

Supplementary material

Supplementary methods

Study design and population

This was a single-center, retrospective observational cohort study carried out at Tianjin Cancer Hospital Airport Hospital. The objective of this research was to describe the feasibility, safety, as well as early clinical outcomes of a uniform sequential treatment pathway consisting of induction therapy with nimotuzumab plus gemcitabine and nab-paclitaxel (AG), followed by consolidative irreversible electroporation (IRE), in patients with pancreatic ductal adenocarcinoma (PDAC).

A retrospective review of institutional electronic medical records was performed to identify consecutive advanced PDAC patients who received first-line systemic therapy with nimotuzumab plus AG at our institution from January 2023 to December 2025. Patients were incorporated into the final analysis if the following requirements were satisfied: planned induction therapy was completed; subsequently underwent consolidative IRE as part of routine multidisciplinary management; and if complete clinical, radiographic, and follow-up data were available.

Eligibility and exclusion criteria

To characterize a cohort that completed the full sequential treatment pathway in routine clinical practice, the following criteria were applied retrospectively.

Patients were eligible for inclusion if all of the following criteria were met: (1) age ≥ 18 years; (2) histologically or cytologically confirmed PDAC; (3) receipt of first-line induction therapy with nimotuzumab plus AG for advanced disease with completion of at least 3 planned 21-day cycles; (4) absence of radiographic disease progression at the primary pancreatic site following induction therapy, as assessed by multidisciplinary team (MDT) review according to RECIST (version 1.1); (5) adequate performance status following induction therapy [Eastern Cooperative Oncology Group performance status of 0–1 or a Karnofsky Performance Status (KPS) ≥ 70]; (6) subsequent receipt of consolidative IRE for the primary pancreatic tumor following the MDT recommendation; and (7) availability of complete medical records documenting treatment delivery, toxicity, imaging assessments, and follow-up outcomes.

Patients were not included in the study for the following reasons: other forms of systemic therapy were administered in the treatment of advanced disease before the nimotuzumab-AG regimen (except neoadjuvant and adjuvant chemotherapy administered after >6 months but still before a recurrence);

radiographic disease progression during treatment or immediately after induction therapy; or incomplete clinical records or absence of follow-up data before or shortly after the IRE procedure.

MDT evaluation and treatment workflow

The key treatment decisions were made in the context of regular MDT discussions at Tianjin Cancer Hospital Airport Hospital. Medical oncologists, pancreatic surgeons, radiologists, anesthesiologists, and interventional specialists were members of the MDT.

All patients received induction therapy with nimotuzumab in combination with nab-paclitaxel (125 mg/m^2) and gemcitabine ($1,000 \text{ mg/m}^2$ [200 mg weekly] intravenously on days 1, 8, and 15 of every 21-day cycle. There were to be at least three cycles before the evaluation of responses. Premedication and supportive care, which consisted of corticosteroids, antiemetics, and granulocyte colony-stimulating factor, were provided in compliance with the institutional standards. Changes of doses, delays, or omissions were permitted based on treatment toxicities.

Following completion of induction therapy, a comprehensive MDT review was performed to assess eligibility for consolidative IRE. The post-treatment images, clinical status, and laboratory findings were evaluated. The decision to proceed was based on a consensus recommendation derived from the following criteria: (1) Disease control at the primary site [radiographic assessment (contrast-enhanced CT/MRI) confirming stable disease or partial response per RECIST v1.1 with no evidence of local progression]; (2) absence of prohibitive systemic progression (lack of new distant metastatic lesions or clinically significant progression at existing non-target sites that would preclude a localized approach); (3) sustained performance status (maintenance of a KPS ≥ 70 , reflecting adequate physiologic reserve for an invasive procedure); (4) favorable tumor anatomy post-induction (reassessment of tumor-vascular relationships on cross-sectional imaging to confirm technical feasibility of achieving a margin-negative ablation while sparing critical adjacent structures, e.g., major mesenteric vessels); and (5) biochemical response [a documented significant reduction (typically $\geq 50\%$) in serum CA19-9 levels from baseline was considered a supportive factor, recognizing the descriptive rather than validated prognostic role in this context]. The approval for consolidative IRE, or in the case of synchronous oligometastatic liver disease for a combined local approach, was a consensual clinical judgment grounded in the above multidisciplinary assessment.

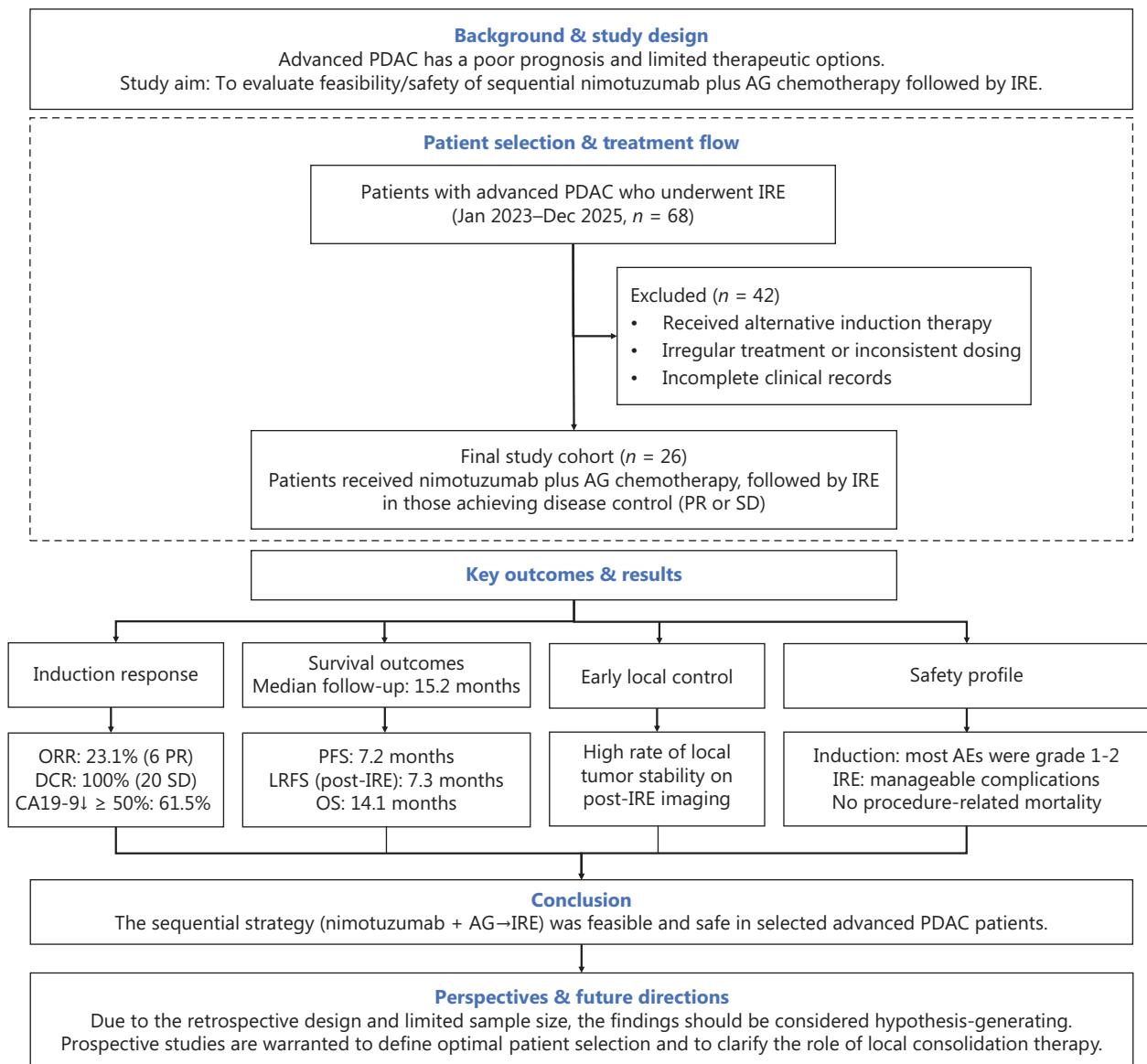


Figure S1 Study flowchart depicting the design, patient selection, treatment flow, outcomes, and conclusions of this retrospective real-world analysis. AEs, adverse events; AG, gemcitabine plus nab-paclitaxel; CA19-9, carbohydrate antigen 19-9; DCR, disease control rate; IRE, irreversible electroporation; LRFS, local recurrence-free survival; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; SD, stable disease.

The local treatment of lesions in the liver during the same operation was determined through intraoperative assessment in the case of patients with synchronous oligometastatic liver disease.

Detailed induction therapy management

Induction therapy was administered in accordance with institutional standards. Nimotuzumab was administered

intravenously at a fixed weekly dose of 200 mg. Nab-paclitaxel (125 mg/m²) as well as gemcitabine (1,000 mg/m²) were administered intravenously on days 1, 8, and 15 of each 21-day cycle. Premedication with corticosteroids and antiemetics was provided per institutional protocol.

Dose modifications, treatment delays, or omission of scheduled doses were performed according to hematologic and non-hematologic toxicities. Toxicities were treated by temporarily stopping treatment and reducing the dosage, as clinically

Table S1 Baseline demographic and clinical characteristics of the study cohort ($n = 26$)

Cases ($n = 26$)		
Age	Years, mean (SD)	62 (7)
	Years, median (range)	63 (48–75)
	<65 years	15 (57.7%)
	≥65 years	11 (42.3%)
Gender	Male	17 (65.4%)
	Female	9 (34.6%)
BMI	kg/m ² , mean (SD)	22.3 (2.9)
	kg/m ² , median (range)	22.7 (16.9–27.5)
Tumor location	Pancreatic head	17 (65.4%)
	Pancreas other than the pancreatic head	9 (34.6%)
CA19-9	U/mL, median (range)	215.7 (17.3–2,999.0)
	<37 U/mL	4 (15.4%)
	37–1,000 U/mL	16 (61.5%)
	>1,000 U/mL	6 (23.1%)
CEA	ng/mL, median (range)	3.4 (1.45–21.0)
	<5.0 ng/mL	19 (73.1%)
	≥5.0 ng/mL	7 (26.9%)
Status	LAPC	13 (50.0%)
	LMPC	13 (50.0%)
Diabetes	Yes	8 (30.8%)
	No	18 (69.2%)
Hypertension	Yes	7 (26.9%)
	No	19 (73.1%)
Pain VAS score	0	14 (53.8%)
	1	10 (38.5%)
	2	2 (7.7%)
KPS score	100	8 (30.8%)
	90	18 (69.2%)

BMI, body mass index; ECOG PS, Eastern Co-operative Oncology Group Performance Score; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LAPC, locally advanced pancreatic cancer; LMPC, liver metastatic pancreatic cancer; VAS, Visual Analog Scale; KPS, Karnofsky Performance Status.

demonstrated. Granulocyte colony-stimulating factor was administered prophylactically or therapeutically at the discretion of the treating physician for patients due to prolonged or severe neutropenia.

Table S2 Radiographic and biochemical response following induction therapy with nimotuzumab plus gemcitabine and nab-paclitaxel chemotherapy ($n = 26$)

Response	Cases ($n = 26$)
PR, n (%)	6 (23.1)
SD, n (%)	20 (76.9)
ORR, n (%)	6 (23.1) (95% CI: 8.9–42.8)
DCR, n (%)	26 (100.0) (95% CI: 86.7–100.0)
CA19-9 response, n (%) (≥50% reduction)	16 (61.5) (95% CI: 40.6–79.8)

PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate; CA19-9, carbohydrate antigen 19-9; CI, confidence interval.

Table S3 Detailed treatment-related adverse events during induction therapy ($n = 26$)

Adverse event	Grade 1–2, n (%)	Grade 3–4, n (%)
Any AE	20 (76.9)	3 (11.5)
Nausea	12 (46.2)	0 (0)
Vomiting	7 (26.9)	0 (0)
Thrombocytopenia	2 (7.7)	2 (0) [†]
Leukopenia	4 (15.4)	2 (0) [†]
AST increased	8 (30.8)	0 (0)
ALT increased	4 (15.4)	0 (0)
Pyrexia	1 (3.8)	0 (0)
Electrolyte disturbance	16 (61.5)	0 (0)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[†]The same patient experienced grade 3–4 thrombocytopenia and leukopenia after induction therapy, both of which resolved prior to the IRE procedure.

IRE procedure and details

All IRE procedures were performed using an IRE therapeutic system (Tianjin Intelligent Health Medical Co., Ltd, China) *via* an open surgical approach under general anesthesia with complete neuromuscular blockade. Following surgical exposure of the pancreas, electrode placement was performed under combined direct visualization and intraoperative ultrasound guidance to delineate tumor boundaries and adjacent critical structures.

The arrangement and spacing of electrodes were personalized based on the geometry of tumors. The distance between electrodes was modified in real-time and the aim was to obtain a non-thermal IRE effect. A target electric field strength of approximately 1500 V/cm was used. The voltage applied,

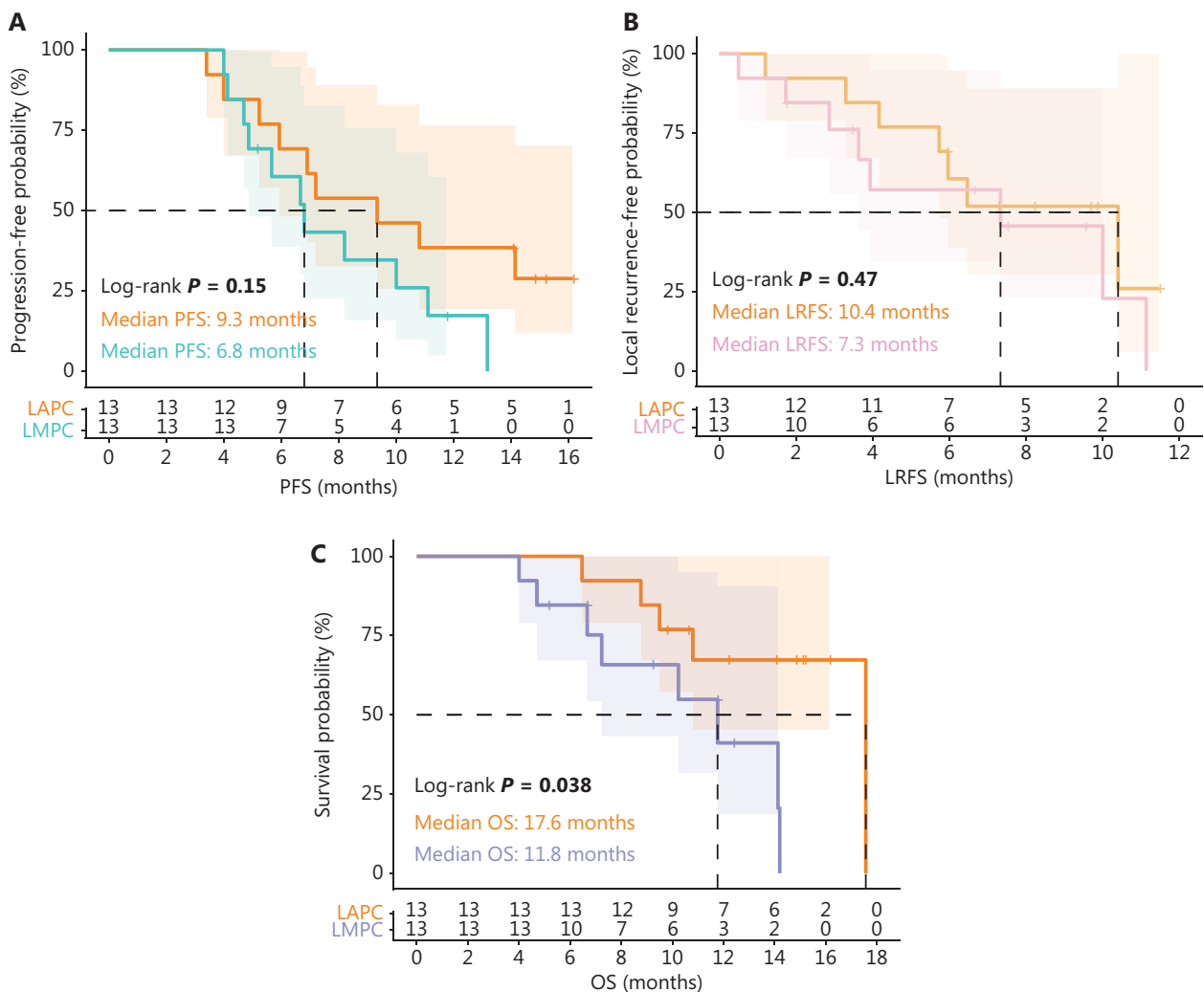


Figure S2 Exploratory comparison of survival outcomes between patients with locally advanced pancreatic cancer (LAPC) and liver-metastatic pancreatic cancer (LMPC). Kaplan–Meier curves showing (A) progression-free survival, (B) local recurrence-free survival from the date of irreversible electroporation, and (C) overall survival for the LAPC subgroup ($n = 13$) versus the LMPC subgroup ($n = 13$). P -values were calculated using the log-rank test for descriptive purposes only; the analysis was not powered for formal subgroup comparison. LAPC, locally advanced pancreatic cancer; LMPC, liver-metastatic pancreatic cancer; LRFS, local recurrence-free survival; OS, overall survival; PFS, progression-free survival.

typically within a range of 1,800–3,000 V, was individualized for each patient based on real-time assessment of electrode spacing and tumor geometry to ensure delivery of the target electric field strength across the intended ablation zone while respecting the proximity of critical adjacent structures. Pulse delivery was gated to the cardiac cycle through electrocardiography to minimize the risk of arrhythmia. The pulse number and pulse width were also varied intraoperatively based on feedback of the system and tissue response.

Technical success was characterized by the successful execution of planned ablation protocol with intraoperative ultrasound confirmation of coverage of the intended ablation zone.

Management of synchronous liver metastases

Hepatic lesions were addressed locally using the same operation as pancreatic IRE in patients who presented with synchronous oligometastatic liver disease because the procedure is considered suitable by the MDT. This measure was performed using intraoperative ultrasonography to determine the size, location, and proximity to great vascular or biliary structures of the lesions.

Lesions that were in a vascular or biliary anatomy were treated more commonly with IRE and those in more favorable locations in the parenchyma were treated with radiofrequency

Table S4 Exploratory univariate analyses of baseline factors related to survival outcomes ($n = 26$)

Variable	Progression-free survival			Local recurrence-free survival			Overall survival		
	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI
Age (per-year)	0.88	1.00	0.95–1.07	0.86	0.99	0.92–1.07	0.12	1.07	0.98–1.16
Gender (female vs. male)	0.95	0.97	0.37–2.54	0.74	0.83	0.28–2.49	0.94	1.05	0.31–3.48
BMI (per-kg/m ²)	0.04	0.84	0.71–1.00	0.32	0.91	0.76–1.09	0.05	0.83	0.68–1.00
Tumor size (per-cm)	0.93	0.98	0.68–1.42	0.53	0.84	0.50–1.43	0.61	0.86	0.49–1.52
Tumor location (other vs. head)	0.32	0.61	0.23–1.60	0.50	0.67	0.21–2.12	0.95	1.04	0.31–3.50
CA19-9 (per-100 U/mL)	0.46	1.02	0.96–1.08	0.98	1.00	0.92–1.09	0.33	1.04	0.96–1.12
CEA (per-ng/mL)	0.09	1.11	0.98–1.24	0.43	1.06	0.92–1.09	0.03	1.16	1.02–1.32
Status (LAPC vs. LMPC)	0.16	0.51	0.20–1.29	0.47	0.69	0.25–1.91	0.05	0.29	0.09–1.00
KPS score (100 vs. 90)	0.79	0.87	0.31–2.42	0.99	0.99	0.31–3.17	0.70	0.77	0.20–2.91

Gender, female vs. male; Tumor location, pancreas other than the pancreatic head vs. pancreatic head; Status, LAPC vs. LMPC; KPS score, 100 vs. 90. BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LAPC, locally advanced pancreatic cancer; LMPC, liver metastatic pancreatic cancer; KPS, Karnofsky Performance Status; CI, confidence interval; HR, hazard ratio.

Table S5 Exploratory multivariate analyses of baseline factors related to survival outcomes ($n = 26$)

Variable	Progression-free survival			Local recurrence-free survival			Overall survival		
	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI
Age (per-year)	0.03	0.91	0.84–0.99	0.16	0.93	0.84–1.03	0.70	0.98	0.86–1.11
Gender (female vs. male)	0.35	0.57	0.18–1.86	0.36	0.51	0.12–2.13	0.90	1.12	0.20–6.31
BMI (per-kg/m ²)	0.00	0.67	0.53–0.85	0.07	0.80	0.64–1.01	0.00	0.53	0.35–0.82
Tumor size (per-cm)	0.60	1.14	0.69–1.87	0.73	0.90	0.48–1.67	0.82	0.90	0.37–2.17
Tumor location (other vs. head)	0.03	0.24	0.07–0.87	0.18	0.35	0.08–1.64	0.77	0.77	0.14–4.16
CA19-9 (per-100 U/mL)	0.11	1.06	0.99–1.15	0.77	1.01	0.93–1.11	0.16	1.09	0.96–1.24
CEA (per-ng/mL)	0.04	1.16	1.01–1.35	0.07	1.19	0.98–1.43	0.06	1.23	1.00–1.53
Status (LAPC vs. LMPC)	0.04	0.19	0.04–0.94	0.24	0.39	0.08–1.84	0.01	0.02	0.00–0.38
KPS score (100 vs. 90)	0.77	1.23	0.30–4.97	0.73	1.30	0.28–5.99	0.12	6.13	0.63–59.82

Gender, female vs. male; Tumor location, pancreas other than the pancreatic head vs. pancreatic head; Status, LAPC vs. LMPC; KPS score, 100 vs. 90. BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LAPC, locally advanced pancreatic cancer; LMPC, liver metastatic pancreatic cancer; KPS, Karnofsky Performance Status; CI, confidence interval; HR, hazard ratio.

ablation. Selection of the ablation modality was not dependent on any comparative efficacy presumption, rather on the technical feasibility and safety.

Follow-up and outcome assessment

Patients were followed from initiation of induction therapy until death, loss to follow-up, or administrative censoring on 26 December 2025. Clinical data were retrospectively retrieved from electronic medical records. Follow-up assessments included a physical examination, laboratory testing

[including serum carbohydrate antigen 19-9 (CA19-9)] with contrast-enhanced computed tomography or magnetic resonance imaging. The radiographic tumor response was evaluated drawing on RECIST (version 1.1) and treatment-related adverse events were graded using the Common Terminology Criteria for Adverse Events (version 4.0).

Post-IRE follow-up data were reviewed to describe early local disease status at the primary pancreatic site, changes in patient-reported pain, and changes in performance status, as measured by KPS scale, in addition to survival and radiographic outcomes.

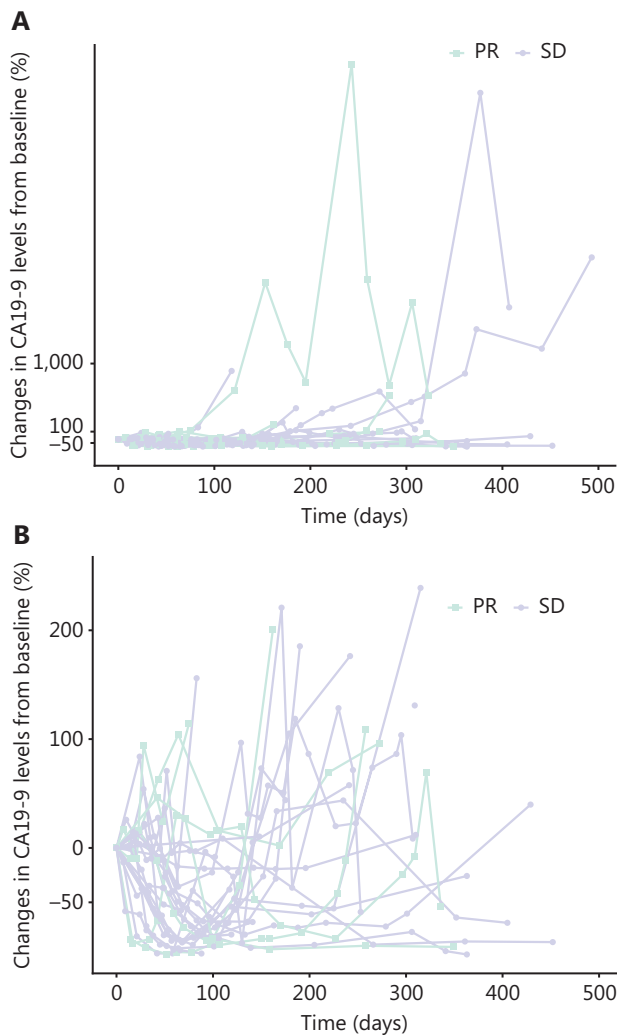


Figure S3 Longitudinal changes in serum CA19-9 levels. (A) Spider plot depicting individual patient trajectories of percent change from baseline in serum CA19-9 for all 26 patients during induction therapy and post-IRE follow-up. To preserve data integrity, all values including outliers are shown. (B) The same plot with the y-axis truncated to a range of -100% to 250% to provide a detailed view of the trajectories for most patients and to illustrate the interpatient variability over time. Lines are shown descriptively. CA19-9, carbohydrate antigen 19-9; IRE, irreversible electroporation; PR, partial response; SD, stable disease.

Assessment of local disease status and symptom outcomes

Radiographic evaluation of the local disease status following IRE was directly achieved by contrast-enhanced computed tomography or magnetic resonance imaging during regular follow-up. The lack of radiographic progression at the primary

site of the pancreatic tumor was regarded as a descriptive definition of local disease control.

Patient-reported pain outcomes were extracted from clinical documentation and recorded qualitatively as absolute relief, enhancement, no alteration, or decline compared to baseline. Status of performance was measured with the KPS scale and measured at baseline and at post-IRE follow-up visits; changes were reported descriptively.

Study endpoints

The primary endpoints were feasibility and safety of the sequential treatment strategy consisting of nimotuzumab plus AG induction therapy followed by consolidative IRE in this retrospective analysis. Overall survival, denoting the duration from initiation of induction therapy-to-death from any cause, was assessed descriptively as a key exploratory outcome.

Secondary endpoints included progression-free survival (measured from treatment initiation-to-radiologic or clinical disease progression or death), local recurrence-free survival (delineated as the time elapsed from the date of the IRE procedure-to-radiologic evidence of local progression at the primary pancreatic tumor site or death), objective response rate as well as disease control rate assessed according to RECIST version 1.1, the proportion of patients achieving a biochemical response (characterized by a $\geq 50\%$ decline in the serum CA19-9 level from baseline) and descriptive assessment of IRE procedural success and treatment-related adverse events.

Statistical analysis

This was a retrospective, descriptive study with a predefined treatment pathway rather than a hypothesis-testing trial. Therefore, no *a priori* sample size or statistical power calculation was performed. Descriptive statistics were used to summarize the data. Continuous variables are presented as the mean with standard deviation (SD) or median with range based on the distribution and clinical conventions. Categorical variables are presented as frequencies and percentages. The Kaplan–Meier method was used to estimate survival curves for time-to-event endpoints (overall survival, progression-free survival, and local recurrence-free survival) and censored observations were handled using standard non-informative censoring assumptions. The associations between selected baseline variables and survival outcomes were evaluated using exploratory univariate and multivariable Cox proportional hazards analyses. Given the exploratory and descriptive nature of this study, which aims to generate hypotheses rather than test confirmatory ones, no correction for multiple comparisons was applied. All reported *P*-values and associations from these analyses were interpreted with caution as hypothesis-generating. R software (version 4.4.1)

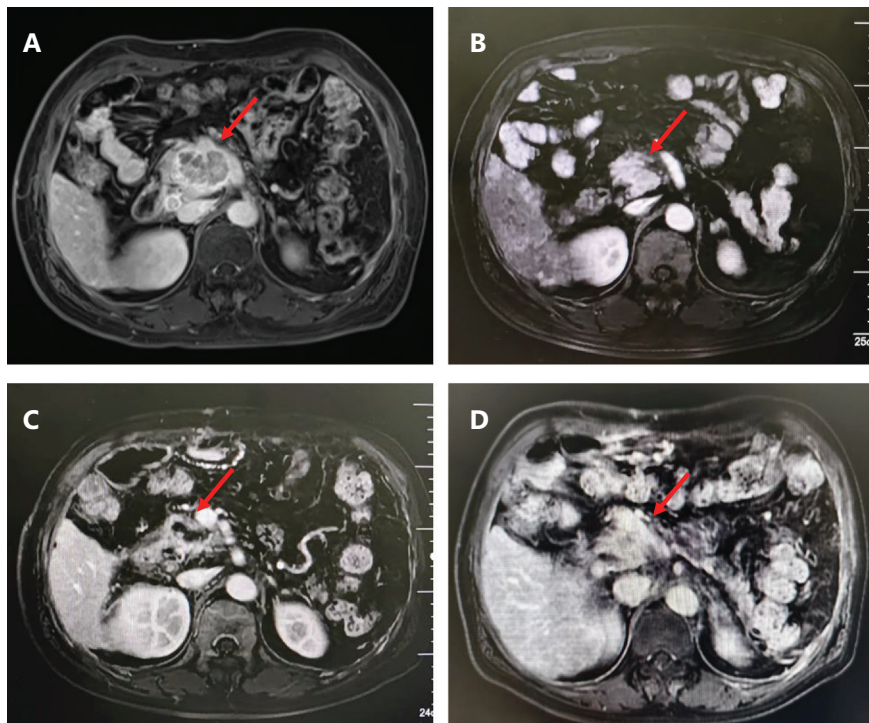


Figure S4 Representative contrast-enhanced magnetic resonance imaging (MRI) images from a patient undergoing sequential therapy. (A) Baseline MRI demonstrates the primary pancreatic head tumor (red arrow). (B) MRI obtained after three cycles of induction therapy with nimotuzumab plus AG shows a reduction in tumor size compared with baseline (red arrow). (C) MRI acquired 1 month after IRE demonstrates the ablation zone with peri-ablational reactive changes (red arrow). (D) MRI obtained 6 months after IRE shows contraction and maturation of the ablation zone, appearing as a stable, non-enhancing region without radiographic evidence of local progression at the primary site (red arrow).

and SPSS (version 27.0) were used to make statistical analyses. The statistical significance was considered less than a two-sided *P*-value of 0.05.

Data collection and quality control

Clinical, laboratory, procedural, and follow-up data were extracted retrospectively from electronic medical records. Imaging assessments were reviewed by experienced radiologists as part of routine clinical care. Data accuracy and

completeness were verified through cross-checking of source documents prior to analysis.

Notes on interpretation

All analyses presented in this study are descriptive and exploratory in nature. The Supplementary Methods are intended to provide transparency regarding treatment delivery and procedural details rather than to support mechanistic or comparative efficacy conclusions.