



# Prospective Evaluation of Irreversible Electroporation With Clustered Electrodes as a Novel Palliative Approach for Locally Advanced Pancreatic Cancer

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**Objective:** This study aimed to evaluate the feasibility, safety, and oncologic outcomes of irreversible electroporation (IRE) using a clustered electrode in patients with locally advanced pancreatic cancer (LAPC).

**Materials and Methods:** In this single-center prospective cohort study, 13 patients with LAPC (median age, 60 years; range, 48–78 years) underwent clustered electrode IRE between September 2022 and September 2024. Patient characteristics, procedural details, and clinical outcomes were recorded. Endpoints included technical success, procedure-related complications, overall survival (OS), and progression-free survival (PFS).

**Results:** Tumors were located in the pancreatic head in four patients (30.8%) and in the body/tail in nine (69.2%). The median tumor size was 2.4 cm (1.5–4.0 cm), and vascular invasion was present in all patients. Technical success was achieved in all patients. Intraoperative IRE was performed in 11 (84.6%) patients, and 2 (15.4%) patients underwent percutaneous IRE. Gastrointestinal bleeding events as major complications occurred in two patients (15.4%) and, both were successfully controlled by embolization. No 60-day mortality was observed. At a median follow-up of 24.5 months (range, 9.9–33.4 months) after IRE, median OS and PFS from IRE were 20.1 and 14.5 months, respectively.

**Conclusion:** IRE using clustered electrodes for LAPC appears to be a feasible therapeutic approach, offering reliable technical success and acceptable safety. Survival outcomes are encouraging; however, larger, controlled studies are required.

**Keywords:** Locally advanced pancreatic cancer; Irreversible electroporation; Clustered electrode; Clinical outcomes; Complications

## INTRODUCTION

Pancreatic cancer is one of the leading causes of cancer-related mortality worldwide, with a 5-year overall survival (OS) rate of approximately 11% across all cancer stages [1].

At diagnosis, approximately 30% of patients present with locally advanced pancreatic cancer (LAPC), defined by tumor encasement of major arterial structures in the absence of distant metastases, which precludes surgical resection [2,3]. Although systemic chemotherapy has advanced with regimens

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such as oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and gemcitabine-based combinations, the prognosis for LAPC remains poor, with median OS typically reported between 9 and 15 months [4,5].

Irreversible electroporation (IRE) is a non-thermal ablation technique that induces apoptosis by generating permanent nanopores in the cell membranes through the application of high-voltage electrical pulses. Unlike thermal ablation, IRE preserves surrounding connective tissue, bile ducts, and blood vessels, making it particularly suitable for treating LAPC located adjacent to major vascular structures [6,7]. Clinical evidence to date has established IRE as a feasible and safe therapeutic option for LAPC, with all published studies to date employing multiple monopolar electrodes [6,8].

However, electrode convergence, divergence, or inadequate parallel alignment can create significant technical challenges, as misplacement may reduce the effective ablation zone or generate excessive current, thereby compromising the safety and efficacy of the procedure. Meticulous attention is therefore required to maintain correct parallel alignment and an optimal interelectrode distance of 1.5–2.0 cm between each pair. Meeting these conditions can prolong the procedure and render IRE technically demanding, particularly in deep or anatomically complex regions of the pancreas [9,10]. To address these limitations, a novel clustered unipolar electrode system has been developed.

We aimed to evaluate the technical feasibility, safety, and oncologic outcomes of IRE using a clustered electrode system in patients with LAPC.

## MATERIALS AND METHODS

### Patient Selection

This single-center prospective study was approved by the Institutional Review Board of Severance Hospital (IRB No. 1-2024-0034), and written informed consent was obtained from all participants for study enrollment, the ablation procedure, and use of clinical data. Between September 2022 and September 2024, 13 patients (median age, 60 years; range, 48–78 years) with LAPC underwent IRE using a clustered electrode system. All patients were deemed unsuitable for curative surgical resection after chemotherapy or chemoradiation. The treatment plans were reviewed by a multidisciplinary tumor board to ensure agreement among the treating physicians before IRE. Patient records included

demographic data, treatment history, laboratory findings, and tumor characteristics.

### Eligibility Criteria

Patients were eligible for IRE if they were suitable candidates for general anesthesia, had a tumor measuring  $\leq 4$  cm, and had no history of ventricular cardiac arrhythmia. A serum CA 19-9 level  $< 2,000$  U/mL at the time of scheduling was also required. However, in a few cases, CA 19-9 levels exceeded this threshold immediately before IRE, and treatment was administered at the treating physician's discretion. The exclusion criteria were distant metastasis, transmucosal invasion into adjacent gastrointestinal (GI) structures (stomach, duodenum, or colon), uncontrolled infection, and severe comorbidities that precluded general anesthesia. Notably, the presence of a biliary metal stent was not considered a contraindication and such patients were treated at the operator's discretion.

### Definitions

LAPC was defined as stage III disease, characterized by  $> 180^\circ$  encasement of major arterial structures (superior mesenteric artery and/or celiac axis), involvement or occlusion of the portal vein, and absence of distant organ or nodal metastases, thereby rendering the tumor unresectable [8]. Disease status was assessed according to the RECIST 1.1 criteria using contrast-enhanced CT performed within 4 weeks and classified as partial response, stable disease, or progressive disease [11]. Technical success was defined as successful placement of the clustered electrode within the target pancreatic lesion under image guidance, followed by the delivery of the planned number of electric pulses. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [12]. Procedure-related complications were defined as events occurring within 30 days of IRE. Major complications were defined as those of CTCAE grade 3 or higher. OS was measured from the date of IRE or initial diagnosis to the date of death from any cause. Disease progression was defined as a focal or diffuse increase in tumor size, specifically a  $> 20\%$  increase in the longest axial diameter of the lesion within 1 cm of the ablation zone, relative to the second baseline scan obtained 4 weeks after IRE [11].

### IRE Procedure

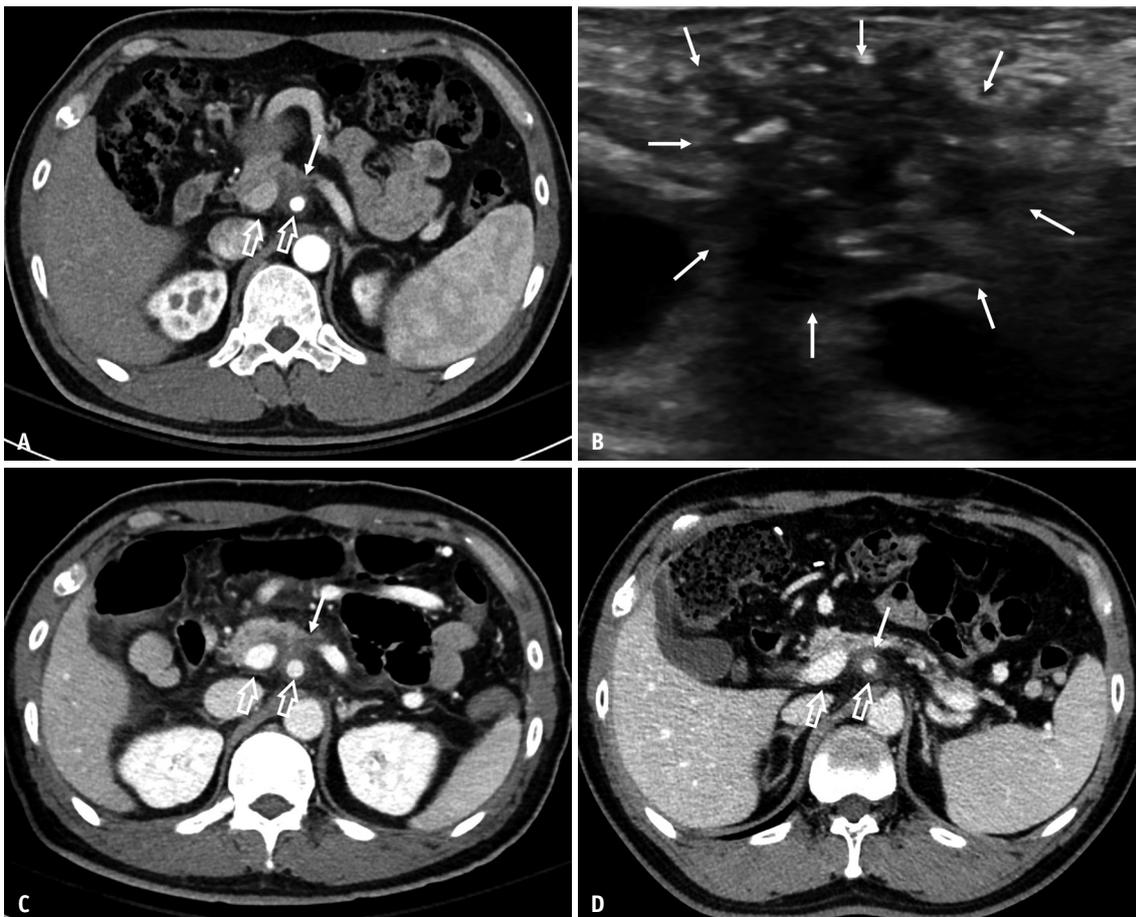
Before IRE, contrast-enhanced CT was performed to evaluate the tumor size, morphology, and its relationship

with adjacent structures (Figs. 1A, 2A). These images were used to determine the number, type, and insertion trajectories of the electrodes. For pancreatic head tumors, a biliary stent was placed 2–3 weeks before IRE to prevent obstructive cholangitis.

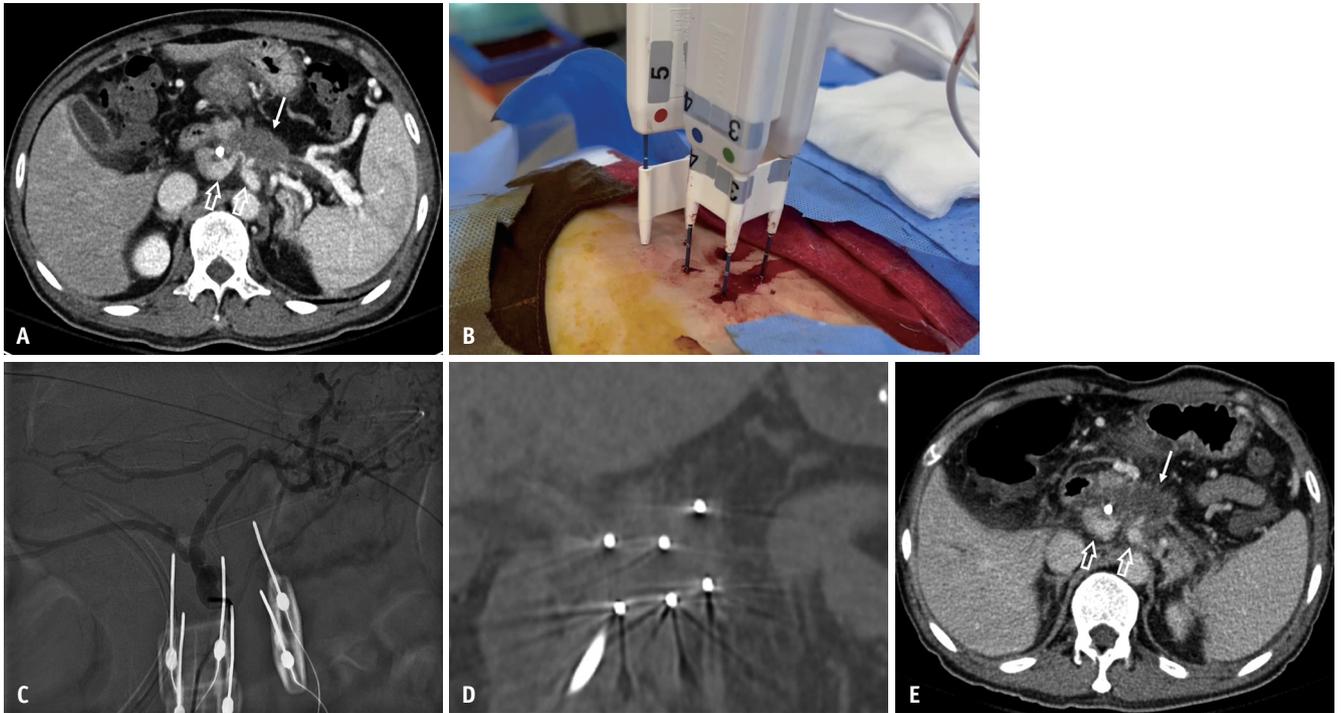
IRE was performed under general anesthesia with complete neuromuscular blockade in all patients. Intraoperative procedures were coordinated by hepatobiliary surgeons, and direct ultrasound guidance was used for electrode placement. Percutaneous IRE was performed in the CT angiography suite with arteriography, portography, and CT for imaging guidance. All procedures used an EPO-IRE system with a generator and 18-gauge electrodes (The Standard Co., Gunpo, South Korea). Dual, triple (equilateral triangular), or square-shaped quadruple clustered electrode configurations, with fixed

interelectrode spacings of 1.5, 1.7, or 2.0 cm, were selected according to tumor morphology (Fig. 3). Clustered electrodes are commercially available in South Korea and were used with institutional approval.

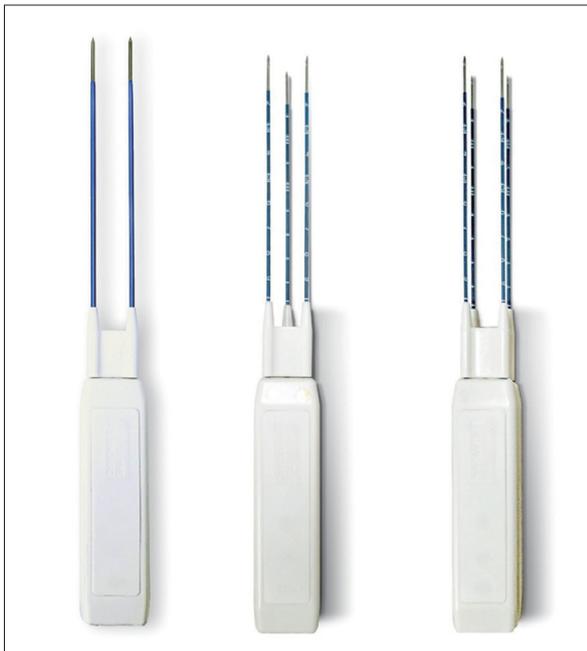
The active tip length of each electrode was fixed at 1.5 cm. In selected cases, additional single or double electrodes were inserted to ensure complete tumor coverage. Electrodes were inserted perpendicular to the long axis of the pancreas (ventral to dorsal) under ultrasound, fluoroscopic, and CT guidance (Figs. 1B, 2B-D). After electrode placement, ten test pulses at 1,500–2,000 V/cm (maximum, 3,000 V) were delivered to assess tissue conductivity and ensure adequate electrical current delivery. If the measured current was excessive, the voltage, pulse width, or both were adjusted. Once calibrated, IRE was performed using a standardized



**Fig. 1.** Locally advanced pancreatic cancer treated with IRE in a 48-year-old male. **A:** Contrast-enhanced CT shows a 2.6 cm hypoattenuating mass in the pancreatic body (arrow) with invasion of the celiac trunk and the splenic and portal veins (open arrows). **B:** Intraoperative US demonstrates a hypoechoic mass (arrows), and IRE was performed under US guidance using two double-clustered electrodes with a fixed interelectrode spacing of 1.5 cm. **C:** Contrast-enhanced CT obtained 1 day after IRE shows an ablation zone encompassing the mass (arrow) with preservation of the celiac trunk and the splenic and portal veins (open arrows). **D:** Contrast-enhanced CT obtained 22 months after IRE demonstrates stable disease (arrow) with continued preservation of the celiac trunk and the splenic and portal veins (open arrows). IRE = irreversible electroporation, US = ultrasound



**Fig. 2.** IRE in a 54-year-old male with locally advanced pancreatic cancer. **A:** Contrast-enhanced CT shows a 3.9 cm hypoattenuating mass in the pancreatic body (arrow) with invasion of the celiac trunk, portal vein, and splenic vein (open arrows). **B:** Percutaneous placement of a square-shaped quadruple electrode and a double-clustered electrode with a fixed interelectrode spacing of 1.7 cm. **C:** Electrodes inserted under fluoroscopic and angiographic guidance. **D:** Coronal CT image showing clustered electrode placement with a quadruple and double configuration. **E:** Contrast-enhanced CT obtained 1 day after IRE demonstrates an ablation zone encompassing the mass (arrow) with maintained patency of the celiac trunk, portal vein, and splenic vein (open arrows). IRE = irreversible electroporation



**Fig. 3.** Clustered electrode arrays for irreversible electroporation. Photographs of 18-gauge clustered unipolar electrode arrays (EPO-IRE system; The Standard Co.) showing dual, triple, and quadruple configurations.

protocol of 90 pulses per treatment cycle, with a pulse width of 70–90  $\mu$ s and an output voltage of 2,000–3,000 V. Pulses were delivered sequentially through each electrode pair with electrocardiographic synchronization. If the current difference remained below 10 A after 90 treatment pulses, an additional 90 pulses were delivered. If the current difference failed to exceed 10 A after 180 pulses, the procedure was terminated to prevent thermal injury. Subcutaneous low-molecular-weight heparin (enoxaparin, Klexane<sup>®</sup>, Sanofi-Aventis, Paris, France; 7,500 U/day) was administered for 5 to 14 days after the procedure to prevent venous thromboembolic events.

#### Follow-Up

During hospitalization, patients were closely monitored for clinical signs and symptoms. Routine laboratory tests included the measurement of inflammatory markers, complete blood count, liver function tests, and pancreatic enzyme levels. To assess acute procedure-related complications, contrast-enhanced CT was performed the day after IRE (Figs. 1C, 2E). After discharge, follow-up

contrast-enhanced CT was conducted 1 and 3 months post-IRE and every 3 months thereafter (Fig. 1D). Additional chemotherapy was administered after IRE according to each patient's general condition and evaluation by a multidisciplinary team.

### Statistical Analysis

Statistical significance was defined as a two-sided *P*-value of <0.05. Progression-free survival (PFS) and OS were estimated using the Kaplan–Meier method. Data management and statistical analyses were performed using the SPSS

**Table 1.** Baseline patient and tumor characteristics

Characteristic	Value
Patient characteristics	
Age at IRE, yrs	60 (48–78)
Sex, female:male	4:9
Previous therapy	13 (100)
FOLFIRINOX	13 (100)
FOLFIRINOX and radiation	3 (23.1)
Gemcitabine + nab-paclitaxel	1 (7.7)
Time from diagnosis to IRE, mos	14 (7.4–45.5)
ECOG performance status at IRE	
0	3 (23.1)
1	9 (69.2)
2	1 (7.7)
Disease status at IRE	
Stable disease	9 (69.2)
Partial response	1 (7.7)
Disease progression	3 (23.1)
CA 19-9	
At diagnosis	352.5 (5.5–4,076)
At IRE	94.6 (5.3–2,750)
Tumor characteristics (at IRE)	
Location	
Head	4 (30.8)
Body/tail	9 (69.2)
Size, cm	2.4 (1.5–4.0)
Vascular invasion	
Celiac trunk	8 (61.5)
SMA	7 (53.8)
SMV/PV/SV	11 (84.6)
Bowel abutment	
Stomach	1 (7.7)
Duodenum	1 (7.7)

Values are expressed as number (%) unless otherwise specified, or as median (range).

IRE = irreversible electroporation, FOLFIRINOX = oxaliplatin, irinotecan, fluorouracil, and leucovorin, ECOG = Eastern Cooperative Oncology Group, SMA = superior mesenteric artery, SMV = superior mesenteric vein, PV = portal vein, SV = splenic vein

software (version 23.0; IBM Corp., Armonk, NY, USA).

## RESULTS

### Patient Characteristics

The baseline patient and tumor characteristics are summarized in Table 1. The median interval between diagnosis and IRE was 14 months (range, 7.4–45.5 months). The tumor was located in the pancreatic head in four patients (30.8%) and in the body or tail in nine patients (69.2%). The median maximum tumor diameter was 2.4 cm (range, 1.5–4.0 cm). For patients with pancreatic head tumors (*n* = 4, 30.8%), biliary stents were placed before IRE to prevent obstructive cholangitis. Two patients received plastic stents and two had previously inserted metal stents. In the latter cases, the metal stents were placed outside the hospital because of obstructive biliary complications and could not be replaced with plastic stents; therefore, IRE was performed with the metal stents in situ at the operator's discretion.

### Technical Details and Outcomes

The details of the procedures are summarized in Table 2. Technical success was achieved in all patients. Eleven (84.6%) patients underwent intraoperative IRE, and 2 (15.4%) underwent percutaneous IRE. A total of 35 clustered electrodes were used in all the procedures. The dual-electrode configuration was the most common (45.7%), followed by the single (42.9%), triple (8.6%), and quadruple (2.9%) configurations.

**Table 2.** Irreversible electroporation procedure details

Variable	Value
Approach	
Intraoperative	11 (84.6)
Percutaneous	2 (15.4)
Electrodes used (total = 35)	
Single	15 (42.9)
Dual	16 (45.7)
Triple	3 (8.6)
Quadruple	1 (2.9)
Pulses per electrode pair	180 (90–180)
Pulse width, $\mu$ s	70 (70–90)
Median voltage, V	2,500 (2,000–3,000)
Interelectrode spacing, cm	1.5 (1.5–2.0)

Values are expressed as number (%) or median (range)

**Postprocedural Complications**

The median in-hospital stay after IRE was 8 days (range, 6–42 days). The procedure-related complications are summarized in Table 3. Major complications occurred in two patients (15.4%), both of which involved GI bleeding (grade 3). The first patient, whose tumor abutted the stomach, developed hypotension at day 10. Transcatheter angiography demonstrated active bleeding from the right gastroepiploic artery, which was successfully treated with N-butyl cyanoacrylate (NBCA) embolization. The second patient presented with hematochezia at 2 weeks. Although angiography did not demonstrate definite extravasation, bleeding was presumed to arise from vascular injury along the needle track near the pancreaticoduodenal branches, and empiric embolization was performed with NBCA. Both patients

recovered completely without recurrent bleeding. Seventeen minor complications were observed in 10 patients (76.9%), all of whom were successfully managed conservatively. No procedure-related deaths occurred within the first 60 days. Additionally, in all 13 patients, the median serum amylase and lipase levels before IRE were 48 U/L (range, 30–124 U/L) and 16 U/L (range, 16–76 U/L), respectively. These values increased to 89 U/L (range, 31–409 U/L;  $P = 0.006$ ) and 130 U/L (range, 14–1,208 U/L;  $P = 0.023$ ), respectively, one day after IRE. Mild elevations in pancreatic enzyme levels were frequently observed after IRE but normalized within 1 week; these biochemical changes were not considered complications if clinically significant pancreatitis was absent.

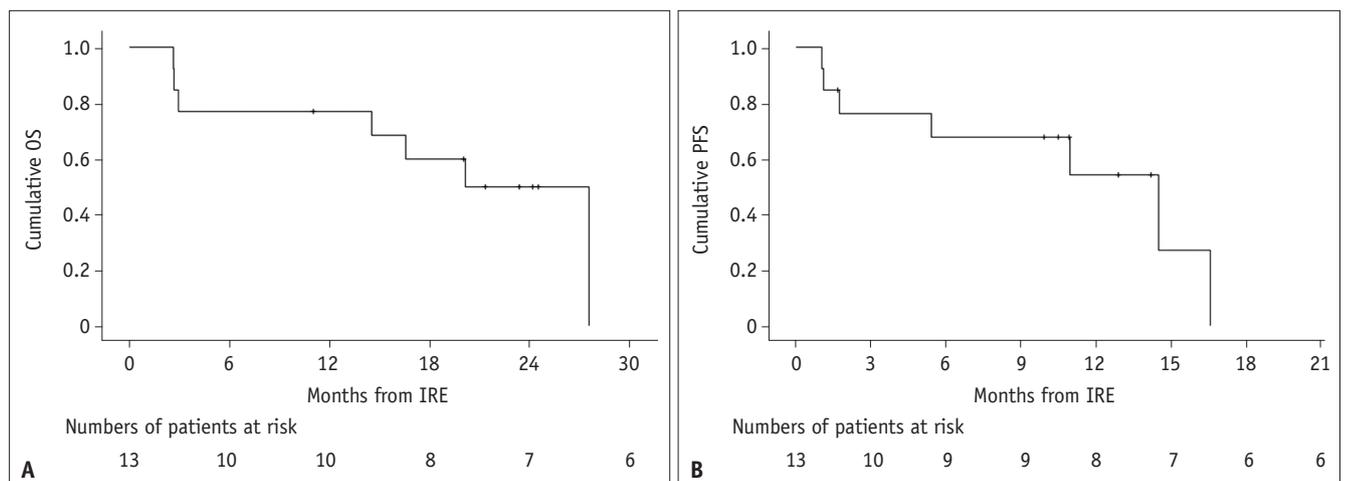
**Follow-Up and Oncologic Outcomes**

Among these 13 patients, 11 (84.6%) received additional chemotherapy after IRE. Of these, two did not undergo chemotherapy for 17 and 6 months after IRE because their tumors remained stable and tumor marker levels were within the normal range. Chemotherapy was later resumed despite stability at the primary site because of lung metastases and increasing tumor marker levels. Two patients (15.4%) did not undergo further systemic therapy after IRE because of poor general health. The median follow-up duration after IRE was 24.5 months (range, 9.9–33.4 months). After IRE, the median CA 19-9 levels were 109.1 U/mL at 1 day, 140.1 U/mL at 3 months, and 181.8 U/mL at 6 months. The median OS from IRE was 20.1 months (95% confidence interval, 10.9–21.6 months), and the median PFS from IRE was 14.5 months (95% confidence interval, 5.1–12.0 months) (Fig. 4).

**Table 3.** Complications

Characteristic	Value
Major complications	
Gastrointestinal bleeding: grade 3	2 (15.4)
Minor complications	
Abdominal pain	8 (61.5)
Grade 1	5 (38.5)
Grade 2	3 (23.1)
Dyspepsia: grade 1	2 (15.4)
Nausea/vomiting: grade 2	1 (7.7)
Fever with chills: grade 1	2 (15.4)
Acute pancreatitis: grade 2	2 (15.4)
Ascites: grade 2	1 (7.7)
Portal vein thrombosis: grade 2	1 (7.7)
60-day mortality	0 (0)

Values are expressed as number (%)



**Fig. 4.** Kaplan–Meier plots of oncologic outcomes after IRE. **A:** OS from IRE. **B:** PFS from IRE. IRE = irreversible electroporation, OS = overall survival, PFS = progression-free survival

## DISCUSSION

IRE provides nonthermal tumor ablation while preserving the perivascular connective tissue and ductal structures, making it particularly suitable for LAPC adjacent to major vessels [6,7]. When performed with multiple single electrodes, however, precise parallel insertion with an optimal interelectrode spacing of 1.5–2.0 cm is required. This is technically challenging in the deep retroperitoneal pancreas and may lead to electrode misalignment, convergence, or divergence, prolonged procedure and anesthesia times, and increased reliance on imaging. These factors can generate heterogeneous electric fields, resulting in undertreatment or overtreatment and a higher risk of thermal or vascular injury [9,10]. Clustered electrodes, with fixed interelectrode spacings of 1.5, 1.7, or 2.0 cm, may help overcome these technical limitations and reduce the procedure duration.

When ablation with a clustered electrode alone was insufficient to cover the tumor, it was combined with either an additional clustered electrode or a single auxiliary electrode. Depending on the tumor size and geometry, newer clustered electrode designs, including diamond, pentagonal, and hexagonal configurations, are under development and may further enhance the efficiency and applicability of IRE in complex pancreatic tumors.

Across the contemporary IRE series in LAPC, the reported median OS typically ranged from 10 to 14 months after the IRE procedure. Median PFS generally ranges from 8 to 15 months, with time to local progression around 12 months [6-8,13-15]. In the present cohort, the median OS was 20.1 months and the median PFS was 14.5 months after IRE, both longer than those reported in most previous studies. These differences may be attributable to the use of a clustered electrode, which could have improved electric field homogeneity and increased the likelihood of more effective ablation. In addition, this cohort, characterized by a favorable performance status (ECOG 0–1 in 92.3%), smaller tumors (median, 2.4 cm), and frequent post-IRE chemotherapy (84.6%), differs from more heterogeneous populations in previous studies and may partly explain the longer survival observed. At the time of IRE, all patients either showed insufficient or no further response to chemotherapy or, despite a treatment response, elected to undergo additional local therapy. The median interval of 14 months between diagnosis and IRE suggests that many of the included patients may have had relatively

indolent tumor biology, which could also have contributed to the favorable outcomes. Future larger controlled studies are needed to validate these findings and isolate the incremental effects of clustered electrode IRE.

In the PANFIRE-1 and PANFIRE-2 studies, approximately 50% and one-third of the patients, respectively, did not receive systemic chemotherapy before IRE, and even fewer patients underwent systemic therapy afterwards [6,13]. In contrast, all patients in this study received systemic chemotherapy before IRE, and 11 of 13 (84.6%) patients also received post-IRE chemotherapy. Notably, the two patients who did not continue systemic therapy after IRE maintained stable disease and normal tumor marker levels for 17 and 6 months, respectively, reflecting an intentional pause in treatment rather than treatment intolerance. The consistent integration of systemic therapy may have contributed to the improved outcomes observed in our cohort. Consistent with this observation, other studies combining IRE with systemic therapy have reported improved outcomes compared with chemotherapy alone [16-18]. Nonetheless, this study is limited by its relatively small patient population and potential selection bias.

Across contemporary palliative regimens for LAPC, the median OS with multiagent chemotherapy, such as FOLFIRINOX, typically ranges from 10 to 23 months from the start of the regimen, with a median PFS of 7–12 months [19,20]. SBRT series and meta-analyses generally report a 1-year OS of 60%–70%, with a median PFS of 8–12 months [21,22]. Thermal ablation using radiofrequency ablation has limited evidence for LAPC, and comparative cohorts have not shown a clear survival advantage over systemic therapy/chemoradiation alone [23]. Against this background, the present cohort's IRE-based outcomes appear numerically within or above the ranges reported for other palliative strategies, but the differences should be interpreted cautiously given the selection and design effects.

In a previous pancreatic IRE series, the most common major complication was GI hemorrhage, with perforation and severe pancreatitis reported less frequently. Major complication rates range from 7% to 24%, with most events managed endovascularly or surgically, and are associated with low early mortality [6-8,16]. Post-IRE GI bleeding is thought to result from vascular injury with pseudoaneurysm formation and subsequent delayed erosion or fistulization into adjacent bowel, leading to hemorrhage from splanchnic branches that is typically managed endovascularly [6,7,17,18]. In this study, 2 major

complications occurred, both involving GI hemorrhage at 10 days and 2 weeks after IRE, requiring embolization. To mitigate post-IRE GI bleeding, prior reports emphasized meticulous trajectory planning to avoid bowel and gastroduodenal branches, maintain adequate electrode spacing and sufficient clearance from major vessels and the bowel, and use adjunctive image guidance, such as transcatheter arteriography, to optimize visualization and distance [13,24,25].

Although only 2 of the 13 patients in this study underwent percutaneous clustered electrode IRE, our broader institutional experience with 46 procedures suggests that percutaneous access under arteriography, with or without portography, offers important advantages. These include more precise electrode placement, real-time vascular assessment, and the avoidance of major vessels. However, intraoperative access remains valuable, particularly in cases requiring open exploration or where percutaneous placement is not feasible.

In conclusion, clustered electrode IRE for LAPC was technically feasible and safe, demonstrating consistent procedural success, an acceptable safety profile, favorable survival outcomes, and the potential to shorten the procedure time. These findings are exploratory and require validation in larger, preferably multicenter, controlled studies to define comparative effectiveness and optimal patient selection.

#### Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

#### Conflicts of Interest

Jiwon Suk and Seung Jeong are affiliated with Standard Co., Ltd, but declare no competing financial interests related to this work. The remaining authors have declared no conflicts of interest.

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Kim. Methodology: Joon Ho Kwon, Man-Deuk Kim, Kichang Han. Project administration: Man-Deuk Kim. Software: Jiwon Suk, Seung Jeong. Supervision: Man-Deuk Kim, Seungmin Bang, Jong Yun Won. Validation: Man-Deuk Kim, Seungmin Bang. Writing—original draft: Joon Ho Kwon, Man-Deuk Kim. Writing—review & editing: Joon Ho Kwon, Man-Deuk Kim.

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