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Review Article

Is irreversible electroporation safe and effective in the treatment of hepatobiliary and pancreatic cancers?

Li-Ming Wu, Le-Le Zhang, Xin-Hua Chen, Shu-Sen Zheng*

Division of Hepatobiliary and Pancreatic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou, 310003, China

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ABSTRACT

Background: Irreversible electroporation (IRE) is a novel ablative technique for hepatobiliary and pancreatic cancers. This review summarizes the data regarding the safety and efficacy of IRE in the treatment of hepatobiliary and pancreatic cancers.

Data sources: Studies were identified by searching PubMed and Embase for articles published in English from database inception through July 31, 2017. For inclusion, each clinical study had to report morbidity and survival data on hepatobiliary and pancreatic cancers treated with IRE and contain at least 10 patients. Studies that met these criteria were included for analysis. Two authors assessed each clinical study for data extraction. The controversial parts were resolved through discussion with seniors.

Results: A total of 24 clinical studies were included. Fourteen focused on hepatic ablation with IRE comprising 437 patients with 666 lesions of different tumor types. Two patients (0.5%) died after the IRE procedure. Morbidity of hepatic ablation with IRE ranged from 7% to 35%. Most complications were mild. Complete response for hepatic tumors was reported as 57%–97%. Ten studies with 455 patients focused on pancreatic IRE. The overall mortality of IRE in pancreatic cancer was 2%. Overall severe morbidity of IRE in pancreatic cancer ranged from 0 to 20%. The median overall survival after IRE ranged from 7 to 23 months. Patients treated with IRE combined with surgical resection showed a longer overall survival.

Conclusions: IRE significantly improves the prognosis of advanced hepatobiliary and pancreatic malignances, and companied with less complications. Hence, IRE is a relatively safe and effective non-thermal ablation strategy and potentially recommended as an option for therapy of patients with hepatobiliary and pancreatic malignances.

Introduction

Hepatobiliary and pancreatic (HBP) cancers remain highly lethal with dismal outcomes due to high invasiveness, metastasis, recurrence and insensitivity to chemotherapy [1–5]. The most effective therapy for HBP cancers is complete surgical resection. However, only 20%–30% of hepatic cancers [6] and approximately 10% of pancreatic cancers [7] are surgically resectable at the time of diagnosis.

In recent decades, various ablation techniques, including irreversible electroporation (IRE), radiofrequency ablation (RFA) and microwave ablation (MWA) have been increasingly implemented in HBP cancers [8–10]. RFA and MWA are both thermal ablative techniques through destroying tumor tissue by generating heat. However, thermal ablative modalities cannot completely kill tumor tissues adjacent to major vessel because of the heat sink effect, resulting in residual lesions and a high degree of local relapse [9,10]. Furthermore, some complications, including pancreatic fistula and bile leakage, may occur due to heat damage to the biliary duct and pancreatic duct [11]. IRE is a novel non-thermal ablative technique that can avoid the detrimental heat sink effect during the ablation procedure. This technique causes cell apoptosis by creating nanoscale pores in the phospholipid bilayer on the cell membrane, and leads to irreversible destruction of intracellular homeostasis, thus sparing adjacent blood vessels and important ducts (pancreatic and biliary) [12–14]. The IRE procedure can be performed percutaneously, laparoscopically, or by open surgery [15,16]. Based on these distinctive characteristics, IRE is considered an effective therapy for tumors in an anatomically complex area of major blood vessels, bile ducts, pancreatic duct, porta hepatis and the urinary collecting system, where thermal ablation and surgical resection are contraindicated [17–22].

In recent years, a growing number of reports focused on the utilization of IRE in HBP cancers. To determine whether the IRE

* Corresponding author.
E-mail address: shusenzheng@zju.edu.cn (S.-S. Zheng).

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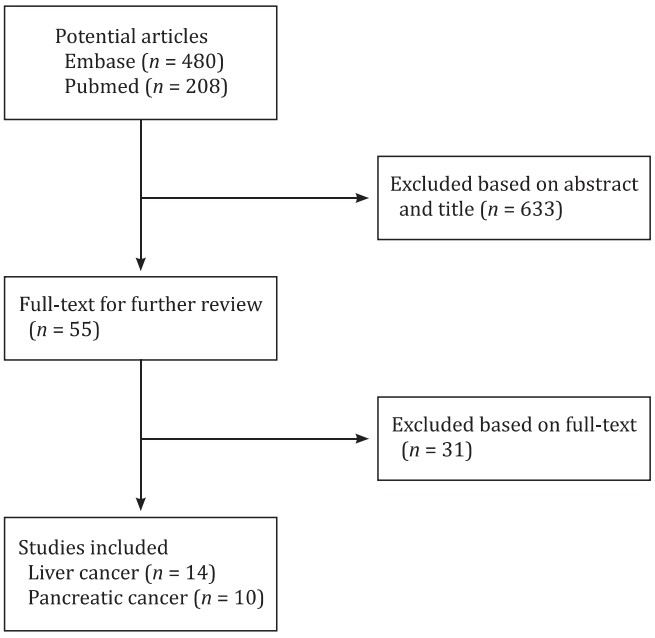

Fig. 1. Flow diagram of selecting eligible articles.

technique is an effective therapy for HBP cancers, we performed this systematic review.

Search strategies and selective criteria

Studies were identified by searching PubMed and Embase for articles published in English from database inception through July 31, 2017. The keywords for the search were "irreversible electroporation", "IRE", "nanoknife", "liver cancer", "pancreatic cancer", "cholangiocarcinoma" and "bile duct cancer". Relevant references were further screened manually for completeness. Details of the specific search process are shown in Fig. 1.

Inclusion criteria were as follows: (i) at least 10 patients; (ii) retrospective or prospective studies; (iii) HBP cancers treated with IRE; (iv) outcomes with morbidity, recurrence free survival (RFS) and overall survival (OS); and (v) the study with the latest and the most cases were chosen if the same author or institution had published several articles. Studies were excluded if they met any of the following criteria: (i) review, meta-analysis, case reports, in vitro studies and animal studies; and (ii) benign lesions.

Liver cancer

Fourteen studies on hepatic IRE were included for analysis. Eight articles were prospective studies and 6 were retrospective. A total of 437 patients with 666 lesions of different tumor types [23–36] were included (Table 1). The median age ranged from 51 to 70 years old. Among the selected studies, the median sizes of treated tumors were 1–3 cm. The median follow-up time ranged from 6 months to 35.7 months. Hepatocellular carcinoma (HCC) and colorectal cancer liver metastasis (CRLM) were the relatively common tumor types in the included cases, although other metastases (neuroendocrine tumor, cholangiocellular carcinoma, renal cell cancer, squamous cell carcinoma, breast cancer, ampullary carcinoma, testicular cancer, leiomyosarcoma, pancreatic cancer, esophageal cancer, gastrointestinal stromal tumor, and malignant melanoma) were also reported. Tumors in all 14 studies were not amenable to conventional thermal ablation or surgical resection because they were located in proximity to critical structures, such as large blood vessels, the bile duct or digestive tract. The IRE procedure was performed percutaneously in 81.7% (357 of 437) of patients, laparoscopically in 0.5% (2 of 437), and by laparotomy in 17.8% (78 of 437).

Most patients in the 7 studies [23,25–27,29,33,36] received at least one form of treatment (chemotherapy, surgical resection, RFA, hepatic arterial therapy or liver-directed therapy) before undergoing the IRE procedure. After IRE, additional thermal ablations, chemotherapy, TACE, surgery or other therapies were performed in 8 studies [23–27,32–34].

Morbidity and mortality

There were two documented deaths within a short period of time after hepatic IRE. One patient suffered a left hepatic vein thrombosis at 1-month follow-up and died shortly thereafter. However, it is unclear whether the death was related to the IRE procedure [33]. The other patient with poor liver function (Child-Pugh B) succumbed to liver failure at 2.5 months after the IRE procedure, resulting in a hepatic IRE-related mortality rate of 1.7% (1 of 58) [34].

Table 2 presents the details of complications and outcomes of the patients underwent hepatic IRE. Twelve studies [23–27,29,31–36] had morbidity data available for further analysis. Morbidity of hepatic IRE ranged from 7% to 35%. A total of 78 complications were noted, of which 16 were major according to the Society of Interventional Radiology [37], Clavien-Dindo [38] or Common Terminology Criteria for Adverse Events version (CTCAE) classifications. Niessen et al. [29] evaluated the safety and efficacy of hepatic IRE in 34 patients with 65 tumors. Six major complications were observed after IRE. A patient whose lesion was close to the left branch of the portal vein suffered partial thrombosis of the portal vein and received moderate anticoagulation. Another patient had a severe complication of diffuse intraperitoneal bleeding; the patient received a blood transfusion and was admitted to the intensive care unit (ICU) for further observation. The remaining 4 complications were liver abscesses that occurred after the IRE intervention. Two of the abscesses were drained percutaneously under CT guidance and treated with systemic antibiotics. Eller et al. [32] treated 18 malignant lesions near large vessels or bile ducts in 14 patients. One patient experienced progressive intraperitoneal bleeding during the IRE procedure and underwent immediate laparotomy for hemostasis. Three other complications, including two cases of hematothorax and one of slight abdominal bleeding were rated as grade 1 (CTCAE 3.0). In a retrospective study including 58 patients who underwent IRE on 75 tumors reported by Sutter et al. [34], three major complications (grade 3 or higher) were observed. Two patients had liver failure after IRE treatment, manifested as jaundice and ascites. Another patient with Child-Pugh B died of liver failure after the IRE procedure. Niessen et al. [35] published a retrospective study of 71 patients with 103 tumors who underwent 83 interventions by IRE. A total of 5 major complication including 4 liver abscesses and 1 myocardial infarction were observed. However, no further information about treatment-related adverse events was reported in this study. Frühling et al. [36] conducted a single-center non-randomized clinical trial, which included 30 patients with 38 liver malignances. Only one major complication was recorded after IRE. A CRLM patient showed portal vein and biliary duct stenosis in the IRE-ablated area with increased bilirubin and was treated by portal vein stent placement and biliary drainage. Hosein et al. [27] conducted a retrospective study of 29 patients of CRLM with 58 tumors. Two IRE-related complications including ventricular arrhythmia and a trial fibrillation were recorded. Both were treated without sequelae. Other reported adverse events were minor or not related to IRE. The relevant minor hepatic IRE-associated complications included neurogenic bladder, urinary retention,

Table 1
Baseline characteristics of patients with hepatic cancer.

Studies	Design	No. of patients (lesions)	Male/Female	Age (yr)	Tumor type	Tumor size (cm)	Approach
Cannon et al. [23]	Prospective study	44 (46)	23/21	60	14 HCC; 20 CRLM; 10 other	HCC 2.1 (1.3–4.5); CRLM 2.7 (1.2–11); Other 2.5 (1.1–5.0)	Perc 28; Lap 2; open 14
Cheung et al. [24]	Prospective study	11 (18)	8/3	70	11 HCC	2.4 (1.0–6.1)	Perc
Kingham et al. [25]	Retrospective study	28 (65)	11/17	51	21 CRLM; 2 HCC; 5 other	1.0 (0.5–5)	Perc 6; open 22
Silk et al. [26]	Retrospective study	11 (22)	4/7	60	16 CRLM; 6 other	3.0 (1.0–4.7)	Perc 11
Hosein et al. [27]	Retrospective study	29 (58)	NA	NA	29 CRLM	2.7 (1.2–7.0)	Perc
Padia et al. [28]	Retrospective study	20 (20)	14/6	62	20 HCC	2.0 (1.0–3.3)	Perc18; open 2
Niessen et al. [29]	Prospective study	34 (65)	27/7	59	33 HCC; 22 CRLM; 10 other	2.4 (0.2–7.1)	Perc
Barabasch et al. [30]	Prospective study	27 (37)	14/13	62	15 CRLM; 12 other	1.5 (0.1–45.0) mL	Perc
Granata et al. [31]	Prospective study	20 (24)	12/8	65	20 HCC	2.0 (1.0–3.0)	Perc
Eller et al. [32]	Prospective study	14 (18)	11/3	58	5 HCC; 11 CRLM; 2 other	2.0 (1.1–3.7)	Perc
Langan et al. [33]	Prospective study	40 (77)	30/10	53	57 CRLM; 7 HCC; 13 other	1.3 (0.5–6.0)	Open
Sutter et al. [34]	Retrospective study	58 (75)	43/15	65	75 HCC	2.4 (0.6–9.0)	Perc
Niessen et al. [35]	Retrospective study	71 (103)	57/14	64	43 HCC; 42 CRLM; 18 other	2.3 (0.6–5.1)	Perc
Frühling et al. [36]	Prospective study	30 (38)	21/9	63	23 CRLM; 8 HCC; 7 other	2.4 (0.8–4.0)	Perc

CRLM: colorectal cancer liver metastasis; HCC: hepatocellular carcinoma; Lap: laparoscopic; Perc: percutaneous; NA: not available.

abdominal pain, flank pain, intraoperative arrhythmia, portal vein thrombosis, bile duct dilatation, hematoma, pneumothorax, peripheral arteriovenous shunt, slight abdominal bleeding, hepatic vein perfusion defect, transient jaundice, asymptomatic gastric fistula, transient encephalopathy, decompensated chronic bronchitis, and high blood pressure. Most of these complications were self-limiting and did not require further treatment. Of note, arrhythmia is an IRE-specific complication due to the delivery of high electrical voltage. The use of cardiac synchronization during the procedure could effectively reduce the risk of cardiac arrhythmias [24,33].

Efficacy

All studies reported efficacy through different parameters, including complete response (CR) rate, local recurrence (LR) rate, local recurrence free survival (LRFS), OS and progression-free survival (PFS).

In an analysis of 44 patients who underwent 48 IRE procedures, 100% technical success rate was reported. Moreover, the authors reported a 59.5% LRFS at 12 months, and for those tumors < 3 cm, the LRFS reached 98% at 12 months [23]. Similarly, Niessen et al. [29] reviewed 65 malignant hepatic tumors with the diameter of 2.4 cm treated by IRE and found a LRFS of 74.8% at 1-year. In the study reported by Eller et al. [32], 10 of 14 (71%) patients were successfully cured with no local recurrence after 388 days of follow-up. According to another retrospective study reported by Hosein et al. [27], the 2-year OS and PFS after IRE were 62% and 18%, respectively.

Cheung et al. [24] reviewed 18 HCC lesions treated with IRE and observed 93% CR rate for lesions ≤ 3 cm and 100% for lesions < 2 cm, which was comparable to the results reported by Hosein et al. [27], Padia et al. [28], Niessen et al. [29,35], Granata et al. [31] and Sutter et al. [34] with a larger sample size or longer follow-up periods. Of the 5 tumors incompletely ablated after two IRE procedures, 4 were larger than 3 cm in diameter [24]. Furthermore, there was no local recurrence over the follow-up time of 18 months. It is also worth noting that the IRE procedure was successfully performed in tumors located adjacent to critical structures (major hepatic vein, digestive duct, heart and gallbladder) [24]. Kingham et al. [25] also analyzed 65 hepatic malignant tumors treated with IRE, of which 57% were within 1 cm of a major portal vein and 40% were within 1 cm of major bile ducts. During 6-month follow-up, the researchers observed 3 local recurrences and 1 of persistent disease, which constituted a combined local failure rate of 7.5%. However, Barabasch et al. [30] reported a 57% (21 of 37) CR rate over an average of 14-week follow-up after IRE.

In 2017, Langan et al. [33] reported a cumulative incidence for LR of 13.4% for tumors of median size of 1.3 cm at 25.7 months of follow-up. Moreover, they found that body mass index (BMI) and ablation zone size were associated with LR. A higher LR rate of 31.7% at 35.7 months of follow-up was reported by Niessen et al. [35]. Silk et al. [26] also reported a 54.5% (6 of 11) LR rate following IRE in 22 peribiliary hepatic metastases with a median size of 3 cm. Similarly, Frühling et al. [36] reported on 38 malignant hepatic tumors with a LR of 34.2% at 6 months following IRE. Furthermore, they analyzed the LR rate in different tumor types and found that all recurrences occurred in metastatic tumors. There was a tendency for the risk of tumor recurrence to increase with larger tumor size [23–26,36].

A retrospective study reported by Sutter et al. [34] analyzed 75 HCC tumors with a median diameter of 2.4 cm that were treated with IRE. The overall local tumor PFS was 70% at the 1-year point. Of note, the authors found that the only factor associated with local tumor PFS was a pre-IRE serum alpha-fetoprotein (AFP) level higher than 200 ng/mL.

Pancreatic cancer

The search strategy yielded 10 clinical studies of IRE in pancreatic cancer [20,22,39–46] (prospective: 6; retrospective: 4). A total of 455 patients were included in the pancreatic IRE review (Table 3). Of the 387 tumors in the 8 studies [20,22,39–43,45] that reported the tumor location, 231 tumors were in the head, 151 in the neck/body/tail or isthmus and 5 were located in the uncinate process. Most of the included patients had locally advanced pancreatic carcinoma (LAPC), but Kluger et al. [40] also treated 3 patients with neuroendocrine tumors. Most patients were deemed unsuitable for surgery and conventional thermal ablation because of an unfavorable tumor location, but Kulger et al. [40] and Martin et al. [22] also performed concurrent surgical procedures in patients with resection potential during open IRE. The median age of the included patients ranged from 58 to 68.5 years; the median tumor size ranged from 2.8 to 4.2 cm. The surgical approach to the IRE procedure in pancreatic cancer was percutaneous in 33.2% (151 of 455) and via laparotomy in 66.8% (304 of 455).

Morbidity and mortality

There were 9 documented deaths within a short time after the intervention (Table 4). Martin et al. [22] reported 3 deaths within 90 days after IRE, resulting in an overall mortality rate of 1.5% (3 of 200); all of the deaths occurred in the group of patients who

Table 2
Results of IRE therapy in hepatic cancer.

Studies	Follow-up time (mon)	Treatment pre-IRE	Treatment post-IRE	Complications (major)	Outcomes
Cannon et al. [23]	12	32 (72%) received chemotherapy, resection, RFA, hepatic arterial therapy, liver-directed therapy	7 (16%) performed concurrent abdominal procedure	5 (0)	Technical success rate: 100%, LRFS at 3-, 6-, and 12-mon was 97.4%, 94.6%, and 59.5%
Cheung et al. [24]	18	NA	4 performed RFA, 1 received TACE, 1 went on LT, 1 treated with sorafanib for metastases	4 (0)	Overall rate of CR was 72%, LRFS was 18 mon, distance recurrence was 14 mon
Kingham et al. [25]	6	24 (86%) treated with pre-IRE chemotherapy	20 (71%) treated with post-IRE chemotherapy, 2 (7%) treated with perioperative pump chemotherapy	2 (NA)	Persistent disease rate: 1.9%, tumors recurred locally rate: 5.7%
Silk et al. [26]	9	100% surgery, 91% chemotherapy, 9% radiotherapy, 27% embolization	8 additional IRE, RFA, MVA, 1 transarterial embolization	1 (NA)	Local tumor recurrence rate: 54.5%
Hosein et al. [27]	48	100% received pre-IRE chemotherapy, more than half undergone liver-directed therapy	24 (83%) post-IRE chemotherapy, 7 (24%) liver-directed therapies	2 (NA)	Median PFS: 4 mon, 2-year PFS rate: 18%, CR rate: 97%
Padia et al. [28]	12	NA	NA	NA	Primary efficacy rate: 90%
Niessen et al. [29]	14	58.5% surgery, 44.1% system therapy, 20.6% liver-directed therapies, 11.8% hepatic arterial therapy, 8.8% RFA	NA	14 (6)	CR rate: 95.4%, LRFS at 3-, 6-, and 12-mon was 87.4%, 79.8%, and 74.8%
Barabasch et al. [30]	23	NA	NA	NA	CR rate: 57%
Granata et al. [31]	6	NA	NA	2 (0)	CR rate: 91.7%
Eller et al. [32]	13	NA	2 additional RFA, TACE, IRE	4 (1)	Technical success rate: 86%, local recurrence rate: 17%, LRFS: 71%
Langan et al. [33]	26	79.5% pre-IRE systemic therapy, 39% of CRLM pre-IRE HAIP	65.9% post-IRE systemic therapy, 33% of CRLM post-IRE HAIP	14 (NA)	The cumulative incidence for local recurrence was 13.4%
Sutter et al. [34]	9	NA	4 LT	11 (3)	CR rate: 92%, overall LTP rate: 28%, the overall local tumor PFS at 6- and 12-mon was 87% and 70%, 96.5% alive, 20.7% distant intrahepatic tumor progression
Niessen et al. [35]	36	NA	NA	12 (5)	CR rate: 92.2%, LR rate: 31.7%, 50.7% alive, median total survival time was 26.3 mon
Frühling et al. [36]	23	60% pre-IRE surgery, 66.7% MWA or RFA	NA	7 (1)	LR at 3- and 6-mon was 21.1% and 34.2%

IRE: irreversible electroporation; RFA: radiofrequency ablation; TACE transarterial chemoembolization; LT: liver transplantation; MVA: microwave ablations; CR: complete response; PFS: progression free survival; LR: local recurrence LRFS: local recurrence free survival; CRLM: colorectal cancer liver metastasis; HAIP: hepatic artery infusion pump; LTP: local tumor progression; NA: not available.

received IRE alone. These deaths resulted from liver failure, pulmonary embolism and severe upper gastrointestinal bleeding. Six deaths (11%) were reported by Kluger et al. [40] within 90 days after IRE procedure; five of these underwent IRE alone, while one was reported in the IRE + resection group.

Severe morbidity of IRE in pancreatic cancer, on the other hand, ranged from 0 to 20%. No morbidity was reported in the study conducted by Belfiore et al. [43], in which percutaneous IRE procedures were followed by chemotherapy for the treatment of LAPC in 29 patients. Narayanan et al. [44] treated 50 patients with LAPC percutaneously with CT guidance. Ten (20%) patients experienced serious complications, including abdominal pain (7), pancreatitis (1), sepsis (1) and gastric leak (1). Another 21 patients experienced at least 1 adverse event that was mild or self-limiting. In a phase I study of 25 patients with LAPC published by Scheffer et al. [45] in 2017, 12 minor complications and 11 major complications were reported in 10 patients. Two of the 11 major complications were classified as grade IV according to CTCAE. These patients experienced life-threatening edematous pancreatitis and hematemesis requiring treatment with fluid resuscitation, intravenous antibiotics and blood transfusions. The remaining 9 complications were grade III. Post-procedure biliary obstruction was observed in three patients without biliary obstruction before IRE; they were treated by stent placement or percutaneous transhepatic cholangiography drain. One patient experienced stenosis of the superior mesenteric artery after IRE, resulting in postprandial abdominal cramps, who was treated by vascular stent placement. Four grade III complications were gastrointestinal tract complaints that were treated symptomatically. Mansson et al. [20] conducted a prospective study to assess the efficacy and safety of percutaneous IRE in

Table 3
Baseline characteristics of patients with pancreatic cancer.

Studies	Design	No. of patients	Male/Female	Age (yr)	Location	Tumor size (cm)	Approach
Mansson et al. [20]	Prospective study	24	12/12	65 (42–77)	19 head; 5 body	3.5	Perc
Martin et al. [22]	Retrospective study	200	101/99	62 (27–88)	108 head 92 body/neck	2.8	Open
Paiella et al. [39]	Prospective study	10	4/6	66	7 head; 3 body	3.0 (2.5–3.9)	Open
Kluger et al. [40]	Prospective study	50 (53 IRE procedures)	31/19	67 (60.2–70)	32 head; 21 neck/body	3.0 (1.7–5)	Open
Lambert et al. [41]	Prospective study	21	10/11	68	17 head; 3 body; 1 tail	3.9 (2.1–6.5)	Perc 2; open 19
Yan et al. [42]	Retrospective study	25	19/6	58 (49–80)	15 head; 10 body/neck	4.2 (2.8–4.9)	Open
Belfiore et al. [43]	Retrospective study	29	16/13	69 (55–81)	15 head; 5 isthmus; 9 body-tail	NA	Perc
Narayanan et al. [44]	Retrospective study	50	27/23	63 (46–91)	NA	3.2 (1.5–8)	Perc
Scheffer et al. [45]	Prospective study	25	12/13	61 (41–78)	18 head; 2 body; 5 uncinate process	4.0 (3.3–5.0)	Perc
Zhang et al. [46]	Prospective study	21	NA	NA	NA	3.5 (2.0–6.7)	Perc

IRE: irreversible electroporation; Perc: percutaneous; NA: not available

Table 4
Results of IRE therapy in pancreatic cancer.

Studies	Follow-up time (mon)	Treatment pre-IRE	Treatment post-IRE	Complications (major)	Outcomes
Mansson et al. [20]	NA	All had chemotherapy or radiotherapy; 5 received surgical exploration	14 additional chemotherapy	11 (3)	Median OS: 7 mon; median local recurrence: 6.1 mon; median distant recurrence 2.7 mon
Martin et al. [22]	29	All had chemotherapy (GEM-based or FOLFIRINOX); partial patients received radiotherapy	60% of margin group and 69% of in situ group had adjuvant chemotherapy; 11% of margin group and 13% of in situ group had adjuvant radiotherapy	74 (NA)	90-day mortality: 1.5%; median LRFS: 12.4 mon; median distant PFS: 16.8 mon; median OS for resection + IRE group:23 mon; median OS for IRE alone: 18 mon
Paiella et al. [39]	8	All had chemotherapy (GEM-based) or radiotherapy	NA	1 (0)	Median OS: 7.5 mon
Kluger et al. [40]	9	46 had chemotherapy (multiple regimes); 39 had radiotherapy	NA	23 (10)	90-day mortality: 11%; median OS for IRE alone group: 7.7 mon; median LR: 8.6 mon; median distant recurrence 9.2 mon
Lambert et al. [41]	NA	NA	7 received chemotherapy; 5 had neoadjuvant chemotherapy	5 (NA)	Median OS: 10.2 mon
Yan et al. [42]	3	1 patient received chemotherapy; 2 received radiotherapy	7 chemotherapy or radiotherapy	9 (2)	36% PR; 28% SD
Belfiore et al. [43]	29	NA	All received chemotherapy (GEMOX); 3 received resection	0	Median OS: 14 mon; recurrence rate: 3%
Narayanan et al. [44]	6	All had chemotherapy (multiple regimes); 60% had radiotherapy	50% resumed chemotherapy; 3 received resection	31 (10)	Median OS: 14.2 mon
Scheffer et al. [45]	12	13 received chemotherapy (GEM-based or FOLFIRINOX); 9 received surgical bypass; 7 plastic retrievable endoprosthesis	NA	10 (NA)	Median OS: 11 mon; median local PFS: 12 mon
Zhang et al. [46]	NA	NA	NA	4 (0)	No recurrence at 1 mon

GEMOX: gemcitabine and oxaliplatin; FOLFIRINOX: 5-fluourouracil, leucovorin, irinotecan, oxaliplatin; OS: overall survival; LRFS: local recurrence free survival; PFS: progression-free survival; IRE: irreversible electroporation; PR: progressive disease; SD: stable disease; NA: not available.

24 patients with LAPC who received pre-IRE chemotherapy and/or radio-chemotherapy. After treatment, complications attributed to the IRE procedures were observed in 11 (46%) patients. Three (12.5%) patients experienced serious complications. One of them developed a thrombosis of the superior mesenteric vein after IRE, necessitating portography with a stent. Another patient had gastric retention that necessitated endoscopy and subsequent surgery. The remaining patient experienced postoperative bleeding caused by an ulcer in the duodenum; this was treated with endoscopy and angiographic embolization. Another prospective study of 50 patients with 53 IRE sessions reported relatively high mortality (11%) [40]. Within 90 days after IRE, 10 patients developed major complications. These serious adverse events included upper gastrointestinal bleeding, gastric ulcer perforations, bile duct stricture, delayed gastric emptying, surgical-site infection and wound dehiscence. Of the patients who experienced minor complications, one had a duodenal ulceration/perforation that was considered to be IRE-associated. In another study, of the 21 IRE procedures, 2 were percutaneous and 19 were laparotomy. Complications were noted in 5 patients and included peripancreatic abscess, liver abscess, abdominal wall abscess, peritonitis, cholangitis, pancreatic fistula and bleeding; the severity of these complications was not graded [41]. Martin et al. [22] published a retrospective study of 200 LAPC patients treated with open IRE. Fifty patients were treated by IRE combined with surgical resection, while the remaining 150 were treated with IRE alone. A total of 149 complications were observed in 74 patients, resulting in an overall morbidity of 37%. However, among the 149 complications, only 47 were grade 3 or higher and were considered to be serious. In a study reported by Paiella et al. [39], 10 patients with LAPC were treated with IRE during laparotomy. Following IRE, one patient experienced 2 procedure-associated complications: a pancreatic abscess and a pancreoduodenal fistula. A single-center retrospective study analyzed 25 patients with unresectable LAPC who underwent open IRE [42]. There were 9 post-IRE complications, two of which, upper gastrointestinal hemorrhage and portal vein thrombosis, were classified as Clavien-Dindo grade 3. Zhang et al. [46] conducted a prospective study of 21 patients who underwent percutaneous IRE treatment. Five complications were observed in 4 patients, including 1 of hypoglycemia, 1 of chest tightness and high blood pressure, 1 of hypokalemia, and 1 of occasional premature ventricular contractions. All of these complications were minor and resolved within 24 hours. These evidences supported that IRE is a safe ablation technique for HBP cancer therapy.

Efficacy

The median OS reported by Narayanan et al. [44] was 16.2 months for patients with tumors ≤ 3 cm and 9.9 months for patients with tumors > 3 cm treated with IRE. Median OS for all patients was 14.2 months. They confirmed that tumor size was the only parameter that was significantly associated with survival. Similar results were found by Belfiore et al. [43], who reported median OS of 14 months. Of note, all patients received chemotherapy 24 h after IRE treatment and showed a higher median OS and better quality of life than patients treated with traditional chemotherapy alone. In addition, a low recurrence rate of 3% was reported after a median follow-up of 29 months, which was comparable to findings reported by Martin et al. [22]. Later, Scheffer et al. [45] evaluated the efficacy of percutaneous IRE in patients with LAPC. Median OS was 11 months, and the median local PFS was 12 months. However, Mansson et al. [20] reported a relatively short median OS (7 months). Median local and distant recurrences were 6.1 months and 2.7 months, respectively. In addition, one patient with previously unresectable LAPC underwent R0 resection after IRE. Similar results were reported by Paiella et al. [39], who published a prospective study of 10 patients undergoing IRE treatment and reported a median OS of 7.5 months. In the study by Kluger et al. [40], 50 patients underwent 53 IRE procedures were classified into two groups: the primary treatment group, who were unsuitable for resection and underwent open IRE alone, and the margin extension group, who underwent IRE at the time of surgical resection. The median OS for the primary group was 7.7 months and was not reached in the resected group. Median local and distant recurrences were 8.6 months and 9.2 months, respectively. Similarly, patients in the study of Martin et al. [22] were also divided into two groups. The median OS from the IRE procedure in the margin accentuation group was 23 months, while it was 18 months for IRE alone group. Median local and distant recurrences were 12.4 and 16.8 months, respectively. Lambert et al. [41] performed the IRE procedure in 21 patients with unresectable LAPC. Their results were compared with a control group that received palliative surgery or chemotherapy. Patients who underwent IRE had a median OS after the procedure of 10.2 months, compared to 9.3 months in patients of the matched group. Yan et al. [42] did not use the OS to indicate the outcomes of the patients who underwent IRE. Instead, they reported a stable disease rate of 28% and a partial response rate of 36% at the last evaluation. The study conducted by Zhang et al. [46] was excluded for survival analysis because of the short follow-up time.

Discussion

HBP cancers remain the most difficult malignancies to treat due to their high recurrence and low survival rates. While progress has been made in diagnosis and treatment, the combined 5-year survival rate of localized HBP cancers is only approximately 30% [47]. Complete surgical resection is the most effective therapy for HBP cancers, but unfortunately only 20% to 30% of hepatic cancer [6] and approximately 10% of pancreatic cancer [7] are considered to be surgically resectable. Ablation is a minimally invasive therapy for patients who are not candidates for surgery. However, the use of conventional ablation such as RFA in HBP cancers remains controversial because of its high complication rates [48].

IRE is a new ablative method without thermal effects. Vital structures in ablation area such as blood vessels, bile and pancreatic ducts, have been shown to remain intact during the IRE procedure [14,49]. This advantage makes IRE particularly suitable for HBP cancers.

This analysis included several clinical studies of IRE in the treatment of HBP cancer, focusing on its safety and efficacy. Two deaths occurred shortly after hepatic IRE. Although the hepatic IRE-related mortality was low, it is important to assess liver function before IRE treatment. The morbidity associated with hepatic IRE ranged from 7% to 35%. This unusual large variation of mortality was mainly due to the difference in individual investigators' experience, clinical setting or patient selection because there is no standard operate criterion. Most complications were minor and required no further treatment. Serious complications included diffuse intraperitoneal bleeding, portal vein thrombosis, liver abscesses, and progressive intraperitoneal bleeding. All of the severe complications were treated. The different incidences of complications in different studies are potentially caused by the following reasons: (i) the standard operating procedure of IRE treatment for HBP cancer was absent; (ii) patients were accompanied with different diseases background which was not analyzed in some reports; (iii) IRE is a new technique, and the operators did not have uniform training. Furthermore, in IRE process, the operating software was used to calculate the field of thermal intensity to control the number of electric pulse to induce tumor cell apoptosis and avoid destroying the matrix structure of large blood vessel or bile duct. But limited precision of operating software calculation

usually led to excessive number of electric pulse and produced heat enough to damage blood vessel and bile duct.

Of note, IRE was successfully performed in tumors that were located adjacent to critical structures [24,25]. Theoretically, IRE has a non-thermal effect that would therefore not damage the surrounding structures. However, bile duct occlusion caused by thermal damage was observed after the hepatic IRE procedure [26].

Overall, IRE seems to be a safe ablative method, especially in hepatic tumors close to biliary and vascular structures. After IRE treatment, CR rates have been promising, especially in small tumors. Relapse is more likely for hepatic tumors > 3 cm that were not amenable to surgical or thermal ablation. The application of conventional thermal ablation methods in the pancreas was limited because of the delicate characteristics of the pancreas and its vulnerability to thermal damage. RFA has a high morbidity of 28% to 40% and a mortality rate of 7.5% in the treatment of pancreatic cancer [50,51]. The overall mortality of IRE in pancreatic cancer was only 2%. In terms of morbidity, it is difficult to determine those that were directly associated with IRE. However, the overall severe morbidity of IRE in pancreatic cancer ranged from 0 to 20%. Systemic chemotherapy is a common treatment for LAPC, but the effect is not significant.

Martin et al. [52] found a longer OS and local and distant PFS in the IRE + chemotherapy group than in the group receiving chemotherapy alone. Similar results were reported by Belfiore et al. [43]. This suggests that IRE treatment may result in survival benefits. Similar to hepatic tumors, patients with pancreatic tumors ≤ 3 cm have a longer OS than those with tumors > 3 cm.

Furthermore, IRE is thought to have the potential to facilitate surgical resection. On one hand, IRE can downstage the patients with LAPC, allowing them to subsequently undergo surgical resection. On the other hand, IRE can be used for margin accentuation at the time of surgery. Martin et al. [22] demonstrated an improvement in OS and in local and distant PFS in the margin accentuation group compared to the group receiving IRE alone. Further studies of IRE in the treatment of HBP cancers are needed to confirm these conclusions.

Although the safety and efficacy of IRE in the treatment of HBP cancers have been clinically proven, there is also a risk of tumor recurrence. Philips et al. [53] found that recurrent tumor cells are faster growing, more aggressive, overexpressing epithelial cell adhesion molecules and may be resistant to standard chemotherapy after incomplete ablation in a heterotopic murine mode. Therefore, complete ablation of the tumor is the primary condition for reducing recurrence. Several factors must be considered to achieve a complete ablation. Firstly, accurate ablation parameters must be set [54]. Secondly, a standardized stepwise procedure is important to improve technical success. Thirdly, it is necessary to find an indicator to determine whether the ablation is successful during the IRE procedure. Dunki-Jacobs et al. [55] suggest that the slope of the resistance curve and change in resistance of tumor tissue are effective predictors.

In recent years, IRE combined with other therapies in cancer treatment has become the subject of several research efforts. Bhutiani et al. [56] found that increased gemcitabine delivery into tumor cells through cell membrane pores created by IRE ultimately reduce the tumor recurrence rate. Therefore, the use of concurrent electro-chemotherapy could enhance the efficacy of ablation therapy and improve its success rate. Previous studies have demonstrated that IRE has the potential to stimulate the immune system [57] and inhibits carcinogenic inflammation signaling pathways [58]. Lin et al. [59] used IRE combined with allogeneic natural killer cells to treat metastatic pancreatic cancer. The short-term effect was encouraging, suggesting that IRE combined with immunotherapy was an effective treatment that could reduce recurrence and improve the therapeutic effect. However, no matter at pre- or post-IRE treatment, the interval from IRE to radiation, chemotherapy or immunotherapy was not stated in the most of articles. Hence, the impact of radiation, chemotherapy and immunotherapy on IRE was not investigated.

There are several limitations to this study. First, no randomized controlled trials were included. Most studies had a small sample size. In addition, different types of hepatic tumors may have different influence on the effects. Furthermore, the imaging methods and follow-up periods varied among the studies. Nevertheless, despite these limitations, there is a potential prognostic benefit from IRE treatment in pancreatic cancer. Large scales of prospective randomized trials are still needed to validate the utility of IRE treatment on HBP cancers. With advances in technology and further refinement of the protocol of IRE, the reduction of mortality and severe adverse effects could be achieved.

Conclusion

IRE is a potentially promising strategy for treating the HBP tumors where the thermal ablation and surgical resection are contraindicated. Moreover, in the aspect of improving the prognosis of advanced HBP malignances, IRE may play an important role. Hence, IRE is a relatively safe and effective non-thermal ablation option, but still need the further clinical investigation.

Contributors

WLM and ZSS proposed the study. WLM and ZLL performed the research and wrote the first draft. ZLL and CXH collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. ZSS is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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