery group and 31.9% (22/69) in the percutaneous IRE group.

The IRE-related minor AEs reported included infection (*n* = 5), abdominal pain (*n* = 3), diarrhoea (*n* = 2), vomiting (*n* = 2), portal vein thrombosis (*n* = 2), pancreatitis (*n* = 2), hepatitis (*n* = 1), ascites accumulation (*n* = 1) and gastrointestinal bleeding (*n* = 1). Minor AEs not related to IRE included wound infections, deep venous thrombosis, abdominal back pain and haematological complications, among others.

Liver cancer

Intervention-specific mortality

No intervention-specific deaths occurred in any of the studies.

Major adverse events

Overall, the frequency of major AEs was 8.70% (12/138), and ranged from 0% to 28.6% among the studies included. None reported procedure-related mortality.

Niessen et al. [25] reported six grade III complications (four abscesses, one intraperitoneal bleeding and one partial thrombosis of the portal vein) and Eller et al. [23] observed three grade III AEs (two haemothorax and one haemoperitoneum) and one grade IV AE (severe bleeding requiring surgery). Fruhling et al. [20] reported one bile duct dilatation and stricture of the portal vein and bile duct, but did not assign a grade.

Minor adverse events

The recording of minor complications was variable among the studies and not all recorded pain as an AE or used the same considerations concerning its classification. Cheung et al. [21] included all cases of pain as AEs, while Fruhling et al. [20] only considered patients who required morphine. The frequency of minor complications would be 33.1% (41/124) according to the first classification and 28.2% (35/124) in the latter case. This percentage could be underestimated given that the study by Eller et al. [23] did not report on minor complications, although the authors stated that pain was sufficiently controlled.

The minor complications included pain (*n* = 14), haematoma (*n* = 9), urinary retention (*n* = 4), cholestasis (*n* = 5), pneumothorax (*n* = 2), arteriovenous shunt (*n* = 2), arterioportal fistula (*n* = 1), infection (*n* = 1), increased blood pressure (*n* = 1), tachycardia (*n* = 1) and shortness of breath (*n* = 1). The four patients who developed transient urinary retention had a history of prostatic hypertrophy [21] and the authors believed that these complications could be related to the opioid analgesia rather than the hepatic-ablation per se.

No comparisons can be made based on approach as all patients were treated with percutaneous IRE. Niessen et al. [25] reported no association between the complications found in their study (haematoma and pneumothorax) and histological type, location or previous CHEMO.

Other adverse events/complications

Needle-tract seeding was observed by Distelmaier et al. [22], with 30.8% of patients (8/26) experiencing regional recurrence in the needle tract (by tumour: 11/40). Granata et al. [24] found two minor AEs along the needle tract: one peripheral arteriovenous shunt and one segmental dilatation of the intrahepatic biliary ducts.

[C0002] Are the harms related to dosage or frequency of applying IRE?

No evidence was found relating either the dosage or frequency to the harms associated with the treatment.

[C0004] How does the frequency or severity of harms change over the time or in different settings?

No evidence was found to answer this question.

[C0005] What are the susceptible patient groups that are more likely to be harmed through the use of IRE?

No evidence was found to answer this research question.

[B0010] What kind of data/records and/or registry is needed to monitor the use of IRE?

No evidence was identified to answer this research question.

Table 12. Frequency and severity of adverse events in pancreatic cancer (comparative studies)

Author, year, country, study characteristics, AE grading system	Intervention	Intervention mortality	Complications/adverse events						
			Major			Minor		Not graded	Total
			Grade V	Grade IV	Grade III	Grade II	Grade I		
Lambert, 2016, Czech Republic [11] Prospective non-RCT (propensity score-matched analysis), 2012–2014, AEs not graded	IRE	0	0	--	--	--	--	5 pts: • Open surgery: bleeding (1), peripancreatic abscess (1), fistula and abscess (1) • Percutaneous: biliary peritonitis, cholangitis, liver abscess (1) and pancreatic fistula (1) *[Other changes 1–2 mo after IRE (28): peripancreatic oedema (9), pancreatic or peripancreatic necrosis (6), peripancreatic or suprameso-colic inflammatory infiltrate (4), enlarged lymph nodes (4), carcinosis with ascites (4), extension of the tumour into the liver (1)]*	5 pts (out of 21 treated)
	Propensity-matched cohort: noncurative surgery	--	--	--	--	--	--	--	--

Abbreviations: IRE = irreversible electroporation; m = months; p = patients; RCT = randomized controlled trial.

Sources: [11]

Table 13. Frequency and severity of adverse events in pancreatic cancer (single-arm studies)

Author, year, country, study characteristics, grading system	Intervention-specific mortality	Complications/adverse events						
		Major			Minor		Not graded	Total
		Grade V	Grade IV	Grade III	Grade II	Grade I		
Huang, 2018, China [17] Prospective multicentre single-arm study, 2012–2015, Clavien-Dindo classification	0	0	0	3 pts (3 AEs): pseudoaneurysm bleeding (1), pancreatic fistula (1), intraabdominal abscess (1)	13 pts (27 AEs): acute hepatitis, ascites accumulation, gastrointestinal bleeding and ileus			30 AEs (in 70 treated pts)
Scheffer, 2017, Netherlands [16][a] Prospective single-arm study, 2014–2015, CTCAE (90 d after IRE)	0	0	2: pancreatitis (1 pt), bleeding from duodenal ulcer adjacent to the ablation zone (1 pt)	9: pancreatitis (2 pts), biliary obstruction (3 pts), cholangitis and biloma (1 pts), high-grade SMA stenosis (1 pt), vomiting (1 pt), loss of appetite or reduced intake (1 pt)	12: abscess (1 pt), pneumonia (1 pt), nausea (1 pt), vomiting (2 pts), diarrhoea (2 pts), gastroparesis (2 pts), abdominal pain (3 pts)		7 pts: irregular vessel narrowing [immediately after procedure]	23 AEs in 10 pts (out of 25 treated pts)
Mansson, 2016, Sweden [14] Prospective single-arm study, data collection period not reported, Clavien-Dindo (30 d after IRE)	0	• Related to IRE: 0 • Not related to IRE: pneumonia (1 pt)	0	3: thrombosis with bleeding (1 pt), gastroenteroanastomosis (1 pt), bleeding from a prior ulcer (1 pt)	8 pts: infection, pancreatitis, portal vein thrombosis	Not related to IRE: 13 pts	1 pt :bleeding [before discharge]	24 pts (100%) [11/24 (45.8%) considered IRE related complications]
Kluger, 2016, USA [13] Prospective single-arm study, October 2012 onwards, Clavien-Dindo (90 d after IRE)	0 (first dead at 8 d)	6 pts (4 at 30 d): • Not related to IRE: 3 pts • IRE related: duodenal and bile duct necrosis (1), gastrointestinal bleeding (1) and intraperitoneal haemorrhage (1)	10 pts (9 at 30 d) [4 IRE-related]		8 p	5 p		29 AEs (in 50 treated pts) [7 (44%) major complications due to IRE]

Author, year, country, study characteristics, grading system	Intervention-specific mortality	Complications/adverse events						
		Major			Minor		Not graded	Total
		Grade V	Grade IV	Grade III	Grade II	Grade I		
Paiella, 2015, Italy [15][a] Prospective single-arm study, June 2011–December 2011, MedDRA classification system, graded according to CTCAE	0	Not related to IRE Sepsis: 1 pt	• Related to IRE: pancreatic abscess and internal fistula (1 pt) • Non related to IRE: pulmonary embolism (1 pt), systemic candidiasis (1 pt), pneumonia: (1 pt)		Not related to IRE (9): abdominal and back pain (5 pt), portal vein thrombosis (present before IRE, 1 pt), onset of ulcerative colitis (1 pt), peripheral oedema (1 pt), wound infection (1 pt)		1 pt: transient hypertensive episode	14 AEs (in 10 treated pts) [1 considered a procedure-related complication]
Belfiore, 2015, Italy [18] Prospective single-arm study, April 2013– June 2014, no grading system stated	0	0	0	0	2: transient amylase increase in serum (1 pt), mild ascites (1 pt)			2 AE (over 20 patients) [only immediate after treatment]
Martin, 2012, USA [19] [b] Prospective single-arm study, December 2009–March 2011, no grading system stated (90 d after IRE)	0	Portal vein thrombosis: 1 pt	Bile leak: 1 pt	• Related to IRE: bile leak (1 pt) • Not related to IRE: pulmonary (2 pts), renal failure (1 pt), ascites (1 pt)	• Related to IRE: portal vein thrombosis (1 pt) • Not related to IRE (8 AEs): haematologic AE (2), ileus (1), deep venous thrombosis (2), wound infection (3)	Haematologic AE: 1 pt		17 AEs in 9/27 pts (33%) Possible IRE-related complications in 4 pts

[a] Data are the number of complications.
[b] Data are the number of complications. Five patients experienced major adverse events and four patients experienced minor adverse events.
Abbreviations: AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; d = days; IRE = irreversible electroporation; MedDRA = Medical Dictionary for Regulatory Activities; pt = patient; SMA = superior mesenteric artery.
Sources: [13–19].

Table 14. Frequency and severity of adverse events in liver cancer (single-arm studies)

Author, year, country, study characteristics, grading system	Intervention mortality	Complications / adverse events					Not graded	Total
		Major			Minor			
		Grade V	Grade IV	Grade III	Grade II	Grade I		
Fruhling, 2017, Sweden [20] Prospective single-arm study, September 2011–September 2014 SIR grading system (30 days after IRE)	0	None related to IRE: pulmonary embolism (1 pt)	1 pt: bile duct dilatation and stricture of portal vein and bile duct		12:[1] postprocedural pain (7 pts (1 required morphine for chest pain)), haematoma (1 pt), shortness of breath (1 pt), tachycardia (1 pt), infection (1 pt), increased blood pressure (1 pt)		Other changes: 13 transient increase in liver transaminases	14 (among 30 treated pts)
Distelmaier, 2017, Germany [22] Prospective single-arm study, February 2012–June 2015 SIR grading system	0	0	0	0	8: cholestasis (5 pts), arterioportal fistula (1 pt (periprocedural)), haematoma (2 pts (immediately after IRE))		8 (30.8%) needle tract seeding	8 (among 29 pts)
Niessen, 2016, Germany [25] Prospective single-arm study, December 2011–June 2013 SIR grading system	0	0	0	6: intraperitoneal bleeding (1 pt), partial thrombosis of portal vein (1 pt), abscess (4 pts)	0	8: haematoma (6 pts), pneumothorax (2 pts)		14 (among 51 procedures; 27.5%)
Granata, 2016, Italy [24] Prospective single-arm study, January 2012–July 2013 No grading system stated	0	0			2: peripheral arteriovenous shunt (1 pt) [2], segmental dilation of intrahepatic biliary ducts (1 pt) [2]		Capsular retraction (4 pts), changes in vascular perfusion during the arterial phase (6 pts)	2 (among 20 pts)
Eller, 2015, Germany (23) Prospective single-arm study, data collection period not reported CTCAE version 2	0		1: severe abdominal bleeding requiring surgery	3: haemoperitoneum (1), haemothorax (2)				4 (among 14 pts)
Cheung, 2013, Australia (21) Prospective single-arm study, November 2008–December 2009 No grading system stated	0	0	0	0	11:[1] transient urinary retention (4 pts), pain post procedure (7 pts)			

[1] Possible duplication of patients with complications.
[2] Occurred along the needle tract
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IRE = irreversible electroporation; pt = patient; SIR = Society of Interventional Radiology.
Sources: [12,20–25].

7 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

7.1 Research questions

One specific question concerning ORG aspects was identified from the rapid REA checklist (Appendix 3): Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes? Therefore, three critical issues were chosen from the ORG aspects of the HTA Core Model Application for Medical and Surgical Interventions (3.0).

Element ID	Research question
G0003	What kind of process ensures proper education and training of staff?
G0006	What are the costs of processes related to acquisition and setting up of IRE?
G0007	What are the likely budget impacts of implementing IRE?

7.2 Results

[G0003] What kind of process ensures proper education and training of staff?

IRE can be carried out by existing professionals, but they must have acquired previous experience with the technique. The NanoKnife procedure is intended to be performed under the direction and supervision of a primary treating physician who has been thoroughly trained on advanced IRE procedures. The training to perform IRE includes determination of eligibility for IRE treatment, physical set-up for the procedure, establishing procedure protocols, monitoring the progress of procedures and stopping the procedure. Detailed physician and clinical support training are required for safe and effective use of the NanoKnife System. Training involves both didactic and animal laboratory training [26].

[G0006] What are the costs of processes related to acquisition and setting up IRE?

[G0007] What are the likely budget impacts of implementing IRE?

No information exists regarding the costs of the processes related to acquisition and setting up of IRE. However, given that IRE requires anaesthesia and radiological and/or surgical operating equipment, it is deemed costlier in terms of resources than other ablative methods [5].

No information regarding the acquisition cost of the NanoKnife System was provided. According to Martin et al. [19] the probes cost approximately $2000 per unit.

8 PATIENT INVOLVEMENT

Two patients aged ≥70 years with liver cancer agreed to participate and were interviewed in *Hospital Clínico Universitario de Santiago de Compostela* about their experiences and views regarding their clinical condition and the use of ablative methods and other treatments received. The patients were asked about their disease, diagnosis and treatment and were encouraged to discuss any issue they considered relevant. In addition, they were asked about the relevance of the patient-related outcomes included in the PICO question (health-related QoL and pain) and were invited to include any other outcomes they considered important.

Both patients had undergone MWA of their tumours. One of the patients had undergone one ablation procedure and received a transplant afterwards. The second patient received more than seven ablation procedures and TACE. It was not possible to recruit patients who had undergone IRE as it is not authorized for this indication in this centre. The inclusion of LAPC patients was also not possible because clinicians were against interviewing these patients given their poor condition.

8.1 Views of patients

Benefits/risks ablative procedure

The patients highlighted that they did not experience any major complication or pain during or after MWA. The only AE noted was nausea related to sedation in one case. The patient that had to undergo TACE twice because of the impossibility of MWA owing to the risk of the heat-sink effect stated that the TACE procedure was much more uncomfortable and did lead to pain. The transplant patient had a positive view of the MWA procedure as it did not require general anaesthesia and a hospital stay of only 1 day in hospital, but reported that he had feared the surgery. Both patients stated that they would certainly undergo an ablative procedure again, specifying that the only drawback was travelling to hospital and the hospital stay. One patient also mentioned the inconvenience of having to stop his medication for 2 days.

Patient reported outcomes

Neither of the patients experienced symptoms or pain before or after the procedure, except for the pain that occurred after TACE. Both stated that the disease and treatment had not notably affected their QoL. They also confirmed that they did not experience anxiety or depression as a result of the disease or treatment.

Relevancy of the outcomes

Patients highlighted the importance of the pain and QoL aspects and did not propose any additional items.

9 DISCUSSION

IRE is an ablative modality that destroys soft-tissue tumours using low-energy electrical pulses to create nanoscale defects in cell membranes, resulting in loss of homeostasis and subsequent cell death. As the effect of IRE is supposed to be confined to the cell membrane, it is claimed that it could kill cancer cells while avoiding damage to surrounding structures, such as vessels, ducts and nerves [88]. Owing to this potential to spare critical structures, IRE has been proposed as an alternative option for solid tumours of the pancreas and liver that are not suitable for surgery or thermal ablation techniques because of vicinity to vulnerable tissue. The treatment of these cancers is very challenging and OS for these patients, especially those with pancreatic cancer, remains quite poor despite advances in systemic cancer therapies.

The exact mechanism of action of IRE is still unknown. While the ability of IRE to induce nanopores in perfused porcine liver has been demonstrated via electron microscopy [89], there are doubts regarding the specific mechanism of cell death in practice. Some experimental studies revealed an increase in tissue temperature [90,91], raising the question of whether the effect of IRE could also be partly attributed to a thermal effect [56]. Likewise, it has also been suggested that IRE could contribute to cell death by inducing a type of immune response, although the connection between IRE and the immune system is still under investigation [15].

The performance of IRE is considered to be influenced by many technical factors, such as the electrical current, the pulses, and the number and correct placement of electrode probes [24], for both the electrode distance and the parallelism of the insertion path have to remain exact [12]. We observed that the studies included used different currents (20–50 A) and numbers of needles (ranging from 2 to 6) according to the size and location of the tumour. In several studies it was reported that needles needed to be repositioned or replaced according to radiological findings, highlighting the complexity of the procedure, which is further complicated by the fact that the patient requires general anaesthesia with deep sedation and complete muscle relaxation [18]. Patients who were interviewed considered this an important issue. Overall, the authors agree that IRE is more complicated and demanding than other thermoablative methods, but consider that it could represent a feasible option for patients for whom thermal ablation is not suitable [23].

However, the evidence from the studies included is not consistent regarding the effectiveness of IRE for achieving complete ablation. Information regarding success, defined as the ability to complete the IRE procedure as planned and the absence of any residual tumour, is lacking in many of the studies included, while those that do provide similar definitions show variable results. Regarding LAPC, we observed one study that claimed ablation success of close to 100% [19]. Other studies found that the tumour size remained unchanged [11]. For liver cancer, incomplete/similar definitions of success ranged from 54.5% to 93%. Commonly, studies attribute these differences in success and local recurrences to the different characteristics of the tumours ablated, prior treatments or how the surgical or IRE procedure was planned and performed [17]. For example, large tumour volumes were associated with incomplete ablation in the study by Cheung et al. [21], who reported a success rate of 93% for tumours <3 cm versus 0% for tumours <4 cm (p = 0.003). Paiella et al. [15], who found that the pancreatic tumour size initially increased by day 60 and then decreased by day 90, hypothesised that the initial increase might have being caused by local inflammation and that the lack of enhancement might have impeded discrimination of oedema from ablated tissue. Several other authors mentioned difficulty in assessing ablative success and local recurrence using conventional imaging modalities [19,20,24].

The available evidence is also insufficient to establish if IRE would be effective in improving OS for patients with pancreatic or liver cancer when compared to the standard of care. For LAPC, only one low-quality nonrandomised trial [11] complied with the eligibility criteria and found no significant difference in mean OS despite comparing IRE to noncurative surgery (10.03 months versus 9.3 months). It should be noted that the internal validity of this trial was very limited, given that it was a nonrandomised study with a small sample size that compared patients who were not matched in terms of prior and post-IRE adjuvant treatments. The authors reported that some patients in the IRE group were given adjuvant therapy, but it is unknown how many in the control arm received this.

The prospective single-arm observational trials on LAPC provided few relevant outcome data. Most studies reported on mean OS after IRE or time to local recurrence after IRE, but these are not valid outcome measures given that the times between diagnosis and IRE were different and the follow-up schemes varied greatly among studies. The most appropriate EFF-related survival outcome would be OS after diagnosis or PFS after diagnosis, but only three studies provided the OS or data to allow for its calculation using the Kaplan-Meier method. Only one trial reported on PFS after diagnosis. For pancreatic cancer, the trials reported mean OS after diagnosis in the range of 12.5–17.5 months, which is in the range found in the latest CHEMO trials [27], but no assumptions can be made given that the studies lack comparability. It should be noted that the patients included in the trials were treated with different CHEMO and/or CRT regimens before or concurrent with IRE, and it is not known how these might have contributed to OS or control rates. According to the results of Huang et al. [17], who noted that survival was significantly longer for patients who received TS-1 CHEMO (28.7 months) than those given gemcitabine (19.1 months), it seems reasonable to assume that the effect is not negligible. It was recently proposed that IRE combined with CHEMO could result in an additive effect. Given the potential to enhance CHEMO by disrupting the dense stroma of pancreatic tumours, IRE could be used in combination with first-line CHEMO [48,92].

The data for liver tumours are even more limited, as no comparative trials were identified and only one of the single-arm studies provided long-term survival data [20]. On the basis of these data we estimated that OS at 12, 18 and 24 months after IRE would be 89.76%, 69.05% and 65.21%, respectively, but these calculations are prone to important biases given that patient follow-up ranged from 2.5 to 55 months.

It is noteworthy that although it is one of the most relevant goals in the management of locally advanced cancers, only a few studies report on QoL. Results from the studies considered here, including the one non-RCT [11], do not support significant improvements with respect to the standard of care. On the contrary, one of the studies [15] found a decrease in the median QoL score of 36% at 2 weeks and 43% at 3 months after IRE. This study also reported increases in pain score in comparison to baseline values. Similarly, Scheffer et al. [16] observed that some of the pain items in the QoL domain deteriorated after IRE, although the clinical relevance of the results are uncertain given that the authors only provide *p* values. Further studies are required to elucidate how IRE affects QoL, especially in relation to symptom alleviation, because from an ethical point of view the benefits of a small increase in survival should always be weighed against QoL and AEs.

Overall, the safety of IRE is a concern. Although no intervention-specific mortality was reported, at least four (1.62%) of the patients recruited in LAPC studies suffered from IRE-related AEs that led to death (grade V) during the next 30–90 days. The frequency of other severe IRE-related complications was also relatively high in several of the trials [13,16,25]. It appears that some of the severe complications are related to heating (portal vein thrombosis, duodenal and bile duct necrosis, penetrating/bleeding ulcers, cholangitis), reinforcing the idea that IRE does have a thermal effect. In addition, IRE might also be prone to more complications related to needle-tract seeding than thermal methods, since needle tract ablation is not possible with current IRE equipment [22]. However, no definitive conclusions can be drawn regarding comparison of these methods given the lack of comparative data.

The reporting of AEs was very heterogeneous in the studies included. These differences could be attributed in part to the use of different scales for defining AE severity, with some stricter than others, or the lack of clear consensus on the classification of IRE-related complications [16]. For instance, we observed that wound infection, abdominal and back pain and ascites were considered to be IRE-related in some studies [16,20] but not in others [15,19]. It is possible that these types of complication were not reported in all studies, which would probably explain why Scheffer et al. [16] found a very high rate of gastrointestinal complications while others did not record any at all. Another problem we encountered is that complications were counted differently, with some providing the number of AEs [15,16] and others the number of patients who experienced major or minor AEs. To provide an overall estimate, we tried to calculate the number of patients affected in all studies. We cannot exclude the possibility of slight overestimation owing to duplication of patients with minor AEs. The studies that did not provide a grading of complications were not included in these calculations.

9.1 Limitations of the present report

An important limitation of the present systematic review is that it was not possible to carry out a comparative analysis to assess how the tumour location and size and the approach could affect SAF outcomes. We observed that the overall frequency of IRE-related severe AEs was higher in the pancreatic studies that used a percutaneous approach in comparison to open surgery, although, as already noted, there are few studies available and these are not comparable in terms of other confounding factors. Nonetheless, it is important to note that some authors reported that the percutaneous approach was abandoned because of discouraging complications [11].

9.2 Quality of evidence

The quality of the evidence is very low for both indications. To date, there are no published RCTs and the only comparative trial included for LAPC is a small propensity-matched trial comparing IRE to noncurative surgery (laparotomy, nonradical resection, biopsy, etc.), with previous or concurrent treatments not taken into account [11]. The single-arm trials included to ascertain the effect on critical EFF or SAF outcomes were very limited by small size, short follow-up and highly selected populations, which had undergone different types of systemic therapy. Data for calculating OS and PFS from the time of diagnosis, as well as other critical EFF outcome measures such as QoL, were also missing in many of the trials, and this constituted an important impediment to drawing any conclusion regarding the potential of IRE to treat these tumours. This was especially noticeable for liver cancer, for which most trials only reported local recurrence during follow-up. Among other important shortcomings are the lack of standardised definitions regarding success, the unclear classification of IRE-related complications and the possible underreporting of some types of AE.

9.3 Applicability

The applicability of the EFF and SAF results is also very doubtful. We observed that IRE application within the treatment algorithm was inconsistent across studies, raising uncertainties regarding the use of this technique in real practice. For example, whilst some studies restricted IRE to patients unresponsive to standard treatment [15], others only applied this technique when patients had a favourable survival profile [14] or when the disease did not progress after previous CHEMO treatment. The treatment protocols also varied substantially; some offered CHEMO before IRE and others offered CRT or induction CHEMO and CRT before IRE; in addition, several applied CHEMO after IRE. Differences were also noted regarding the number of ablative sessions, imaging modalities and IRE technique, with no formal consensus regarding the considerations that should be taken into account to identify tumours for which IRE might be more beneficial.

It is essential that appropriately designed prospective comparative trials are carried out to be able to determine the comparative effectiveness and safety of IRE. Ideally, these would be randomised trials that would allow evaluation of whether there are additional benefits in terms of safety, survival, QoL and pain.

9.4 Ongoing studies

A search for ongoing studies identified 22 trials in pancreatic cancer, most of them single-arm trials. One of the studies is a patient registry. At least 16 are still recruiting patients. Two of the studies are comparative trials, one comparing the treatment arm with a historic control group and another with surgical resection. Another trial evaluated the effect of IRE when combined with natural killer cells. Further information is provided in Table A5. During the fact check, the manufacturer informed us that AngioDynamics is currently sponsoring a clinical study for pancreatic cancer. For liver cancer, 16 trials were found, of which at least eight are still recruiting. Most of them are single-arm trials and some are complete but no publication was found. In addition, one trial compares IRE with microwave treatment and another evaluates the effect of IRE combined with natural killer cells. Further information is provided in table A6.

10 CONCLUSION

Pancreatic cancer

There is insufficient evidence to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (CHEMO, CRT or palliative therapy) for the treatment of unresectable LAPC.

There is insufficient evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (CHEMO, CRT or palliative therapy) for the treatment of unresectable LAPC.

The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of unresectable LAPC.

The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for LAPC. Currently, it is unclear whether IRE needs to be combined with CHEMO and, if so, which regimens are optimal.

There are uncertainties regarding the occurrence of severe AEs when IRE is used for the treatment of unresectable LAPC.

Liver cancer

There is a lack of data to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (TACE, sorafenib or palliative therapy) for the treatment of patients with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.

There is a lack of evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (TACE, sorafenib or palliative therapy) for the treatment of patients with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.

The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of primary or secondary unresectable liver tumours that are not suitable for thermal ablation.

The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for primary or secondary liver tumours that are not suitable for thermal ablation.

There are uncertainties regarding the occurrence of severe AEs when IRE is used for the treatment of liver tumours that are not suitable for thermal ablation.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search strategy for Medline on 26th September 2018

	Search terms	Nº
#1	((((((Electropermeabilizat*[TIAB]) OR ((“Electroporation”[Mesh] OR electroporat*[TIAB] OR electro-porat*[TIAB]) AND irreversib*[TIAB])) OR (IRE[TIAB] OR Nanoknife[TIAB] OR “Nano knife”[TIAB] OR NTIRE[TIAB] OR “NT IRE”[TIAB]))) AND ((“Liver Neoplasms”[Mesh]) OR (((“Liver”[Mesh] OR liver[TIAB] OR hepatic*[TIAB] OR hepatocel*[TIAB] OR hepato-cel*[TIAB])) AND (“Neoplasms”[Mesh] OR neoplas*[TIAB] OR cancer*[TIAB] OR tumor*[TIAB] OR tumour*[TIAB] OR carcinom*[TIAB] OR hepatocarcinom*[TIAB] OR hepato-carcinom*[TIAB] OR metastas*[TIAB] OR malignanc*[TIAB])))) OR ((((((IRE[TIAB] OR Nanoknife[TIAB] OR “Nano knife”[TIAB] OR NTIRE[TIAB] OR “NT IRE”[TIAB])) OR ((“Electroporation”[Mesh] OR electroporat*[TIAB] OR electro-porat*[TIAB]) AND irreversib*[TIAB])) OR Electropermeabilizat*[TIAB])) AND ((“Pancreatic Neoplasms”[Mesh]) OR (((neoplas*[TIAB] OR cancer*[TIAB] OR tumor*[TIAB] OR tumour*[TIAB] OR carcinom*[TIAB] OR adenocarcinom*[TIAB] OR adeno-carcinom*[TIAB] OR “Neoplasms”[Mesh])) AND (“Pancreas”[Mesh] OR pancreas[TIAB] OR pancreat*[TIAB] OR hepatopancrea*[TIAB])))) Filters activated: English, French, Italian, Portuguese, Spanish	331

Search strategy for Embase on 26th September 2018

	Search terms	Nº
1	(“IRE” or “NT IRE” or NTIRE or “Nano knife” or Nanoknife).ti,ab.	2841
2	exp irreversible electroporation/ or (Electropermeabilization or ((Electroporation or electro-poration) and Irreversib*)).ti,ab.	1636
3	1 or 2	3647
4	(liver* or hepatic* or hepatocel* or hepato-cel*).ti,ab.	1134412
5	liver/	401224
6	4 or 5	1218064
7	neoplasm/	406306
8	(neoplas* or tumor* or tumour* or cancer* or hepatocarcinom* or hepato-carcinom* or malignanc* or metastas*).ti,ab.	3528418
9	7 or 8	3566545
10	6 and 9	277811
11	liver tumor/	44723
12	10 or 11	294541
13	3 and 12	420
14	limit 13 to embase (english or french or italian or portuguese or spanish)	195
15	(IRE or Nanoknife or “Nano knife” or NTIRE or “NT IRE”).ab,ti.	2841
16	exp irreversible electroporation/	479
17	(((electroporation or electro-poration) and irreversib*) or Electropermeabilization).ab,ti.	1550
18	15 or 16 or 17	3647

19	neoplasm/	406306
20	(neoplas* or cancer* or tumor* or tumour* or carcinom* or adenocarcinom* or adeno-carcinom* or malignanc*).ab,ti.	3700523
21	19 or 20	3738245
22	(pancreas or pancreat* or hepatopancreat*).ab,ti.	341820
23	21 AND 22	136301
24	pancreas tumor/	24324
25	23 OR 24	142721
26	18 AND 25	300
27	limit 26 to embase (english or french or italian or portuguese or spanish)	146
28	14 OR 27	286

Search strategy for Scopus on 26th September 2018

	Search terms	**Nº**
#1	((TITLE-ABS-KEY (liver OR hepatic* OR hepatocel*) AND TITLE-ABS-KEY (neoplas* OR cancer* OR tumor* OR tumour* OR carcinom* OR hepatocarcinom* OR malignanc* OR metastas*) AND TITLE-ABS-KEY (ire OR nanoknife OR “Nano knife” OR ntire OR “NT IRE” OR “irreversible electroporation” OR “irreversible electro-poration” OR electropermeabilization))) OR (TITLE-ABS-KEY (pancreas OR pancreat* OR hepatopancrea*) AND TITLE-ABS-KEY (neoplas* OR cancer* OR tumor* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR malignanc*) AND TITLE-ABS-KEY (ire OR nanoknife OR “Nano knife” OR ntire OR “NT IRE” OR “irreversible electroporation” OR “irreversible electro-poration” OR electropermeabilization)) AND (LIMIT-TO (LANGUAGE , “English”) OR LIMIT-TO (LANGUAGE , “Spanish”) OR LIMIT-TO (LANGUAGE , “French”) OR LIMIT-TO (LANGUAGE , “Italian”))	593

Search strategy for Web of Science on 26th September 2018

	Search terms	**Nº**
# 1	TS = (liver or hepatic* or hepatocel* or hepato-cel*) OR TI = (liver or hepatic* or hepatocel* or hepato-cel*) AND LANGUAGE: (English OR French OR Italian OR Portuguese OR Spanish) Indexes = SCI-EXPANDED Timespan = All years	988789
# 2	TS = (neoplas* OR cancer* OR tumor* OR carcinom* OR tumour* OR hepatocarcinom* OR metastas* OR malignanc*) OR TI = (neoplas* OR cancer* OR tumor* OR carcinom* OR tumour* OR hepatocarcinom* OR metastas* OR malignanc*) AND LANGUAGE: (English OR French OR Italian OR Portuguese OR Spanish) Indexes = SCI-EXPANDED Timespan = All years	3258551
# 3	TS = (ire OR nanoknife OR “Nano knife” OR ntire OR “NT IRE” OR “irreversible electroporation” OR “irreversible electro-poration” OR electropermeabilization) OR TI = (ire OR nanoknife OR “Nano knife” OR ntire OR “NT IRE” OR “irreversible electroporation” OR “irreversible electro-poration” OR electropermeabilization) AND LANGUAGE: (English OR French OR Italian OR Portuguese OR Spanish) Indexes = SCI-EXPANDED Timespan = All years	9371
# 4	#3 AND #2 AND #1	499
# 5	TS = (pancrea* OR hepatopancrea*) OR TI = (pancrea* OR hepatopancrea*) AND LANGUAGE: (English OR French OR Italian OR Portuguese OR Spanish) Indexes = SCI-EXPANDED Timespan = All years	308830
# 6	TS = (neoplas* OR cancer* OR tumor* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR tumour* OR malignanc*) OR TI = (neoplas* OR cancer* OR tumor* OR carcinom* OR adenocarcinom* OR adeno-carcinom* OR tumour* OR malignanc*) AND LANGUAGE: (English OR French OR Italian OR Portuguese OR Spanish) Indexes = SCI-EXPANDED Timespan = All years	3260225

# 7	TS = (ire OR nanoknife OR “Nano knife” OR ntire OR “NT IRE” OR “irreversible electroporation” OR “irreversible electro-poration” OR electropermeabilization) OR TI = (ire OR nanoknife OR “Nano knife” OR ntire OR “NT IRE” OR “irreversible electroporation” OR “irreversible electro-poration” OR electropermeabilization) AND LANGUAGE: (English OR French OR Italian OR Portuguese OR Spanish) Indexes = SCI-EXPANDED Timespan = All years	9402
# 8	#5 AND #6 AND #7	218
# 9	#4 OR #8	656

Search strategy for CRD on 26th September 2018

	Search terms	**Nº**
1	(Electroporation OR IRE OR Nanoknife OR “Nano knife”) AND (liver* OR hepat*):TI	6
2	(Electroporation OR IRE OR Nanoknife OR “Nano knife”) AND (pancrea*):TI	6
3	1 OR 2	9

Search strategy for Cochrane Library on 26th September 2018

	Search terms	**Nº**
#1	((Electroporation or electro-poration) and Irreversible):ti,ab,kw (Word variations have been searched)	41
#2	(Electropermeabilization):ti,ab,kw (Word variations have been searched)	0
#3	IRE or (NT IRE) or NTIRE or (Nano knife) or Nanoknife:ti,ab,kw (Word variations have been searched)	101
#4	#1 OR #2 OR #3	114
#5	(liver or hepatic* or hepatocel* or hepato-cel*):ti,ab,kw (Word variations have been searched)	39325
#6	MeSH descriptor: [Neoplasms] explode all trees	67290
#7	neoplas* or cancer* or tumor* or tumour* or malignanc* or metastas* or carcinom*:ti,ab,kw (Word variations have been searched)	166941
#8	#6 OR #7	172135
#9	#5 AND #8	11884
#10	MeSH descriptor: [Liver Neoplasms] explode all trees	2576
#11	#9 OR #10	11884
#12	#4 AND #11	14
#13	MeSH descriptor: [Neoplasms] explode all trees	67290
#14	neoplas* or cancer* or tumor* or tumour* or carcinom* or adenocardinom* or adeno-carcinom* or malignanc*:ti,ab,kw (Word variations have been searched)	166829
#15	#13 OR #14	172010
#16	(pancrea* OR hepatopancrea*):ti,ab,kw (Word variations have been searched)	11976
#17	#15 AND #16	5146
#18	MeSH descriptor: [Pancreatic Neoplasms] explode all trees	1408
#19	#17 OR #18	5154
#20	#4 AND #19	14
#21	#12 OR #20	14

Search strategy for identification of ongoing studies

clinicaltrials.gov, on 26th September 2018

Pancreatic cancer

	Search terms
#1	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND pancreas [DISEASE] AND Irreversible electroporation [TREATMENT]
#2	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND pancreatic [DISEASE] AND Irreversible electroporation [TREATMENT]
#3	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND hepatopancreatic [DISEASE] AND Irreversible electroporation [TREATMENT]
#4	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND hepatopancreatic [DISEASE] AND nanoknife [TREATMENT]
#5	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND pancreas [DISEASE] AND nanoknife [TREATMENT]
#6	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND pancreatic [DISEASE] AND nanoknife [TREATMENT]
#7	neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocardinoma OR adenocarcinomas OR malignancy OR malignancies | pancreas | nanoknife
#8	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND pancreas [DISEASE] AND “nano knife” [TREATMENT]
#9	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND pancreatic [DISEASE] AND “nano knife” [TREATMENT]
#10	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies) AND hepatopancreatic [DISEASE] AND “nano knife” [TREATMENT]

Liver cancer

	Search terms
#1	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND liver[DISEASE] AND irreversible electroporation [TREATMENT]
#2	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND hepatic [DISEASE] AND irreversible electroporation [TREATMENT]
#3	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND hepatocellular [DISEASE] AND irreversible electroporation [TREATMENT]
#4	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND liver [DISEASE] AND “nano knife” [TREATMENT]
#5	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND hepatic [DISEASE] AND “nano knife” [TREATMENT]
#6	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND hepatocellular [DISEASE] AND “nano knife” [TREATMENT]
#7	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND hepatic [DISEASE] AND nanoknife [TREATMENT]
#8	(neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastasis) AND liver [DISEASE] AND nanoknife [TREATMENT]
#9	neoplasm OR neoplasms OR neoplasia OR neoplasias OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocardinoma OR adenocarcinomas OR malignancy OR malignancies OR metastases OR metastais | hepatocellular | irreversible electroporation

International ClinicalTrials Registry Platform (ICTRP)

Pancreatic cancer

	Search terms
#1	[search field condition]:Liver Neoplasms AND [Search field inetrvention]irreversible electroporation
#2	[search field condition]:Liver* OR hepat* AND [Search field inetrvention]:IRE or “NT IRE” or NTIRE or “Nano knife” or Nanoknife

Liver cancer

	Search terms
#1	[search field condition]:Pancreatic Neoplasms AND [Search field inetrvention]:Irreversible electroporation
#2	[search field condition]:Pancrea* AND [Search field inetrvention]:IRE or “NT IRE” or NTIRE or “Nano knife” or Nanoknife

EU clinical Registry

Pancreatic cancer

	Search terms
#1	Pancreatic AND “Irreversible electroporation”
#2	Pancreas AND “Irreversible electroporation”
#3	hepatopancreatic AND “Irreversible electroporation”
#4	hepatopancreatic AND IRE
#5	hepatopancreatic AND NT-IRE
#6	hepatopancreatic AND “Nano knife”
#7	hepatopancreatic AND Nanoknife
#8	pancreas AND Nanoknife
#9	pancreas AND “Nano knife”
#10	pancreas AND NT-IRE
#11	pancreas AND IRE
#12	pancreas AND electroporation
#13	pancreatic AND IRE
#14	pancreatic AND NT-IRE
#15	pancreatic AND “Nano knife”
#16	pancreatic AND Nanoknife

Liver cancer

	Search terms
#1	liver AND “Irreversible electroporation”
#2	hepatic AND “Irreversible electroporation”
#3	hepatocellular AND “Irreversible electroporation”
#4	liver AND IRE
#5	liver AND NT-IRE
#6	liver AND “Nano knife”
#7	liver AND Nanoknife
#8	hepatic AND Nanoknife
#9	hepatic AND “Nano knife”
#10	hepatic AND NT-IRE
#11	hepatic AND IRE
#12	hepatocellular AND “Irreversible electroporation”
#13	hepatocellular AND IRE
#14	hepatocellular AND NT-IRE
#15	hepatocellular AND “Nano knife”
#16	hepatocellular AND Nanoknife

QUESTIONS FOR PATIENT INTERVIEWS

These are the set of questions that were defined for the two patients who were diagnosed with liver cancer and had undergone tumour ablation with a thermal ablative method.

1. What are the diagnosis you have had?
2. How was the diagnostic process?
3. How do you feel in relation to the diagnosis?
4. What was your experience with the disease and what treatments have you received?
5. What ablative treatment have you received? How many sessions did you receive? What was the approach? How long were you in the hospital? How was the recovery process? Did you have any complications after the ablation? How did the ablation affect your quality of life? How did ablation affect your pain?
6. Would you undergo another ablation treatment?
7. The included outcomes related to patients in the assessment are health related quality of life and pain. Do you agree with the included outcomes? Do you think we should consider any other outcome?
8. Is there anything else that you would like to say about your experience with the disease and the ablative treatment?

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A 1. Overview of guidelines

Name of society/ organisation issuing guidance	Date of issue	Country/ ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Pancreatic cancer				
ESMO	2015	Europe	Ablative techniques, such us IRE or other thermal techniques are not considered	-
KCE	2017	Belgium	Ablative techniques, such us IRE or other thermal techniques are not considered	-
NCCN	2017	USA	Ablative techniques, such us IRE or other thermal techniques are not considered	-
ASCO	2016	USA	Ablative techniques, such us IRE or other thermal techniques are not considered	-
NICE	2017	UK	Little evidence was found on ablative therapies so the committee agreed not to make any recommendations for clinical practice about ablative techniques	-
SEOM	2016	Spain	Ablative techniques, such us IRE or other thermal techniques are not considered	-
Liver cancer				
EASL	2018	Europe	IRE is a novel form of tissue ablation that could preserve sensible areas. However, delivery of IRE requires general anaesthesia with deep muscular blockade, given the muscular contraction induced by IRE stimuli, making its performance more demanding than RFA/MWA, and making it costlier in terms of resources. No recommendations regarding IRE are made.	-
BSG	2003	UK	Ablative techniques as radiofrequency ablation may be a good alternative ablative therapy but data are limited. No recommendations regarding IRE is made.	-

Name of society/ organisation issuing guidance	Date of issue	Country/ ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
ESMO-ESDO	2012	Europe	Local ablation is an alternative for resection in some patients but no recommendations regarding IRE are made.	-
IKNL	2014	Netherlands	It advises radiofrequency ablation in some patients, but no recommendations regarding IRE are made.	-
AISF	2013	Italy	Percutaneous ablation is recommended in some patients. No recommendations regarding IRE are made.	-
AASLD	2018	USA	The comparative effectiveness of ablative strategies (other than RFA techniques) remain unclear. IRE is not considered.	-
NCCN	2017	USA	Ablation is recommended in some patients. No recommendations regarding IRE are made.	-
Consensus Spanish Associations: AEEH, SEOM, SERAM, SERVEI and SETH	2016	Spain	Ablation is recommended in some patients. No recommendations regarding IRE are made.	-

Abbreviations: AASLD = American Association for the Study of Liver Diseases; AEEH = Asociación Española para el Estudio del Hígado; AISF = Italian Association for the Study of the Liver; ASCO = American Society of Clinical Oncology; BSG = British Society Gastroenterology; EASL = European Association for the Study of the Liver; ESDO = European Society of Digestive Oncology; ESMO = European Society for Medical Oncology; IKNL = Integraal Kankercentrum Nederland; IRE = irreversible electroporation; KCE = Belgian Health Care Knowledge Centre; MWA = microwave ablation; NCCN = National Comprehensive Cancer Network; NICE = The National Institute for Health and Care Excellence; RFA = radiofrequency ablation; SEOM = Sociedad Española de Oncología Médica; SERAM = Sociedad Española de Radiología Médica; SERVEI = Sociedad Espanola de Radiología Vascular e Intervencionista; SETH = Sociedad Española de Trasplante Hepático.
Sources: (5, 27-29, 31, 32, 50, 74, 76, 81-85).

Evidence tables of individual studies included for clinical effectiveness and safety

Table A 2. Characteristics of comparative studies for the effectiveness and safety for pancreatic cancer

Author, year, reference number	Lambert, 2016 (11)		
Country	Czech Republic		
Centre	NR		
Funding	IGA NT/13263-4 and the Ministry of Health No. RVO VFN 64 165.		
Conflict of interest	NR		
Registration trial number	NR		
Study Design	Prospective non-RCT study (propensity score matched analysis)		
Data collection period	June 2012 – December 2014		
Inclusion/exclusion criteria	Inclusion: • Unresectable pancreatic carcinoma Stage III (without metastatic disease) • Tumour size ≤6.5 cm in axial plane • Good performance status (Karnofsky performance status ≥80)		
Patient characteristics	**IRE**	**Matched cohort** (based on age and size of the tumour 1.5:1)	
Number of patients: n	21	32	
Age: years; mean ± SD	68 ± 8.4	65.2 ± 8.7	*p = 0.22*
Gender: n (%)	Female: 11 (52.4%)	Female: 10 (31.3%)	*p = 0.10*
Clinical stage	Stage III LAPC	Stage III LAPC	
Tumour type and location: n (%)	Type: • Ductal adenocarcinoma: 16 (76%) • Mucinous adenocarcinoma: 2 (10%) • Acinary adenocarcinoma: 1 (5%) • Dedifferentiated: 0 • Not specified: 2 (10%) Location: • Head: 17 (81%) • Body: 3 (14%) • Tail: 1 (5%)	Type: • Ductal adenocarcinoma: 22 (69%) • Mucinous adenocarcinoma: 2 (6%) • Acinary adenocarcinoma: 1 (3%) • Dedifferentiated: 5 (16%) • Not specified: 2 (6%) Location: • Head: 24 (75%) • Body: 5 (16%) • Tail: 3 (10%)	
Tumour size: cm; mean ± SD	3.82 ± 1.15	3.73 ± 1.39	*p = 0.80*
Treatments before IRE: n (%)	Chemotherapy: 5 (23.8%)		
Simultaneous treatments: n (%)	• Gastroenteroanastomosis (GEA): 1 (4.8%) • GEA and cholecystectomy: 1 (4.8%) • Hepaticojejunoanastomosis (HJA): 1 (4.8%) • Cholecystectomy: 1 (4.8%)		
Treatments after IRE: n (%)	Chemotherapy: 7 (33.3%)		
Intervention			
IRE device	Nanoknife		

Approach: n (%)	Open surgery: 19 (90.5%) Percutaneous: 2 (9.5%)		
Imaging guidance	NR		
Number and length of interventions: min; mean ± SD	Length: • Open approach: 79 ± 23 • Percutaneous: 26		
IRE intention: ablation or margin accentuation	Ablation		
Comparator	Matched cohort: patients that had undergone surgery(explorative laparotomy, non-radical resection, bypass surgery, cholecystectomy, biopsy) or percutaneous biopsy only, with or without chemotherapy		
Hospital stay: days; mean (range)	23 (6-150)	26 (2-166)	*p = 0.35*
Length of follow-up: months; median (range)	8.19 (1.25-26.84) **Calculated with individual data provided by the author*		
Effectiveness-related outcomes			
Success of the procedure	0% *[the size of the tumours after IRE did not change]*		
Overall survival: months; median (95% CI) Survival at X months:	10.03 (5.26, 15.39) **calculated with individual data provided by the author. In the text: 10.2*	9.3	HR = 0.54 *p* = 0.053
	At 3 months: 90.48 (67.00, 97.53) At 6 months: 75.00 (49.81, 88.80) At 12 months: 47.62 (24.37, 67.71) At 18 months: 13.61 (2.33, 34.71)		
	**Calculated with individual data provided by the author*		
Cancer specific survival	NR		
Disease free survival	NR		
Progression free survival	NR		
Time to recurrence	NR		
Time to progression	NR [8/19 (42.1%) patients had disease progression]		
Time to local recurrence	NR		
Health-related quality of life	81% of time after IRE KPS ≥70 (IQR 65%-98%)	74% of time after surgery KPS ≥70 (IQR: 14,88)	*p* = 0.076
Pain	NR		
Safety-related outcomes			
Intervention specific mortality	0 *(one month after IRE)*		

Adverse events: n (%)	5 (23.8%) patients: • Open surgery: - Bleeding: 1 - Peripancreatic abscess: 1 - Fistula and abscess in the abdominal wall: 1 • Percutaneous approach: - biliary peritonitis, cholangoitis, liver abscesses: 1 - Pancreatic fistula: 1	
Other adverse events/ complications	Among 19 (90.5%) patients (who underwent computed tomography): • Peripancreatic edema: 9 • Pancreatic or peripancreatic necrosis: 6 • Peripancreatic or supramesocolic inflammatory infiltrate: 4 • Enlarged lymph nodes: 4 • Carcinosis with ascites: 4 • Extension of the tumour into the liver: 1	

Table A 3. Characteristics of other relevant studies for the effectiveness and safety for pancreatic cancer

Author, year, reference number	Huang, 2018 (17)
Country	China
Centre	Multicentre
Funding	No financial support or material support
Conflict of interest	None
Registration trial number	201210008DIC
Study Design	Prospective multicentre single-arm study
Data collection period	2012-2015
Inclusion/exclusion criteria	Inclusion: • confirmed LAPC • induction chemotherapy without radiation and no disease progression • tumour dimension maximum 4 cm • tolerance to anaesthesia and complete muscle relaxant. Exclusion criteria: • history of heart problems or existing metallic implants.
Patient characteristics	
Number of patients: n	70
Age	NR
Gender	NR
Clinical stage	Stage III LAPC
Tumour type and location: n (%)	Head: 24 (34.2%) Body: 28 (40%) Tail: 8 (11.4%) Uncinate process: 10 (14.3%)
Tumour size: n (%)	≤3 cm: 37 (52.9%) 3-4 cm: 33 (47.1%)
Treatments before IRE: n (%)	Gemcitabine: 42 (60%) TS-1 (Tegafur, Gimeracil and Oteracil): 28 (40%)
Simultaneous treatments	NR
Treatments after IRE	The same regime as before IRE *(until evidence of tumour progression was noted)*
Intervention	
IRE device	Nanoknife
Approach: n (%)	Open surgery: 65 (92.9%) Laparoscopic: 5 (7.1%)
Imaging guidance	Ultrasound
Number and length of interventions: n; min (median)	70 procedures Length: 165
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay: days; median	Open surgery: 7.2 Laparoscopic: 5.6
Length of follow-up: months; median	28.1

<table>
<tr><th colspan="2">Effectiveness-related outcomes</th></tr>
<tr><td>Success of the procedure: (%)</td><td>NR
[No residual contras-enhanced tumour by dynamic imaging after 3 months: 100 %]</td></tr>
<tr><td>Overall survival: months; median (95% CI) [range]

Survival at X months:</td><td>Median 22.6 (19.60 - 25.60) [6.6-52.3]<table><tr><td>Gemcitabine</td><td>TS-1</td><td>p</td></tr><tr><td>19.1 months</td><td>28.7 months</td><td>0.04</td></tr></table>At 3 months: 100%
At 6 months: 100%
At 12 months: 90%
At 24 months: 37%
*Data provided by the author. Only uncensored patients included.</td></tr>
<tr><td>Cancer specific survival</td><td>NR</td></tr>
<tr><td>Disease free survival</td><td>NR</td></tr>
<tr><td>Progression free survival: months; median (range)</td><td>15.4 (5.3-52.3)<table><tr><td>Gemcitabine</td><td>TS-1</td><td>p</td></tr><tr><td>13.2 months</td><td>26.4 months</td><td>0.025</td></tr></table></td></tr>
<tr><td>Time to recurrence</td><td>NR</td></tr>
<tr><td>Time to progression</td><td>NR
[Distant progression recurrence: 24/70 (34.2%)]</td></tr>
<tr><td>Time to local recurrence</td><td>NR
[Local recurrence percentage: 6/70 (8.6%)]</td></tr>
<tr><td>Health-related quality of life</td><td>NR</td></tr>
<tr><td>Pain</td><td>NR</td></tr>
<tr><th colspan="2">Safety-related outcomes</th></tr>
<tr><td>Intervention specific mortality</td><td>0</td></tr>
<tr><td>Adverse events: n (%)
Clavien-Dindo Classification:</td><td>• Major complications:
3 Grade III in 3 patients (4.3%): pseudoaneurysm bleeding, pancreatic fistula and intra-abdominal abscess.
• Minor complications:
27 Grade I-II in 13 patients: acute hepatitis, ascites accumulation, gastrointestinal bleeding and ileus.</td></tr>
<tr><td>Other adverse events/complications</td><td>NR</td></tr>
</table>

Author, year, reference number	Scheffer, 2016 (16)
Country	Netherlands
Centre	NR
Funding	National Foundation Against Cancer (Amsterdam, the Netherlands) Foundation for Image- guided Cancer Therapy (Diemen, The Netherlands) Needle electrodes partially funded by AngioDynamics (Lathan, NY)

Conflict of interest	One of the authors is a paid consultant for AngioDynamics
Registration trial number	NCT01939665 (PANFIRE study)
Study Design	Prospective single-arm study
Data collection period	January 2014 – June 2015
Inclusion/exclusion criteria	Inclusion: • radiologic confirmation • maximum tumour size 5 cm • histologic or cytologic confirmation • written informed consent • ASA classification 0-3 • age ≥18 • adequate bone narrow, liver and renal function Exclusion: • successful downstaging QT/RT from previous unresectable and/or borderline tumour to resectable tumour • CHEMO/RT < = 6 weeks before • allergy to contrast • history of epilepsy • implanted stimulation device • ventricular arrhythmias • compromised liver function • metallic biliary stent
Patient characteristics	
Number of patients	25
Age: years; median (range)	61 (41-78)
Gender: n (%)	Female: 13 (52%)
Clinical stage	LAPC (NCCN classification)
Tumour type and location: n (%)	Location: • Head: 18 (72%) • Body: 2 (8%) • Uncinate process: 5 (20%)
Tumour size (diameter): cm, median (range)	4.0 (3.3-5.0)
Treatments before IRE: n	Chemotherapy: 25 (100%) • Gemcitabine: 2 • FOLFIRINOX: 10 • Gemcitabine + nab-paclitaxel: 1
Simultaneous treatments	NR
Treatments after IRE	NR
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Contrast-enhanced computed tomography
Number and length of interventions	NR
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay: days; median (range)	3 (2-20)
Length of follow-up: months; median (IQR)	12 (7-16)

Effectiveness-related outcomes	
Success of the procedure (%)	NR [A computed tomography scan was performed after IRE to confirm technical success (absence of any residual tumour enhancement) but no results were given Needle placement and pulse delivery were successful in all patients.]
Overall survival: months; median (95% CI) [IQR]	From IRE: 11 months (9, 13) [8-17] From diagnosis: 17 months (10, 24)
Cancer specific survival	NR
Disease free survival	NR
Progression free survival: months; median (95% CI)	From IRE: 8 (4, 12) From diagnosis**:** 15 (10, 20) [the study defined it as “event free survival”, as local or distant progression or death of disease
Time to recurrence	NR
Time to progression	NR
Time to local recurrence: months; median (95% CI)	12 (8, 16)
Health-related quality of life: QLQ-C30 and QLQ-PAN26	At 6 weeks: • Reduced appetite (p = 0.048) At 3 months: • diminished general functioning at (p = 0.040) At 6 months: • diminished general functioning (p = 0.028) • feeling or weak arms and/or legs (p = 0.0.31) • indigestion problems (p = 0.007)
Pain	• Day after IRE: median 2 (range 0-5) • Deteriorated items at 6 weeks: the impact of pain on (a) gait (p = 0.016), (b) normal work (p = 0.039), and (c) daily activities (p = 0.023). • Pain increased after 6 months and was more difficult to treat with analgesics (p = 0.039).
Safety-related outcomes	
Intervention specific mortality	0
Adverse events *CTCAE version 4.0:*	23 adverse events in 10 patients [within 90 days]* Grade IV: 2 p (pancreatitis, bleeding from duodenal ulcer) Grade III: 9 p (pancreatitis, biliary obstruction, cholangitis and biloma, high-grade SMA stenosis, vomiting, loss of appetite/reduced intake) Grade I/II: 12 p (abscess, pneumonia, nausea, vomiting, diarrhea, gastroparesis, abdominal pain) **Discrepancies in the number of patients who experienced 23 adverse events*
Other adverse events/complications	Irregular vessel narrowing in 7 patients (resolved at 6 weeks)

Author, year, reference number	Mansson, 2016 (14)
Country	Sweden
Centre	Uppsala University Hospital
Funding	Grants from Uppsala University Hospital
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	NR
Inclusion/exclusion criteria	Inclusion: • Patients over 18 years old • Biopsy proven • Unresectable LAPC Exclusion: • Implanted electronic devices • ASA-score IV • Expected survival <3 months • Pregnancy • Epilepsy • Severe heart disease • Tumour diameter >5.0 cm
Patient characteristics	
Number of patients: n	24
Age: years; median (range)	65 (42-77)
Gender: n (%)	Female: 12 (50%)
Clinical stage	Unresectable LAPC *(classification equivalent to NCCN criteria)*
Tumour type and location: n (%)	Location: • Caput: 19 (79.2%) • Corpus: 5 (20.8%)
Tumour size: volume; cm^3	27 ± 15.5 cm^3
Treatments before IRE: n (%)	• Chemotherapy + radio-chemotherapy: 7 (29.2%) • Radiochemotherapy alone: 3 (12.5%) • Chemotherapy alone: 14 (58.3%)
Simultaneous treatments	NR
Treatments after IRE: n (%)	Chemotherapy: 14 (58.3%) Surgery: • Pancreaticoduodenectomy with portal vein resection: 1 (4.2%)
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Ultrasound guidance
Number and length of interventions: n	24 procedures
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA

Hospital stay: days; median (range)	5 (2-65) **It is said that all patients were observed for at least 3 days in hospital. According to the table, one patient was observed only 2 days*
Length of follow-up: months; median (range)	6.96 (1.12-18.75)
Effectiveness-related outcomes	
Success of the procedure	NR
Overall survival: months; mean (95% CI) [median (95% CI)] **Survival at X months:**	**From IRE:** 7.66 (4.57-11.35) [8.95 (6.79-11.11)] At 3 months: 95.83% (73.92-99.40) At 6 months: 58.33% (36.45-74.99) At 12 months: 29.55% (12.45-48.99) **From diagnosis:** 17.52 months (13.18, 21.83) *[calculated with individual data. In the article it is said 17.9]* At 3 months: 100% At 6 months: 100% At 12 months: 79.17% (56.98, 90.75) At 18 months: 50% (29.10, 67.76) At 24 months: 13.89% (3.54, 31.14) **Kaplan-Meier Analysis, with individual data provided in the article*
Cancer specific survival	NR
Disease free survival	NR
Progression free survival: months; mean (95% CI) [median (95% CI)] **Progression free survival at X months:**	4.51 (3.25-5.78) [3.19 (2.14-6.18)] At 3 months: 58.33 (36.45-74.99) At 6 months: 33.33 (15.90-51.87) **Kaplan-Meier Analysis, with individual data provided in the article*
Time to recurrence	NR
Time to progression: months; mean (95% CI) [median (95% CI)]	4.86 (3.53-6.19) [3.32 (2.30-6.38)] **Kaplan-Meier Analysis, with individual data provided in the article* [Time to distant progression (median): 2.7 months] [Distant progression percentage: 13 (54.2%)]
Time to local recurrence: months; mean (95% CI) [median (95% CI)]	7.25 (5.52-8.99) [6.81 (4.87-8.78)] **Kaplan-Meier Analysis, with individual data provided in the article* [Local recurrence percentage: 14 (58.3%)]
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality	0
Adverse events: n (%) **Clavien-Dindo Classification:**	24 (100%) patients *[during the first 30 days after IRE]* • Minor (<3) Grade 1: 13 patients (no IRE related) Grade 2: 8 patients [infection, pancreatitis, portal vein thrombosis] • Serious: 3 patients [thrombosis with bleeding (1), gastroenteroanastomosis (1), bleeding from a prior ulcer (1)] • 1 patient died 2 weeks after IRE due to pneumonia (no IRE related) [11/24 (45.8%) are considered IRE related complications] **Discrepancies in the number of minor adverse events between the text and tables*
Other adverse events	Bleeding: 1 [before discharge]

Author, year, reference number	**Kluger, 2016 (13)**		
Country	United States		
Centre	NewYork-Presbyterian/Columbia University Medical Center		
Funding	NR		
Conflict of interest	None		
Registration trial number	NR		
Study Design	Prospective single-arm study		
Data collection period	From October 2012 onwards		
Inclusion/exclusion criteria	Inclusion: • at least 180º encasement of the celiac and/or superior mesenteric artery (T4 according to the AJCC) Exclusion: • ECOG ≥3 • Atrial fibrillation • M1 or distant N1 disease • Tumour size >3 cm • Borderline resectable		
Patient characteristics	** data presented by number of procedures (n = 53)*		
	All	Ablative treatment	Margin accentuation
Number of patients: n	50		
Age*: years; median (range)	66.5 (60.2-72.0)	68.6 (63.4-73.8)	62.4 (56.1-68.6)
Gender*: n (%)	Female: 22 (41.5%)	Female: 14 (48.3%)	Female: 8 (33.3%)
Clinical stage	LAPC (NCCN)		
Tumour type: n (%)	Adenocarcinoma: 47 (94%) Neuroendocrine: 3 (6%) *3 patients had recurrence and were treated with a second IRE (7,9,19 months after first IRE)*	Adenocarcinoma: 24 patients	Adenocarcinoma: 23 patients
Tumour location*: n (%)	Head: 32 (60.4%) Neck/body: 21 (39.6%)	Head: 17 (58.6%) Neck/body: 12 (41.4%)	Head: 15 (62.5%) Neck/body: 9 (37.5%)
Tumour size*: cm; median (IQR)	3.0 (1.7-5.0)	2.7 (2.4-4.0)	3.2 (2.0-4.5)
Treatments before IRE			
Chemotherapy: n (%)	46 (92%) patients: GTX/GAX: 29 (63.0%) FOLFIRINOX: 7 (15.2%) Other: 10 (21.8%)	 14 (58.3%) 3 (12.5%) 7 (29.2%)	 15 (68.2%) 4 (18.2%) 3 (13.6%)
Radiotherapy: n (%)	39 (78%) patients: Intensity-modulated: 5 (12.8%) Stereotactic body: 34 (87.2%)	3 (16.7%) 15 (83.3%)	2 (9.5%) 19 (90.5%)
Simultaneous treatments*: n (%)		Gastrojejunostomies: 2 (6.9%) Double-bypass operation: 2 (6.9%)	Wipple: 15 (63%) Distal: 7 (29%) Appleby: 2 (8%) Venous reconstruction: 12 patients (52%)

Treatments after IRE	NR		
Intervention	All	Ablative treatment	Margin accentuation
IRE device	Nanoknife		
Approach	NR		
Imaging guidance	NR		
Number and length of interventions: n; minutes, median ± range	53 procedures; 42 min (26-91)	29 procedures; 84 min (54-118)	24 procedures; 26.5 min (17-33.5)
IRE intention: ablation or margin accentuation; n (%)		29 (55%)	24 (45%)
Comparator	NA		
Hospital stay*: days, median (range)	6 (2-40)	4 (2-34)	8 (3-40)
Length of follow-up: months; median (IQR)	8.69 (0.26-16.26)		
Effectiveness-related outcomes	*Data reported only for patients with adenocarcinoma*		
Success of the procedure	NR		
Overall survival: months; median (95% CI)	12.03 (7.71-23.12)	7.71 (6.03-12.0)	-
Cancer specific survival	NR		
Disease free survival	NR		
Progression free survival	NR		
Time to recurrence	NR		
Time to progression	NR [Percentage of progression (local + distant recurrence): 58%] [Time to distant recurrence: median of 90.2 months (95% CI, 6.66-16.98)]		
Time to local recurrence: months, CI 95%	8.6 (5.51- Not reached) [Percentage of local recurrence: 11%]		
Health-related quality of life	NR		
Pain	NR		
Safety-related outcomes			
Intervention specific mortality	0 [6 patients died within 90 days after IRE, median postoperative mortality: 26 days (range 8-42)]	0 [5 postoperative mortality]	0 [1 postoperative mortality]

Adverse events: n (%) *Clavien-Dindo classification:*	30 days: • Grade 3-4: 9 (16.9) (4 IRE related) • Grade 5: 4 (7.6) (1 IRE related: duodenal and bile duct necrosis) 90 days: • Grade 3-4: 1 (2.0) • Grade 5: 2 (3.8) (2 IRE related: upper gastrointestinal bleeding, intraperitoneal haemorrhage) **At 30 days: in the text 5 grade 1 complication and 8 grade 2 complications are mentioned.* **there were no statistically differences in the incidence of adverse events adjusted by needle-placement, tumour size or primary treatment versus margin extension.*	30 days: • Grade 3-4: 4 (13.7) • Grade 5: 3 (10.3) 90 days: • Grade 3-4: 1 (3.4) • Grade 5: 2 (6.9)	30 days: • Grade 3-4: 5 (20.8) • Grade 5: 1 (4.2) 90 days: • Grade 3-4: 0 (0) • Grade 5: 0 (0)
Other adverse events/ complications	NR		

Author, year, reference number	**Paiella, 2015 (15)**
Country	Italy
Centre	Single center: University of Verona Hospital Trust
Funding	None
Conflict of interest	NR
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	June 2011-December 2011
Inclusion/exclusion criteria	Inclusion: • Male or female • 18 years of age • Meets criteria for locally advanced unresectable pancreatic adenocarcinoma • Tumour size must be <4 cm (longest axis) and must be measurable • Must have an INR <1.5 • Must be unresponsive to chemotherapy as demonstrated with either computed tomog-raphy or MRI imaging and not have taken any chemotherapy agents within 14 days of treatment with the NanoKnife LEDC System • Are willing and able to comply with the protocol requirements • Are able to comprehend and willing to sign an Informed Consent Form

	Exclusion: • A baseline creatinine reported as >2.0 mg/dl • Have any reported baseline lab values with a grade 3 or 4 toxicity as defined by the CTCAE Version 3.0 • Inability to stop antiplatelet and Coumadin therapy for 7 days prior to and 7 days post treatment with the NanoKnife System • Known history of contrast allergy that cannot be medically managed • Known hypersensitivity to the metal in the electrodes (stainless steel 304L) that cannot be medically managed • Unable to be treated with a muscle blockade agent (e.g., pancuronium bromide, atricurium, cisatricurium, etc.) • Women who are pregnant or currently breast feeding • Women of childbearing potential who are not utilizing an acceptable method of contraception • Have taken an investigational agent within 30 days of visit 1 • Have implanted cardiac pacemakers or defibrillators • Have implanted electronic devices or implants with metal parts in the immediate vicinity of a lesion • Have a history of epilepsy or cardiac arrhythmia (atrial or ventricular fibrillation) • Have a recent history of myocardial infarction (within the past 2 months) • Have Q-T intervals greater than 550 ms unless treated with an Accusync Model 72 synchronization system controlling the NanoKnife system's output pulses
Patient characteristics	
Number of patients	10
Age: years; median	66
Gender: n (%)	Female: 6 (60%) ** Discrepancies between the text and the tables: 5 females were included according to the abstract*
Clinical stage	LAPC; any of the following features: • Infiltration or thrombosis of one or more large arterious vessels surrounding the pancreas (celiac axis, and/or superior mesenteric artery and/or hepatic artery) • Infiltration of the venous vessels wall (portal vein, and/or superior mesenteric vein) • Contact >180º for more than 2 cm in length.
Tumour type and location: n (%)	Type: 10 adenocarcinoma (100%) Location: • Head: 7 (70%) • Body: 3 (30%)
Tumour size: cm; median (range)	3 (2.5-3.9)
Treatments before IRE: n (%)	Chemotherapy: 10 (100%) • Gemcitabine: 2 • GEMOX: 5 • GEMOX first line, FOLFIRINOX second: 2 • PEXG: 1 Radiotherapy: 4 (40%)
Simultaneous treatments	Double bypass (gastric and biliary) in one patient
Treatments after IRE: n (%)	Chemotherapy: 3 (30%)
Intervention	
IRE device	Nanoknife

Approach	Open surgery
Imaging guidance	US
Number and length of interventions: min; median (range)	79.5 (20-148)
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay: days; median (range)	9.5 (8-17)
Length of follow-up: months; median	7.6
Effectiveness-related outcomes	
Success of the procedure	NR [IRE procedure 100% successful]
Overall survival: months; median (95% CI) [mean (95% CI)] Survival at X months (95% CI):	**From IRE*:** 4.3 m (2.9, 10.1) [Mean 7.5 (24.95,10.03)] At 3 months: 90% (47.30, 98.53) At 6 months: 50% (18.36, 75.32) At 12 months: 20% (3.09, 47.47) **From diagnosis*:** 12.5 months (95% CI: 8.5, 24.1) [16.79 (95% CI: 12.40, 21.18)] At 3 months: 100% At 6 months: 100% At 12 months: 60% (25.27, 82.72) At 18 months:50% (18.36, 75.32) At 24 months: 30% (7.11, 57.79) * *Kaplan-Meier Analysis, with individual data provided in the article. Important discrepancies between the text and the tables: in the text it is said that a patient died because of septic shock 2 weeks after IRE.*
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression	NR [One patient developed metastases 30 days after IRE] Two patients developed metastases 60 days after IRE]
Time to local recurrence	NR
Health-related quality of life:	• EORTC QLQ 30/ PAN26: Preoperatively: 58.3 2 weeks after IRE: 37.5 3 months:33.5 • KPS Performance status: Baseline: 100 30 days after IRE: 80 60 days after IRE: 77.5 90 days after IRE: 70
Pain	• Visual Analogue Scale Baseline: 0.5 30 days after IRE: 3 60 days after IRE: 4 90 days after IRE: 1
Safety-related outcomes	
Intervention specific mortality	0

Adverse events: n (%) *MedDRA classification system; severity of toxicities according to the CTCAE, whenever possible*	• Severe adverse events: ◊ Pulmonary embolism: 1 ◊ Systemic candidiasis: 1 ◊ Pneumonia: 1 ◊ Sepsis: 1 ◊ Pancreatic abscess and internal fistula: 1 (*considered procedure-related abdominal complication*) • Non severe adverse events : ◊ Abdominal and back pain: 5 ◊ Portal vein thrombosis: 1 ◊ Onset ulcerative colitis: 1 ◊ Peripheral oedema: 1 ◊ Wound infection: 1
Other adverse events/complications	• Intraoperativerly: 1 patient (10%) transient hypertensive episode
Author, year, reference number	**Belfiore, 2015 (18)**
Country	Italy
Centre	Single center: S. Anna - S. Sebastiano Hospital
Funding	None
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	April 2013 - June 2014
Inclusion/exclusion criteria	Inclusion: • LAPC according to the NCCN guidelines • Maximal axial diameter ≤6 cm • No metastases Exclusion: • Moderate or severe cardio-pulmonary failure • Coagulation disorders • Contraindication to general anesthesia and/or chemotherapy
Patient characteristics	
Number of patients: n	20
Age: years; mean (range) [median]	69.2 (55-82) [70]
Gender: n (%)	Female: 10 (50%)
Clinical stage	LAPC (not reported if histologically confirmed)
Tumour type and location: n (%)	Type: NR Location: • Head: 10 (50%) • Body: 1 (5%) • Body-tail: 5 (25%) • Isthmus: 3 (15%) • Isthmus-head: 1 (5%)
Tumour size (volume): cm^3; mean (range)	93 (39-170)
Treatments before IRE	NR
Simultaneous treatments	NR

Treatments after IRE: n (%)	20 patients (100%): combination of gemcitabine (100mg/mq) + oxaliplatin (100 mg/mq) biweekly 3 (15%) patients underwent surgery because of lesions downstaging
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Computed tomography
Number and length of interventions: n	20
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay	NR
Length of follow-up: months; mean (range)	8.55 (3-14)
Effectiveness-related outcomes	
Success of the procedure	NR [IRE procedure 100% successful. Residual tumour was observed in all patients after a 6 months of follow-up]
Overall survival: months; mean (CI 95%) Survival at X months (95% CI):	12.95 (11.57-14.33) At 3 months: 95% (69.5 - 99.3) At 6 months: 90% (65.6 - 97.4) At 12 moths: 90% (65.6 - 97.4) **Kaplan-Meier Analysis, with individual data provided in the article.*
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression	NR [No progression in 18/20 (90%) of patients at the last follow-up]
Time to local recurrence	NR [Local control at 6 months: 18/20 (90%)]
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality: n	0
Adverse events: n (%) *Not grading system stated*	Minor complication: 2 (10%) • Transient amylase increase in serum: 1 • Mild ascites: 1 Major complication: 0
Other adverse events/complications	NR

Author, year, reference number	**Martin, 2012 (19)**
Country	United States

Centre	Multicenter: Henry Ford Hospital and University of Louisville
Funding	Partial support of an educational grant from Angiodynamics
Conflict of interest	First author is a paid consultant for Angiodynamics
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	December 2009 - March 2011
Inclusion/exclusion criteria	Inclusion: • Locally advanced pancreatic cancer (Stage III) by the AJCC staging system Exclusion: • Borderline resectable lesions
Patient characteristics	
Number of patients: n	27
Age: years; median (range)	61 (45-82) **Discrepancies between the text and the table: in the abstract the range is 45-80*
Gender: n (%)	Female: 13 (48.1%)
Clinical stage	LAPC Stage III (AJCC staging system)
Tumour type and location: n (%)	Location: • Head: 15 (55.6%) • Body/neck: 12 (44.4%)
Tumour size: cm; median (range)	Axial: 3 (1-5.5) Anterior to posterior: 2.8 (1-5.3) Caudal to cranial: 2.6 (1-4.1)
Treatments before IRE: n (%)	Previous treatment in 23 (85%) of patients: • Chemotherapy: ◊ Gemzar: 8 ◊ FOLFOX: 3 ◊ FOLFIRI:1 ◊ Oxaliplatin:1 ◊ Avastin: 1 ◊ Cisplatin: 2 ◊ Taxol: 1 ◊ FOLFIRINOX: 4 ◊ Other: 15 • Radiotherapy: ◊ 5FU and radiation: 3 ◊ Gemzar and radiation: 6 **FOLFIRI: folinic acid, fluorouracil and irinotecan* *FOLFIRINOX: oxaliplatin, irinotecan, fluorouracil and leucovorin* *FOLFOX: 5-FU, leucovorin and oxaliplatin*
Simultaneous treatments	• Resection + IRE: 8 ◊ Whipple procedure: 4 ◊ Subtotal pancreatectomy: 4 • Hepticojejunostomy: 4 • Gastrojejunostomy: 9 • Partial gastrectomy: 3 • Other: 17
Treatments after IRE	NR

Intervention	
IRE device	Nanoknife
Approach: n (%)	Open: 26 (96.3%) Percutaneous: 1 (3.7%)
Imaging guidance	Ultrasound
Number and length of interventions: n; min; median (range)	27 procedures Length of IRE: 10 (2-97) Length of procedure: 160 (40-365)
IRE intention (ablation or margin accentuation): n (%)	Ablation: 19 (70.4%) Margin accentuation: 8 (29.6%)
Comparator	NA
Hospital stay: days; median (range)	9 (1-58)
Length of follow-up: days	90
Effectiveness-related outcomes	
Success of the procedure: %	96.3% (26/27) [Definition: ability to deliver the planned therapy in the operative room and at 3 months to have no evidence of residual tumour] [One patient died on day 70]
Overall survival	At 3 months: 26 (100%)
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression	NR
Time to local recurrence	NR
Health-related quality of life	NR
Pain	Before IRE: 5 points (range 3-9)
Safety-related outcomes	
Intervention specific mortality	0
Adverse events: n (%) *Not grading system stated*	9 (33%) patients, 17 adverse events: • Grade 1: hematologic (1) • Grade 2: hematologic (2), ileus(1), portal vein thrombosis (1), Deep venous thrombosis (2), wound infection (3) • Grade 3: Bile leak (1), pulmonary (2), renal failure (1), ascites (1) • Grade 4: bile leak(1) • Grade 5: portal vein thrombosis (1) [Possible IRE-related adverse events in 4 patients] **Discrepancies between the text and the table: in the text 18 complications*
Other adverse events/complications	NR

Table A 4. Characteristics of other relevant studies for the effectiveness and safety for liver cancer

Author, year, reference number	Frühling, 2017 (20)
Country	Sweden
Centre	Single center: Uppsala University Hospital
Funding	Non-industry sponsored
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	September 2011 - September 2014
Inclusion/exclusion criteria	Inclusion criteria: • contraindicated for other ablation modalities • size of <30 mm • a maximum of 2 tumours • performance, status according to Eastern Co-operative Oncology Group (ECOG) <2 Exclusion: • American Society of Anaesthesiologists (ASA) classification score IV • Pacemakers • epilepsy • severe cardiac disease **A inclusion criteria is a tumour size <30 mm but they include 6 patients with a marginally larger tumour.*
Patient characteristics	
Number of patients: n	30
Age: years; median (range)	63 (46-78)
Gender: n (%)	Female: 9 (30%)
Clinical stage: n (%)	NR
Tumour type and location: n (%)	38 tumours: • Primary tumours: ◊ HCC: 8 (21.1%) • Secondary tumours: ◊ CRLM: 23 (60.5%) ◊ Other metastases: 7 (18.4%)
Tumour size: cm; median (range)	2.4 (0.8-4)
Treatments before IRE: n	Liver surgery: 18 MWA/RFA: 20
Simultaneous treatments	NR
Treatments after IRE	NR
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	CE-US
Number and length of interventions: n	38 treated tumours (2 patients were treated on two different occasions and 8 patients had 2 tumours)

<table>
<tr><td>IRE intention: ablation or margin accentuation</td><td>Ablation</td></tr>
<tr><td>Comparator</td><td>NA</td></tr>
<tr><td>Hospital stay: days; median (range)</td><td>2 (1-4)</td></tr>
<tr><td>Length of follow-up: months; median (range)</td><td>22.3 (2.5-55.6)</td></tr>
<tr><td colspan="2">Effectiveness-related outcomes</td></tr>
<tr><td>Success of the procedure</td><td>NR
[Ablation success defined as acceptable ablation zone in the treated area and no evidence of residual tumour. Imaging techniques were performed 1 month after IRE but the results were not provided]</td></tr>
<tr><td>Overall survival: months; mean (95% CI)
Survival at X months (95% CI):</td><td>37.92 (30.28,45.57)
At 3 months: 96.67 (78.61, 99.52)
At 6 months: 96.67 (78.61, 99.52)
At 12 months: 89.76 (71.51, 96.58)
At 18 months: 69.05 (48.93, 82.54)
At 24 months: 65.21 (44.92, 79.58)
*Discrepancies between the text and the tables (number of deaths, range follow-up) were clarified by the author
*Kaplan-Meier Analysis, with individual data provided in the article.</td></tr>
<tr><td>Cancer specific survival</td><td>NR</td></tr>
<tr><td>Disease free survival</td><td>NR</td></tr>
<tr><td>Progression free survival</td><td>NR</td></tr>
<tr><td>Time to recurrence</td><td>NR</td></tr>
<tr><td>Time to progression</td><td>NR</td></tr>
<tr><td>Time to local recurrence</td><td>NR
Local recurrence percentages:
<table>
<tr><td></td><td>3 months</td><td>6 months</td></tr>
<tr><td>All tumours</td><td>21.1%</td><td>34.2%</td></tr>
<tr><td>CRLM</td><td>26.1%</td><td>47.8%</td></tr>
<tr><td>HCC</td><td>0%</td><td>0%</td></tr>
<tr><td>Other metastases</td><td>28.6%</td><td>28.6%</td></tr>
</table></td></tr>
<tr><td>Health-related quality of life</td><td>NR</td></tr>
<tr><td>Pain</td><td>Post-procedural pain: 7 patients</td></tr>
<tr><td colspan="2">Safety-related outcomes</td></tr>
<tr><td>Intervention specific mortality: n</td><td>0 (30 days after IRE)</td></tr>
<tr><td>Adverse events: n (%)
SIR grading system
(30 days after IRE)</td><td>• Major complication (2):
Grade V: pulmonary embolism (non-IRE related) (1)
Grade III-IV: bile duct dilatation and stricture of portal vein and bile duct (1)
• Minor complications (12):*
◊ Post-procedural pain: 7 patients (one patient required morphine for chest pain)
◊ Hematoma (1)
◊ Shortness of breath (1)
◊ Tachycardia (1)
◊ Infection (1)
◊ Increased blood pressure (1)
Other changes: 13 transient increase in liver transaminases
*Possible duplication of patients</td></tr>
<tr><td>Other adverse events/complications</td><td>NR</td></tr>
</table>

Author, year, reference number	Distelmaier, 2017 (22)
Country	Germany
Centre	Single center: Academic comprehensive cancer centre
Funding	NR
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	February 2012 to June 2015
Inclusion/exclusion criteria	Inclusion criteria: • not considered suitable for RFA or MWA because of the close proximity (<0.5 cm) to major hepatic or portal vein branches and bile duct structures • no more than three malignant liver tumours, each smaller than 4 cm
Patient characteristics	
Number of patients: n	29
Age: years; mean ± SD	63 ± 12
Gender: n (%)	Female: 14 (48.3%)
Clinical stage	NR
Tumour type and location	Total 29 patients, 43 tumours: Primary tumours (8 tumours): • Hepatocellular carcinoma 2 patients, 4 target tumours Secondary tumours (35 tumours): • Breast cancer 4 patients, 4 target tumours • Colorectal cancer 13 patients, 21 target tumours • Cholangiocellular carcinoma 2 patients, 4 target tumours • Pancreatic cancer 2 patients, 2 target tumours • Melanoma 1 patient, 1 target tumour • Mesothelioma 1 patient, 1 target tumour • Esophageal carcinoma 2 patients, 2 target tumours • Renal cell carcinoma 1 patient, 3 target tumours • Gastrointestinal stromal tumour 1 patient, 1 target tumour
Tumour size: volume (mL); mean ± SD	6.4 ± 11.39
Treatments before IRE	NR
Simultaneous treatments	NR
Treatments after IRE	NR
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Computed tomography
Number and length of interventions	NR
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA

Hospital stay	NR
Length of follow-up: mean ± SD	24 ± 7
Effectiveness-related outcomes	
Success of the procedure: % (95% CI) [n]	NR [No residual tumour and the ablation zone cover the target tumour with an adequate safety margin: By patients: 90% (95% CI: 73, 98) [26/29] By tumours: 93% (95% CI: 85,100) [40/43]]
Overall survival	NR
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR [Recurrence (local + regional): by patient: 10/26 (38%; 95% CI: 20,59)]
Time to progression	NR [Distant progression: 5/29 (17.2%) patients (range: 8 weeks-24 months)]
Time to local recurrence	NR Range: 2-18 months [Local recurrence 7.70% (2/26)] [Regional recurrence: 30.8% (8/26) (along the needle tract seeding)]
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality: n	0
Adverse events: n *SIR grading system:*	• Minor: 8 ◊ Cholestasis 2-6 weeks after IRE: 5 ◊ Hematoma: 2 [inmmediate (within 24 hours after IRE)] ◊ Arterioportal fistula: 1 [periprocedural (within 30 days after IRE)]
Other adverse events/complications: n (%)	8/26 (30.8%) patients needle tract seeding

Author, year, reference number	**Niessen, 2016 (25)**
Country	Germany
Centre	Single center: University Hospital Regensburg
Funding	NR
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	December 2011 - June 2013

Inclusion/exclusion criteria	Inclusion: • Diagnosis of primary or secondary liver cancer based on positive biopsy or noninvasive criteria (1 tumour <5cm, 3 tumours <3 cm) • Noncandidacy for conventional thermal ablation • Age 18-85 • Written informed consent Exclusion: • Resectable disease • Severe coagulation disorders • Vascular invasion, multifocal hepatic disease or extrahepatic spread on imaging • Previous treatment of target nodule • Patients who received systemic chemotherapy whiting 30 days of IRE • Severe heart failure, recent myocardial infarction, coronary artery disease, arrhythmia, implantable devices • Pregnancy or women childbearing age not using contraception
Patient characteristics	
Number of patients	34
Age: mean ± SD (range)	59.4 ± 11.2 (22-81)
Gender: n (%)	Female: 7 (20.6%)
Clinical stage	NR
Tumour type and location: n	34 patients, 65 tumours: • Primary tumours (33) ◊ Hepatocelular carcinoma: 15 p, 33 tumours • Secondary tumours (32) ◊ Colorrectal liver metastases: 12 p, 22 tumours ◊ Cholangiocellular carcinoma: 4 p, 5 tumours ◊ Testicular metastases: 1 p, 2 tumours ◊ Neuroendocrine metastases: 2 p, 3 tumours
Tumour size (diameter): cm; median ± SD (range)	2.4 ± 1.4 (0.2 – 7.1)
Treatments before IRE: n (%)	Surgical treatment: 20 (58.8%) Systemic therapy: 15 (44.1%) RFA: 7 (20.6%) Hepatic arterial therapy: 4 (11.8%) Radiation therapy: 3 (8.8%)
Simultaneous treatments	NR
Treatments after IRE	NR
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Computed tomography and US
Number and length of interventions: n; minutes, mean ± range	51 procedures Length: 163.5 min ± 59.5 (62-400)
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA

Hospital stay	NR
Length of follow-up: months; median (range)	13.9 (1.8-19.5)
Effectiveness-related outcomes	
Success of the procedure: n (%)	NR [Successful delivery of all planned pulses to the target volume as calculated by the IRE generator and complete tumour coverage (assessed by computed tomography or MR performed 6 weeks after ablation): 62/65 tumours (95.4%)]. [3 patients with incomplete ablation at 6 weeks and 9 patients with recurrence at 3 or 6 months were retreated]
Overall survival	NR [One patient died 9.8 months after first IRE]
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression: months; median	15.6
Time to local recurrence: months; mean Local recurrence free survival at X months:	By tumour: 15.5 At 3 months: 87.4% At 6 months: 79.8% At 12 months:74.8%
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality	NR
Adverse events: n (%) *SIR grading system, graded according the CTCAE:*	14/51 procedures (27.5%) • Major complications: 6 (11.8%) ◊ Intraperitoneal bleeding: 1 (2.0%) [CTCAE 3] ◊ Partial thrombosis of portal vein 1(2.0%) [CTCAE 3] ◊ Abscess: 4 (7.8%) [CTCAE 3] • Minor complications: 8 (15.7%) ◊ Hematoma: 6 (11.8%) [CTCAE 1] ◊ Pneumothorax: 2 (3.9%) [CTCAE 1]
Other complications/adverse events	NR

Author, year, reference number	**Granata, 2016 (24)**
Country	Italy
Centre	Single center: National Cancer Institute
Funding	NR
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single arm study
Data collection period	January 2012 - July 2013

Inclusion/exclusion criteria	Inclusion: • Histologically proven diagnosis of HCC • Not suitable for surgical resection with tumour sites unfavourable to radiofrequency ablation • 3 HCC nodules or less • Nodule size ≤3 cm • Child-Pugh class A • ECOG performance status of 0 • ASA score of 3 • Prothrombin time ratio >50% • Platelets count >50 × 109/L Exclusion: • Distant metastases • Tumour infiltration of the major liver vessels • Recent myocardial infarction • Cardiac arrhythmias, implanted pacemaker, renal failure • Sepsis • Poor life expectancy
Patient characteristics	
Number of patients: n	20
Age: years; mean (range)	65 (48-80)
Gender: n (%)	Female: 8 (40%)
Clinical stage	BCLC classification: Stage A
Tumour type and location: n (%)	24 primary tumours Tumour type: • Well-differentiated HCC: 20/24 (83.3%) • Moderately differentiated nodule: 3/24 (12.5%) • Poorly differentiated lesion: 1/24 (4.17%) Tumour location: • Location in difficult sites: 8/24 (33.3%) • Non-difficult sites: 16/24 (66.7%)
Tumour size: cm; mean (range)	2 (1-3)
Treatments before IRE	NR
Simultaneous treatments	NR
Treatments after IRE	NR
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	US
Number and length of interventions: n	22 procedures
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay	NR
Length of follow-up: months	6
Effectiveness-related outcomes	

Success of the procedure: n (%)	NR [Complete response (disappearance of any enhancement in all target lesions): 22/24 (91.7%)] [The two residual tumours underwent an additional single session of IRE achieving complete response]
Overall survival	100%
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression	NR
Time to local recurrence	NR
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality	0
Adverse events	Minor (2): • Peripheral arteriovenous shunt: 1/20 (5%)* • Segmental dilation of the intrahepatic biliary ducts: 1/20 (5%)* **Occurred along the needle tract*
Other adverse events/complications: n (%)	Capsular retraction: 4/24 (17%) Alterations of vascular perfusion during the arterial phase: 6/20 (30%)

Author, year, reference number	**Eller, 2015 (23)**
Country	Germany
Centre	Single center: University Hospital Erlangen
Funding	NR
Conflict of interest	None
Registration trial number	NR
Study Design	Prospective single-arm study
Data collection period	NR
Inclusion/exclusion criteria	Inclusion: • Primary or secondary liver tumours in perivascular locations • No surgical or thermo-ablative candidate
Patient characteristics	
Number of patients: n	14
Age: years; mean ± SD (range)	58 ± 11 (36-73)
Gender: n (%)	Female: 3 (21.4%)
Clinical stage	NR

Tumour type and location: n (%)	14 patients, 18 tumours: • Primary: 3/14 (21.4%) ◊ Hepatocellular carcinoma: 3/18 • Secondary: 11/14 (78.6%) ◊ Neuroendocrine: 1/14 ◊ Squamous cell carcinoma: 1/14 ◊ Colorrectal carcinoma: 9/14
Tumour size: cm; median (range)	2 ± 0.5 (1.1-3.7)
Treatments before IRE: n	1 patient treated with TACE
Simultaneous treatments	NR
Treatments after IRE: n	1 patient unsuccessful treated: RFA 4 weeks later 1 patient treated with MWA of further lesions 2 patients treated with RFA of recurrent lesions
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Computed tomography
Number and length of interventions: n; hours	14 procedures; range: 2-5 h
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay	NR
Length of follow-up: days; mean ± SD (range)	388 ± 160 (120-594) [among 10 patients without local recurrence]
Effectiveness-related outcomes	
Success of the procedure (%)	NR [Total inclusion in the devascularized area in the initial posinterventional computed tomography performed the first following day after IRE: 12/14 (86%)]
Overall survival	NR
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression	NR • Progression percentage: 6/12 (50%)
Time to local recurrence: months; mean	NR Local recurrence percentage: 2/12 (17%)
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality	*0*

Adverse events *Classified according CTCAE version 2:*	• Major complications 4/14 (29%): ◊ Severe abdominal bleeding requiring surgery: 1 [CTCAE 4] ◊ Hemoperitoneum:1 [CTCAE grade 3] ◊ Hematothorax: 2 [CTCAE grade 3] No long-term complications
Intervention specific mortality	NR

Author, year, reference number	**Eisele, 2014 (12)**			
Country	Germany			
Centre	NR			
Funding	None			
Conflict of interest	None			
Registration trial number	NR			
Study Design	Prospective single-arm study			
Data collection period	NR **10 months of recruitment*			
Inclusion/exclusion criteria	Inclusion: • Unresectable tumour • Small solitary tumour centrally sited in combination with a high probability for recurrent disease and/or not more than 3 tumours • Abscense of coagulation disorders • Normal blood cell count • Tumours in the vicinity of larger vessels (predominantly portal or hepatic veins) • Small tumours* ** Initially <2 cm. In the two most recent applications, tumour sizes were increased up to 2.4 cm* Exclusion: • Severe cardiac arrhythmia • Inability to undergo general anaesthesia			
Patient characteristics				
Number of patients: n	13			
Age: years; mean ± SD	63 ± 10			
Gender: n (%)	Female: 4 (30.8%)			
Clinical stage	NR			
Tumor type and location: n (%)	14 tumours: • Primary tumours: 8 ◊ Hepatocellular carcinoma: 5 p, 5 tumours (35.7%) ◊ Intrahepatic recurrent cholangiocarcinoma: 2 p, 2 tumours (14.3%) • Secondary tumours: 6 ◊ Colorectal liver metastases: 6 p, 7 tumours (42.9%)			
Tumour size: cm; mean ± SD	1.5 ± 0.5			
Treatments before IRE: n		Percutaneous	Laparoscopic	Open surgery
		Intersticial brachytherapy: 1	NR	NR

Simultaneous treatments: n		Hernia repair: 1	Hepatic resection: 2	Hepatic resection: 2
Treatments after IRE: n		Brachytherapy: 2	TACE: 1	
Intervention	**Overall**	**Percutaneous**	**Laparoscopic**	**Open surgery**
IRE device	Nanoknife			
Approach: n (%)		7 (53.8%)	4 (30.8%)	2 (15.4%)
Imaging guidance	US			
Number and length of interventions: n; min, mean ± SD	Procedures:	7	4	2
	Length:	62 ± 27	155 ± 75	240 ± 10
IRE intention: ablation or margin accentuation	Ablation			
Comparator	NA			
Hospital stay: days; mean		2	4	9
Length of follow-up: months; median (range)	8 (3-12) **Calculated with data from table II. In the text is stated 6 months*			
Effectiveness-related outcomes				
Success of the procedure: n (%)	NR [Complete ablation: By patient: 10/13 (76.9%) By tumour: 11/14 (78.6)] [One procedure was prematurely aborted due to technical failure of the generator]	NR [4/7 (57.1%)]	NR [4/4 (100%)]	NR [2/2 (100%)]
Overall survival	100% [No deaths occurred]			
Cancer specific survival	NR			
Disease free survival	NR			
Progression free survival	NR			
Time to recurrence	NR			
Time to progression	NR [Progression percentage: 2/10 (20%)]			
Time to local recurrence	NR			
Health-related quality of life	NR			
Pain	NR			
Safety-related outcomes				

Intervention specific mortality: n	0
Adverse events	NR
Other adverse events/complications	NR

Author, year, reference number	**Cheung, 2013 (21)**
Country	Australia
Centre	The Alfred Hospital. Melbourne.
Funding	Research equipment: AngioDynamics
Conflict of interest	Research equipment support for the Department of Radiology at The Alfred Hospital was received from AngioDynamics
Registration trial number	Australian New Zealand Clinical Trial Registry: #00083436
Study Design	Prospective single-arm study
Data collection period	November 2008 - December 2009
Inclusion/exclusion criteria	Inclusion: • HCC histologically proven or stablished according to the American Association for the Study of Liver Disease practice guideline criteria • No evidence of macrovascular invasion or extrahepatic metastases • Unresectable (because of liver disease severity, portal hypertension and/or tumour location • Tumour not amenable to RFA because of tumour proximity to essential tissue vulnerable to thermal injury or major blood vessels
Patient characteristics	
Number of patients: n	11
Age: years; mean ± SD (range)	70 ± 8.7 (52-84)
Gender: n (%)	Female: 3 (27.3%)
Clinical stage	NR
Tumour type and location	18 tumours
Tumour size: cm; mean ± SD (range)	2.44 ± 0.99 (1.0 - 6.1)
Treatments before IRE	NR
Simultaneous treatments	NR
Treatments after IRE: n	4/5 incompletely ablated lesions: RFA 1/5 incompletely ablated lesions: TACE 1 patient: liver transplant 1 patients: Sorafenib for metastatic disease 1 patient: RFA for distant recurrence
Intervention	
IRE device	Nanoknife
Approach	Percutaneous
Imaging guidance	Ultrasound/Computed tomography

Number and length of interventions: n; hours, median (range)	154 procedures: • Lesion <3 cm: median 4 procedures • Lesion >3 cm: median 16 procedures Length: • Per treatment: 2.4 (1-3) • Per tumour: 1.25 (0.6-2.75)
IRE intention: ablation or margin accentuation	Ablation
Comparator	NA
Hospital stay	NR
Length of follow-up: months; mean ± SD (range)	18 ± 4 (14-24)
Effectiveness-related outcomes	
Success of the procedure: n (%)	NR [Complete ablation: no recurrent or residual disease at or directly adjacent to the treated location after up to two ablation treatments and at least six months of follow-up By tumour: After 1st procedure: 12/18 (66.67%) After 1st and 2nd procedure: 13/18 (72%) [after 6 months] [4/5 (80%) incompletely ablated lesions were larger than 3 cm] By patient (1st and 2nd IRE): 6/11 (54.5%)]
Overall survival	NR
Cancer specific survival	NR
Disease free survival	NR
Progression free survival	NR
Time to recurrence	NR
Time to progression: months; mean ± SD (range)	NR [6 patients with complete response: time to distant recurrence 14 ± 6 (9-22)]
Time to local recurrence: months; mean ± SD	NR [Local recurrence percentage: 0/6 (0%), among 6 patients treated successfully]
Health-related quality of life	NR
Pain	NR
Safety-related outcomes	
Intervention specific mortality	0
Adverse events	Major complications: 0 Minor complications: 4 patients developed transient urinary retention (all had previous history of prostatic hypertrophy) 7 (64%) patients experienced pain post procedure
Other adverse events/complications	NR

List of ongoing and planned studies

Table A 5. List of ongoing studies with irreversible electroporation for pancreatic cancer

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
2017-003775-62	Not available (ongoing)	Single-arm trial	75	FOLFIRINOX followed by local therapy (resection, RT and/or IRE)	NA	Inclusion criteria: • LAPC (Karolinska Type B, C or D1) • Cytologically or histologically verified adenocarcinoma/ carcinoma • The patient is operable (i.e. no co-morbidity which can preclude anaesthesia or sur-gery) • No sign of M1 disease • WHO performance status 0-1 • Age ≥18 years • Adequate hematological, renal, and hepatic function • Patients with obstruction of bile duct or gut must be drained before start of therapy • Oral and written informed consent must be obtained prior to registration with planned date of first treatment within 14 days from registration	Primary outcomes: • 2 year survival for all patients starting chemotherapy • Secondary outcomes: • QoL (EORTC QLQ-PAN26) • PFS • OS • Response rate (RECIST v1.1) • Histological tumour regression • Adverse events grade 2-5 (CTCAE 4.0) • Surgical complications, including IRE (Clavien) • Number of patients with progression during chemotherapy • Number of patients with R0 resection
NCT03673137	November 2021 (not yet recruiting)	Randomized controlled trial	120	Synchronous treatment group: Gemcitabine was administered over 30 minutes immediately following percutaneous IRE	Traditional treatment group: gemcitabine administration on day 7 following IRE treatment	Inclusion criteria: • Histologically or cytologically confirmed pancreatic cancer • Radiologic confirmation of AJCC stage III LAPC • Histological or cytological confirmation of pancreatic adenocarcinoma • The maximum diameter of tumour is less than 5 cm • Biliary drainage in patients with biliary obstruction • PS 0-1 • Written informed consent	Primary outcomes: • OS Secondary outcomes: • Time to progression • Time to local recurrence • PFS • Response rate
NCT03484299	December 2023 (recruiting)	Single-arm trial	20	IRE and treatment with either FOLFIRINOX or Gemcitabine (based upon which chemotherapy regimen received prior to IRE)	NA	Inclusion criteria: • greater than or equal to 18 years of age • diagnosed with stage III pancreatic cancer • tumour is measurable • GFR > m L/min/1.73 m^2 • willing and able to comply with protocol requirements • AST/ALT >3 times upper limit of normal • stable surgical post-operative course as defined by operative surgeon	Primary outcomes: • Incidence of Adverse and Serious Adverse events will be captured (safety and tolerability) Secondary outcomes: • PFS

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT03614910	May 2023 (recruiting)	Single-arm	30	IRE	NA	Inclusion criteria: • age >18 • locally advanced unresectable pancreatic ductal adenocarcinoma as demonstrated by computed tomography or MRI • must have received standard chemotherapy and completed at least four cycles of treatment at least 5 weeks prior to therapy with Nanoknife • INR <1.5 • able to tolerate laparotomy (medical/cardiac clearance as needed) • able to comply with protocol requirements • women of childbearing potential must have a negative serum pregnancy test and be practicing an effective form of birth control	Primary outcomes: • OS • Local progression-free survival • Distant disease-free survival • Tumour response Secondary outcomes: • Complications • QoL • Tumour markers • Biliary obstruction • Gastric outlet obstruction • Cancer related pain
NCT02674100	January 2030 (recruiting)	Prospective cohort (registry)	500	IRE	NA	Inclusion criteria: • Adult patients (greater than 18 years of age) diagnosed with pancreatic cancer that are eligible for soft tissue ablation per the treating physician.	Primary outcomes: • Adverse events (IRE related or non-IRE related) Secondary outcomes: • OS
NCT02952859	January 2024 (recruiting)	Prospective cohort	36	IRE	Historic control group	Inclusion criteria: • Patients with histology proven or highly suspected potentially resectable or borderline resectable pancreatic cancer will be included. • Age ≥18 years • Able to undergo general anesthesia (ASA ≤3) • Performance status ECOG < = 2 (Eastern Cooperative Oncology Group) • Life expectancy of at least 6 months • Resectable or borderline resectable proven pancreatic adenocarcinoma of the pancreas	Primary outcomes: • Time from diagnosis to death for any reason

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT03069599	January 2024 (recruiting)	Prospective cohort	30	IRE	Surgical resection	Inclusion Criteria: • Age ≥18 years • Able to undergo general anesthesia (ASA ≤4) • Performance status ECOG < = 2 • Life expectancy of at least 6 months • Resectable, borderline resectable, or locally advanced pancreatic cancer • Patients who have locally advanced disease have to show no tumour progression after 3 month of neo-adjuvant chemotherapy+/-radiotherapy before undergoing in situ IRE	Primary outcomes: • Immunological outcome Secondary outcomes: • Number of local tumour recurrences • Number of distant tumour recurrences • OS • Cancer specific survival
NCT03080974	April 2022 (recruiting)	Single arm trial	10	IRE and Nivolumab	NA	Inclusion Criteria: • ≥18 years if age • Diagnosed with stage III pancreatic cancer • Tumour is measurable • Glomerular Filtration Rate >60 m/L/min/1.73 m(2) • Willing and able to comply with the protocol requirements • Able to comprehend and have signed the informed consent to participate	Primary outcomes: • Safety and Tolerability of combination IRE and Nivolumab treatment Secondary outcomes: • PFS • OS
NCT03257150	September 2021 (recruiting)	Single arm trial	47	IRE	NA	Inclusion Criteria: • Histologically proven pancreatic ductal adenocarcinoma • Age ≥18 years • Locally advanced unresectable primary tumour • Tumours ≤5 cm in largest dimension at the time of enrolment that is technically amenable to treatment with IRE • At least 4 months of combination chemotherapy • ECOG performance status of ≤2 • Acceptable organ and bone marrow function • Life expectancy estimated ≥6 months • Ability and willingness to sign informed consent form • Have a measurable primary tumour at the time of study enrolment • Suitable and fit to undergo general anesthetic and laparotomy • Women of child-producing potential must agree to use effective contraceptive methods prior to study entry, during study participation, and for at least 30 days after the last administration of study medication.	Primary outcomes: • Adverse event rate • OS rate Secondary outcomes: • PFS rate • OS rate of disease • PFS rate of disease

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02041936	December 2019 (recruiting)	Single-arm trial	12	IRE	NA	Inclusion Criteria: • Male or female • 18 years of age • Must be found to have locally advanced unresectable disease following standard chemotherapy ± radiotherapy as demonstrated with either computed tomography/MRI imaging and surgical evaluation, and not have taken any chemotherapy/radiotherapy within 5 weeks of treatment with the NanoKnife IRE System • Must have an INR <1.5 • Are willing and able to comply with the protocol requirements • Are able to comprehend and willing to sign an informed consent form	Primary outcomes: • Number of Participants with Adverse Events as a Measure of Safety and Tolerability Secondary outcome • Pain Scores on the Visual Analogue Score • QoL on the EORTC QLQ-PAN26 and EORTC QLQ-C30
NCT02898649	August 2019 (recruiting)	Single-arm trial	100	IRE	NA	Inclusion criteria: • Pathologically confirmed pancreatic cancer patients • LAPC patients. Vascular encasement by tumour was noted in radiological evaluation (computed tomography, MRI or PET-computed tomography) • Older than 19 years old and younger than 70 years old • Previously treated with systemic chemotherapy or chemoradiotherapy due to locally advanced pancreatic cancer.	Primary outcome • OS • Safety (frequency of procedure-related complication and death) Secondary outcome • Time to progression • Tumour control • Pain control • Change in CA 19-9
NCT02926040	September 2023 (recruiting)	Single-arm trial	20	IRE	NA	Inclusion Criteria: • Age ≥18 years • Able to undergo general anesthesia (ASA ≤3) • Performance status ECOG < = 2 (Eastern Cooperative Oncology Group) • Locally advanced, unresectable, histology proven pancreatic adenocarcinoma • Partial response or stable disease after a minimum of 3 months of (radio-) chemotherapy after diagnosis of pancreatic adenocarcinoma without signs of liver or lung metastases • Last chemo-/radiotherapy procedure >4 weeks ago	Primary outcomes • Change from baseline in Health related QoL measured by health questionnaire

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT03105921	June 2020 (recruiting)	Single-arm trial	20	IRE	NA	Inclusion Criteria: • Patients with histologically proven adenocarcinoma of the head of the pancreas (fine needle aspiration or biopsy) • Pancreatic adenocarcinoma locally advanced on imaging at diagnosis • Tumour of less than 7 cm in largest diameter • No chemotherapy or abdominal radiotherapy within five years before the inclusion in the study	Primary outcomes • R0 resection rate
NCT02841436	October 2018 (status unknown)	Single-arm trial	40	IRE	NA	Inclusion Criteria: • LAPC • Biliary tract or intestine is compromised by tumour, palliative bypass operation (hepaticojejunostomy and/or gastrojejunostomy) is considered to be performed. • ECOG score of 0-1, • ASA score ≤3, • Adequate bone marrow, liver and renal function. • Prior Informed Consent Form • Life expectancy of at least 3 months.	Primary outcomes • Tumour response • Secondary outcomes • ECOG evaluation • Haematology test • Tumour marker measurement • Conduct computed tomography or MRI scans for tumour response evaluation • Review concomitant medications • Assess for presence of adverse event
NCT03239184	September 2018 (completed)	Randomized trial (Parallel Assignment)	120	Ablation (IRE or cryosurgery)	• Life information rehabilitation therapy • Combination therapy • Control	Inclusion Criteria: • All standard therapies have failed according to NCCN guidelines or the patient refuses standard therapies • Body tumour 1-6, with at least one tumour length >2 cm • KPS ≥70, lifespan >6 months • Platelet count ≥80×109/L white blood cell count ≥3×109/L, neutrophil count ≥2×109/L, hemoglobin ≥80 g/L	Primary outcome • Relief degree of tumours Secondary outcome • PFS • OS

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02981719	October 2020 (recruiting)	Single arm trial	20	IRE combined with chemotherapy (Gemcitabine)	NA	Inclusion Criteria: • Radiologic confirmation of unresectable pancreatic cancer by at least computed tomography of chest and abdomen • Screening must be performed no longer than 2 weeks prior to study inclusion • Maximum tumour diameter ≤5 cm • Histological or cytological confirmation of pancreatic adenocarcinoma; • Age ≥18 years • ASA-classification 0-3 • Life expectancy of at least 12 weeks • Adequate bone marrow, liver and renal function • Written informed consent	Primary outcome • Safety (adverse effects) Secondary outcomes • Efficacy (percentage of lesions that show no sign of recurrence 12 months after • Voltage (A minimum and maximum range of voltage for safe and effective IRE) • OS
NCT02822716	June 2020 (recruiting)	Single-arm trial	35	IRE	NA	Inclusion criteria • Signed informed consent by patient • Age older than 18 years. • Any kind of histologically or radiologically diagnosed malignant pancreatic tumour. • Tumour size < = 3 cm in largest dimension • Surgical treatment is considered not an option because of patient factors or tumour factors, such as those with vascular encasement or regional lymph node metastasis • Locally recurrent pancreatic tumour after surgical resection • KPS of 50% or greater. • Life expectancy greater than 3 months. • Normal coagulation profile (INR <1.5; platelet count >50 10^9/L). • Willingness and ability to complete follow-up interviews and imaging investigations following the treatment.	Primary outcome • Radiological assessment

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02514421	July 2017 (status unknown)	Single-arm trial	24	IRE combined with chemotherapy (Gemcitabine/nab-paclitaxel)	NA	Inclusion Criteria: • Histologically or cytologically proven pancreatic carcinoma which is safely accessible by percutaneous methods; • LAPC; • At least one measurable lesion according to RECIST criteria • WHO PS <2 or ECOG <2; • Age >18; • Life expectancy >3 months; • No history of gastric or esophageal varices; • No active, uncontrolled infection; • All patients must have adequate physiologic (hematologic, renal and hepatic) reserves • Pain and biliary obstruction controlled before the start of the study • Absence of psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; • Women of childbearing potential (defined as sexually mature woman who 1) has not undergone hysterectomy or bilateral oophorectomy or 2) has not been naturally post-menopausal for at last 24 consecutive months) must have a negative pregnancy test prior to starting therapy. Men and women of childbearing potential must be willing to use effective contraceptive while on treatment and for a reasonable period thereafter.	Primary outcome • Number of participants who experienced dose limiting toxicities Secondary outcome • Number of participants who demonstrated no clinical change or clinical improvement in pancreatic adenocarcinoma outcome as assessed by time to progression • Number of participants who demonstrated no clinical change or clinical improvement in pancreatic adenocarcinoma outcome as assessed by one year survival • Number of participants who demonstrated no clinical change or clinical improvement in pancreatic adenocarcinoma outcome as assessed by tumour imaging • Number of participants who demonstrated diffusion weighted MRI changes • Number of participants who demonstrated MR changes • Number of groups of patients who have similar pancreatic tumour gene expression characteristics and associated imaging characteristics after electrochemotherapy • Number of groups of patients who have similar pancreatic tumour gene expression characteristics and associated clinical outcomes after electrochemotherapy

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02343835	January 2020 (recruiting)	Single-arm trial	20	IRE	NA	Inclusion criteria • Radiologic confirmation of unresectable pancreatic cancer by at least computed tomography of chest and abdomen • Screening must be performed no longer than 2 weeks prior to study inclusion • Maximum tumour diameter ≤5 cm; • Histological or cytological confirmation of pancreatic adenocarcinoma; • Age ≥8 years; • ASA-classification 0-3 • Life expectancy of at least 12 weeks; • Adequate bone marrow, liver and renal function • Written informed consent	Primary outcome: • Characterization of the intra-tumoural and systemic immune response to IRE in unresectable pancreatic cancers Secondary outcome: • Comparison immune response between non-ablated and ablated pancreatic cancer and pre-ablated and post ablated serum Other outcomes: • OS and (local and distant) PFS
NCT02791503	May 2019 (recruiting)	Randomized trial (parallel assignment)	138	Chemotherapy (FOLFIRINOX) and IRE	Chemotherapy (FOLFIRINOX) with stereotactic ablative radiotherapy (a form of external beam radiation therapy)	Inclusion Criteria: • Radiologic confirmation of LAPC by at least computed tomography of chest and abdomen (with the upper abdomen scanned according to a dedicated 3mm slice multiphase pancreatic tumour protocol); • Maximum tumour diameter ≤5 cm; • Histological or cytological confirmation of pancreatic adenocarcinoma; • Age >18 years; • ASA-classification 0-3; WHO performance status 0-1 ; • Adequate bile drainage in case of biliary obstruction; • Written informed consent	Primary outcome • OS Secondary outcome • PFS • Untreatable PFS • Number of participants with treatment-related adverse events as assessed by CTCAE v4.0 • Pain assessment • Cost-effectiveness analysis • QoL • Change in immune status and reactivity after the procedure (IRE/ stereotactic ablative radiation) by assessing the level of immune cells pre- and post-IRE • Tumour marker CA 19.9
NCT02718859	March 2017 (status unknown)	Randomized trial (parallel assignment)	60	IRE	IRE and natural killer cells	Inclusion Criteria: • Age: 18-80 • Advanced and active pancreatic cancer • The tumour is measurable • ECOG score : 0~2 : 3 but has no relationship with tumour • Vital organ function is normal • Non pregnant and lactating patients • Non allergic reactions to biological products • Informed and consent	Primary outcome • Relief degree Secondary outcome • PFS • OS

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
JPRN-UMIN000016423	Not available (status unknown)	Single-arm trial	6	IRE	NA	Inclusion criteria • It does not matter whether the pre-treatment but it is necessary that 4 weeks was passed from the pre-treatment • It has been confirmed pathologically is adenocarcinoma or adenosquamous carcinoma • Patient of unresectable LAPC • Major organs (heart, lung, kidney, liver, etc.) function are maintained • ECOG score 0 or 1 • Life expectancy of at least 4 weeks • Written informed consent	Primary outcome: • Effectiveness of IRE for treatment of unresectable locally advanced pancreatic cancer according to local control rate using computed tomography or MRI performed 6 months after treatment Secondary outcome • Incidence and kind of adverse events of up to 1 month after treatment

Abbreviations: AJCC = American Joint Committee on Cancer; ALT = alanine aminotransferase; ASA = American Society of Anaesthesiologists; AST = Aspartate Aminotransferase; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organisation for Research and Treatment of Cancer- Quality of Life Questionnaire; GFR = glomerular filtration rate; INR = International Normalized Ratio; IRE = Irreversible electroporation; KPS = Karnofsky performance status; LAPC = locally advanced pancreatic cancer ; MRI = magnetic resonance imaging; NA = not applicable; NCCN = National Comprehensive Cancer Network; SGPT = serum glutamic-pyruvic transaminase; OS = overall survival; PET = Positron-emission tomography; PFS = progression free survival; PS = performance status; QoL = quality of life; RECIST = Response Evaluation Criteria In Solid Tumours; RT = radiotherapy; UPL = upper limit normal; WHO = world health organization .
Sources: Clinicaltrials.gov, Cochrane Central EU clinical trials, International ClinicalTrials Registry Platform (ICTRP), UK Clinical Trails gateway.

Table A 6. List of ongoing studies with irreversible electroporation for liver cancer

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
2017-004679-29	Not available (status: ongoing)	Single-arm trial	50	Nivolumab (neoadjuvant and adjuvant) in IRE treated patients	NA	• Male or female patients superior or equal 18 years • Histological or cytological documentation of HCC or non-invasive diagnosis of HCC as per AASLD criteria in patients with a confirmed diagnosis of cirrhosis, BCLC stage Category B or C • Patients with HCC amenable for IRE as assessed by multidisciplinary board corresponding to the following extension: ◊ Uninodular HCC >3 cm and <5 cm ◊ Multinodular HCC • At least one uni-dimensional measurable lesion by computed tomography scan or MRI according to modified RECIST for HCC • Liver function status Child-Pugh Class A • ECOG Performance Status inferior or equal 2 • Adequate bone marrow, liver and renal function • Life expectancy superior or equal 3 months • WOCBP need to accept one effective method of contraception until 5 months after the last Nivolumab infusion • Men who are sexually active with WOCBP partners need to accept one effective method of contraceptionuntil 7 months after the Nivolumab infusion and men must agree to use adequate contraception • Patients affiliated to a Social Security System • Written informed consent signed	Primary outcomes: • Local recurrence-free survival during a 2-years follow-up Secondary outcomes: • Changes of tumourous and non-tumourous perfusion parameters observed with compression ultrasound and MRI after one months of neoadjuvant treatments • Per nodule rates of early response (one month) after a single procedure of IRE • Incidences of intra segmental/extra segmental distant recurrence • OS at 2-years following IRE procedure • Compliance to neoadjuvant and adjuvant treatments • Tolerance of Nivolumab in the setting of neo- and adjuvant therapy to IRE • Tumoural and non tumoural assessment (histological and molecular study) of the effect of Nivolumab at 1 month • Peripheral blood approach of the effect of immunotherapy

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT03630640	September 2020 (recruiting)	Single-arm trial	50	Nivolumab up to 12 months after IRE	NA	Inclusion Criteria: • Male or female patients ≥18 years of age • Histological or cytological diagnosis of HCC • Patients with HCC eligible for IRE as assessed by multidisciplinary board • At least one uni-dimensional measurable lesion by computed tomography scan or MRI according to modified RECIST for HCC • Liver function status Child-Pugh Class A • ECOG Performance Status ≤2 • Adequate bone marrow, liver and renal function • Life expectancy ≥3 months • Women of childbearing potential and men must agree to use adequate contraception • Patients affiliated to a Social Security System • Written informed consent signed	Primary outcomes: • Local recurrence-free survival Secondary outcomes: • Changes of tumourous and non-tumourous perfusion parameters • Per nodule rates of early response • Incidences of intra segmental/ extra segmental distant recurrence • Assessment of OS • Assessment of tolerance of the immunotherapy treatment • Compliance to neoadjuvant treatments • Compliance to adjuvant treatments • Frequency of severe adverse events • Frequency of discontinuations treatment due to adverse events
NCT02828865	October 2018 (recruitment status unknown)	Single-arm trial	40 participants	IRE	NA	Inclusion criteria: • HCC or metastatic liver cancers • Unsuitable for surgical resection but local ablation is indicated, however, the distance between tumour and vessels is smaller than 5 mm. • Have at least one, but less than or equal to 3 tumours, • Each tumour must be ≤5 cm in diameter, • Child-Pugh class A-B, • ECOG score of 0-1, • ASA score ≤3, • Adequate bone marrow, liver and renal function • Prior Informed Consent Form • Life expectancy of at least 3 months. • The disease status is not suitable to receive surgical resection, percutaneous alcohol injection, transarterial chemoembolization or other standard treatment.	Primary outcome: • Tumour response Secondary outcome: • ECOG evaluation • Change of vital signs • Physical examination • Clinical laboratory assessments • Urinalysis • Conduct computed tomography or MR scans for tumour response evaluation • Review concomitant medications • Assess for presence of adverse events

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02333773	January 2020 (recruiting)	Single-arm trial	15	IRE	NA	Inclusion Criteria: • Liver cancer diagnosed by positive biopsy or non-invasive criteria, • Liver cancer with Portal venous tumour emboli, • Not suitable for surgical resection or transplantation, • Child-Pugh class A,B • ECOG score of 0-1, • A prothrombin time ratio >50%, • Platelet count >80 × 10^9/L, • Ability of patient to stop anticoagulant and anti-platelet therapy for seven days prior to and seven days post NanoKnife procedure, • Able to comprehend and willing to sign the written informed consent form, • Have a life expectancy of at least 3 months.	Primary outcomes: • Safety (adverse effects) Secondary outcomes: • Efficacy (percentage of lesions that show no sign of recurrence 12 months after IRE) • Voltage (A minimum and maximum range of voltage for safe and effective IRE) • Progress free disease • OS
NCT02329106	January 2020 (recruiting)	Single arm trial	30	IRE	NA	Inclusion Criteria: • Liver cancer diagnosed by positive biopsy or non-invasive criteria, • Tumours from diaphragm is <1 cm • not suitable for surgical resection or transplantation, • have at least one, but less than or equal to 3 tumours, • of the tumour(s) identified, each tumour must be ≤5 cm in diameter, • Child-Pugh class A, B • ECOG score of 0-1, • a prothrombin time ratio >50%, • platelet count >80 × 109/L, • ability of patient to stop anticoagulant and anti-platelet therapy for seven days prior to and seven days post NanoKnife procedure, • are able to comprehend and willing to sign the written informed consent form, • have a life expectancy of at least 3 months.	Primary outcomes: • Evaluate the safety of IRE for unresectable liver cancer close to diaphragmatic dome using CTCAE Secondary outcomes: • Evaluate the efficacy of IRE for unresectable liver cancer close to diaphragmatic as measured by cell death of CRLM after IRE is demonstrated macroscopically by using vitality-staining with triphenyl-tetrazoliumchloride

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
JPRN-UMIN000014522	Not available (status: recruiting)	Single arm trial	20	IRE	NA	Inclusion criteria: • Older than 20 years, • Male or female • Diagnosis of hepatocellular carcinoma, metastatic liver cancer or cholangiocarcinoma based on positive biopsy or noninvasive criteria • Not suitable for surgical resection and patients who are not willing ot surgical resection • Primary tumour is controlled • The target nodule must have a diammeter of < = 10 cm • Child-Pugh class A, • Liver lesion visible on US, computed tomography, or MRI • ECOG score 0, 1 • ASA score < = 3 • Life expectancy of at least 12 weeks • Written informed consent	Pimary outcome • Effectiveness of IRE for treatment of hepatic malignancies according to modified RECIST criteria using computed tomography or MRI performed 6 months after treatment. Secondary outcomes • Safety within 30 days post-intervention. All adverse events will be classified according to CTCAE version 4.0 criteria
NCT01442324	September 2012 (status unknown)	Single arm trial	5	IRE	NA	Inclusion Criteria: • older than 18 years, • male or female, • diagnosis of secondary liver cancer or cholangiocarcinoma based on positive biopsy or noninvasive criteria, • presence of at least one lesion untreatable by surgical resection or ablation for microwave or radio frequency, • the target nodule must have a diameter of ≤5 cm • ECOG score 0, • ASA score ≤3, • prothrombin time ratio >50% • platelet count >50 × 10^9/l, • patient's ability to discontinue anticoagulant and antiplatelet therapy for seven days before and seven days after surgery with NanoKnife™, • ability to understand and willingness to sign the written informed consent form, • life expectancy of at least 3 months.	Primary outcome: • Effectiveness of IRE for the treatment of metastatic liver cancer or cholangiocarcinoma Secondary outcomes: • Safety • Time to in situ recurrence

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02787954	Terminated (no publication found)	Cohort	10	IRE, TACE, Y-90 or MWA	NA	Inclusion Criteria: • Diagnosis or suspicion of primary or metastatic liver cancer deemed eligible for TACE, Y-90, percutaneous ablation, and /or electroporation.	Primary Outcome: • Time to progression Secondary Outcome Measures : • 1 year survival
NCT03040453	September, 2018 (status unknown)	Non-Randomized trial (parallel assignment)	40	IRE	MWA	Inclusion Criteria: • Hepatocellular carcinoma, maximum 3 lesions, maximum 30 mm in any cross section diameter • Physically fit to undergo general anaesthesia • Fully understand Swedish instructions regarding the study	Primary outcome: • Immunological response Secondary outcome: • Number of participants with complete radiological response at follow-up 3, 6, 9 and 12 months.
NCT03239158	Completed	Randomized trial (Parallel Assignment)	120	Ablation (IRE or cryosurgery)	• Life information rehabilitation therapy • Combination therapy • Control	Inclusion criteria: • All standard therapies have failed according to NCCN guidelines or the patient refuses standard therapies • Body tumour 1-6, with at least one tumour length >2 cm • KPS ≥70, lifespan >6 months • Platelet count ≥80 × 109/L white blood cell count ≥3 × 109/L, neutrophil count ≥2 × 109/L, hemoglobin ≥80 g/L	Primary outcome: • Relief degree of tumours Secondary outcome: • PFS • OS
NCT03008343	December 2019 (recruiting)	Randomized trial (Parallel Assignment)	20	IRE	IRE and natural killer	Inclusion criteria: • All standard therapies have failed according to NCCN guidelines or the patient refuses standard therapies after cancer recurrence • Body tumour 1-6, the maximum tumour length <5 cm • KPS ≥70, lifespan >6 months • Platelet count ≥80 ×109/L white blood cell count ≥3×109/L, neutrophil count ≥2 × 109/L, hemoglobin ≥80 g/L	Primary outcome: • Relief degree of tumours Secondary outcome: • PFS • OS

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02332551	January 2020 (recruiting)	Single-arm trial	30	IRE	NA	Inclusion criteria: • Hepatic carcinoma diagnosed by positive biopsy or non-invasive criteria, • Tumour from gallbladder is <0.5 cm • not suitable for surgical resection or transplantation, • have at least one, but less than or equal to 3 tumours, • of the tumour(s) identified, each tumour must be ≤7 cm in diameter, • Child-Pugh class A,B • ECOG score of 0-1, • ASA score ≤3, • a prothrombin time ratio >50%, • platelet count >80 × 109/L, • ability of patient to stop anticoagulant and anti-platelet therapy for seven days prior to and seven days post NanoKnife procedure, • are able to comprehend and willing to sign the written informed consent form, • have a life expectancy of at least 3 months.	Primary outcome: • Treatment efficacy as measured by modified RECIST criteria by computed tomography or MRI Secondary outcome: • Safety using CTCAE Version 3.0 criteria. • PFS
NCT02352935	January 2020 (recruiting)	Single-arm trial	15	IRE	NA	Inclusion Criteria: • Hepatic carcinoma diagnosed by positive biopsy or non-invasive criteria, • not suitable for surgical resection or transplantation, • have at least one, but less than or equal to 3 tumours, • of the tumour(s) identified, each tumour must be ≤5 cm in diameter, • Child-Pugh class B or ≤12 • ECOG score of 0-1, • ASA score ≤3, • a prothrombin time ratio >50%, • platelet count >80 × 109/L, • ability of patient to stop anticoagulant and anti-platelet therapy for seven days prior to and seven days post NanoKnife procedure, • are able to comprehend and willing to sign the written informed consent form, • have a life expectancy of at least 3 months.	Primary outcome: • Safety using CTCAE Version 3.0 criteria Secondary outcome: • Treatment efficacy as measured by modified RECIST criteria by computed tomography or MRI • PFS • OS

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02082782	May 2018 (status unknown)	Single-arm trial	29	IRE	NA	Inclusion Criteria: • Histological or cytological documentation of primary colorectal tumour; • Previous induction chemotherapy due to unresectability; no intra- or extrahepatic disease progression under induction chemotherapy; OR • Previous chemotherapy for other CRLM, now presenting with renewed CRLM unsuitable for resection or thermal ablation; • Liver metastases PET avid and visible on computed tomography, size ≤3,5 cm and not eligible for resection or thermal ablation due to location close to a vessel or bile duct; • Age more than 18 years; • ASA classification 0-3; • Adequate bone marrow, liver and renal function • Written informed consent	Primary outcome: • Efficacy
NCT02010801	December 2013 (completed)	Single-arm trial	20	IRE	NA	Inclusion Criteria: • The diagnosis of HCC or other cancers with hepatic metastatic with pathologic proven. • The diagnosis of HCC will be made by pathology / cytology or according to the AASLD (2010) diagnostic criteria. • Suitable for surgical resection, but the distance between tumours and preserved vessels is less than 5 mm. Adequate safe margin can not be obtained. • There are at least one tumour, but less than or equal to 3 tumours, • Each tumour must be ≤5 cm in diameter, • Child-Pugh class A-B, • ECOG score of 0-1, • American Society of Anaesthesiologists (ASA) score ≤3, • Platelet count ≥100 K/l • Total bilirubin ≤2 mg/dL • ALT and AST <5 × upper limit of normal • PT-INR ≤2.0, or PT <6 seconds above control • Serum creatinine ≤1.5 × upper limit of normal • Prior Informed Consent Form • Life expectancy of at least 3 months.	Primary outcome: • Complete treatment Secondary outcome: • adverse effect

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01078415	June 2013 (completed)	Single-arm trial	26	IRE	NA	Inclusion Criteria: • HCC diagnosed by positive biopsy or non-invasive criteria, • not suitable for surgical resection or transplantation, • have at least one, but less than or equal to 3 tumours, • of the tumour(s) identified, each tumour must be ≤3 cm in diameter, • Child-Pugh class A, • ECOG score of 0, • ASA score ≤3, • a prothrombin time ratio >50%, • platelet count >50 × 109/L, • ability of patient to stop anticoagulant and anti-platelet therapy for seven days prior to and seven days post NanoKnife procedure, • are able to comprehend and willing to sign the written informed consent form, • have a life expectancy of at least 3 months.	Primary outcome: • Treatment efficacy as measured by modified RECIST criteria by computed tomography or MRI. Secondary outcome: • Safety using CTCAE Version 3.0 criteria.

Abbreviations: AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; ASA = American Society of Anesthesiologists; BCLC = Barcelona Clínic Liver Cancer; CRLM = colorectal liver metastases ; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; IRE = irreversible electroporation; KPS = Karnofsky performance status; LRFS = local recurrence free survival; MRI = magnetic resonance imaging; NA = not applicable; NCCN = National Comprehensive Cancer Network; OS = overall survival; PET = Positron-emission tomography; PT-INR = Prothrombin time-international normalized ratio; RECIST = Response Evaluation Criteria In Solid Tumours; TACE = Transarterial chemoembolisation; US = ultrasound; WOCBP = Women of childbearing potential.
Sources: Clinicaltrials.gov, Cochrane Central EU clinical trials, International ClinicalTrials Registry Platform (ICTRP), UK Clinical Trails gateway.

Risk of bias tables

Table A 7. Risk of bias – study level-non-randomised study (matched analysis)

Study	Lambert, 2016 (11)
Domain 1: Confounding	Critical (no details about the number of patients in the control group who received chemotherapy was given)
Domain 2: Selection	Serious (Inclusion criteria KPS>80; no details of exclusion criteria, no details about control group selection criteria)
Domain 3: Classification of intervention	Critical (intervention in the control group not clearly defined)
Domain 4: deviation from intervention	Low (no deviation)
Domain 5: missing data	Low (no missing data)
Domain 6: measurement of outcomes	Moderate (due to not blinding outcome assessors)
Domain 7: selection of reported result	Serious (no data provided about QoL (only graphical information); no information given about complications for patients in the control group)
Overall risk of Bias	**Critical**

Abbreviations: KPS = Karnosfsky Performance Status; QoL = quality of life.
Sources: (11).

Table A 8. Risk of bias – single-arm studies (IHE-20-Criteria checklist) in pancreatic cancer

Y/N/Partial/ Unclear		Huang, 2018 (17)	Scheffer, 2016 (16)	Mansson, 2016 (14)	Kluger, 2016 (13)	Paiella, 2015 (15)	Belfiore, 2015 (18)	Martin, 2012 (19)
Study objective								
1	Was the hypothesis/aim/objective of the study clearly stated?	No	Yes	Yes	Yes	Yes	Yes	Yes
Study design								
2	Was the study conducted prospectively?	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear
3	Were the cases collected in more than one centre?	Yes	Unclear	No	No	No	No	Yes
4	Were patients recruited consecutively?	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Study population								
5	Were the characteristics of the patients included in the study described?	No	Yes	Partial	Partial	Yes	Partial	Yes
6	Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Partial
7	Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intervention and co-intervention								
8	Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Were additional interventions (co-interventions) clearly described?	Yes	Partial	Yes	Yes	Yes	Partial	Yes
Outcome measure								
10	Were relevant outcome measures established a priori?	No	Yes	Yes	Yes	Yes	Partial	Yes
11	Were outcome assessors blinded to the intervention that patients received?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
12	Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	No	Yes	Yes

Y/N/Partial/ Unclear		Huang, 2018 (17)	Scheffer, 2016 (16)	Mansson, 2016 (14)	Kluger, 2016 (13)	Paiella, 2015 (15)	Belfiore, 2015 (18)	Martin, 2012 (19)
Statistical analysis								
14	Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Results and conclusions								
15	Was follow-up long enough for important events and outcomes to occur?	Yes	Unclear	Yes	Unclear	Yes	No	No
16	Were losses to follow-up reported?	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes
17	Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Partial	Yes	No	Yes	Yes	Yes	Partial
18	Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Were the conclusions of the study supported by results?	No	Yes	No	Yes	Yes	Yes	No
Competing interests and sources of support								
20	Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes	Partial	Partial	Yes	Yes
Total		11/20	14/20	12/20	14/20	15/20	13/20	13/20
Overall risk of bias		Serious	Serious	Serious	Serious	Serious	Serious	Serious

Sources: (13-19)

Table A 9. Risk of bias – single-arm studies (IHE-20-Criteria checklist) in liver cancer

Y/N/Partial/Unclear		Fruhling, 2017 (20)	Distelmaier, 2017 (22)	Niessen, 2016 (25)	Granata, 2016 (24)	Eller, 2015 (23)	Eisele, 2014 (12)	Cheung, 2013 (21)
Study objective								
1	Was the hypothesis/aim/objective of the study clearly stated?	Partial	Yes	Partial	Yes	Yes	Yes	Yes
Study design								
2	Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Were the cases collected in more than one centre?	No	No	No	No	No	Unclear	No
4	Were patients recruited consecutively?	Unclear	Yes	Unclear	No	Yes	Unclear	Unclear
Study population								
5	Were the characteristics of the patients included in the study described?	Yes	Partial	Partial	Yes	Partial	Partial	Partial
6	Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Partial	Yes	Yes	Partial	Yes	Partial
7	Did patients enter the study at a similar point in the disease?	No	No	No	Yes	No	No	Unclear
Intervention and co-intervention								
8	Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Were additional interventions (co-interventions) clearly described?	Partial	No	Partial	No	Yes	Yes	Partial
Outcome measure								
10	Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Partial	No	Yes
11	Were outcome assessors blinded to the intervention that patients received?	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear
12	Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Y/N/Partial/Unclear		Fruhling, 2017 (20)	Distelmaier, 2017 (22)	Niessen, 2016 (25)	Granata, 2016 (24)	Eller, 2015 (23)	Eisele, 2014 (12)	Cheung, 2013 (21)
13	Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Statistical analysis								
14	Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Results and conclusions								
15	Was follow-up long enough for important events and outcomes to occur?	Yes	Unclear	Unclear	No	Yes	Yes	Unclear
16	Were losses to follow-up reported?	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
17	Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Partial	Partial	No	Partial
18	Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	No	Yes
19	Were the conclusions of the study supported by results?	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Competing interests and sources of support								
20	Were both competing interests and sources of support for the study reported?	Partial	Partial	Partial	Partial	Partial	Yes	Partial
Total		12/20	12/20	10/20	13/20	10/20	10/20	10/20
Overall risk of bias		Serious	Serious	Serious	Serious	Serious	Serious	Serious

Sources: (12, 20-25)

Table A 10. GRADE assessment of irreversible electroporation in pancreatic cancer (comparative study)

Quality assessment							Summary of findings					Importance
							Number of patients / Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IRE	Comparator	Relative (95% CI)	Absolute (95% CI)		
Effectiveness												
Success of the procedure												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		0	Not available	Not estimable	NA	Very low	Important
Overall survival												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[6]		10.03 months	9.3 months	HR 0.54 (p = 0.053)	NA	Very low	Critical
Overall survival at 3 months												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[7]		90.48 (95% CI: 67.0, 97.5)	Not available	Not estimable	NA	Very low	Critical
Overall survival at 6 months												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[6]		75.00 (95% CI 49.81,88.80)	Not available	Not estimable	NA	Very low	Critical
Overall survival at 12 months												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[6]		47.62 (95% CI 24.37,67.71	Not available	Not estimable	NA	Very low	Critical
Overall survival at 18 months												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[6]		13.61 (95% CI 2.33, 34.71	Not available	Not estimable	NA	Very low	Critical
Overall survival at 24 months: Not available												
Cancer specific survival: Not available												
Disease free survival: Not available												
Progression free survival: Not available												

Quality assessment							Summary of findings					Importance
							Number of patients / Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IRE	Comparator	Relative (95% CI)	Absolute (95% CI)		
Time to recurrence: Not available												
Time to progression: Not available												
Time to local recurrence: Not available												
Health related quality of life (Karnofsky Performance Status)												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[5]	Very serious[6]		81% of time after IRE KPS ≥70 (IQR: 65,98)	74% of time after IRE KPS ≥70 (IQR: 14,88)	Not available	NA	Very low	Critical
Pain: Not available												
Safety												
Intervention specific mortality												
1	Observational (matched analysis)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		0	Not available	Not estimable	NA	Very low	Critical
Major adverse events: Not available												
Minor adverse events: Not available												

[1] No randomization, patients received different adjuvant therapies, lack of information on patient selection, follow-up, and incomplete data from the control.
[2] Only one trial
[3] Heterogeneous treatments
[4] Small sample size
[5] Small sample size, no 95% CI available, p = 0.053
[6] Small sample size, wide CI
Abbreviations: HR = hazard ratio; IQR = interquartile range; IRE = irreversible electroporation; NA = applicable; KPS = Karnofsky Performance Status
Sources: (11)

Table A 11. GRADE assessment of irreversible electroporation in pancreatic cancer (single-arm studies)

Quality assessment							Summary of findings					Impor-tance
							Number of patients/ Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other con-siderations	Pre-IRE	Post-IRE	Relative (95% CI)	Absolute (95% CI)		
Effectiveness												
Success of the procedure												
1	Observational (single-arm)	Very serious[1]	NA (oonly one trial)	Very serious[2]	Very serious[4]		--	96.3%	Not estimable	NA	Very low	Important
Overall survival												
6	Observational (single-arm)	Very serious[1]	Very serious (highly variable: 4.3 vs 22.6)	Very serious[2]	Very serious[4]		--	4.3-22.6 months (Median)	Not estimable	NA	Very low	Critical
Overall survival at 3 months												
4	Observational (single-arm)	Very serious[1]	Not serious (95-100)	Very serious[2]	Very serious[4]		--	95%-100%	Not estimable	NA	Very low	Critical
Overall survival at 6 months												
4	Observational (single-arm)	Very serious[1]	Very serious (highly variable: 50 vs 100)	Very serious[2]	Serious[4]		--	50%-100%	Not estimable	NA	Very low	Critical
Overall survival at 12 months												
4	Observational (single-arm)	Very serious[1]	Very serious (highly variable: 20 vs 90)	Very serious[2]	Serious[4]		--	20%-90%	Not estimable	NA	Very low	Critical
Overall survival at 18 months: Not available												
Overall survival at 24 months												
1	Observational (single-arm)	Very serious[1]	NA[5]	Very serious[2]	Very serious[6]		--	37%	Not estimable	NA	Very low	Critical

Quality assessment							Summary of findings					Importance
							Number of patients/ Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-IRE	Post-IRE	Relative (95% CI)	Absolute (95% CI)		
Cancer specific survival: Not available												
Disease free survival: Not available												
Progression free survival												
3	Observational (single-arm)	Very serious[1]	Very serious (highly variable: 3.19 vs 15.4)	Very serious[2]	Serious[4]		--	3.19-15.4 months (median)	Not estimable	NA	Very low	Critical
Time to recurrence: NA												
Time to progression												
1	Observational (single-arm)	Very serious[1]	NA[5]	Very serious[2]	Very serious[4]		--	3.32 months (median)	Not estimable	NA	Very low	Critical
Time to local recurrence												
3	Observational (single-arm)	Very serious[1]	Serious (6.81 vs 12)	Very serious[2]	Serious[4]		--	6.81-12 months (median)	Not estimable	NA	Very low	Critical
Health related quality of life (QLQ C30/PAN26)												
2	Observational (single-arm)	Very serious[1]	Not serious	Very serious[2]	Very serious[3]			QoL decreased compared with baseline	Not estimable	NA	Very low	Critical
Pain												
2	Observational (single-arm)	Very serious[1]	Not serious	Very serious[2]	Very serious[3]			Pain increased compared with baseline	Not estimable	NA	Very low	Critical

Quality assessment							Summary of findings					Impor-tance
							Number of patients/ Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other con-siderations	Pre-IRE	Post-IRE	Relative (95% CI)	Absolute (95% CI)		
Safety												
Intervention specific mortality												
7	Observational (single-arm)	Very serious[1]	Not serious	Very serious[2]	Very serious[3]		0/226	0/226 (0%)	Not estimable	NA	Very low	Critical
Major adverse events												
7	Observational (single-arm)	Very serious[1]	Very serious (0% vs 50%)	Very serious[2]	Very serious[3]		0/226	44/226 (19.47%)	Not estimable	NA	Very low	Critical
Minor adverse events												
7	Observational (single-arm)	Very serious[1]	Very serious (10% vs 87.5%)	Very serious[2]	Very serious[3]		0/226	74/226 (32.74%)	Not estimable	NA	Very low	Important

[1] Single-arm studies, several bias and lack of information
[2] No control group
[3] Small sample size
[4] Small sample size in most studies, wide CI
[5] Only one trial
[6] Small sample size, no CI available
Abbreviations: IRE = irreversible electroporation; NA = applicable; QoL = quality of life.

Table A 12. GRADE assessment of irreversible electroporation in liver cancer (single-arm studies)

Quality assessment							Summary of findings					Importance
							Number of patients/Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consid-erations ations	Pre-IRE	Post-IRE	Relative (95% CI)	Absolute (95% CI)		
Effectiveness												
Success of the procedure: Not available												
Overall survival												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	37.92 months 95% CI: 30.28, 45.57)	Not estimable	NA	Very low	Critical
Overall survival at 3 months												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	96.67% (78.61, 99.52)	Not estimable	NA	Very low	Critical
Overall survival at 6 months												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	96.67% (78.61, 99.52)	Not estimable	NA	Very low	Critical
Overall survival at 12 months												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	89.76% (71.51, 96.58)	Not estimable	NA	Very low	Critical
Overall survival at 18 months												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	69.05% (48.93, 82.54)	Not estimable	NA	Very low	Critical
Overall survival at 24 months												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	65.21% (44.92, 79.58)	Not estimable	NA	Very low	Critical
Cancer specific survival: Not available												
Disease free survival: Not available												
Time to recurrence: Not available												

Quality assessment							Summary of findings					Importance
							Number of patients/Effect		Effect		Quality	
Number of studies	Study design	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other consid-erations ations	Pre-IRE	Post-IRE	Relative (95% CI)	Absolute (95% CI)		
Time to progression												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	15.6 months (median)	Not estimable	NA	Very low	Critical
Time to local recurrence												
1	Observational (single-arm)	Very serious[1]	NA[2]	Very serious[3]	Very serious[4]		--	15.5 months (mean)	Not estimable	NA	Very low	Critical
Health-related quality of life: Not available												
Pain: Not available												
Safety												
Intervention specific mortality												
6	Observational (single-arm)	Very serious[1]	Not serious	Very serious[3]	Very serious[4]		0/138	0/138 (0%)	Not estimable	NA	Very low	Critical
Major adverse events												
6	Observational (single-arm)	Very serious[1]	Very serious (0% vs 28.6%)	Very serious[3]	Very serious[4]		0/138	12/138 (8.7%)	Not estimable	NA	Very low	Critical
Minor adverse events												
5	Observational (single-arm)	Very serious[1]	Very serious (10% vs 100%)	Very serious[3]	Very serious[4]		0/124	41/124 (33.1%)	Not estimable	NA	Very low	Important

[1] Single-arm studies, several bias and lack of information
[2] Only one trial
[3] No control group
[4] Small sample size
Abbreviations: IRE = irreversible electroporation; NA = applicable; QoL = quality of life.

Applicability tables

Table A 13. Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Whilst irreversible electroporation (IRE) is intended to be used as the first line of treatment in histologically proven unresectable LAPC patients or patients with primary or secondary liver cancer that are not eligible for thermoablation. However, the enrolled population was highly heterogeneous in terms of theapplication of IRE. For LAPC, some studies restricted IRE to patients unresponsive to standard chemotherapy and/or radiochemotherapy treatment and others only applied this technique when patients had a favourable survival or when the disease did not progress after previous chemotherapy treatment. The majority of liver studies reported that patients had received several treatments before IRE, including surgical treatments, systematic therapy, radiofrequency/microwave ablation, brachytherapy, radiotherapy and transarterial chemoembolization, among others. These reduce the applicability of the evidence.
Intervention	The Nanoknife System was used in all studies but the treatment algorithm was inconsistent across studies. Some studies offered chemotherapy prior IRE others chemoradiotherapy or induction chemotherapy and chemoradiotherapy prior to IRE and in addition, several applied chemotherapy after IRE. Differences were also noted regarding the number of ablative sessions, imaging modalities and IRE technique, not existing a formal consensus regarding the considerations that should be taken into account in order to identify the tumours for who IRE might be more beneficial.
Comparators	The only one comparative study compared IRE for pancreatic cancer with some type of non-curative surgery, including exploratory laparotomy, non-radical resection, bypass surgery, cholecystectomy or percutaneous biopsy only. No more information regarding the comparator was given. There were no other comparative studies.
Outcomes	Included LAPC trials provided few relevant outcome data. Most studies reported on mean overall survival after IRE or time to local recurrence after IRE but these are not a valid outcome measures given that the time at which IRE was performed and the follow-up schemes varied greatly among studies. The definition of success of the procedure also differed among studies. With regard to complications/adverse events, it was often not stated over what time period they were reported. Some authors did not grade adverse events according to severity and the classification of IRE related complications was unclear in most of the studies. The follow-up period for these outcomes in some of the studies was commonly very short. Overall survival was not considered in most liver studies. Therefore, it was not possible to provide conclusions about safety or effectiveness of IRE.
Setting	Studies came from different countries from Europe and also from the United States, Asia and Australia. Therefore, there is no concern about the applicability of evidence related to this aspect. However, clinical settings were not described in the studies.

Abbreviations: IRE = Irreversible electroporation; LAPC = locally advanced pancreatic cancer, MWA = microwave ablation
Sources: Evidence retrieved for the effectiveness and safety domains.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A 14. Regulatory status

Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)
Europe	CE mark (Notified Body)	Yes	Cell membrane electroporation	-	March 10, 2010
Australia	The Therapeutic Goods Administration Australian Department of Health	Yes	Cell membrane electroporation	-	January 30, 2013
Canada	Health Canada	Yes	Cell membrane electroporation	-	May 29, 2009
China	National Medical Product Administration (formerly CFCA)	Yes	The intended use of this product is surgical ablation of liber and pancreatic cancer	-	June 18, 2015
Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	Yes	Cell membrane electroporation	-	June 16, 2016
Costa Rica	Ministry of Health	Yes	Cell membrane electroporation	-	June 14, 2016
Egypt	Egyptian Drug Authority	Yes	Cell membrane electroporation	-	February 12, 2013
Hong Kong	Medical Device Control Office (MDCO)	Yes	Cell membrane electroporation	-	October 17, 2014
Israel	Israeli Ministry of Health (AMAR)	Yes	Cell membrane electroporation	-	August 29, 2012
Mexico	Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)	Yes	Cell membrane electroporation	-	February 7, 2017
New Zealand	New Zealand Medicines and Medical Devices Safety Authority (Medsafe)	Yes	Cell membrane electroporation	-	November 17, 2014
Panama	Ministry of Health of the Republic of Panama	Yes	The Nanoknife system with six outputs is indicated for the surgical ablation of soft tiussue	-	May 5, 2018
Peru	General Directorate of Pharmaceuticals, Devices and Drugs	Yes	Cell membrane electroporation	-	March 22, 2017

Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)
Russia	Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (ROSZDRAVNADZOR)	Yes	Cell membrane electroporation	-	October 30, 2014
Saudi Arabia	Saudi Food and Drug Authority (SFDA)	Yes	Cell membrane electroporation	-	April 10, 2018
Singapore	Health Sciences Authority (HSA)	Yes	Cell membrane electroporation	-	October 19, 2016
South Korea	The Ministry of Food and Drug Safety (MFDS)	Yes	Cell membrane electroporation	-	May 24, 2013
Thailand	Food and Drug Administration of Thailand (Thailand FDA)	Yes	Cell membrane electroporation	-	August 21, 2017
United States of America	Food and Drug Administration (FDA)	Yes	The Nanoknife System with six outputs is indicated for the surgical ablation of soft tissue	-	November 21, 2006

Abbreviations: CE = Conformité Européenne; FDA = Food and Drug Administration
Sources: (26)

Table A 15. Summary of (reimbursement) recommendations in European countries for the technology

Country and issuing organisation e.g. G-BA, NICE	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
UK; NICE	Negative; research context only	
Germany; Ministry of Health	Positive coverage	2017 Pancreas G-DRG code (€): • H09B (9,686€) • H01B (16,320€) 2017 Liver G-DRG code (€): • H09B (9,686€) • H12B (5,398€)

Abbreviations: NICE = National Institute for Health and Care Excellence; UK = United Kingdom.
Sources:
Reimbursement Guide Irreversible Electroporation for Liver and Pancreas. Angiodyamics, Inc. Published January 2017.
Germany Ministry of Health, G-DRG System 2017.

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2	**Organisational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
	Introduction of IRE could require some organisational changes as it is required the device and the training for the staff, and leads to increased costs	
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the MAH/manufacturer(s) (fact check), as well as responses from authors, is available on the EUnetHTA website.