Article published online: 2025-02-03

Original Article

Complications of Percutaneous Irreversible Electroporation for Pancreatic Cancer: A Systematic Review

Harsimran Bhatia[1] Muniraju Maralakunte[1] Mudita Gulati[1] Vishal Sharma[2] Pankaj Gupta[1]

[1] Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[2] Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence Pankaj Gupta, MD, Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh, India (e-mail: pankajgupta959@gmail.com).

J Clin Interv Radiol ISVIR

Abstract

Objective The aim of the study was to systematically review the percutaneous irreversible electroporation (IRE) complications for pancreatic ductal adenocarcinoma (PDAC).

Methods This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers conducted a detailed search in PubMed and EMBASE databases from inception till May 2024. The studies reporting the complications of percutaneous IRE in PDAC using standard scales were included. The primary outcome of interest was the complication rate (including total number of complications and major and minor complications) associated with the percutaneous IRE. IRE-related mortality was also recorded.

Results Of the 2,324 studies, 14 (9 prospective and 3 retrospective) met the inclusion criteria. Of the 748 complications, 114 were major complications (15.2%) and 634 were minor complications (84.7%). The most common complications were abdominal pain ($n = 137$), diarrhea ($n = 57$), and nausea and/or vomiting ($n = 45$). Pancreatitis ($n = 57$), vascular thrombosis ($n = 21$), bleeding ($n = 21$), and biliary complications ($n = 26$), including bile leaks, cholangitis, and strictures, were other common complications. The overall IRE mortality was 4/584 (0.68%). IRE-related fatal complications included duodenal perforation ($n = 2$), hepatic artery and superior mesenteric artery thrombosis ($n = 1$), and purulent peritonitis ($n = 1$).

Conclusion Although complications are common after IRE for PDAC, most are minor complications. Major complications include bleeding and pancreaticobiliary complications.

Keywords
- irreversible electroporation
- pancreatic cancer
- complications

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related mortality and morbidity. It carries a dismal prognosis with a reported 5-year survival rate as low as 8%.[1] The standard treatment regime consists of surgical resection in resectable tumors and a combination of systemic chemotherapy and surgery in borderline resectable tumors.[2,3] Unfortunately, due to the lack of specific symptoms, most patients present with locally advanced pancreatic cancer (LAPC) or unresectable cancer. Patients with LAPC have major vascular encasement and are thus offered

DOI https://doi.org/10.1055/s-0045-1801889.
ISSN 2457-0214.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

gemcitabine-based chemotherapy and radiation. However, the prognosis is abysmal.[4–6] Additionally, the recurrence rate in patients undergoing curative resection is high.[7]

Local ablative therapies offer a nonsurgical method for patients with LAPC.[8–13] Radiofrequency ablation (RFA) has been extensively used in this setting, but the complication rate is high.[14] Microwave ablation (MWA) and cryoablation are the two other techniques utilized for PDAC. The thermal ablative techniques cause complications due to heat-induced peripancreatic vasculature, bile duct, and duodenum necrosis. Irreversible electroporation (IRE) is a novel nonthermal ablative technique that uses high-voltage electrical pulses.[15] These electrical pulses irreversibly damage the cell membrane and induce apoptosis.[16,17] Owing to its distinct mechanism of action, IRE has been traditionally proposed as a relatively safer option for treating hepatobiliary and pancreatic malignancies at high risk locations compared with thermal ablation.[18–20] Systemic symptoms like transient abdominal pain, fever, and diarrhea are common.[21–24] Additionally, recent literature suggests that the procedure may also be associated with severe complications.[21] There is a lack of literature exclusively reporting the complications of percutaneous IRE for PDAC. Moreover, factors associated with complications of IRE have not been assessed in the published literature.

Thus, this study systematically reviews the complications associated with percutaneous IRE in patients with PDAC.

Materials and Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] Our institutional ethics committee does not review systematic reviews and meta-analyses. Two independent reviewers (H.B., M.M.) conducted a detailed search in the PubMed and EMBASE databases from inception till May 2024. The search was conducted with the terms "pancreas adenocarcinoma" OR "pancreatic ductal adenocarcinoma" OR "pancreas cancer" OR "pancreas carcinoma" AND "irreversible electroporation" OR "irreversible electroporation device" OR "ablation therapy" OR "catheter ablation" OR "non-thermal irreversible electroporation." There were no time or language restrictions. The references of selected studies were also reviewed for articles meeting the inclusion criteria. If there were differences between the two reviewers regarding the inclusion or exclusion of the articles, a third reviewer (P.G.) was involved.

Selection Criteria

The studies that reported the safety of IRE in the management of the PDAC and graded the severity of complications using standard reporting guidelines were included for analysis. Only human studies were included. Studies reporting technical efficacy alone were not included. Case reports, case series (<10 cases), review articles, and duplicate publications were excluded from the analysis. Studies reporting the safety of the open surgical technique of IRE were also excluded. Studies including both open and percutaneous IRE were included only if a separate complication rate for the latter was reported. Studies were also excluded if no specific grade of severity of complications was mentioned.

Outcome Measures

The primary outcome of interest was the complication rate associated with the percutaneous IRE procedure. Only complications related to the IRE procedure were included. The grades of the reported complications were recorded.[26,27] The major/severe complications were defined as a Clavien–Dindo scale of greater than 2, Common Terminology Criteria for Adverse Events (CTCAE) grade of greater than 3, or Society of Interventional Radiology (SIR) grades C to F. The IRE-related mortality was also recorded. It was defined as major IRE-related complications that lead to death.

Data Extraction

Study design, study year, number of subjects, age, sex, and origin of the study cohort were extracted. The tumor size, stage, and image guidance for percutaneous IRE were recorded. The complications (including overall rate and major and minor complications) were recorded. Finally, the IRE-related mortality was recorded for each study.

Risk of Bias and Quality Assessment

The Newcastle-Ottawa scale was used for evaluating the quality of the studies by two reviewers (H.B. and M.G.) independently. A third reviewer (P.G.) resolved the ensuing discrepancies. In this study, rating was defined as good, fair, and poor based on the selection, comparability, and outcome domains.

Results

Study Details

A total of 2,324 nonoverlapping studies were identified, of which 1,638 were excluded based on the titles. The abstracts of the remaining articles were screened independently by two investigators. Fifty-one articles were then subjected to full-text reading. Data from 14 articles were finally included. Of these, nine were prospective[21–24,30,32,33,35,37] and five were retrospective[28,29,32,34,36] (►**Fig. 1**). A total of 600 patients were included, of which 584 were subjected to percutaneous IRE. Patient and tumor characteristics are shown in ►**Table 1**. All the studies employed adjuvant chemotherapy/radiotherapy, which is detailed in ►**Table 1**.

Complications

Prevalence of Complications

The total number of reported complications was 748. One-hundred fourteen complications were major complications, while 634 were minor complications. The overall IRE-related mortality was 4/584 (0.68%; ►**Table 2**).

Severity of Complications

CTCAE was used by most of the studies to grade the adverse events.[21,22,28,29,32,34,36,37] Few studies used the

Total identified: 2,324

PubMed	1,724
Embase	600
Duplicates	268

Remaining screened	2,056
Excluded based on titles	1,638

Full text articles and abstracts assessed for eligibility	418

Excluded :

Abstract not relevant	210
Languages other than English	7
Book page	3
Case reports	11
Review articles	64
Meta-analysis	11
Expert survey	2
Open IRE	19
Complications exclusive to percutaneous IRE not specified	2
No specific complication severity scale used	10
Complications not specified	12
Murine models	23
Manual search	7
Sample size <10 patients	9
Final included	14

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. IRE, irreversible electroporation.

Clavien–Dindo scale to grade the complications' severity.[23,24,30,31,35] Belfiore et al used the SIR classification.[33] The details of the severity of the complications are presented in ►**Table 2**.

Interval between IRE and Complications

Only a few studies mentioned the exact time interval of onset of complications.[22,24,29–32,34,35,37] The rest of the studies mentioned a follow-up period post-IRE procedure[21,23,28,33,36] (►**Table 2**).

Specific Complications

The most common complications were abdominal pain ($n = 137$;18.3%), diarrhea ($n = 57$;7.6%), pancreatitis ($n = 57$; 7.6%), and nausea/vomiting ($n = 45$; 6%) reported by 14 studies.[21–24,28–37] The system-wise complications are reported in ►**Table 3**. ►**Table 4** details the major complications.

IRE-Related Mortality

IRE-related mortality was reported in four studies.[21,23,24,31] The overall mortality rate was 0.68% (4/584; ►**Table 4**). Causes included duodenal perforation in two cases (50 days after IRE in both).[21,24] Other causes included vascular thrombosis involving hepatic artery and superior mesenteric artery (SMA; 3.6 months after IRE)[23] and purulent peritonitis (<30 days after IRE).[31]

Review of Factors Associated with Complicationsf

As the data reported by studies was variable and heterogenous, meta-regression could not be performed. A review of the individual studies revealed that the complication rate was higher with larger tumors and those undergoing repeat IRE.[23,24,31] Other factors like adjuvant treatment, location of tumor, image guidance for IRE, and voltage settings of IRE were not reported to influence the rate of

Table 1 Patient and tumor characteristics in studies reporting percutaneous irreversible electroporation (IRE) complications in locally advanced pancreatic cancer

Sl. no.	Study	Country	Year	Study design	No. of patients	Age (mean/median), y	Gender distribution (M/F)	Stage	Size of tumor	Site in pancreas	Adjuvant therapy (CT, RT)
1	Ruarus et al[21]	The Netherlands	2019	P	50	Median age, 61 (IQR, 56–69)	25/25	40: LAPC 10: recurrent	4 cm	Head/ body/ uncinate (21/12/7)	Pre-IRE CT
2	Pan et al[22]	China	2020	P	92	Mean age, 57.6 ± 10.6	52/40	LAPC	4.1 cm	All sites	Natural killer (NK) therapy
3	Månsson et al[23]	Sweden	2020	P	10	Mean age, 65.9 ± 11.7	4/6	Recurrent	< 5 cm	Not reported	Pre-IRE CT
4	Månsson et al[24]	Sweden	2019	P	24	Median age, 68 (IQR, 60.5–74.5)	15/9	LAPC	Median: 3 cm	Head/body (18/6)	Post-IRE CT
5	Narayanan et al[28]	USA	2012	R	14	Median age, 57 (range, 51–72)	7/7	11: LAPC 3: metastatic	Median: 3.3 cm	Head/ uncinate/ body (6/1/7)	Pre-IRE CT and adjuvant RT
6	Scheffer et al[29]	The Netherlands	2017	R	25	Median age, 61 (range, 41–78)	13/12	LAPC stage III	Median: 4 cm	Head/body/ uncinate	Pre-IRE CT and adjuvant RT
7	Månsson et al[30]	Sweden	2016	P	24	Mean age, 63.1 ± 8.5	12/12	LPAC	< 5 cm	Not reported	Pre-IRE CT and adjuvant RT
8	Flak et al[31]	Denmark	2019	P	33	Mean age, 671. (range, 50–81)	18/15	LAPC	Median 3 cm	Head, body	Pre- and post-IRE CT
9	Narayanan et al[32]	The Netherlands	2016	R	50	Median age, 62.5 (range, 46–91)	23/27	LAPC	Mean: 3.2 ± 1.3 cm	Not reported	Pre-IRE CT and RT
10	Belfiore et al[33]	Italy	2017	P	29	Mean age, 68.5 (range, 55–81)	16/13	LAPC stage III	Not reported	All sites	Post-IRE CT
11	Leen et al[34]	UK	2018	R	75	Median age, 63.4 (range, 32–79)	53/22	LAPC	Mean 3.4 ± 1.2	All sites	Pre-IRE CT
12	Liu et al[35]	China	2019	P	54	Median age, 61 (range, 41–73)	26/28	LAPC stage III/IV	4.9 ± 1.6 cm	All sites	Pre-IRE CT
13	Ma et al[36]	China	2023	R	103	Median ages, 55 (range, 26–80) and 62 (range, 34–78)	31/72	LAPC	Median: 4.1 cm (group A) 3.8 cm (group B)	All sites	Pre-IRE CT in all PD-1/PD-L1 blockade (immunotherapy) post-IRE in 25 patients
14	Tasu et al[37]	France	2024	P	17	Median age, 61 (range, 37–77)	6/11	LAPC	< 7 cm	Head, body, and uncinate process	Pre-IRE CT

Abbreviations: CT, chemotherapy; IQR, interquartile range; LAPC, locally advanced pancreatic cancer; P, prospective; R, retrospective; RT, radiotherapy.

Table 2 Prevalence and severity of complications in studies reporting percutaneous irreversible electroporation (IRE) complications in locally advanced pancreatic cancer

Sl. no.	Study	Image guidance	Scale used	Total no. of patients	No. of complications	Major	Grade I/II	III	IV	V	Time interval
1	Ruarus et al[21]	CT	CTCAE	50	35 complications in 29 patients	21	14	17	2	2	Follow-up: 3 mo
2	Pan et al[22]	CT	CTCAE v 4	92	69 patients (75%)	None	All				<30 d
3	Månsson et al[23]	US	Clavien–Dindo	10	4 patients (40%)	2	2	1		1	Follow-up: 3 mo
4	Månsson et al[24]	US	Clavien–Dindo	24	9 patients (37.5%)	6	3	2	3	1	<30 d
5	Narayanan et al[28]	CT	CTCAE v 4	14	3 patients (21.4%)	None	3				Follow-up: variable
6	Scheffer et al[29]	CT	CTCAE v 4	25	23 complications in 10 patients	11	12	9	2		3 mo
7	Månsson et al[30]	US	Clavien–Dindo	24	12 patients (50%)	3	9	3			<30 d
8	Flak et al[31]	US	Clavien–Dindo	33	Complications in 21/40 procedures	8	13	6	1	1	3 mo
9	Narayanan et al[32]	CT	CTCAE v 4	50	45 complications in 31 patients	10	35		10		30 d
10	Belfiore et al[33]	CT	SIR	29	No major complications	None					Follow-up: 1, 3, and 6 mo
11	Leen et al[34]	CT	CTCAE	75	24 patients (32%)	6	12	5	1		3 mo
12	Liu et al[35]	US/CT	Clavien–Dindo	54	44 complications	3	41	3			<3 wk
13	Ma et al[36]	US/CT	CTCAE	103	437 complications	32	405	32			Follow-up: 1, 3, and 6 mo
14	Tasu et al[37]	CT	CTCAE	17	22 complications in 10 patients	12 in 3 patients	10	9	3	0	3 mo

Abbreviations: CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; SIR, Society of Interventional Radiology; US, ultrasound.

Table 3 System-wise complications in studies reporting percutaneous irreversible electroporation (IRE) complications in locally advanced pancreatic cancer

Sl. no.	Study	Infection			Biliary		Vascular				Gastrointestinal (GI)							Others
	Ruarus et al[21]	Abscess	Pneumonia	Peritonitis	Obstruction	Cholangitis	GI bleeding	Vascular stenosis	Bleeding duodenal ulcer (DU)	Portal vein thrombosis	Pancreatitis	Ascites	Reduced appetite	Diarrhea	Gastroparesis	Duodenal perf	Nausea/ vomiting	Pain/arrythmia/fever
1	Pan e t al[22]	3	1		4	2		2	1	3	3 Fistula: 1		2	3	3	1	1	Pain: 2 Arrythmia: 1 Chyle leakage: 1
2	Månsson et al[23]						1								2		9	Hypoglycemia: 7 Fever: 31 Fatigue: 19
3	Månsson et al[24]	Sepsis:1						1						1				Pain = 1
4	Narayanan et al[28]	Infection: 2			Common bile duct perforation: 1	Bile leakage:1					1 Pancreatic abscess: 1			1	1			Pneumoperitoneum: 1
5	Scheffer et al[29]										1							Pneumothorax: 1 Subcutaneous hematoma: 1
6	Månsson et al[30]	1	1		3	1		1	1		3		1	2	2		4	Pain = 3
7	Flak et al[31]	5					1		1	2	2				1			
8	Narayanan et al[32]	4		1			3		1	1	Pseudocyst: 1 Pancreatic enzyme deficiency: 5	2						Abdominal pain: 3
9	Belfiore et al[33]	Sepsis:1								3	6						7	Abdominal pain: 19 Gastric leak: 1 Hematoma: 3 Fever: 1 Constipation: 1 Urinary discomfort: 1 Back pain: 1 Malaise: 1
10	Leen et al[34]	Not elaborated																
11	Liu et al[35]	Sepsis: 5					16											Abdominal pain: 16 Needle tract bleed: 3
12	Ma et al[36]							3				10			3		4	Pleural effusion: 9 Fever: 6 Pain: 4 Hypokalemia: 4 Arrythmia: 1
13	Tasu et al[37]	20			Biliary fistula: 23						29	12	11	50			19	Fever: 13 Pain: 80 Hypertension: 48 Arrythmia: 38 Pleural effusion: 6 Abdominal distention: 6
14	Ruarus et al[21]	1						4		1	3 Pancreatic fistula: 1		1				1	Duodenal stenosis: 1 Pain: 9

Table 4 System-wise major complications in studies reporting percutaneous irreversible electroporation (IRE) complications in locally advanced pancreatic cancer

Sl. no.	Study	Major complications (*n*)	Infection	Biliary	Vascular	Gastrointestinal (GI)	Others	IRE-related mortality
1	Ruarus et al[21]	21	Abscess = 1	6	Superior mesenteric artery (SMA) stenosis = 2 Bleeding duodenal ulcer (DU) = 1	Pancreatitis = 3 Pancreatic fistula = 1 Reduced appetite = 1 Gastroparesis = 3 Duodenal perforation = 1	Chyle leakage = 1	1 Cause: duodenal perforation leading to euthanasia
2	Pan et al[22]	None						None
3	Månsson et al[23]	2	Sepsis: 1		Thrombosis:1			1 Cause: vascular thrombosis (hepatic artery and SMA)
4	Månsson et al[24]	6	1	Common bile duct (CBD) perforation = 1 Bile leakage = 1		Duodenal perforation = 1 Pneumoperitoneum = 1 Pancreatic abscess = 1		1 Cause: duodenal perforation
5	Narayanan et al[28]	None	1					None
6	Scheffer et al[29]	11		4	Bleeding DU = 1 SMA stenosis = 1	Pancreatitis = 3 Vomiting = 1 Reduced appetite = 1		None
7	Månsson et al[30]	3			Superior mesenteric vein (SMV) thrombosis with bleeding = 1 Bleeding DU = 1	Gastroparesis = 1		None
8	Flak et al[31]	8	Abscess = 2 Peritonitis = 1		Bleeding DU = 1 GI bleeding = 1	Pancreatic pseudocyst = 1	Ascites = 2	1 Cause: peritonitis
9	Narayanan et al[32]	10	Sepsis = 1			Pancreatitis = 1 Gastric leak = 1	Abdominal pain = 7	None
10	Belfiore et al[33]	Not elaborated						None
11	Leen et al[34]	6	Sepsis = 5				Nausea = 1	None
12	Liu et al[35]				Hemorrhage = 3			None
13	Ma et al[36]	32		Biliary fistula = 3	Hemorrhage = 3	Pancreatitis = 5	Cardiac arrythmia = 9 Hypertension = 12	None
14	Tasu et al[37]	12	Septicemia = 1		Intraperitoneal bleeding = 4 Portal vein thrombosis = 1	Pancreatitis = 3 Pancreatic fistula = 1 Duodenal stenosis = 1 Loss of appetite = 1		None

Table 5 Factors associated with complications in studies reporting percutaneous irreversible electroporation (IRE) complications in locally advanced pancreatic cancer

Study	Factor reported	Complication rate outcome
Ruarus et al[21]	Location of tumor	No correlation
Pan et al[22]	Adjuvant therapy (natural killer [NK])	No significant difference between IRE and IRE-NK group
Månsson et al[23]	Larger tumor size	Higher vascular complications
Månsson et al[24]	Timing of adjuvant therapy (chemotherapy)	Higher rate of severe complications in IRE prior to chemotherapy (25%) v/s IRE post-chemotherapy (12.5%)
Månsson et al[30]		
Flak et al[31]	Tumor size	Higher overall and major complications in size $>$3.5 cm (67 and 28%, respectively) vs. size $\leq$3.5 cm (41 and 14%, respectively)
Factors extracted		
Månsson et al,[23] Månsson et al,[24] Månsson et al,[30] and Flak et al[31] Ruarus et al,[21] Pan et al,[22] Narayanan et al,[28] Scheffer et al,[29] Narayanan et al,[32] Leen et al,[34] and Tasu et al[37]	**Guidance for IRE** Ultrasound (US) vs. computed tomography (CT)	US 40, 37.5, 50%, and 63.6% CT 58, 75, 21.4, 40, 62, 32, and 58.8%
Ruarus et al,[21] Pan et al,[22] Månsson et al,[23] Månsson et al,[24] Narayanan et al,[28] Scheffer et al,[29] and Månsson et al[30] Narayanan et al,[32] Leen et al,[34] and Tasu et al[37]	**Technique of IRE** 1,000–1,500 V vs. Up to 3,000 V	58, 75, 40, 37.5, 21.4, 40, and 50% 62, 32, and 58.8%
Månsson et al,[24] Narayanan et al,[28] Flak et al,[31] Narayanan et al,[32] and Leen et al[34] Ruarus et al,[21] Pan et al,[22] and Scheffer et al[29]	**Tumor size** $<$ 3.5 cm vs. ≥3.5 cm	37.5, 21.4, 63.6, 62, and 32% 58, 75, and 40%
Ruarus et al,[21] Månsson et al,[23] Leen et al,[34] and Tasu et al[37] Narayanan et al,[28] Scheffer et al,[29] Månsson et al,[30] and Narayanan et al[32] Pan et al[22] Månsson et al[24]	**Adjuvant therapy** Pre-IRE chemotherapy Pre-IRE chemoradiotherapy NK therapy followed by IRE Post-IRE chemotherapy	58%, 40, 32, and 58.8% 21.4, 40, 50, and 62% 75% 37.5%

complications.[21,22,30,31] These factors are summarized in ►**Table 5**.

Risk of Bias and Quality Assessment

►**Table 6** shows Newcastle-Ottawa quality assessment scores.

Discussion

The results of our systematic review reveal that major complications associated with percutaneous IRE for PDAC are uncommon. Most are minor. The IRE-related mortality is rare.

IRE is a novel ablative technique used for local ablation of various hepatobiliary malignancies, particularly PDAC.[38,39] It offers substantial benefits in patients with unresectable PDAC who have a dismal prognosis and a low survival rate. PDACs are detected at an advanced stage due to nonspecific abdominal complaints; hence, most patients fall into the LAPC/metastatic category.[1,40] Since major vascular encasement constitutes an inoperable disease, using other local thermal ablative techniques like RFA, MWA, or cryoablation are less effective due to the heat sink effect and the risk of vascular/biliary damage.[41,42] IRE offers advantages as it theoretically preserves the vascular structures surrounding the tumor. It acts by disrupting the cellular homeostatic mechanism and inducing cell apoptosis.[43–46] It has now been increasingly used in combinations with adjuvant chemotherapy/radiotherapy to downgrade the tumor, offer them resectability, or, in metastatic disease, to ensure better survival.[34]

Few studies have compared RFA and MWA in the ablation of PDAC and reported that MWA is safer and more efficacious than RFA.[47,48] The overall survival following RFA has been reported to be 19 to 26.5 months.[47] The overall survival data following MWA are not available. Both these techniques are associated with complications including pancreatitis, pancreatic fistula, ascites, vascular thrombosis, and biliary and duodenal injury, with a higher incidence of the latter three complications in patients undergoing RFA.[47] The overall complication rates of RFA and MWA are reported to be 0 to 26% and 20 to 40%, respectively. However, it is pertinent to note that there is very limited literature on percutaneous RFA and MWA.[47,48] Few studies have thus reported IRE as a safer

Table 6 The Newcastle-Ottawa Scale (NOS) for quality assessment of the included studies

Study	Selection								Comparability				Outcome/exposure						Total score		
	Reader 1				Reader 2				Reader 1		Reader 2		Reader 1			Reader 2			Reader 1	Reader 2	Consensus
	1	2	3	4	1	2	3	4	1a	1b	1a	1b	1	2	3	1	2	3			
Ruarus et al[21]	*		*	*	*		*	*			*	*	*	*	*	*	*	*	6	8	7
Pan et al[22]	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	9	9	9
Månsson et al[23]	*		*	*	*		*	*			*	*	*	*	*	*	*	*	6	8	7
Månsson et al[24]	*	*	*	*	*	*	*	*			*		*	*		*	*	*	6	8	7
Narayanan et al[28]	*		*	*	*	*					*		*		*	*			5	4	5
Scheffer et al[29]	*		*	*	*		*	*			*	*	*	*	*	*	*	*	6	8	7
Månsson et al[30]	*		*	*	*		*	*			*	*	*	*	*	*	*		6	7	7
Flak et al[31]	*	*	*	*	*		*	*	*		*	*	*	*	*	*	*	*	8	8	8
Narayanan et al[32]	*		*	*	*	*					*		*	*	*	*	*		6	5	6
Belfiore et al[33]	*	*	*	*			*	*	*		*		*	*		*			7	4	5
Leen et al[34]	*		*	*	*	*							*	*		*			5	3	4
Liu et al[35]	*	*	*	*	*	*	*	*	*		*		*	*		*	*	*	7	8	8
Ma et al[36]	*	*			*	*	*	*	*	*			*	*	*	*	*	*	7	7	7
Tasu et al[37]	*	*		*	*	*	*	*			*		*	*	*	*	*	*	6	8	8

technique than RFA in PDAC, associated with lower mortality and a better safety profile.[12,39,49]

Literature regarding the use of cryoablation in pancreatic cancer is also limited. Complications of cryoablation are attributed to the small volume and fragility of the pancreatic parenchyma and its proximity to structures like the stomach, duodenum, colon, and vascular structures at the porta.[50–52] Reported complications range from delayed gastric emptying to biliary injury and intra-abdominal bleeding.[13,53,54]

In a systematic review by Scheffer et al evaluating the safety and efficacy of IRE for various malignancies, it was reported that the complication rate was highest for the lung (50%), followed by renal (36%), pancreas (19%), and liver tumors (16%). Major complications, including CTCAE III, IV, and V, and procedure-related mortality were observed only with pancreatic tumors.[55] Gupta et al reported a complication rate of 23.7% and major complications in 6.9% of patients undergoing IRE for liver malignancies.[56] Few studies compared percutaneous and open IRE for pancreatic cancer.[31,35] Liu et al enrolled patients undergoing IRE with both open and percutaneous techniques. Percutaneous IRE was reported to have a higher number of overall complications and major complications than patients undergoing open IRE.[35] We note that most of the complications after percutaneous IRE are minor. Intraprocedural complications like muscle weakness, cardiac arrhythmias, and hypotension are common and self-resolving. Postprocedure gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and abdominal pain, and systemic symptoms like fever, fatigue, and chills predominate.

Although IRE is a nonthermal technique of ablation and theoretically does not damage the extracellular matrix and collagenous structures, it is still reported to cause biliary epithelial and vascular endothelial damage producing major complications.[17,49] Biliary complications include bile leaks and strictures. Scheffer et al recommended prophylactic biliary stent placement/percutaneous biliary drainage even without preexisting biliary obstruction.[29] The vascular complications include portal vein thrombosis, superior mesenteric vein thrombosis, and SMA occlusion. These had variable outcomes requiring prolonged anticoagulation and/or stenting.[21,23,29–31,35] Intra-abdominal bleeding is another major complication. Duodenal ulcer leading to perforation or bleeding is seen in the cases where the tumor is close to the duodenum.[21,29–31,35] Liu et al reported duodenal hemorrhage only in patients with duodenal/gastric and vascular invasion.[35]

There were a few limitations to our study. First, the available data on percutaneous IRE are limited. Second, many studies had a heterogenous population with PDAC as one of the subgroups rather than exclusive tumor type. Third, many studies included both percutaneous and open surgical methods of IRE. Fourth, the severity grading system used by the studies was variable. Fifth, a few studies may have overlapping patients.[28,32] Finally, it would have been helpful to compare the complication rate of IRE with other ablative techniques. However, there are very few comparative studies.

In conclusion, our systematic review provides insight into the complications associated with percutaneous IRE for PDAC. Although most complications are minor, significant hemorrhagic and biliary complications can occur, despite IRE being theoretically considered safe for blood vessels and bile ducts. Thus, caution must be exercised in treating tumors causing vascular encasement. Due to the limitations of available data, trials comparing different ablative techniques and open versus percutaneous methods must be conducted to identify the safest method to treat patients with LAPC.

Ethics Approval
As per the institute ethics committee, ethical approval is not required for systematic review and meta-analysis.

Availability of Data and Materials
All data associated with the manuscript have been presented in the paper.

Authors' Contributions
H.B., M.G., M.M. screened the studies, extracted data, performed quality assessment, and wrote the initial draft. V.S. and P.G. wrote the initial draft and critically revised the manuscript.

Funding
None.

Conflict of Interest
None declared.

References
1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(01):7–30
2 American Cancer Society. Cancer Facts & Figures 2011. Atlanta, GA: American Cancer Society; 2011
3 Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009;16(07):1727–1733
4 Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 2007;25(03):326–331
5 Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol 2008;19(09):1592–1599
6 Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011;29(31):4105–4112
7 Jones RP, Psarelli EE, Jackson R, et al; European Study Group for Pancreatic Cancer. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg 2019;154(11):1038–1048
8 Hadjicostas P, Malakounides N, Varianos C, Kitiris E, Lerni F, Symeonides P. Radiofrequency ablation in pancreatic cancer. HPB (Oxford) 2006;8(01):61–64

9 D'Onofrio M, Barbi E, Girelli R, et al. Radiofrequency ablation of locally advanced pancreatic adenocarcinoma: an overview. World J Gastroenterol 2010;16(28):3478–3483
10 Lygidakis NJ, Sharma SK, Papastratis P, et al. Microwave ablation in locally advanced pancreatic carcinoma: a new look. Hepatogastroenterology 2007;54(77):1305–1310
11 Thanos L, Poulou LS, Mailli L, Pomoni M, Kelekis DA. Image-guided radiofrequency ablation of a pancreatic tumor with a new triple spiral-shaped electrode. Cardiovasc Intervent Radiol 2010;33 (01):215–218
12 Wu Y, Tang Z, Fang H, et al. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. J Surg Oncol 2006;94(05):392–395
13 Li J, Chen X, Yang H, et al. Tumour cryoablation combined with palliative bypass surgery in the treatment of unresectable pancreatic cancer: a retrospective study of 142 patients. Postgrad Med J 2011;87(1024):89–95
14 Pezzilli R, Serra C, Ricci C, et al. Radiofrequency ablation for advanced ductal pancreatic carcinoma: is this approach beneficial for our patients? A systematic review. Pancreas 2011;40(01): 163–165
15 Charpentier KP, Wolf F, Noble L, Winn B, Resnick M, Dupuy DE. Irreversible electroporation of the liver and liver hilum in swine. HPB (Oxford) 2011;13(03):168–173
16 Ruarus A, Vroomen L, Puijk R, Scheffer H, Meijerink M. Locally advanced pancreatic cancer: a review of local ablative therapies. Cancers (Basel) 2018;10(01):E16
17 Kalra N, Gupta P, Gorsi U, et al. Irreversible electroporation for unresectable hepatocellular carcinoma: initial experience. Cardiovasc Intervent Radiol 2019;42(04):584–590
18 Maor E, Ivorra A, Leor J, Rubinsky B. The effect of irreversible electroporation on blood vessels. Technol Cancer Res Treat 2007;6 (04):307–312
19 Au JT, Wong J, Mittra A, et al. Irreversible electroporation is a surgical ablation technique that enhances gene transfer. Surgery 2011;150(03):474–479
20 José A, Sobrevals L, Ivorra A, Fillat C. Irreversible electroporation shows efficacy against pancreatic carcinoma without systemic toxicity in mouse models. Cancer Lett 2012;317(01):16–23
21 Ruarus AH, Vroomen LGPH, Geboers B, et al. Percutaneous irreversible electroporation in locally advanced and recurrent pancreatic cancer (PANFIRE-2): a multicenter, prospective, single-arm, phase II study. Radiology 2020;294(01):212–220
22 Pan Q, Hu C, Fan Y, Wang Y, Li R, Hu X. Efficacy of irreversible electroporation ablation combined with natural killer cells in treating locally advanced pancreatic cancer. JBUON 2020;25(03): 1643–1649
23 Månsson C, Nilsson A, Nygren P, Karlson BM. Ultrasound-guided percutaneous irreversible electroporation for treatment of locally recurrent pancreatic cancer after surgical resection. Anticancer Res 2020;40(05):2771–2775
24 Månsson C, Brahmstaedt R, Nygren P, Nilsson A, Urdzik J, Karlson BM. Percutaneous irreversible electroporation as first-line treatment of locally advanced pancreatic cancer. Anticancer Res 2019; 39(05):2509–2512
25 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(71):n71
26 National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. NIH publication # 09–7473 Bethesda, MA: NIH; 2010
27 Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250(02):187–196
28 Narayanan G, Hosein PJ, Arora G, et al. Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. J Vasc Interv Radiol 2012;23(12): 1613–1621
29 Scheffer HJ, Vroomen LG, de Jong MC, et al. Ablation of locally advanced pancreatic cancer with percutaneous irreversible electroporation: results of the phase I/II PANFIRE study. Radiology 2017;282(02):585–597
30 Månsson C, Brahmstaedt R, Nilsson A, Nygren P, Karlson BM. Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy. Eur J Surg Oncol 2016;42(09):1401–1406
31 Flak RV, Stender MT, Jensen TM, et al. Treatment of locally advanced pancreatic cancer with irreversible electroporation: a Danish single center study of safety and feasibility. Scand J Gastroenterol 2019;54(02):252–258
32 Narayanan G, Hosein PJ, Beulaygue IC, et al. Percutaneous image-guided irreversible electroporation for the treatment of unresectable, locally advanced pancreatic adenocarcinoma. J Vasc Interv Radiol 2017;28(03):342–348
33 Belfiore G, Belfiore MP, Reginelli A, et al. Concurrent chemotherapy alone versus irreversible electroporation followed by chemotherapy on survival in patients with locally advanced pancreatic cancer. Med Oncol 2017;34(03):38
34 Leen E, Picard J, Stebbing J, Abel M, Dhillon T, Wasan H. Percutaneous irreversible electroporation with systemic treatment for locally advanced pancreatic adenocarcinoma. J Gastrointest Oncol 2018;9(02):275–281
35 Liu S, Qin Z, Xu J, et al. Irreversible electroporation combined with chemotherapy for unresectable pancreatic carcinoma: a prospective cohort study. OncoTargets Ther 2019;12:1341–1350
36 Ma Y, Xing Y, Li H, et al. Irreversible electroporation combined with chemotherapy and PD-1/PD-L1 blockade enhanced antitumor immunity for locally advanced pancreatic cancer. Front Immunol 2023;14:1193040
37 Tasu JP, Herpe G, Damion J, et al. Irreversible electroporation to bring initially unresectable locally advanced pancreatic adenocarcinoma to surgery: the IRECAP phase II study. Eur Radiol 2024; 34(10):6885–6895
38 Zimmerman A, Grand D, Charpentier KP. Irreversible electroporation of hepatocellular carcinoma: patient selection and perspectives. J Hepatocell Carcinoma 2017;4:49–58
39 Sutter O, Calvo J, N'Kontchou G, et al. Safety and efficacy of irreversible electroporation for the treatment of hepatocellular carcinoma not amenable to thermal ablation techniques: a retrospective single-center case series. Radiology 2017;284(03): 877–886
40 Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15(08):1028–1061
41 Casadei R, Ricci C, Pezzilli R, et al. A prospective study on radiofrequency ablation locally advanced pancreatic cancer. Hepatobiliary Pancreat Dis Int 2010;9(03):306–311
42 Girelli R, Frigerio I, Salvia R, Barbi E, Tinazzi Martini P, Bassi C. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. Br J Surg 2010;97(02):220–225
43 Bower M, Sherwood L, Li Y, Martin R. Irreversible electroporation of the pancreas: definitive local therapy without systemic effects. J Surg Oncol 2011;104(01):22–28
44 Martin RC II, McFarland K, Ellis S, Velanovich V. Irreversible electroporation therapy in the management of locally advanced pancreatic adenocarcinoma. J Am Coll Surg 2012;215(03): 361–369
45 Paiella S, Butturini G, Frigerio I, 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(02):90–97
46 Martin RC II, Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with

irreversible electroporation: safety and efficacy. Ann Surg 2015; 262(03):486–494, discussion 492–494
47 Narayanan G, Daye D, Wilson NM, Noman R, Mahendra AM, Doshi MH. Ablation in pancreatic cancer: past, present and future. Cancers (Basel) 2021;13(11):2511
48 Vogl TJ, Panahi B, Albrecht MH, et al. Microwave ablation of pancreatic tumors. Minim Invasive Ther Allied Technol 2018;27 (01):33–40
49 Varshney S, Sewkani A, Sharma S, et al. Radiofrequency ablation of unresectable pancreatic carcinoma: feasibility, efficacy and safety. JOP 2006;7(01):74–78
50 Maiettini D, Mauri G, Varano G, et al. Pancreatic ablation: minimally invasive treatment options. Int J Hyperthermia 2019;36 (02):53–58
51 Xu KC, Niu LZ, Hu YZ, et al. A pilot study on combination of cryosurgery and (125)iodine seed implantation for treatment of locally advanced pancreatic cancer. World J Gastroenterol 2008; 14(10):1603–1611
52 Niu LZ, Li HB, Wen WF, et al. Feasibility and safety of percutaneous cryoablation for locally advanced pancreatic cancer. Zhonghua Yixianbing Zazhi 2011;11:1–4
53 Song ZG, Hao JH, Gao S, Gao CT, Tang Y, Liu JC. The outcome of cryoablation in treating advanced pancreatic cancer: a comparison with palliative bypass surgery alone. J Dig Dis 2014;15(10): 561–569
54 Niu L, He L, Zhou L, et al. Percutaneous ultrasonography and computed tomography guided pancreatic cryoablation: feasibility and safety assessment. Cryobiology 2012;65(03):301–307
55 Scheffer HJ, Nielsen K, de Jong MC, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol 2014;25(07):997–1011, quiz 1011
56 Gupta P, Maralakunte M, Sagar S, et al. Efficacy and safety of irreversible electroporation for malignant liver tumors: a systematic review and meta-analysis. Eur Radiol 2021;31(09): 6511–6521

