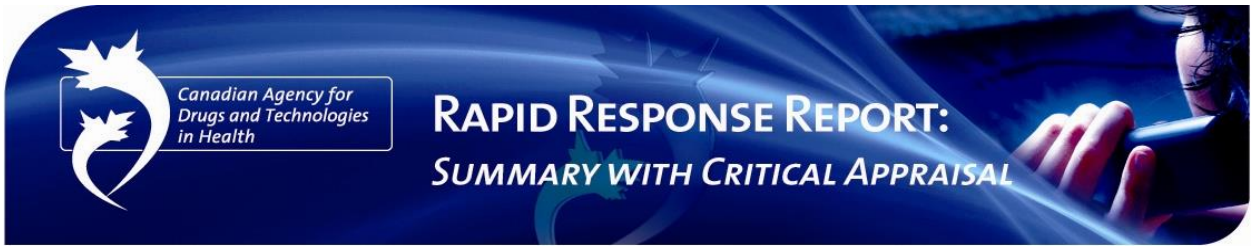


TITLE: Irreversible Electroporation for Tumors of the Pancreas or Liver: A Review of Clinical and Cost-Effectiveness

DATE: 10 February 2016

CONTEXT AND POLICY ISSUES

Pancreatic cancer is an aggressive cancer with a world-wide one-year survival rate of 27% and a 6% five-year survival rate.[1] According to the Canadian Cancer Society, in 2015 approximately 4,800 Canadians were expected to be diagnosed with pancreatic cancer and 4,600 were expected to die from it.[2] When pancreatic cancer is diagnosed, approximately 10% present with local disease that is considered resectable, 50% present with metastatic disease, and 40% present with local disease that is considered surgically unresectable (for reasons such as proximity to or encasement of a major blood vessel).[1] For patients who are considered surgically unresectable, treatment options include chemotherapy, radiotherapy, chemoradiation, and ablative techniques.[1]

Hepatocellular carcinoma (HCC) is one of the most common types of cancer worldwide.[3] Along with liver metastases and recurrent cholangiocarcinoma, patients with hepatic tumors represent an important percentage of the population with cancer. Approximately 70% to 80% of liver metastases are considered unresectable due to location, limited functional reserve, or comorbidities.[4]

Irreversible electroporation (IRE) is a non-thermal ablation technique that allows tissue ablation without the potential detrimental heat-effects on tissue surrounding the tumor. It delivers short electrical pulses to the tumor with the aim of destroying the cancerous tissue while sparing surrounding tissue.[5] IRE can be performed percutaneously, laparoscopically, or as part of open surgery[1] and requires imaging guidance with computed tomography, magnetic resonance imaging, or ultrasound. Currently, NanoKnife is the only IRE device available for use in Canada.[6]

Due to the high toxicity and poor outcomes associated with chemotherapy options, ablative therapies, such as IRE, are becoming more popular in palliative care for unresectable tumors, however, their effectiveness on cancer outcomes and adverse events are unclear. Additionally, it is unclear as to what role IRE may play in the treatment of resectable tumors. IRE requires the

purchase of a device and requires training, thus the cost-effectiveness is also a factor when considering whether or not to bring the technology into use. The current review seeks to determine the clinical effectiveness, safety, and cost-effectiveness of IRE for the treatment of patients with resectable and unresectable pancreatic or liver tumors.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of irreversible electroporation (IRE) in patients with tumors of the pancreas or liver?

2. What is the cost-effectiveness of irreversible electroporation (IRE) in patients with tumors of the pancreas or liver?

KEY FINDINGS

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

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2011 and Jan 13, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients with tumors of the pancreas or liver. Tumors can be benign, malignant, primary, metastatic, resectable, or unresectable.
Intervention	Irreversible electroporation (IRE)
Comparator	Any or none
Outcomes	Q1: Progression-free survival, measurable response rate, procedure-related complications, other adverse events or toxicities Q2: Cost-effectiveness
Study Designs	Health technology assessment, systematic review, meta-analysis, economic evaluations, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, were clinical studies that had been reviewed in an included systematic review, were systematic reviews that only reviewed citations that were included in other included SRs, or were published prior to 2011. Studies were not included if they did not report a patient-related outcome. Due to the number of studies identified, case series were not considered for inclusion as they are considered to be low quality evidence.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR)[7] and non-randomized studies were critically appraised using the Downs and Black checklist.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 207 citations were identified in the literature search. Following screening of titles and abstracts, 170 citations were excluded and 37 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 24 publications were excluded for various reasons, while 16 publications (two of which reported on the same study) met the inclusion criteria and were included in this report. Appendix 1 shows the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design

Pancreatic Tumors

Two of the included studies[9,10] were systematic reviews. The Rombouts SR[10] reviewed four non-randomized studies that included patients with pancreatic tumors and the Scheffer SR[9]

reviewed non-randomized studies of patients with pancreatic cancer and patients with liver cancer; four of the studies were in patients with pancreatic cancer.

Five of the included primary studies examined patients with pancreatic tumors.[11-15] Three of the studies[11-13] were prospective before and after studies without a control group and two of the studies were retrospective before and after studies without a control group.[14,15]

No relevant economic studies were identified.

Liver Tumors

One of the included SRs reviewed studies of patients with either liver or pancreatic cancer,[9] eight of which included patients with liver cancer.

Nine of the included citations describing eight studies examined patients with liver cancer.[11,16-23] Six citations describing five studies were prospective before and after studies without a control group[11,16-20] and three[21-23] were retrospective before and after studies without a control group.

Country of Origin

Pancreatic Tumors

Both of the systematic reviews that examined studies of patients with pancreatic cancer were conducted in the Netherlands.[9,10] Two of the primary studies were conducted in Italy[11,13] and three in the United States.[12,14,15]

Liver Tumors

The systematic review that included studies of patients with liver cancer (along with studies in patients with pancreatic cancer) was conducted in the Netherlands.[9] Six of the included primary studies were conducted in Germany,[16,17,19,22-24] one in Japan,[20] one in the Netherlands,[18] and one in the United States.[21]

Patient Population

Pancreatic Tumors

All of the studies included patients with locally advanced pancreatic cancer (LAPC).[10-15] The SRs examined the results of 141[10] and 69[9] patients included in the various studies. The number of included patients in the primary studies ranged from ten[13] to 200.[14] Mean and median ages ranged from 62[14] to 69.2 years[11] and the percentage of male participants ranged from 40%[13] to 58.5%.[12] Patients in all studies either received chemotherapy and/or radiation therapy prior to or in conjunction with IRE.

Liver Tumors

The systematic review included 129 patients with hepatocellular carcinoma (HCC), colorectal liver metastases (CRLM), or other liver tumors,[9] and the median age of the patients included in the SR studies ranged from 51 to 65. The number of included patients in the primary studies ranged from five[20] to 52.[22] Mean and median ages ranged from 61[22] to 66.6[20] and the

percentage of male participants ranged from 40[18] to 82%[23] The percentage of male participants ranged from 40%[18] to 82%,[15] and one study did not report the percentages of male or female participants.[21]

Interventions and Comparators

Pancreatic Tumors

All of the studies performed IRE using the NanoKnife. The systematic reviews included studies that used open, percutaneous, and laparoscopic approaches to IRE.[9,10] One of the included primary studies used a percutaneous approach,[11] one used a laparoscopic approach,[13] and two used an open surgical approach.[14,15] The approach was unclear in one study, but as most of the IRE procedures were done in conjunction with an operative procedure, it is likely the open approach was used.[12]

Liver Tumors

All of the included studies performed IRE using the NanoKnife. The systematic review included studies that used open, percutaneous, and laparoscopic approaches to IRE.[9] Six of the included primary studies used a percutaneous approach,[16,20-24] and one used a laparoscopic approach.[18] One study included patients who underwent open, laparoscopic, or percutaneous IRE.[19]

Outcomes

Pancreatic Tumors

The included studies reported survival outcomes, complications, and outcomes related to disease response and progression. More specifically:

- seven studies reported general adverse events or complications,[10-15,25]
- one reported IRE related adverse events or complications,[10]
- four reported overall mortality,[9-12]
- one reported IRE related mortality,[10]
- one reported disease progression,[9]
- two reported disease recurrence following IRE,[12,14]
- two reported tumor response to IRE[13,15]
- one reported progression-free survival,[14]
- one reported change in tumor volume.[11]

Liver Tumors

Similarly, the studies examining liver tumors also reported survival outcomes, complications, and outcomes related to disease response and progression. More specifically:

- eight studies reported general adverse events or complications[9,18-24]
- four reported IRE related complications or adverse events[9,16,18,23]
- two studies reported mortality[9,21]
- one studies reported disease progression[9]
- two reported disease recurrence following IRE[19,24]
- two reported tumor response to IRE.[16,20]

Additional information regarding study and patient characteristics is reported in Appendix 2.

No relevant economic studies were identified, however, four studies[13-15,19] reported length of hospitalization. This information is reported in Appendix 4.

Summary of Critical Appraisal

The authors of the two included systematic reviews[9,10] both reported that they conducted the review according to PRISMA guidelines, and while it is assumed that this was followed, neither reported an a priori design in the text. Rombouts et al. reported that two authors performed selection of articles, but they did not report two authors performing data extraction or critical appraisal. There was no mention of critical appraisal at all, so it is unclear if it was done or if study quality was considered in the conclusions.[10] Scheffer et al.[9] did not mention double screening, extraction, or quality appraisal. Although the database searches were comprehensive for both SRs, it was unclear if the Rombouts review included a grey literature search.[9] Although that may normally pose a potential risk for publication bias, the Scheffer review[9] was conducted in a similar time period, searched the grey literature, and did not find any relevant inclusions from the grey literature. The authors of both SRs did not perform a meta-analysis, however complication rates were combined to aggregate the results. It is unclear if this was the least biased approach, however the authors did discuss the limitations of their reviews. None of the included studies in the SRs used a design that included a comparator group, thus the results are only descriptive and not comparative.[9,10] Additionally, Scheffer et al.[9] considered most of the results of the included studies together, as opposed to separating the results based on the surgical approach, it was therefore difficult to determine whether the type of surgery (open, laparoscopic, or percutaneous) was taken into account. As open surgeries are generally more lengthy and are often associated with more adverse events when compared with less invasive approaches, this may not have been an appropriate choice. Rombouts et al.[10] considered outcomes together as well as separated by surgical approach and did differentiate between open and percutaneous approaches in their conclusions.

None of the included primary studies randomized patients to interventions, had a comparator group, or attempted blinding of study participants or staff. Thus, the results of all of the included studies are descriptive and are not indicative of comparative results. Additionally, due to the lack of blinding, it is possible that patients or staff could be biased toward new technology.

Most of the included studies clearly reported the interventions, methods, and characteristics of patients,[11-16,18,19,22-24] though Sugimoto[20] and Hosein[21] did not report a description of the 5 and 29 patients who participated in their studies. Although a patient was recruited to replace the patient who could not receive IRE in the Eisele study,[19] the characteristics of the patient who did not receive IRE were not well reported. Compliance with IRE was reliable in all studies.[11]

The Scheffer et al. primary study[18] included a population that was 60% female. As liver cancer is more prevalent in men than women (the Canadian Cancer society statistics suggest that 75% of those diagnosed with liver cancer in 2016 will be men), this sample was likely not representative of the general population with liver cancer. Eller et al. included a population that was 79% male – while liver cancer is indeed more prevalent in men, women were likely underrepresented in the sample. While pancreatic cancer tends to be more prevalent in men in other countries (American men are 30% more likely to get pancreatic cancer than their female counterparts[26]), Canadian statistics suggest a more even distribution between the sexes[2] and

thus the 50/50 sex representation in the Belfiore study[11] may be representative of the Canadian population with pancreatic cancer.

The included studies for both liver and pancreatic cancer examined patients with either unresectable primary cancers or unresectable metastatic cancer (one study also included patients with borderline resectable cancers)[15] The patient populations were generally similar and the results are likely generalizable to the general population of patients with unresectable liver and pancreatic cancers.

Further detail regarding critical appraisal is available in Appendix 3.

Summary of Findings

What is the clinical effectiveness and safety of irreversible electroporation (IRE) in patients with tumors of the pancreas or liver?

Pancreatic Tumors

IRE Efficacy, Disease Progression, Survival

In the Rombouts SR,[10] one study of patients receiving open surgery IRE (n = 54 patients) reported that IRE increased survival from an average of 11 months to an average of 20 months. These patients received IRE following unresectability and received IRE in conjunction with palliative bypass (where indicated) and chemotherapy. In the study using percutaneous IRE, the 6-month overall survival was 70% though patients with metastatic disease showed no improvement in survival following IRE and died "soon after the IRE procedure."[10] In the Scheffer SR,[9] one study compared IRE patients to propensity score matched chemo-radiation patients. IRE was associated with improved local (14 months versus 6 months, *P* = 0.01), distant (15 months versus 9 months, *P* = 0.02), and overall survival (20 months versus 13 months, *P* = 0.03). After 20 months, there was no difference in survival between the groups.

Mean survival ranged from 7.5 months (range: 2.9 to 15.9) in the Paiella study (N = 10)[13] to 12.95 months (95% Confidence Interval [CI] 11.57 to 14.33) the Belfiore study (N = 20).[11] Median survival from the day of IRE was 12.03 months (95 CI, 7.71 to 23.12 months) in the Kluger study[12] 22 months (95% CI, 17.9 to 24.9) in the Kwon study[15] and 24.9 months (range: 12.4 to 85 months) in the Martin study.[14] Historical data on chemotherapy and chemoradiotherapy options reported by Martin et al.[14] show a median survival of approximately 12 months.

Two studies reported median progression free survival; 11 months (95% CI, 3 to 10) in the Kwon study,[15] 12.4 months (range: 4.4 to 8.9) in the Martin study.[14]

Overall recurrence rate ranged from 29% in the Martin study[14] 58% in the Kluger study[12] The Local disease control at the last available follow-up (range 6 to 14 months) was reported in all living patients (18/20) in the Belfiore study.[11]

Complications and Adverse Events

The Rombouts systematic review[10] reported an overall complication rate of 48% (in 4 studies), with open surgeries having a complication rate of 51% and percutaneous approaches having a

rate of 27%. Two studies reported complications that were specifically judged to be IRE-related; the IRE-related complication rate was 13% (15% in open, 9% in percutaneous surgery) and the morbidities included duodenal leakage, pancreatic leakage, bile leakage, and (progression of) portal vein thrombosis.[10] The Scheffer SR[9] reported an IRE-related complication rate of 19%, with 7% of the IRE-related complications being classified as "major". The authors noted that one study reported general adverse events that were not considered IRE-related but did not describe them in the review.[9]

No major complications were reported in four of the primary studies.[11,13-15] The overall rates of minor complications (mostly gastrointestinal) ranged from 10%[11] to 40%.[14] Major morbidities (e.g. gastrointestinal bleeding, deep surgical site infection, need for stent placement) were reported in one study;[12] the rate of major morbidities was 19%, 44% of which were thought to be IRE-related. Minor IRE-related complication rates were reported in one study; 11% of patients (n = 5) had a complication thought to be IRE-related two of the evets were bleeding events.[15]

Mortality

The overall mortality rate (based on the 4 included studies) reported in the Rombouts SR[10] was 3% (2% in open, 9% in percutaneous surgery) and the IRE-related mortality (reported in 4 studies) was 2% (3% in open, 0% in percutaneous surgery). The Scheffer SR reported no periprocedural deaths, one possible IRE-related death (a rate of 2.3%) and three deaths (N = 43) in the three months following IRE for pancreatic tumors. The cause of these deaths was not reported but they were not attributed to IRE.

None of the included primary studies reported procedure-related mortality. In the Belfiore study (N = 20),[11] two patients died 3- and 4-months after IRE due to disease progression and all patients died in the Paiella study[13] (nine from advanced disease and one from septic shock that was related to ulcerative colitis and not IRE). Median postoperative mortality in the Kluger study[12] was 26 days (interquartile range 8 to 42 days). No patients had died at the 90-day follow up in the Kwon study[15] and the Martin study[14] reported progression free survival, which was included in the section on disease progression.

Liver Tumors

IRE Efficacy, Disease Progression, Survival

The Shaffer SR reported six to 18 month efficacy data for 106 patients in five studies.[9] Primary efficacy (defined as percentage of tumors successfully eradicated after the initial procedure based on follow-up imaging after 3 months) ranged from 67% to 100% and secondary efficacy (defined as successful tumor eradication 6 months after the first treatment) ranged from 55% to 93%.

Tumor control or response rate (generally defined as no tumor recurrence or tumor growth) at the final follow-up was reported in two studies and ranged from 71.4%[24] to 83.3%.[20] Complete response ranged from 18%[21] to 91.7%[16] and partial response 8.3%[16] to 18%[21] in the two studies that reported it. Overall recurrence rate was reported as 38% in the Eisele study.[19]

Overall and 2-year progression free survival was reported as 4.0 months (95%CI 1.4 to 6.6) and 18% (95% CI, 0% to 35%) in the Hosein study.[21]

Complications and Adverse Events

No serious IRE-related adverse events were reported in the Scheffer SR.[9] Both the total and IRE-related complication rates were reported as 16%, 6% of which were stenosis or occlusion of portal vessels or bile ducts.

IRE-related adverse events were reported in 2 of 24 patients in the Granata study,[16,17] neither of which were considered major and one IRE-related event (ventricular extrasystoles without haemodynamic changes) was reported in the Scheffer study.[18] In two patients in two studies, the IRE procedure either had to be prematurely halted (due to bleeding)[24] or could not be performed due to pre-operative complications.[21] Overall complication rate was reported in one study; 18.8% in the Dollinger study.[22] Major adverse events were reported in two studies and ranged from 8%[22] to 28.5%.[24]

Mortality

Mortality was not reported for liver cancer patients in the Schaffer SR.[9] It was not clear if there were no mortalities in the included studies or if the authors did not report them. No treatment related mortalities[16,18-24] occurred in the primary studies.

Further detail regarding the clinical effectiveness and safety reported in the included studies is available in Appendix 4.

What is the cost-effectiveness of irreversible electroporation (IRE) in patients with tumors of the pancreas or liver?

No relevant cost-effectiveness or economic studies were identified.

Limitations

Although 15 studies were included in this review, the majority of the data is based on small, uncontrolled studies that were designed to demonstrate feasibility and early safety of the IRE procedure. The two systematic reviews included case series and case studies and the included primary studies did not include a comparator group. The results of this review are therefore descriptive and no conclusions can be made regarding the comparative efficacy of the IRE procedure versus other procedures or standard care.

The majority of the studies of patients with liver tumors included patients with tumors that were ≤ 3 centimeters (cm), thus the results are likely not generalizable to patients with larger tumors. Tumor sizes in the studies of patients with pancreatic cancer ranged from just under 3 cm to ≤ 6 cm, thus the results may be more generalizable to patients with various sizes of tumors.

In almost all of the included studies, the patients had either previously or were concurrently receiving chemotherapy, radiation therapy, or chemoradiation in order to treat their cancers. It is therefore difficult to determine whether tumor response or absence of disease progression was due to the IRE procedure alone. Additionally most studies examined the use of IRE in unresectable tumors, thus it is unclear whether results could generalize to patients with resectable tumors or if IRE is a treatment option for patients with resectable tumors.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

IRE seems to be a reasonably feasible and safe procedure for patients with unresectable or borderline resectable liver and pancreatic tumors. The percutaneous approach may result in less morbidity than the open approach. The efficacy of IRE is unclear. For liver tumors, it seems to be more successful for tumors ≤ 3 cm that are not suitable for resection or thermal ablation. IRE may also be helpful for improving short-term local control and the survival of patients with pancreatic tumors, however, the results on all patients should be interpreted with caution. The results are based on data from small studies with no control group. The majority of authors expressed the need for larger, controlled trials. For resectable tumors, resection seems to remain the gold standard as it is unclear what role IRE may play for these patients.

More research is needed before making firm conclusions regarding the effectiveness of IRE for patient with pancreatic of liver tumors. This is consistent with 2013 guidance from the National Institutes for Health and Care Excellence on IRE for the treatment of both pancreatic[27] and liver[28] tumors.

No conclusions can be made regarding the cost-effectiveness of IRE due to the lack of available evidence.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Young SJ. Irreversible electroporation and the pancreas: What we know and where we are going? World J Gastrointest Surg [Internet]. 2015 Aug 27 [cited 2016 Jan 15];7(8):138-44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4550840/pdf/WJGS-7-138.pdf

2. Pancreatic cancer statistics [Internet]. Toronto: Canadian Cancer Society; 2016. [cited 2016 Feb 8]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/pancreatic/statistics/?region=on

3. Cheung W, Kavnoudias H, Roberts S, Szkandera B, Kemp W, Thomson KR. Irreversible electroporation for unresectable hepatocellular carcinoma: initial experience and review of safety and outcomes. Technol Cancer Res Treat. 2013 Jun;12(3):233-41.

4. Silk MT, Wimmer T, Lee KS, Srimathveeravalli G, Brown KT, Kingham PT, et al. Percutaneous ablation of peribiliary tumors with irreversible electroporation. J Vasc Interv Radiol. 2014 Jan;25(1):112-8.

5. NICE [Internet]. London: National Institute for Health Care and Excellence. Liver cancers: Individual research recommendation details, recommendation ID IPG445/1; 2013 Feb [cited 2016 Feb 2]. Available from: http://www.nice.org.uk/researchrecommendation/current-evidence-on-the-safety-and-efficacy-of-irreversible-electroporation-for-treating-liver-metastases-is-inadequate-in-quantity-and-quality-therefore-this-procedure-should-only-be-used-in-the-context-of-research-in-particular-studies-should-report-the Comes from guidance "Irreversible electroporation for treating liver metastases".

6. NanoKnife system (AngioDynamics, Inc.) for treating liver cancer [Internet]. Plymouth Meeting (PA): ECRI Institute; 2016. [cited 2016 Feb 9]. Available from: www.ecri.org Subscription required.

7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2016 Feb 2];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2016 Feb 2];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

9. Scheffer HJ, Nielsen K, de Jong MC, van Tilborg AA, Vieveen JM, Bouwman AR, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol. 2014 Jul;25(7):997-1011.

10. Rombouts SJ, Vogel JA, van Santvoort HC, van Lienden KP, van HR, Busch OR, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. Br J Surg. 2015 Feb;102(3):182-93.

11. Belfiore MP, Ronza FM, Romano F, Ianniello GP, De Lucia G, Gallo C, et al. Percutaneous CT-guided irreversible electroporation followed by chemotherapy as a novel neoadjuvant protocol in locally advanced pancreatic cancer: Our preliminary experience. Int J Surg. 2015 Sep;21 Suppl 1:S34-S39.

12. Kluger MD, Epelboym I, Schrope BA, Mahendraraj K, Hecht EM, Susman J, et al. Single-Institution Experience with Irreversible Electroporation for T4 Pancreatic Cancer: First 50 Patients. Ann Surg Oncol. 2015 Dec 29.

13. Paiella S, Butturini G, Frigerio I, Salvia R, Armatura G, Bacchion M, et al. Safety and feasibility of Irreversible Electroporation (IRE) in patients with locally advanced pancreatic cancer: results of a prospective study. Dig Surg. 2015;32(2):90-7.

14. Martin RC, Kwon D, Chalikonda S, Sellers M, Kotz E, Scoggins C, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg. 2015 Sep;262(3):486-94.

15. Kwon D, McFarland K, Velanovich V, Martin RC. Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation. Surgery. 2014 Oct;156(4):910-20.

16. Granata V, de Lutio di Castelguidone E, Fusco R, Catalano O, Piccirillo M, Palaia R, et al. Irreversible electroporation of hepatocellular carcinoma: preliminary report on the diagnostic accuracy of magnetic resonance, computer tomography, and contrast-enhanced ultrasound in evaluation of the ablated area. Radiol Med. 2015 Sep 7.

17. Granata V, Fusco R, Catalano O, Piccirillo M, De Bellis M, Izzo F, et al. Percutaneous ablation therapy of hepatocellular carcinoma with irreversible electroporation: MRI findings. AJR Am J Roentgenol. 2015 May;204(5):1000-7.

18. Scheffer HJ, Nielsen K, van Tilborg AA, Vieveen JM, Bouwman RA, Kazemier G, et al. Ablation of colorectal liver metastases by irreversible electroporation: results of the COLDFIRE-I ablate-and-resect study. Eur Radiol. 2014 Oct;24(10):2467-75.

19. Eisele RM, Chopra SS, Glanemann M, Gebauer B. Risk of local failure after ultrasound guided irreversible electroporation of malignant liver tumors. Interv Med Appl Sci [Internet]. 2014 Dec [cited 2016 Jan 15];6(4):147-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4274353/pdf/IMAS-06-147.pdf

20. Sugimoto K, Moriyasu F, Kobayashi Y, Saito K, Takeuchi H, Ogawa S, et al. Irreversible electroporation for nonthermal tumor ablation in patients with hepatocellular carcinoma: initial clinical experience in Japan. Jpn J Radiol. 2015 Jul;33(7):424-32.

21. Hosein PJ, Echenique A, Loaiza-Bonilla A, Froud T, Barbery K, Rocha Lima CM, et al. Percutaneous irreversible electroporation for the treatment of colorectal cancer liver metastases with a proposal for a new response evaluation system. J Vasc Interv Radiol. 2014 Aug;25(8):1233-9.

22. Dollinger M, Beyer LP, Haimerl M, Niessen C, Jung EM, Zeman F, et al. Adverse effects of irreversible electroporation of malignant liver tumors under CT fluoroscopic guidance: a single-center experience. Diagn Interv Radiol [Internet]. 2015 Nov [cited 2016 Jan 15];21(6):471-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4622394/pdf/dir-21-6-471.pdf

23. Dollinger M, Jung EM, Beyer L, Niessen C, Scheer F, Muller-Wille R, et al. Irreversible electroporation ablation of malignant hepatic tumors: subacute and follow-up CT appearance of ablation zones. J Vasc Interv Radiol. 2014 Oct;25(10):1589-94.

24. Eller A, Schmid A, Schmidt J, May M, Brand M, Saake M, et al. Local control of perivascular malignant liver lesions using percutaneous irreversible electroporation: initial experiences. Cardiovasc Intervent Radiol. 2015 Feb;38(1):152-9.

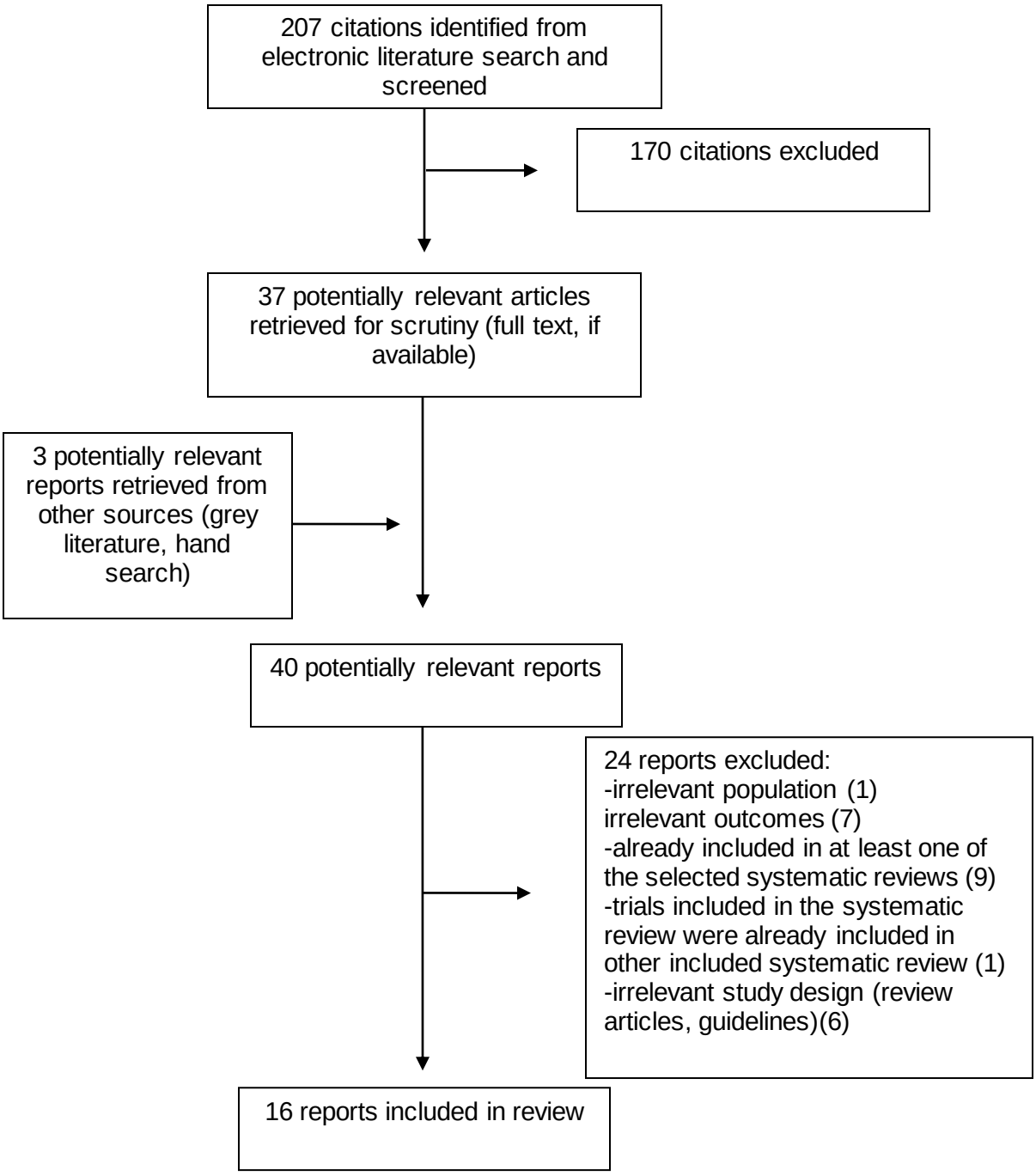
25. Akinwande O, Ahmad SS, Van Meter T, Schulz B, Martin RC. CT Findings of Patients Treated with Irreversible Electroporation for Locally Advanced Pancreatic Cancer. J Oncol [Internet]. 2015 [cited 2016 Jan 15];2015:680319. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4651710

26. Pancreatic cancer [Internet]. Atlanta (GA): American Cancer Society; 2016 Jan 9. [cited 2016 Feb 8]. Available from: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-risk-factors

27. Irreversible electroporation for treating pancreatic cancer [Internet]. London: National Institute for Health Care and Excellence; 2013 Feb 23. [cited 2016 Feb 2]. (NICE Interventional procedure guidance; no. 442). Available from: https://www.nice.org.uk/guidance/ipg442/resources/irreversible-electroporation-for-treating-pancreatic-cancer-1899869746651333

28. Irreversible electroporation for treating liver metastases [Internet]. London: National Institute for Health Care and Excellence; 2010 Nov 8. [cited 2016 Feb 2]. (NICE Interventional procedure guidance; no. 445). Available from: https://www.nice.org.uk/guidance/ipg445/resources/irreversible-electroporation-for-treating-liver-metastases-1899869751690181

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Rombouts et. al., 2015, Netherlands[10]	Other therapies were also included, but 4 studies (3 prospective cohorts and 1 retrospective cohort) examining IRE were included.	Patients with LAPC	Open IRE using the NanoKnife (3 studies, 130 patients) Percutaneous IRE using the NanoKnife (1 study, 11 patients)	None	Overall complications, IRE related complications, overall mortality, IRE related mortality, median survival. Follow-up not reported however, median survival indicates from 6 to 20 months.
Scheffer, 2014, The Netherlands[9]	Liver tumors: 8 studies (1 prospective observational, 1 retrospective comparative, 3 retrospective observational, 3 case reports)* Pancreatic tumors: 4 studies (1 prospective comparative, 1 prospective observational, 1 retrospective observational, 1 case report)* Other tumors:	Patients with liver tumors (HCC = 49 patients; colorectal liver metastases = 57; other = 23) Patients with pancreatic adenocarcinoma (pancreatic head = 41 patients; body/tail = 27; uncinated process = 1) (23 patients with other tumors also included but not relevant to the current review) Median age ranged from 51	Open IRE (4 studies, 115 patients) Laparoscopic IRE (2 studies, 4 patients) Percutaneous IRE (9 studies, 93 patients)	No IRE No comparator	Morbidity Mortality Disease progression

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
	2 studies not relevant to the current review	to 65 for liver cancer and 57 to 78 for pancreatic cancer.			

CT = computed tomography; IRE = irreversible electroporation; LAPC = locally advanced pancreatic cancer;
* As reported by the SR authors; not enough information was provided to classify any differently

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Pancreatic Cancer					
Belfiore, 2015, Italy[11]	Prospective, non-comparative, before and after.	20 patients with LAPC; mean age 69.2 years (range 55 to 82) 50% male lesions ≤ 6 cm	IRE with NanoKnife (percutaneous, CT guided) All patients also received chemotherapy	None	Complications, mortality, change in lesion volume.
Kluger, 2015, USA[12]	Prospective non-comparative before and after	53 patients with LAPC; n = 29 primary, n = 24 margin extension median age: 66.5 (IQR 60.2 to 72.0) 58.5% male median tumor size: 3.0 cm (IQR 1.7 to 5.0)	IRE with NanoKnife (all patients also received chemotherapy and/or radiation)	None	Primary: 90 day Clavien–Dindo complications Secondary: survival, recurrence
Martin, 2015, USA[14]	Retrospective database review	Patients with LAPC who had been treated with chemotherapy, chemoradiation, or both. (N =	IRE with NanoKnife performed during resection. IRE with	None	Recurrence using RECIST criteria Adverse events

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
		200) median age 62 years (range: 27 to 88) 50% male median tumor size: 2.8 cm (longest axis) 62% white, low Charleston comorbidity index, low frailty index.	NanoKnife performed alone (unresectable patients) All IRE procedures were open surgery. n = 50 patients had IRE for margin extension n = 150 patients in situ		Progression-free survival
Paiella, 2015, Italy[13]	Prospective, non-comparative, before and after	10 patients with unresectable, non- metastatic, LAPC mean age 66 years 40% male Tumor size <4 cm mean follow up: 7.6 months	IRE with NanoKnife	None	Complications AEs Response (RECIST criteria)
Kwon, 2014, USA[15]	Retrospective, non-comparative, database review	48 patients with borderline resectable or LAPC. Median age: 61 (range 27 to 81) 54% male mean tumor size: 3.5 cm	IRE with NanoKnife (open surgery) patients were treated initially with chemotherapy and chemoradiation	None	Complications 90 day response (RECIST criteria)

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Liver Cancer					
Dollinger, 2015, Germany[22]	Retrospective database review	Patients with non-resectable liver tumors that were not suitable for thermal ablation. N = 52 (n = 28 with primary tumors; n = 28 with secondary tumors) 75% male median age 61 years (range, 22 to 81 years)	IRE with NanoKnife (percutaneous) median number of IRE sessions per patient was 1 (range, 1 to 4). median procedure time 172 min (range, 55 to 561 min	None	Complications
Eller, 2015,Germany[24]	Prospective, non-comparative before and after	14 patients with liver cancer (3 with HCC and 11 with hepatic metastases 86% male mean age: 58 SD 11 years	IRE with NanoKnife (percutaneous)	None	Adverse Events Recurrence
Granata, 2015, Italy[16,17]	Prospective , non-comparative before and after (non-consecutive sample)	Patients with unresectable HCC (N = 20) Tumor size ≤3 cm 60% male mean age: 65 (range 48 to 80)	IRE (percutaneous) all patients underwent imaging for monitoring	None	Response as determined by imaging and RECIST guidelines.
Sugimoto, 2015, Japan[20]	Prospective, non-comparative, before and after.	5 patients with unresectable HCC. 60% male mean age 66.6 years ± 5.8	IRE using NanoKnife (percutaneous)	None	Tumor response Safety

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Eisele, 2014, Germany[19]	Prospective, non-comparative, before and after.	14 patients with liver tumors (HCC, CRLM, CCC) 69% male mean age 63 years	IRE using NanoKnife (percutaneous n = 7; lapaproscopic n = 4; open surgery n = 2)	None	Recurrence Adverse events
Dollinger, 2014, Germany[23]	Retrospective, non-comparative review	34 patients (with 52 tumors; 30 primary tumors, 22 hepatic metasteses) 82% male mean age 64 years (range 22 to 80)	IRE with NanoKnife (percutaneous)	None	Adverse events
Scheffer, 2014, Netherlands,[18] COLDFIRE-I	Prospective, non-comparative, before and after.	10 patients with CRLM 40% male mean age: 63 (49 to 74) 2 patients had not received systemic chemotherapy lesion size: 2.4 cm (0.8 to 5.3)	IRE with NanoKnife (laparoscopic)	None	Adverse events
Hosein, 2014, USA[21]	Retrospective non-comparative, before and after	29 patients with CRLM unresectable (70% had IRE as a sole modality of treatment, 20% as part of multi-modal treatment, 10% as palliative treatment)	IRE with NanoKnife (percutaneous)	None	Survival Complications

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
		median age: 62 years			

CCC = recurrent cholangiocarcinoma; CRLM = colorectal liver metastases; HCC = hepatocellular carcinoma; IQR = interquartile range; IRE = irreversible electroporation; LAPC = locally advanced pancreatic cancer; min = minutes; RECIST = response evaluation criteria in solid tumors

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[7]	
Strengths	**Limitations**
Rombouts[10]	
• A comprehensive database literature search was performed – information regarding multiple databases, search terms, and search dates were provided. • Included studies are listed, characteristics are provided. • Details of critical appraisal provided in supplemental documents. • The limitations of the studies were discussed in the context of the results of the review. • The authors did not use meta-analysis to combine the results of the studies on IRE – this was appropriate due to the heterogeneity of the studies. • Conflict of interest statement was presented.	• A priori design, two authors performing data extraction (or double checking), and two authors performing (or double checking) critical appraisal were not reported in the text. This, however, may be only a lack of reporting, as the authors indicated that the SR was performed according to PRISMA guidelines. • It is unlikely that grey literature was included; the flow chart of study selection does not have a spot for grey literature. • List of excluded studies not provided. • Assessment of publication bias was not mentioned, however, there were fewer than 10 IRE studies therefore it is not appropriate to assess.
Scheffer[9]	
• Two reviewers independently conducted study selection, data extraction, and quality assessment. • Comprehensive literature review performed; databases listed, search date reported. • Grey literature not referred to by name but literature from “alternative sources” was considered for inclusion. • Included studies are listed, the majority of study characteristics are provided. • Scientific quality is assessed and used appropriately in forming conclusions. • No meta-analysis was performed, this was appropriate given heterogeneity and study type. • Conflict of interest statement is provided.	• A priori design not reported, however authors stated that the review was conducted according to PRISMA. • List of excluded studies no provided. • No diagram of possible publication bias was presented, however, the authors do mention that publication bias could have occurred. • Outcomes were not well described – “local” and “distant” progression were not clearly defined.

IRE = irreversible electroporation; PRISMA = preferred reporting items for systematic reviews and meta-analyses; SR: systematic review ;

Table A4: Strengths and Limitations of Non-Randomized Studies using Downs and Black[8]	
Strengths	**Limitations**
Pancreatic Cancer	
Belfiore[11]	
• Aims and objectives clearly stated • Main outcomes and study intervention clearly described. • Compliance with the intervention was reliable.	• No comparator group • No randomization. • Unclear if the patients were representative of the larger population with LAPC. Lesions were <= 6 cm and population was 50% male. • Patients not clearly described (no mention of comorbidities or characteristics beyond age, sex, tumor size)
Kluger[12]	
• Aims and objectives clearly stated • Main outcomes to be measured clearly described • Characteristics of study patients clearly described, however more detail regarding comorbidities would be ideal. • Intervention clearly described. • Staff, places, and facilities where the patients were treated were likely representative of the treatment the majority of patients receive, however as IRE is not the standard of care, it is possible that the centers are more prone to having leading experts. • Duration of follow-up was consistent in all patients. • Compliance was reliable – all patients received IRE. • Outcome measures were valid and reliable. • The sample was of consecutive patients and thus recruited over a similar time period. • Statistical analyses were appropriate and authors explain why Cox modelling was no appropriate.	• No comparator group. • No randomization • There did not seem to be an attempt at blinding •
Martin[14]	
• Patient characteristics and comorbidities well described. • Aims and objectives clearly stated • Main outcomes to be measured clearly described. • Compliance was reliable – all patients received IRE. • Outcome measures were valid and reliable	• No comparator treatment. • No randomization. • No blinding.
Paiella[13]	
• Patient characteristics and comorbidities well described. • Aims and objectives clearly stated • Main outcomes to be measured clearly described. • Compliance was reliable – all patients received IRE.	• No comparator treatment. • No randomization. • No blinding.

Table A4: Strengths and Limitations of Non-Randomized Studies using Downs and Black[8]	
Strengths	**Limitations**
• Important adverse events were considered. • Outcome measures were valid and reliable.	
Kwon[15]	
• Objectives, interventions and outcomes clearly described. • Outcome measures were reliable and valid. • Staff, places, and facilities where the patients were treated were likely representative of the treatment the majority of patients receive, however as IRE is not the standard of care, it is possible that the centers are more prone to having leading experts. • Compliance with the intervention was reliable. • Patient characteristics were well reported.	• Unclear if subjects asked to participate were representative of patients with borderline or LAPC – 46% female, median tumor size 2.7 cm. • No randomization. • No control group. • No blinding.
Liver cancer	
Dollinger[22]	
• Objectives, interventions, and outcomes being measured clearly described. • Adverse events reported (these are the main outcomes considered). • Staff, places, and facilities where the patients were treated were likely representative of the treatment the majority of patients receive, however as IRE is not the standard of care, it is possible that the centers are more prone to having leading experts. • Compliance to the intervention was reliable.	• Unclear if subjects asked to participate were representative of patients with unresectable liver cancer – the population was 75% male, lesions were ≤ 3 cm. • Blinding was not attempted. • No randomization. • No control group.
Eller[24]	
• Objectives interventions, outcomes being measured clearly described. • Adverse events well reported (these were the main outcomes considered) • Compliance with the intervention was reliable. • Staff, places, and facilities where the patients were treated were likely representative of the treatment the majority of patients receive, however as IRE is not the standard of care, it is possible that the centers are more prone to having leading experts.	• No control group. • No randomization. • Blinding not attempted. • Population characteristics were not well reported. • Unclear if subjects asked to participate were representative of patients with liver cancer – 79% male, • Follow-up not consistent.
Granata[16,17]	
• Objectives, interventions, outcomes well-reported • Compliance with the intervention was reliable. • Staff and facilities were likely representative of the treatment most patients were received – imaging and surgical staff had at least 10 years experience – most hospitals likely have at least some staff with that level of experience.	• No randomization, no control group. • Unclear whether the non-consecutive sample was a limitation or strength – not enough information provided regarding the reasoning for it. • Blinding was not attempted • Inclusion criteria required lesions ≤ 3 cm; may not be indicative of patients with unresectable cancer. • Limited adverse events reported. • Patient characteristics not well reported.

Table A4: Strengths and Limitations of Non-Randomized Studies using Downs and Black[8]	
Strengths	**Limitations**
Sugimoto[20]	
• Objectives and methods well reported. • Compliance with the intervention was reliable. • Staff and facilities were likely representative of the treatment most patients receive – imaging and surgical staff had at least 10 years experience – most hospitals likely have at least some staff with that level of experience.	• Patient characteristics not well-reported. • Blinding was not attempted. • No randomization. • No control group.
Eisele[19]	
• Objectives and methods well reported. • Compliance with the intervention was reliable. • Outcomes were valid and reliable • Staff and facilities were likely representative of the treatment most patients receive	• Characteristics of the patient who was recruited but not followed-up were not well reported. • No randomization. • No control group. • Blinding was not attempted. • Small sample.
Dollinger[23]	
• Objectives, methods, interventions clearly described. • Compliance with intervention reliable. • No losses to follow-up. • Outcomes were valid and reliable.	• No randomization. • No control group. • Blinding was not attempted. • Small sample
Scheffer[18]	
• Objectives, methods, interventions clearly stated. • Patients who could not undergo the intervention were well described. • Outcomes were valid and reliable. • Staff and facilities were likely representative of the treatment most patients receive.	• No randomization – consecutive sample • No control group • Blinding was not attempted • Short follow-up • Unclear if patients were representative of the general population with liver metastases – 60% female and the median tumor size was 2.4 cm
Hosein[21]	
• Objectives, methods, interventions clearly stated. • Outcomes were valid and reliable. • Findings clearly described/	• Patient characteristics were not well reported. • No randomization. • No control group. • Blinding not attempted • Unclear if patients were representative to the population to which the results will be generalized – characteristics not well reported.

cm = centimeter; IRE = irreversible electroporation; LAPC = locally advanced pancreatic cancer

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusions
Rombouts, 2015[10]	

Complication Rate: (4 studies)
• Overall: 48%
• Open Surgery: 51%
• Percutaneous: 27%
IRE-Related Complication Rate: (2 studies)
• Overall: 13%
• Open Surgery: 15%
• Percutaneous: 9%
Mortality: (4 studies)
• Overall: 3%
• Open Surgery: 2%
• Percutaneous: 9%
IRE-related Mortality: (4 studies)
• Overall: 2%
• Open Surgery: 3%
• Percutaneous: 0%
Survival:
• 1 study employing open surgery (n = 54 patients) reported IRE increased survival by 9 months (from 11 to 20 months). These patients received IRE following unresectability and received IRE in conjunction with palliative bypass (where indicated) and chemotherapy.
• 1 study using percutaneous IRE 2/11 patients had margin0negative resection following IRE and 3/11 patients were disease free for 11 months.
  ○ 6 month overall survival: 70%
  ○ Patients with metastatic disease showed no improvement in survival following IRE and died "soon after the IRE procedure"
IRE-related morbidities included duodenal leakage (in patients with transduodenal needle placement, or stent removal), pancreatic leakage, bile leakage and (progression of) portal vein thrombosis. (Number of studies reporting morbidities and number of patients with morbidities not reported)
	• IRE is relatively feasible and safe
	• The percutaneous approach may result in better morbidity and mortality when compared with the open approach.
	• The non-thermal effect of IRE is helpful in preserving adjacent tissue.
	• Ablative therapies may contribute to short-term local control of unresectable pancreatic adenocarcinoma.
	• Authors suggest further studies to determine how IRE can contribute to improving survival in patients with LAPC.

Scheffer, 2014[9]	

• No serious IRE related adverse events were reported.
• IRE related complications:
  ○ 16% (21/129) complication rate for liver
  ▪ Stenosis or occlusion of portal vessels or bile ducts: 6% (9/129)
  ○ 19% (8/42) complication rate for pancreas
	• Results should be interpreted in light of the low quality of the included studies.
	• Results suggest that IRE is a safe procedure.
	• Efficacy on smaller liver tumors seems to be positive (90% ablation rate) but decreases as tumors get larger.
	• IRE seems most useful for tumors <3 cm that are not suitable for resection or thermal ablation.

Table A5: Summary of Findings of Included Systematic Reviews	
Main Study Findings	**Author's Conclusions**
▪ Major complications:7% (3/42) • Total Complications: o Liver: 16% (21/129) (6 of 8 reported) o Pancreas: 19% (8/42) (3 of 4 studies reported complications) • Mortality: o No periprocedural deaths o 3 deaths reported within 3 months of IRE (all patients with pancreatic cancer) ▪ 1 of these deaths was likely IRE related (edema following ablation contributed to progression of portal vein thrombosis) therefore the IRE mortality for pancreatic patients was 1/43 or 2.3% • Efficacy (ablation success, disease progression): o Liver: 5 of 8 studies reported follow-up >3 months; 6 to 18 month efficacy reported for 106 patients. ▪ No deaths resulting from disease progression ▪ Primary efficacy ranged from 67% to 100% ▪ Secondary efficacy ranged from 55% to 93% ▪ Increased risk for recurrence in larger tumors was reported in 5 studies. o Pancreas: (2 studies) ▪ 1 study compared IRE patients to propensity score matched chemo-radiation patients. IRE was associated with Improved local (14 mo vs 6 mo, P = .01), distant (15 mo vs 9 mo, P = .02), and overall survival (20 mo vs 13 mo, P = .03). After 20 months, there was no difference in survival between the groups. ▪ 1 study reported disease related death 3, 4, and 9 months after IRE (all patients with metastatic disease died of progressive disease); for patients with LAPC, local progression occurred between 1 and 7 months (2/7 patients), distant progression at 4	• IRE may result in improved survival and pain reduction in patients with unresectable pancreatic cancer. • IRE seems a promising option but requires more research.

Table A5: Summary of Findings of Included Systematic Reviews	
Main Study Findings	**Author's Conclusions**
months (1/7 patients), 2 patients underwent successful re-ablation and had no evidence of disease at 11 and 14 months follow-up, 2 patients had stable disease at 4 and 6 months. • 1 study found that pain and narcotic use were improved among patients receiving IRE for pancreatic tumors.	

IRE = irreversible electroporation; LAPC = locally advanced pancreatic cancer; mo = months

Table A6: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
Pancreas	
Belfiore, 2015[11]	

• No major complications were observed.
• 2/20 patients experienced minor complications (1 transient amylase increase in serum, 1 instance of ascites that did not require drainage).
• 2 patients died 3- and 4-months after IRE due to disease progression.
• 6-month follow-up: 18/20 (the remaining living patients) had local disease control.
  ○ Mean lesion decrease: 37 cm^3 (SD 16 cm^3)
  ○ Mean % volumetric decrease: 42.89%; 95% CI 34.9% to 54.88%
• Last available follow-up (mean 9 months, range 6 to 14), the 18 living patients had local disease control.
• Mean survival (Kaplan-Meyer analysis): 12.95 months, 95% CI 11.57 to 14.33
	• Findings suggest that the IRE protocol used (followed by chemotherapy) is feasible, safe, and effective for short-term control of LAPC.

Kluger, 2015[12]	
• 16% (9 patients) were readmitted after the procedure • 11% (6 patients) died within 90 days of IRE (83% of the mortalities were being treated for primary tumors) • Median postoperative mortality: 26 days (IQR 8 to 42 days) • 19% (10/53) experienced major morbidity (e.g. gastrointestinal bleeding, deep surgical site infection, need for stent placement) within 90 days of IRE; 44% of those complications were thought to be IRE-related. • Median survival from the day of IRE was 12.03 months (95 CI, 7.71 to 23.12 months) • Overall recurrence rate: 58%	• Authors did not think that IRE should be considered a minimally invasive approach for the management of locally advanced pancreatic cancer due to the rates of major morbidity.

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Martin, 2015[14]	
Complete ablation of tumor: • 50/50 for margin extension; 148/150 for in situ Total IRE delivery time: • 17 min (2 to 58 min) in the margin extension group; 35 min (10 to 125 min) in the in situ group Length of hospital stay: • 7 days (4 to 26 d) in the margin extension group; 6 days (2 to 36) in the in situ group. Adverse Events: • 20/50 patients who underwent IRE for margin extension had 49 AEs; 54/150 patients who underwent IRE in situ had 100 complications. • The most common AEs were GI events, which included anorexia, dehydration, gastritis, heartburn, nausea, vomiting, liver included ascites, biliary anastomotic stricture, liver dysfunction and failure. Most AEs were grade 1 events. Survival: • Median overall survival: 24.9 months (range: 12.4 to 85 months) • Median survival in resection + IRE: 28.3 months (range: 9.2 to 85 months) • Median survival in the IRE in situ: 23.2 months (range: 4.9 to 76.1) Recurrence: • 58/200 patients had recurrence • Local recurrence after IRE success: n = 6 Progression Free Survival: • Overall: mean 12.4 months (range: 4.4 to 8.9) • Local progression free interval: median 10.7 (range: 4.4 to 12.4) mo • Time to distant progression (n = 52 patients): median 16.8 (range: 1.3 to 55)	• Authors conclude that the report demonstrates that IRE can extend the lives of patients with LAPC. • Local disease control, in conjunction with adjuvant chemotherapy and radiation therapy, can prolong survival.
Paiella, 2015[13]	
• Median procedure time was 79.5 min (range: 20 to 148 min) • 1 transient intraoperative hypertensive episode. • Median length of hospital stay: 9.5 days • 8/10 patients experienced 13 adverse events. • 1 patient with procedure-related abdominal complication (abscess and internal fistula in the duodenum. • All patients died – 9 from advanced disease, 1 from septic shock (2 weeks after IRE, related to an ulcerative colitis flare). • Overall survival: 7.5 months (range: 2.9 to 15.9) • 90% of deaths had occurred by 12 months.	• IRE does not seem to result in the intraoperative and postoperative complications associated with other ablative techniques. • IRE can be considered a feasible and safe procedure for patients with LAPC.

Table A6: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
• 6 patients remained in the study to 90 days of follow-up. • 4 patients had partial response based on their last observation. • median tumor size at baseline was 30 mm, remained at 30 mm at day 30 (n = 9), at day 60, median tumor size was 32 mm (n = 9)	
Kwon, 2014[15]	

• Success of IRE delivery (technical success): 100%
• IRE delivery time: median 12 minutes (range 2 to 90 minutes)
• Duration of hospital stay: median 9 days (range 4 to 58)
• Number of patients with AEs: 18 (38%)
  ○ Number of AEs: 44
  ○ 5 (11%) of AEs were deemed potentially IRE-related
  ○ 2 bleeding events were deemed potentially IRE-related.
• 90 day follow-up: no recurrence based on RECIST criteria
• No deaths reported during the 90 day follow-up
• 24 month follow up: 28 (58%) patients developed recurrence
• Median overall survival: 22 months (95% CI, 17.9 to 24.9)
• Median progression free survival: 11 months (95% CI, 3 to 10).
	• For patients with advanced pancreatic cancer, IRE therapy (as an adjunct to resection) may provide an improvement in local control.
	• IRE may prolong the survival of patients with pancreatic cancer.

Liver Cancer	
Eller, 2015[24]	
• Procedural time 2 to 5 hours. • Procedure was had technical success in 12/14 patients • 4/14 experienced major complications. • No bile duct complications, no long-term complications. • Procedure prematurely terminated due to severe GI bleeding in one case. • No treatment-related deaths • Local recurrence occurred in 2/12 of the initially successful cases (at 3 and 14 months). • 10/14 cases had local tumor control at final follow-up •	• Percutaneous IRE seems to be effective for primary and secondary liver tumors. • Suggest further studies in bigger cohorts.
Dollinger, 2015[22]	
Major Complications: • Periprocedural hepatic abscesses: 4 (seemed to be associated with the presence of bilioenteric anastomosis) • Hemorrhage requiring transfusion: 1	• IRE ablation of liver tumors seems to be a fairly safe and well-tolerated procedure.

Table A6: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
• Hemorrhage requiring arterial embolization: 1 • Renal failure: 1 No IRE related deaths occurred Minor Complications: • 18.8% (16/85 procedures; in 3 of the procedures, 2 minor complications occurred) • Most frequent: hemorrhage without requirement of any further therapy (5.9%, 5/85); portal vein branch thrombosis (5.9%, 5/85) Logistic regression models showed no risk factors for major complications.	
Granata, 2015[16,17]	
Complete response:* • 1-, 3-, and 6-month: 22/24 (91.7%) tumors showed a complete response Partial response:* • 1-, 3-, and 6-month: 2/24 (8.3%) tumors showed a partial response No major IRE-related complications were reported. Two minor IRE-related complications (peripheral arteriovenous shunt and a segmental dilation of the intrahepatic biliary ducts) occurred; they did not require treatment.	• IRE is feasible, safe, and efficient for patients with unresectable HCC.
Sugimoto, 2015[20]	
• IRE judged to be technically successful in 5/6 lesions immediately after the procedure. • Residual tumor was diagnosed in 1 patient 7 days after the IRE procedure. • Tumor control achieved in 5/6 lesions. • No procedure-related deaths. • Increases in blood pressure occurred in all patients during IRE.	• Percutaneous IRE was well tolerated and may achieve satisfactory local disease control, particularly for small tumors. • Larger studies are needed.
Eisele, 2015[19]	
• 3 to 12 month follow up • tumor size: 15 SD 0.5 cm Average length of hospital stay: • percutaneous: 2 days • laparoscopy: 4 days • open surgery: 9 days Local recurrence: • percutaneous: 3 • no local recurrence for patients undergoing laparoscopy or open. Incomplete ablations: 21.4% (3/14) tumors, all after percutaneous Rate of overall recurrence: 38%	• Further study needed in order to determine the role of IRE for liver tumors.
Dollinger, 2014[23]	
• At 30-day follow up, 4 patients had clinical signs of infection. • All 4 of the infections were abscesses at the	• CT imaging of ablation sites after IRE were suggestive of more than 4 abscesses • Normal CT imaging of the liver after IRE may

Table A6: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
ablation site; patients received percutaneous drainage and IV-antimicrobial therapy.	resemble hepatic abscess, therefore, careful consideration of imaging results in combination with clinical findings was suggested by the authors.
Scheffer, 2014[18]	
• 1 IRE-related adverse event: ventricular extrasystoles without haemodynamic changes • Blood pressure increased in all patients during the IRE procedure • Mean ablation time: 25 minutes per lesion	• IRE may become an important tool in the treatment of cancer.
Hosein, 2014[21]	
29 patients in the ITT population, 28 in the response population. • 1 patient developed atrial fibrillation during IRE probe placement and did not receive IRE. • Most patients experienced abdominal pain the day of the procedure • 3 patients underwent liver resection 3 to 6 months after IRE Progression free survival: • median: 4.0 months, 95%CI 1.4 to 6.6 • 2-year: 18% (95% CI, 0% to 35%) Overall survival: • 62% (95% CI, 37% to 87%) RECIST response: • Complete response: 5 (18%) • Partial response: 5 (18%) • Stable disease: 13 (46%) • Progressive disease: 5 (18%)	• IRE can be incorporated into future studies on liver tumor ablation • Percutaneous IRE is feasible as a part of a multidisciplinary approach to colorectal liver metastases.

AE = adverse event; CI = confidence interval; cm= centimeter; CT = computed tomography; GI = gastrointestinal; HCC = hepatocellular carcinoma; IRE = irreversible electroporation; ITT = intention to treat; LAPC = locally advanced pancreatic cancer; mm = millimeter; RECIST = Response Evaluation Criteria in Solid Tumors; SD = standard deviation
*According to modified RECIST criteria