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CONTINUING EDUCATION – HEPATOBILIARY TUMORS

Systematic Review of Surgical and Percutaneous Irreversible Electroporation in the Treatment of Locally Advanced Pancreatic Cancer

Dimitrios Moris, MD, MSc, PhD[1,2], Nikolaos Machairas, MD, PhD[3], Diamantis I. Tsilimigras, MD[1,3], Anastasia Prodromidou, MD[3], Aslam Ejaz, MD[1], Matthew Weiss, MD[4], Natasha Hasemaki, MD[3], Evangelos Felekouras, MD, PhD[3], and Timothy M. Pawlik, MD, MPH, PhD, FACS, FRACS (Hon.)[1]

[1]Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, Wexner Medical Center, James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH; [2]Department of Surgery, Duke University Medical Center, Durham, NC; [3]First Department of Surgery, Laikon General Hospital, University of Athens Medical School, Athens, Greece; [4]Department of Surgery, Johns Hopkins Hospital, Baltimore, MD

ABSTRACT

Objective. The aim of the present systematic review was to collect, analyze, and critically evaluate the role of irreversible electroporation (IRE) in locally advanced pancreatic cancer (LAPC). Furthermore, we sought to analyze the different approaches of IRE (open, laparoscopic, and percutaneous) and assess the relative outcomes.

Methods. A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Using the MEDLINE (1966–2018), Scopus (2004–2018), Google Scholar (2004–2018) and ClinicalTrials.gov databases, eligible articles published up to August 2018 were included. The following keywords were applied: 'irreversible electroporation', 'IRE', 'LAPC', 'unresectable pancreatic cancer', 'palliative treatment', 'locally advanced pancreatic cancer', 'ablation' and 'ablative treatment'.

Results. IRE for LAPC was feasible and safe; however, it was associated with morbidity in approximately one in three patients, some of whom experienced serious complications, particularly after surgical IRE. In addition, while mortality following IRE was uncommon, it did occur in 2% of patients. While some studies suggested a survival benefit, others failed to note an improvement in long-term outcomes following IRE compared with other therapies.

Conclusions. Providers and patients need to be aware of the potential morbidity and mortality associated with IRE. In addition, based on the literature to date, the survival benefit of IRE for LAPC remains to be elucidated. Conclusive and definitive evidence to support a survival benefit of IRE does not currently exist. Future multicenter, randomized, prospective trials are needed to clarify the role of IRE in patients with LAPC.

Pancreatic cancer (PC) is one of the most lethal malignancies, with a dismal prognosis and only an 8–10% 5-year overall survival.[1] According to recent estimates,[1] approximately 53,000 new patients are diagnosed with PC and 43,000 PC patients die annually in the US. Surgical resection with microscopically negative margins (R0) offers the best chance for long-term survival. However, at the time of presentation, approximately 80% of patients are not surgical candidates due to the presence of metastatic (50%) or locally advanced disease (30–40%).[2]

Previous management of patients with locally advanced PC (LAPC) utilized gemcitabine-based chemotherapy with or without radiation therapy,[3,4] which provided only a marginal survival benefit.[5] More recently, the use of more efficient chemotherapeutic regimens such as gemcitabine/nab-paclitaxel and FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) in a neoadjuvant setting for LAPC have increased the amount of patients eligible for

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T. M. Pawlik, MD, MPH, PhD, FACS, FRACS (Hon.)
e-mail: tim.pawlik@osumc.edu

curative-intent surgery among patients with LAPC.[6–8] Notably, these regimens have improved response rates by approximately 30%, as well as survival compared with gemcitabine monotherapy.[8] However, due to the limited available data on the superiority of one regimen over the other, a decision regarding which regimen to administer remains a challenge. The awaited outcomes of the S1505 randomized trial are expected to provide stronger evidence on the efficacy of these two novel regimens for patients with LAPC.[9]

Nevertheless, a large proportion of patients with locally advanced tumors remain ineligible for curative-intent resection despite multimodal treatment. In this circumstance, ablation strategies such as cryoablation, radiofrequency ablation, microwave ablation, high-intensity focused ultrasound, and irreversible electroporation (IRE) have been utilized as alternative local therapies.[10] IRE was first utilized in 2009 for LAPC as a consolidative therapy because of its non-thermal injury method of action.[11] Through high-voltage, small microsecond pulse lengths, nanoscale micropores are formed in the lipid bilayer of cell membranes. In turn, this increases permeability to ions and macromolecules and leads to cell swelling and death through apoptosis. Given that IRE causes cell death through apoptosis, structures formed by proteins such as vascular elastin and collagenous structures are not affected, thus surrounding vessels are preserved. Unlike thermal-induced necrosis, which results in fibrosis and scarring, with the application of IRE the apoptotic cells are phagocytosed by immune cells and replaced by innate cellular degeneration.[12] This ablative method can be performed through an open, laparoscopic, or percutaneous approach.

A number of studies have confirmed the safety and feasibility of IRE for patients with LAPC.[13–15] The aim of the present systematic review was to collect, analyze, and critically evaluate the role of IRE in LAPC. Furthermore, we sought to analyze the different approaches of IRE (open, laparoscopic, and percutaneous) and assess the relative outcomes.

MATERIALS AND METHODS

Search Sources and Study Design

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] Three independent authors (NH, NM, AP) meticulously searched for potentially eligible articles published up to August 2018 using the MEDLINE (1966–2018), Scopus (2004–2018), Google Scholar (2004–2018) and ClinicalTrials.gov databases. No language restrictions were applied, however the following keywords were searched: 'irreversible electroporation', 'IRE', 'LAPC', 'unresectable pancreatic cancer', 'palliative treatment', 'locally advanced pancreatic cancer', 'ablation', and 'ablative treatment'. The references of the included studies were manually screened in order to minimize the chance of missing any relevant studies.

Eligibility Criteria

All appropriate observational studies (prospective and retrospective) and case reports addressing the outcomes of patients with unresectable LAPC who were offered only IRE with or without pre-or post-treatment chemotherapy or radiotherapy were considered eligible for inclusion in the present systematic review. Studies reporting outcomes of patients who underwent surgical resection combined with IRE for margin accentuation, but not as primary tumor treatment, were excluded. Specifically, studies reporting on at least one post-IRE outcome (morbidity, mortality, OS, progression-free-survival (PFS), response to therapy and disease progression) were included. Reviews and preclinical studies were also excluded from analysis. After exclusion of studies with overlapping populations, the selected variables were tabulated in structured forms. Articles that fulfilled the inclusion criteria were retrieved for full-text evaluation.

Data Extraction

After reviewing the full-texts of eligible studies, two independent authors (NH, NM) performed the data extraction and crosschecked all results. Potential discrepancies in the selection of articles and extraction of the data were resolved following consensus with a third reviewer (DIT). Data on patient characteristics included age, sex, tumor location, tumor size, IRE approach (percutaneous, open, laparoscopic), previous chemotherapy or radiotherapy, post-treatment chemotherapy, number or IRE probes used, and duration of IRE administration. Survival was defined as the interval from the IRE application during which the patient remained either alive (OS) or without disease progression (PFS). Morbidity and mortality following IRE were also evaluated. Finally, response to therapy with regard to downstaged or stable disease, as well as the distant or local progression of disease, was also assessed.

Definitions

Morbidity was defined as the occurrence of any type of post-treatment complications. Complications were classified and recorded according to the Clavien–Dindo

classification system.[17] Mortality was defined as the number of deaths, both related and unrelated to IRE, following 30, 60, or 90 days from IRE application. IRE-related mortality, if any, was separately addressed in the main text.

RESULTS

Identification of Eligible Studies

The PRISMA flow diagram schematically depicts the article selection process (Fig. 1). A total of 18 original studies incorporating 498 patients with unresectable LAPC who underwent IRE were included.[13,14,18–33] Among all included studies, eight reports were retrospective single-center studies (n = 371 patients),[13,18,19,22,26,28,30,33] three were case reports (n = 3 patients),[21,29,32] and the remaining seven studies were prospective, single-center studies (n = 124 patients).[14,20,23–25,27,31] In addition, a total of 25 ongoing trials were identified through the ClinicalTrials.gov database. Nine studies were excluded from further analysis after reading the full text. Among these studies, two were excluded with the intention to minimize overlap.[34,35] Four studies were excluded because the reports did not detail separate outcomes for patients undergoing IRE for margin accentuation and primary management of disease.[11,36–38] Another study reported outcomes of patients who underwent combined IRE and allogenic natural killer cell immunotherapy.[39] The studies by Vroomen et al. and Philips et al. were excluded due to insufficient data.[40,41]

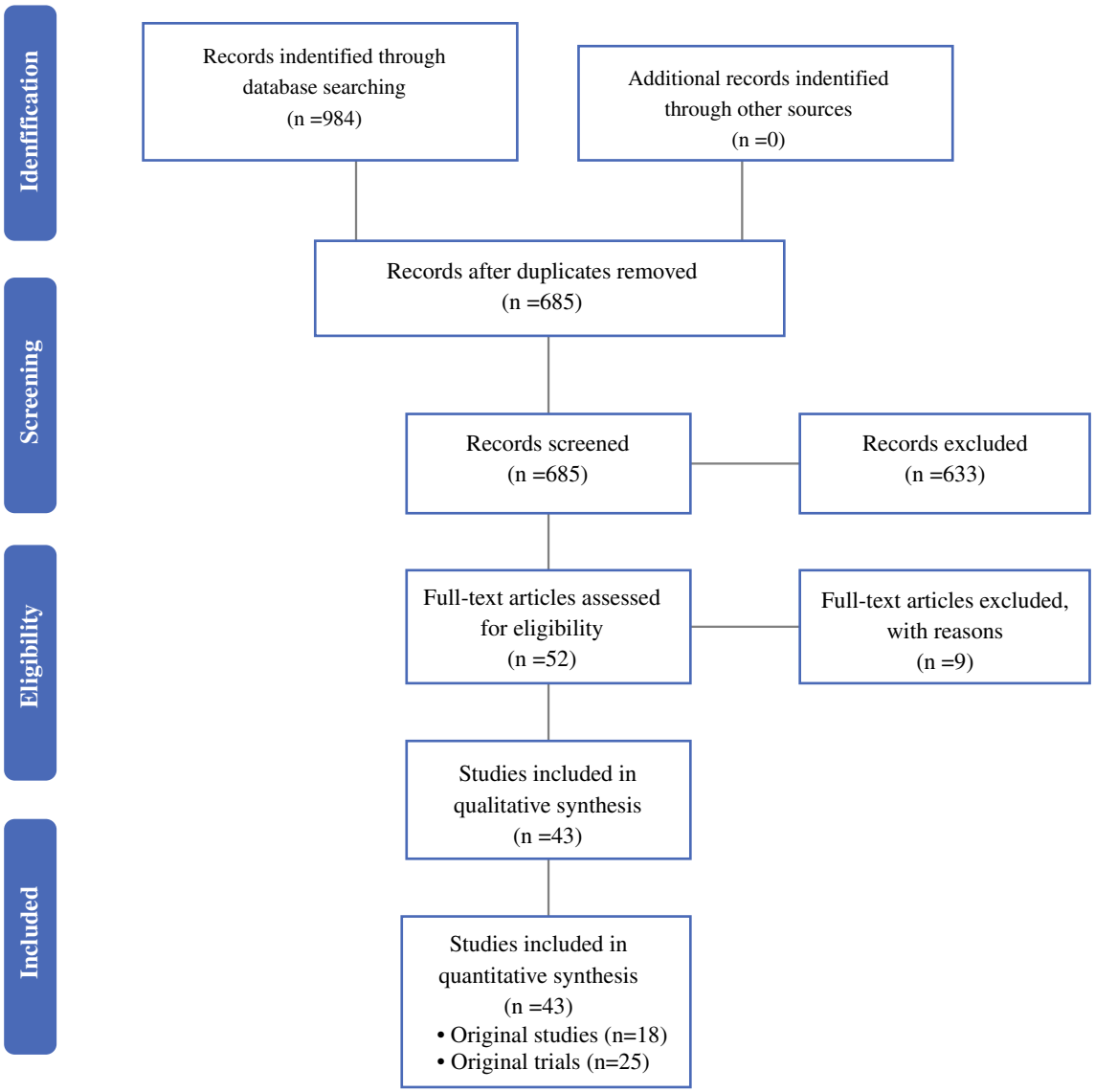

FIG. 1 Study search strategy

TABLE 1 Study and patient characteristics

Year; author	Type of study	Indication for IRE	No. of patients	Age (years)	Male sex	Tumor location	Tumor size (cm)
Open IRE							
2018; Spiliotis et al.[18]	RSC	LAPC	10	62 (48–73)[a]	6	Head, 7 Tail, 3	NA
2017; Vogel et al.[14]	PSC	LAPC	15	NA	NA	NA	NA
2016; Yan et al.[26]	RSC	LAPC (< 5 cm)	25	58 (49–80)[a]	19	Head, 15 Body/neck, 10	4.2 (2.8–4.9)[a]
2015; Kluger et al.[30]	RSC	LAPC T4	29	68.6 (63.4–73.8)[a]	15	Head, 17 Body/neck, 12	2.7 (2.4–4.0)[a]
2015; Martin et al.[13]	RSC	LAPC	150	NA	NA	Head, 95 Body/neck, 55	3 (1–6)[a]
2015; Paiella et al.[31]	PSC	LAPC (< 4 cm)	10	66	4	Head, 7 Body, 3	3 (2.5–3.9)[a]
Laparoscopic IRE							
2018; Tartaglia et al.[21]	CR	LAPC	1	69	0	Neck	3.5
2016; Stillström et al.[33]	RSC	LAPC	3	75 (64–78)[a]	1	Head, 3	3.5 (3–5)[a]
Percutaneous IRE							
2018; Leen et al.[19]	RSC	LAPC	75	63.4 (32–79)[a]	53	Head, 51 Body/tail, 24	3.47 ± 1.2[b]
2017; Belfiore et al.[22].	RSC	LAPC	29	68.5 (55–81)[c]	16	Head, 15 Isthmus, 5 Body/tail, 9	9.7 (4.2–17)[a]
2017; Scheffer et al.[23]	PSC	LAPC (< 5 cm)	25	61 (41–78)[a]	12	Head, 18 Body, 2 Uncinate, 5	4 (3.3–5)[a]
2017; Zhang et al.[24]	PSC	LAPC	21	NA	NA	Head/neck, 16 Body/tail, 5	3.5 (2.0–6.7)
2016; Mansson et al.[27]	PSC	LAPC	24	65 (42–77)[a]	12	Head, 19 Body, 5	3.5 (2.5–4.5)[a]
2016; Narayanan et al.[28]	RSC	LAPC	50	62.5 (46–91)[a]	27	NA	3.2 ± 1.3[b]
2015; Trueba-Arguinarena[29]	CR	LAPC	1	66	1	Body	4
2012; Bagla and Papadouris[32]	CR	LAPC T4	1	76	1	NA	4.1 × 4.1 × 3.5
Open and percutaneous IRE							
2018; Sugimoto et al.[20]	PSC	LAPC	8	64	5	Head, 5 Body, 3	2.95 (2–4.8)[a]
2016; Lambert et al.[25]	PSC	LAPC (≤ 6.5 cm)	21	68.2 ± 8.4[b]	10	Head, 17 Body, 3 Tail, 1	3.82 ± 1.15[b]

TABLE 1 continued

Year; author	Chemotherapy before IRE (%)	Radiation before IRE (%)	Chemotherapy after IRE (%)	No of IRE probes	IRE duration (min)
Open IRE					
2018; Spiliotis et al.[18]	9/10 (90) GEMOX, 7 Gemcitabine, 2	0/10 (0)	NA	NA	NA
2017; Vogel et al.[14]	9/15 (60) FOLFIRINOX, 9	0/15 (0)	NA	NA	NA
2016; Yan et al.[26]	1/25 (4)	3/25 (12)	Chemotherapy or radiotherapy, 7	4 (2–6)[a]	36 (23–101)[a]
2015; Kluger et al.[30]	24/29 (83) GTX/GAX, 14 FOLFIRINOX, 3 Other, 7	18/29 (62)	NA	4 (3–6)[a]	84 (54–118)[a]
2015; Martin et al.[13]	130/150 (89) Gemcitabine-based, 90 FOLFIRINOX, 44	77/150 (47)	104/150 (69)	4 (2–6)[a]	35 (10–125)[a]
2015; Paiella et al.[31]	10/10 (100) Gemcitabine, 2 GEMOX, 5 GEMOX and FOLFIRINOX, 2 PEXG, 1	4/10 (40)	3/10 (30)	4 (2–6)[a]	79.5 (20–148)[a]
Laparoscopic IRE					
2018; Tartaglia et al.[21]	FOLFIRINOX	0/1 (0)	NA	NA	182
2016; Stillström et al.[33]	NA	NA	NA	NA	190 (156–282)[a]
Percutaneous IRE					
2018; Leen et al.[19]	75/75 (100) FOLFIRINOX, 28 Gemcitabine-based, 47	4/75 (5.3)	75/75 (100) NA	NA	32 (25–40)[a]
2017; Belfiore et al.[22].	NA	NA	29/29 (100) GemOx	3 (2–5)[a]	NA
2017; Scheffer et al.[23]	13/25 (52) Gemcitabine, 2 FOLFIRINOX, 10 Gemcitabine + nab-paclitaxel, 1	0/25 (0)	NA	6 (3–9)[a]	NA
2017; Zhang et al.[24]	NA	NA	NA	NA	NA
2016; Mansson et al.[27]	22/24 (91.6)	10/24 (41.6)	14/24 (58)	NA	NA
2016; Narayanan et al.[28]	50/50 (100) Gemcitabine-based, 15 FOLFIRINOX, 14 FOLFIRINOX and gemcitabine-based, 17 Other, 4	30/50 (60)	25/50 (50)	3 (1–6)[a]	NA

TABLE 1 continued

Year; author	Chemotherapy before IRE (%)	Radiation before IRE (%)	Chemotherapy after IRE (%)	No of IRE probes	IRE duration (min)
2015; Trueba-Arguinarena[29]	1/1 (100) Nab-paclitaxel and gemcitabine	0/1 (0)	1/1 (100)	6	NA
2012; Bagla and Papadouris[32]	0/1 (0)	0/1 (0)	1/1 (100)	First IRE, 4 Second IRE, 3	NA
Open and percutaneous IRE					
2018; Sugimoto et al.[20]	8/8 (100) FOLFIRINOX 2 Gemcitabine, 2 Gemcitabine + nab-paclitaxel, 4	4/8 (50)	8/8 (100) NA	4 (3–4)[a]	NA
2016; Lambert et al.[25]	5/21 (23.8)	NA	7/21 (33)	NA	79 ± 23[b] (open) 26[b] (percutaneous)

IRE irreversible electroporation, *RSC* retrospective single-center, *PSC* prospective single-center, *CR* case report, *LAPC* locally advanced pancreatic cancer, *NA* not available, *SD* standard deviation

[a]Median (range)

[b]Mean ± SD

[c]Mean (range)

Patient, Tumor, and Procedure Characteristics

A total of 498 patients underwent open (n = 262, 52.6%), percutaneous (n = 232, 46.6%), or laparoscopic (n = 4, 0.8%) IRE (Table 1). Patient age ranged from 58 to 76 years (median age 65.5 years, interquartile range 62.5–68.3), with males comprising 58.3% (n = 182) of the study sample. The majority of tumors were located in the pancreatic head, neck or uncinate process (n = 296, 68.6%), and 13.6% (n = 59) of tumors were located in the pancreatic body or tail; three studies reported 77 patients (17.8%) with tumors in the pancreatic body or neck. Tumor size ranged from 2.7 to 9.7 cm, and median tumor size was 3.5 cm.

A total of 358 patients (80.6%) received chemotherapy prior to IRE. The most common chemotherapeutic regimens administered were gemcitabine-based (56.1%) and FOLFIRINOX (39.4%) (Table 2). In addition, radiation therapy before IRE was performed in 150 patients (35.4%). Adjuvant chemotherapy after IRE was administered to 274 patients (69.5%). With regard to the IRE procedure, the median number of probes inserted ranged from three to six, while the duration of IRE ranged from 32 to 182 min.

Tumor Response, Morbidity and Mortality

Overall, nine studies reported on tumor response to IRE, although the definition of 'tumor response' was not consistent among eligible studies (Table 2). Following IRE, complete tumor remission was seen in 16% (n = 4/25) of patients, while partial tumor response was achieved in 38.2% (n = 50/131) of patients. Approximately one-half of patients (n = 68/146, 46.6%) had stable disease, whereas 17.2% (n = 23/134) of patients exhibited disease progression. After IRE, 5.3% (n = 10/190) of patients were downstaged and eventually proceeded to curative-intent surgery.[19,22,27,28]

Cumulative overall morbidity was 30% (n = 150/498 patients). Ten studies reported complications according to the Clavien–Dindo classification system;[14,18,20,25–30,33] approximately one-quarter of patients (n = 25/88, 28.4%) experienced grade I–II complications, whereas severe complications (grade III or higher) were reported in 21% (n = 37/176) of patients.

Cumulative mortality after IRE was 2.2% (n = 11/498 patients); 14 studies reported no deaths during the post-IRE period.[18–29,32,33] During follow-up, median OS after IRE varied from 7 to 27 months, and median PFS ranged from 5 to 15 months. Fifty-four (n = 54/164, 32.9%) patients presented with distant metastasis during the follow-up period.

TABLE 2 Short- and long-term outcomes

Year; author	Follow-up (months)	Morbidity (%)	Response to therapy	OS (months)	PFS (months)	Resection feasible (post-IRE)	Mortality (%)	Recurrence (%)
Open IRE								
2018; Spiliotis et al.[18]	10	5/10 (50) 5, CD II	NA	16.7 (4–18)[a]	NA	NA	0/10 (0)	1/1 (100) Local
2017; Vogel et al.[14]	24	8/15 (53) 8, CD III or higher	NA	16	NA	NA	2/15 (13) 90-day	NA
2016; Yan et al.[26]	3	9/25 (36) 7, CD I–II 2, CD III	36% PR 28% SD 36% DP	NA	NA	NA	0/25 (0)	2/25 (8) Distant
2015; Kluger et al.[30]	8.69 (0.26–16.26)[a]	7/29 (24) 4, CD III–IV 3, CD IV	NA	7.71 (6–12)[b]	NA	NA	5/29 (17) 90-day	NA
2015; Martin et al.[13]	29	54/150 (36)	NA	18 (4.9–55.4)[a]	NA	NA	3/150 (2) 90-day	NA
2015; Paiella et al.[31]	7.6	2/10 (20)	40% PR 30% SD 30% DP	7.5 (2.9–15.9)[a]	NA	NA	1/10 (10) 30-day	3/10 (30) Distant
Laparoscopic IRE								
2018; Tartaglia et al.[21]	6	0/1 (0)	100% SD	6	NA	NA	0/1 (0)	NA
2016; Stillström et al.[33]	14 (4–14)[a]	2/3 (66) 2, CD IIIa	33% SD 33% CR 33% DP	14 (4–14)[a]	NA	0/3	0/3 (0)	1/3 (33) Local
Percutaneous IRE								
2018; Leen et al.[19]	11.7 (3–45)[a]	19/75 (25)	31% PR 66% SD 3% DP	27 (21.1–32.8)[b]	15	3 (4)	0/75 (0)	29/75 (38) Distant
2017; Belfiore et al.[22]	29	0/29 (0)	NA	14 (9.8–18.1)[b]	NA	3 (10)	0/29 (0)	NA
2017; Scheffer et al.[23]	12 (7–16)[a]	10/25 (40)	NA	11 (9–13)[b]	12	NA	0/25 (0)	NA
2017; Zhang et al.[24]	1	3/21 (14.3)	42.9% PR 13.6% SD 9.5% CR	NA	NA	NA	0/21 (0)	NA
2016; Mansson et al.[27]	NA	11/24 (100) 8, CD I–II 3, CD III–IV	NA	7 (1–19)[a]	NA	1 (4)	0/24 (0)	14/24 (58) local 13/24 (54) distant
2016; Narayanan et al.[28]	NA	10/50 (20) 10, CD III–IV	NA	14.2 (9.7–16.2)[a]	NA	3 (6)	0/50 (0)	NA
2015; Trueba-Arguinarena et al.[29]	12	1/1 (100) 1, CD III	100% CR	NA	NA	NA	0/1 (0)	No
2012; Bagla and Papadouris[32]	5	0/1 (0)	100% SD	NA	NA	0 (0)	0/1 (0)	1/1 (100) distant

TABLE 2 continued

Year; author	Follow-up (months)	Morbidity (%)	Response to therapy	OS (months)	PFS (months)	Resection feasible (post-IRE)	Mortality (%)	Recurrence (%)
Open and percutaneous IRE								
2018; Sugimoto et al.[20]	17.5	4/8 (50) 2, CD I–II 2, CD III–IV	NA	17.5 (9–20.5)[a]	5	0 (0)	0/8 (0)	3/8 (38) local 5/8 (62) distant
2016; Lambert et al.[25]	NA	5/21 (23.8) 3, CD II 2, CD IIIb	23.8% ≥ 10 mm decrease in size 19% SD 38% DP	10.2	NA	NA	0/21 (0)	8/21 (38) local 1/21 (5) distant

IRE irreversible electroporation, *OS* overall survival, *PFS* progression-free survival, *NA* not available, *CD* Clavien–Dindo classification, *PR* partial response, *SD* stable disease, *DP* disease progression, *CR* complete remission, *CIs* confidence intervals

[a]Median (range)

[b]Median (90% CIs)

Morbidity and Mortality by Type of Irreversible Electroporation (IRE) Approach

After stratifying by IRE approach, patients undergoing open, laparoscopic, and percutaneous IRE had a cumulative morbidity of 35.6% (85/239 patients), 50% (2/4 patients), and 23.9% (54/226), respectively (Table 3). Although the sample size was limited, major morbidity (Clavien–Dindo grade III or higher) appeared to be more common after laparoscopic (n = 2/4, 50%) versus open (n = 17/79, 21.5%) or percutaneous (n = 14/105, 13.3%) IRE.

Cumulative mortality in patients undergoing open IRE was 4.6% (11/239); no deaths were reported for patients undergoing laparoscopic or percutaneous IRE. Further investigation of the deaths pertaining to the open IRE group demonstrated that these 11 reported deaths were attributed to gastrointestinal bleeding (n = 3, 28%),[13,14,30] intraperitoneal hemorrhage (n = 1, 9%),[30] extensive bile duct and duodenal ischemia (n = 1, 9%),[30] liver failure (n = 2, 18%),[13,14] pulmonary embolism (n = 1, 9%),[13] multi-organ failure (n = 1, 9%),[30] and unknown reasons (n = 2, 18%).[30,31] Only one study reported comparative results of open versus percutaneous IRE.[20] Four patients underwent open IRE and four patients underwent percutaneous IRE for tumors of comparable size. No differences were noted in 30- or 120-day morbidity, or 90-day mortality.[20]

Reported median OS in the open IRE group ranged from 7.5 to 18 months compared with 6–14 months in the laparoscopic IRE group. Only one study reported OS for percutaneous IRE, which had a median OS of < 10 months, although one individual had a survival of 27 months.[19]

IRE Versus Surgery

Lambert et al. performed a matched comparison of patients who underwent IRE versus non-curative surgical procedures and noted no difference between the two approaches; the reported median survival in the IRE group was 10.2 months versus 9.3 months in the control group [hazard ratio (HR) 0.54, p = 0.053].[25] Vogel et al. compared patients with LAPC who received neoadjuvant chemotherapy (FOLFIRINOX or gemcitabine-based) for 3 months and, in the case of non-progressive disease, underwent resection (14 patients) or IRE (15 patients), or neither resection nor IRE (7 patients). A survival benefit was noted among patients who underwent resection alone versus IRE alone or no additional local treatment (median OS 34 months vs. 16 and 15 months, respectively, p = 0.003).[14]

TABLE 3 Cumulative morbidity and mortality rates by type of approach

Type of approach	Morbidity (%)	Major morbidity (CD grade III or higher)	Mortality
Open[a]	87/243 (35.8)	17/79 (21.5)	11/243 (4.5)
Laparoscopic	2/4 (50)	2/4 (50)	0/4 (0)
Percutaneous[a]	56/230 (24.3)	14/105 (13.3)	0/230 (0)

CD Clavien–Dindo classification, *NA* not available

[a]The study Lambert et al. was not included due to the mixed results reported

Prognostic Factors After IRE

Two studies reported on prognostic factors associated with OS and PFS among patients who underwent IRE. Narayanan et al. reported that tumor size was the only factor associated with OS in univariate [HR 0.43, 95% confidence interval (CI) 0.20–0.94; $p = 0.035$] and multivariate analysis (HR 0.31, 95% CI 0.12–0.81); patients with tumors ≤ 3 cm had a survival advantage ($p = 0.017$).[28] Scheffer et al. reported that early local progression (< 6 months) following IRE was the only predictor of worse OS in univariate Cox regression analysis (HR 7.02, 95% CI 1.54–31.96; $p = 0.0083$).[23]

Clinical Trials in the Field

Twenty-five clinical trials were identified through the ClinicalTrials.gov database (Electronic Supplementary Table 1); the majority of trials are currently recruiting patients in China (10/25), followed by the US (6/25). All trials pertain to IRE application in the setting of LAPC. Most trials are utilizing IRE as monotherapy ($n = 17$, 68%), with the remaining trials utilizing IRE in combination with chemotherapy ($n = 5$, 20%) or immunotherapy ($n = 3$, 12%). While most trials are using an open approach, three trials are utilizing percutaneous IRE.

DISCUSSION

IRE is a relatively novel local ablation therapy used in the treatment of patients with LAPC. As treatment paradigms continue to evolve, there is an increasing body of evidence that has evaluated the use of IRE. The current systematic review summarized the collective data on IRE, reporting on the safety and outcomes (mortality, morbidity, survival) of IRE among patients with LAPC. Outcomes were stratified based on the technical approach (open, laparoscopic, percutaneous). Of note, the cumulative overall morbidity following IRE was 30%, whereas the cumulative mortality was 2.2%.[15,42] Of particular interest, among patients undergoing surgical (open or laparoscopic) IRE, morbidity was 36% versus 24.3% among patients who underwent percutaneous IRE. Furthermore, mortality among patients undergoing surgical IRE was 4.4%, whereas no periprocedural mortality was reported among patients who underwent percutaneous IRE. While most studies focused largely on perioperative outcomes, a subset of studies did report on survival. Reported median OS following IRE ranged from 6 to 18 months. In addition, whether IRE provided a survival benefit was inconclusive as at least one study failed to find a benefit of IRE compared with non-curative palliative surgical controls.

Data from the current study demonstrated that the open IRE approach was the most commonly employed technique. In order to determine the optimal approach for each patient, several tumor-, patient-, and specialist-specific factors must be taken into account, including tumor size, location, and body structure, as well as relevant expertise of the operator in each approach. While the percutaneous approach has gained popularity over the last few years, some clinicians have argued that an open approach may allow for more precise needle placement under direct visualization.[12] On the other hand, a surgical approach provides the opportunity to assess for the presence or absence of distant disease since approximately 50% of patients with LAPC may have metastatic disease at the time of surgery that was undetectable with preoperative imaging.[43,44] The percutaneous approach is minimally invasive and has lower complication risks compared with a surgical procedure. Nevertheless, the characteristics of patients who are likely to derive the most benefit from this approach are not yet clearly defined. In fact, given that many patients being considered for IRE have been pretreated, the use of neoadjuvant chemotherapy may decrease the sensitivity of preoperative cross-sectional imaging to detect low-burden metastatic disease.[45] In addition, as radiographic response often does not correlate with actual local pathologic response following neoadjuvant therapy, patients with stable, non-metastatic LAPC often proceed to surgery, at which time resection with or without IRE can be considered. Given that surgical IRE was associated with higher perioperative morbidity and mortality, patients with stable LAPC and poor performance status should likely be considered for percutaneous rather than surgical IRE. In contrast, evidence of a marked radiologic tumor response after neoadjuvant chemotherapy should lead to consideration for surgery if resection is possible. For those patients with persistent borderline disease, resection with or without IRE could be considered. In contrast, metastatic disease should be treated with systemic chemotherapy, and the role of IRE should only even be considered when the metastatic disease is limited and has demonstrated durable stability on systemic therapy (Fig. 2).

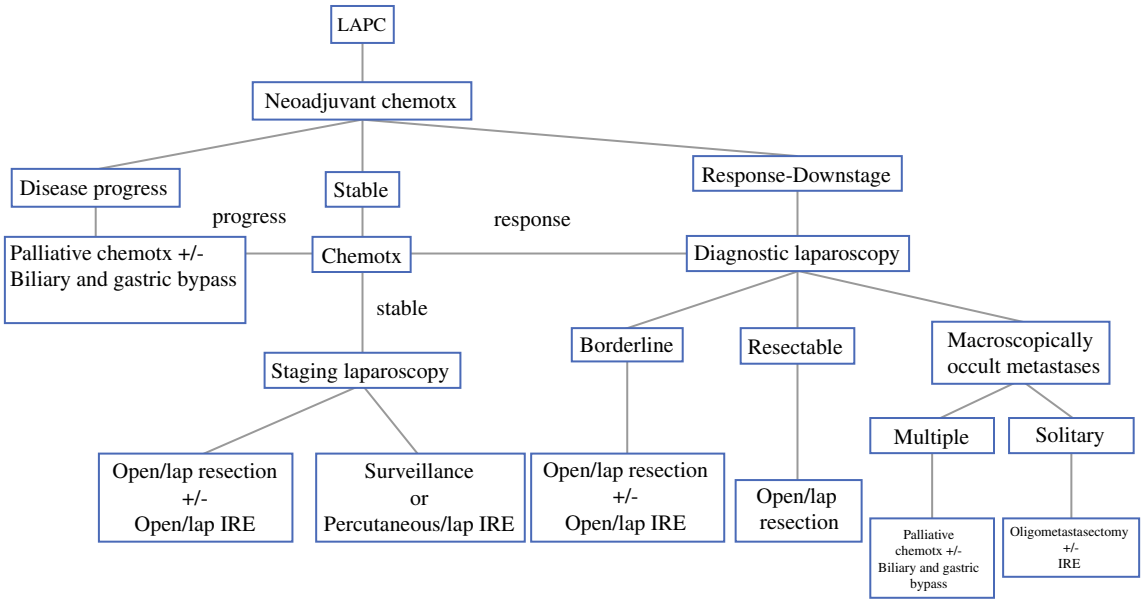

FIG. 2 A proposed treatment algorithm for patients with LAPC. *LAPC* locally advanced pancreatic cancer, *chemotx* chemotherapy, *lap* laparoscopic, *IRE* irreversible electroporation

The potential survival benefit associated with IRE remains to be elucidated. As noted in the current analysis, data from various studies of patients undergoing IRE for LAPC have reported conflicting results. For example, Martin et al. reported a mean OS of 18 months among patients undergoing IRE, and advocated that IRE had a survival benefit compared with patients who did not undergo IRE.[13] Of note, all patients in the study by Martin et al. received induction chemotherapy, most frequently with FOLFIRINOX, and over one-half of patients also received chemoradiotherapy.[13] In a separate report, the Induction Chemotherapy Followed by Resection or Irreversible Electroporation in Locally Advanced Pancreatic Cancer (IMPALA) study noted a median OS of only 16 months among patients undergoing IRE alone, which was not different from an OS of 15 months among patients with non-progressive disease who did not undergo resection or IRE.[14] These discordant results can potentially be explained by different resection rates after neoadjuvant therapy, favorable tumor biology among patients included in the Martin et al. study (e.g. patients had stable or responsive disease after chemotherapy), and the differing characteristics of the underlying patient populations (e.g. comorbidities, post-chemotherapy performance status, access to care). As such, it is difficult to conclude whether or not IRE truly provides a statistically or clinically significant OS benefit compared with a similar cohort of patients treated with chemotherapy alone.

Despite some encouraging preliminary reports, a higher level of evidence is currently lacking to support the routine use of IRE in the treatment of patients with LAPC; randomized trials are imperative in order to validate any potential survival benefit of IRE after neoadjuvant chemotherapy in LAPC. To this point, we identified several ongoing IRE trials. For example, one recent study prospectively examined the application of IRE versus combined IRE and allogeneic natural killer (NK) cell immunotherapy, and demonstrated an improved median PFS (9.3 vs. 8.1 months; $p = 0.0465$) and median OS (13.2 vs. 11.4 months; $p = 0.0411$) among patients with unresectable LAPC in favor of the IRE plus NK group.[39]

The current study had several limitations. The majority of available data on IRE are derived from retrospective or registry databases, which can be influenced by selection and attrition bias. Several studies reported data from overlapping patients; therefore, to account for this, we included only the study with the largest number of patients. In an effort to increase the data available on this emerging technique, study design was not included in the exclusion criteria, and thus caution is warranted when interpreting these results due to potential biases. The cumulative numbers were small and therefore of limited analytic power. One reason is that patients undergoing pancreatic resection combined with IRE were excluded on the basis of analyzing the outcomes of IRE itself in the setting of LAPC. Additionally, there was heterogeneity among some patient and tumor characteristics (location and size), as well as technique (IRE duration). Moreover, while many patients received pre-IRE chemotherapy, the types and duration of chemotherapeutic regimen differed among

patients. Finally, the intent (curative, palliative) of IRE application was not consistently reported among the included studies.

CONCLUSIONS

Based on a systemic cumulative review of the current data, IRE for LAPC was feasible and safe. However, IRE was associated with morbidity in approximately one in three patients, some of whom experienced serious complications, especially after surgical IRE. In addition, while mortality following IRE was uncommon, it did occur in 2% of patients. Therefore, providers and patients need to be aware of the potential morbidity and mortality associated with IRE. Conclusive and definitive evidence to support a survival benefit of IRE does not currently exist. While some studies suggested a survival benefit, other studies failed to note an improvement in long-term outcomes following IRE compared with other therapies. As such, while IRE can be considered for patients with LAPC, future multicenter, randomized, prospective trials are needed to clarify the role of IRE in patients with LAPC.

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