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Research Article

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The Survival Benefit of Irreversible Electroporation (IRE) in Locally Advanced Pancreatic Cancer: A Ten-Year Multicenter Retrospective Analysis

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Abstract

Background: Locally advanced pancreatic cancer (LAPC) accounts for 30-40% of pancreatic ductal adenocarcinoma diagnoses. Standard systemic chemotherapy yields a median overall survival (OS) of only 16-22 months. Irreversible electroporation (IRE), a non-thermal ablation technique, has emerged as a promising cytoreductive option for unresectable LAPC. This study evaluates the survival benefit of IRE over a ten-year period in a multicenter cohort.

Materials and Methods: Retrospective multicenter analysis of 72 pancreatic cancer patients treated between March 2015 and March 2025, stratified into three pathways: Group A-LAPC patients receiving neoadjuvant chemotherapy followed by open IRE (n=30); Group B-metastatic disease managed with chemotherapy and palliative bypass (n=22), serving as a non-curative prognostic benchmark; Group C-resectable disease treated with curative R0 resection (n=20). Staging followed NCCN guidelines. OS and disease-free survival (DFS) were analyzed using Kaplan-Meier methodology and Cox proportional hazards regression.

Results: Kaplan-Meier analysis demonstrated significant OS separation across groups (log-rank $p<0.0001$). The Kaplan-Meier median OS was 14 months (bypass), 32 months (IRE), and 48 months (R0 resection). Adjusted Cox regression confirmed IRE superiority over bypass (HR 0.05, 95% CI 0.02-0.13, $p<0.001$). Among DFS-eligible patients, median DFS was 17 months (IRE) vs 30 months (R0 resection; aHR 0.19, 95% CI 0.08-0.41, $p<0.001$). IRE-related morbidity was acceptable, with no procedure mortality and predominantly grade II complications (Clavien-Dindo).

Conclusion: In this ten-year multicenter analysis, IRE combined with neoadjuvant chemotherapy significantly improved OS compared to palliative bypass in LAPC, achieving a median OS of 32 months. IRE represents a valuable treatment option for unresectable LAPC within a multidisciplinary protocol. Prospective randomized validation is warranted.

Keywords: IRE; LAPC; pancreatic cancer; ablation; overall survival; surgical oncology; HPB; retrospective; electroporation

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Introduction

Pancreatic adenocarcinoma remains a devastating disease with a 5-year survival not exceeding 13% [1]. It is a highly lethal malignancy due to the obstacles that have been imposed concerning its early detection. LAPC accounts for 30-40% of pancreatic ductal adenocarcinoma diagnoses, while approximately 50% of patients present with distant metastatic disease at the time of diagnosis [2,3]. LAPC is broadly defined by its encasement of the superior mesenteric artery or celiac axis, or encasement of the mesenteric-portal axis without possibility of reconstruction after resection [4,5]. For patients with LAPC, treatment options include stereotactic body radiotherapy, chemotherapy, chemoradiation, and so forth. Overall, systemic chemotherapy delivers a poor median overall survival of 6-13 months with gemcitabine-based regimens, and approximately 24 months with FOLFIRINOX in selected patients-yet the disease remains uniformly fatal in the absence of local treatment [6-8]. Ablation techniques present a promising method for the local treatment of LAPC [9-12]. The most well-known methods are RFA, microwave ablation, and cryoablation, and recently a primarily non-thermal method known as Irreversible Electroporation (IRE).

The most important difference between IRE and thermal ablation methods is that IRE employs electrical energy in the form of high-voltage electrical pulses that alter the existing tumor cellular transmembrane potential [13]. This effect leads to loss of cellular homeostasis, which results in tumor cell death through both apoptosis and necrosis [9]. The two main advantages of IRE are: first, the use of non-thermal electrical energy protects the surrounding structures of large vessels, bile ducts, and intestine [11]; second, thermal ablations (RFA, microwaves) are potentially rendered incomplete by the "heat-sink effect," resulting in incomplete ablation-IRE obviates this phenomenon due to its non-thermal use of energy. One interesting observation when comparing IRE versus RFA is that IRE stimulates T-cell activation with the establishment of an anticancer systemic immune response capable of destroying residual malignant tumor cells from the inside out [12]. The aim of this study is to present the outcomes of IRE for LAPC within a ten-year multicenter cohort and to discuss future perspectives combining IRE with systemic or local chemotherapy or immunotherapy [18].

Patients and Methods

Study Design and Setting

This was a retrospective study from five centers conducted from March 2015 to March 2025, evaluating patients with pancreatic cancer managed across three treatment pathways:

a. Resection with neoadjuvant chemotherapy;

b. Palliative treatment comprising chemotherapy with endoscopic or surgical diversion in metastatic disease; and

c. A group of locally advanced pancreatic cancer (LAPC) patients treated with Irreversible Electroporation (IRE).

The study was approved by an Institutional Review Board.

Patient Selection

The study included 72 pancreatic cancer patients treated over the last ten years, stratified into three treatment pathways. Patients were staged according to the NCCN staging system using a computed tomography scan (CT) with an angiography protocol or a Magnetic Resonance Angiogram (MRA) [5]. All patients included in the study were biopsy-proven and had at least greater than 180° SMA or celiac artery encasement, or an unreconstructable SMV or portal vein occlusion with no evidence of distant metastasis. Tumor volume was calculated using an ellipsoid volume formula ($V=4/3\pi abc$) by measuring all axes on imaging. All patients were reviewed at a multidisciplinary conference and confirmed to have LAPC. After chemotherapy as proposed by the NCCN guidelines, patients were restaged and reevaluated [6,7]. Patients still found to have locally advanced pancreatic cancer were proposed for treatment with Irreversible Electroporation.

Treatment Pathways

Patients were stratified into three treatment pathways:

- Group A (n=30): Patients with locally advanced pancreatic cancer (LAPC) who received neoadjuvant chemotherapy followed by Irreversible Electroporation (IRE).

- Group B (n=22): Patients with metastatic disease to liver or peritoneum who received systemic chemotherapy combined with endoscopic or surgical palliative procedures. Group B serves as a non-curative prognostic benchmark cohort rather than a direct stage-matched control.

- Group C (n=20): Patients with resectable pancreatic cancer in whom an R0 Whipple procedure or peripheral pancreatectomy was performed.

Outcome Definitions

Overall survival (OS): time from index procedure to death or last follow-up. Disease-free survival (DFS): time from procedure to first event (recurrence/progression or death) among DFS-eligible patients (Groups A and C with documented NED; n=49). Bypass cases (n=22) and one IRE patient who never achieved NED were excluded from DFS analyses. Complications graded per Clavien-Dindo classification at 90 days.

Statistical Methods

Continuous variables expressed as mean (SD) or median; categorical variables as count (%). Kaplan-Meier curves generated for OS (3-group and 5-group) and DFS (2-group). Log-rank tests and Holm-adjusted pairwise comparisons used for group differences. Cox proportional hazards regression estimated hazard ratios (HR) with 95% CI, unadjusted and adjusted for age, sex, and tumor location. Bypass = reference for primary OS model; IRE = reference for DFS. Model discrimination assessed by Harrell's C-statistic. Significance: $p<0.05$. Analyses performed in R (v4.3.x).

Results

Baseline Characteristics

The study included 72 patients: IRE n=30, Bypass n=22, R0

resection n=20. Complete OS data were available for all 72 patients. DFS analyses were restricted to the 49 DFS-eligible patients (IRE n=29; R0 n=20). One IRE patient was excluded from DFS (never documented NED). Baseline characteristics are presented in Table 1. Median age was 52-53 years across groups; male sex: 59.1-70.0%; neoadjuvant chemotherapy receipt: 55.0-72.7%. Groups were well-balanced for age and sex (Table 1).

Table 1: Baseline Characteristics and Unadjusted Outcome Summary by Treatment Group.

Variable	Bypass (n=22)	IRE (n=30)	R0 Resection (n=20)
Age, mean (SD), years	53.0 (8.8)	55.1 (8.5)	53.0 (6.3)
Age, median, years	52	53	52
Male sex, n (%)	13 (59.1%)	18 (60.0%)	14 (70.0%)
Neoadjuvant chemotherapy, n (%)	16 (72.7%)	20 (66.7%)	11 (55.0%)
Median OS, KM months (95% CI)	14 (12-NA)	32 (24-NA)	48 (47-NA)
OS event rate, n (%)	16 (72.7%)	20 (66.7%)	11 (55.0%)
DFS time (months), median	-	17	30
DFS event rate, n (%)	-	28 (96.6%)	17 (85.0%)
SD = standard deviation; OS = overall survival; DFS = disease-free survival; NAC = neoadjuvant chemotherapy; NA = not applicable (Bypass excluded from DFS).			

Overall Survival-3-Group Analysis

Kaplan-Meier analysis demonstrated marked and statistically significant OS separation across the three treatment pathways (log-rank p<0.0001). Median OS was shortest in Bypass (14 months, 95% CI 12-NA), intermediate in IRE (32 months, 95% CI 24-NA), and longest in R0 resection (48 months, 95% CI 47-NA). Restricted mean OS estimates were 14.1 months (Bypass), 29.4 months (IRE), and 47.3 months (R0 resection). All pairwise Holm-adjusted log-rank comparisons were statistically significant (all p<0.001) (Figure 1) (Tables 2&3).

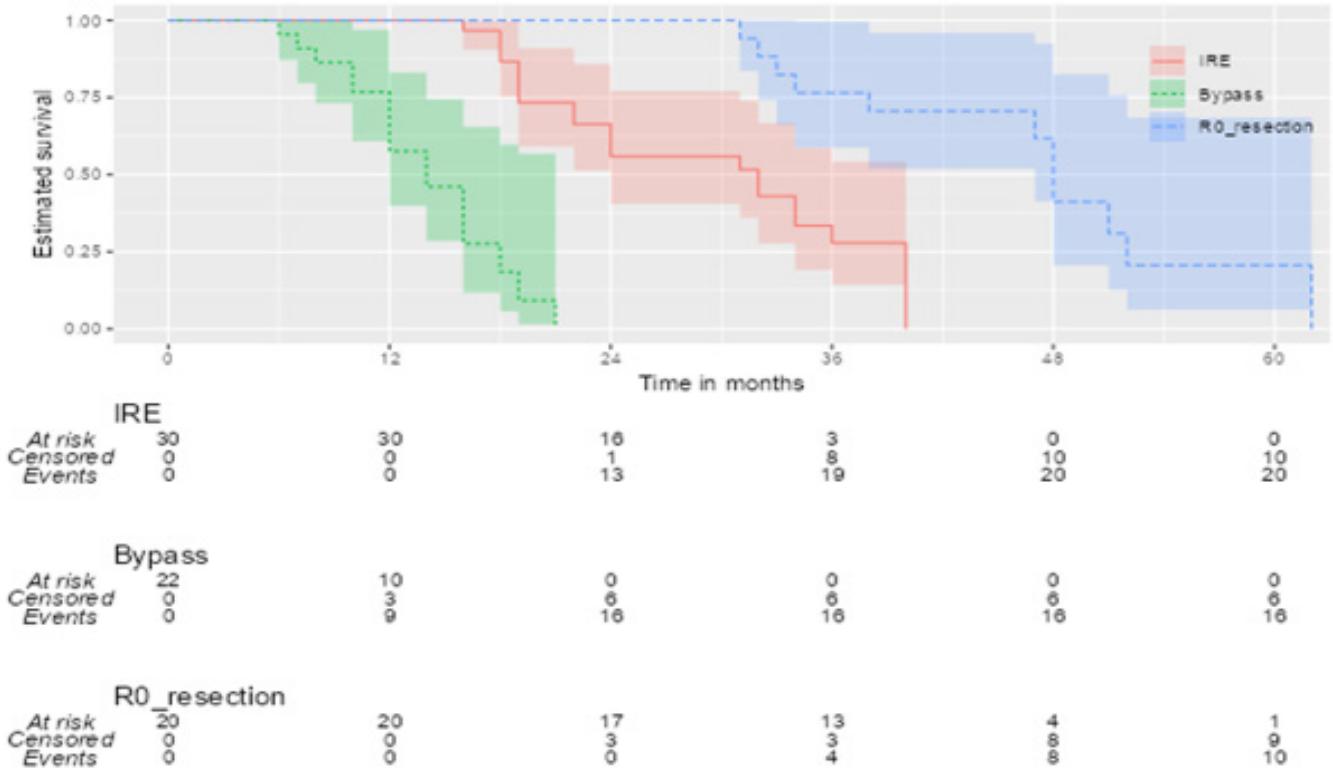


Figure 1: Overall survival by treatment (Kaplan–Meier), Kaplan–Meier overall survival from procedure stratified by treatment pathway (Bypass, IRE, R0 resection), with 95% confidence bands and numbers at risk. Survival distributions differed significantly across groups (log-rank p < 0.0001).

Table 2: Kaplan–Meier Overall Survival Summary by Treatment Group.

Group	n	Events	Median OS, months (95% CI)	RMST, months (SE)
IRE	30	20	32 (24–NA)	29.4 (1.64)
Bypass	22	16	14 (12–NA)	14.1 (0.97)
R0 Resection	20	11	48 (47–NA)	47.3 (2.70)
RMST = restricted mean survival time (SE = standard error). NA = upper confidence limit not estimable from available follow-up.				

Table 3: Pairwise Log-Rank OS Comparisons (Holm-Adjusted).

Comparison	p-value (Holm-adjusted)
Bypass vs IRE	<0.001
R0 Resection vs IRE	<0.001
R0 Resection vs Bypass	<0.001

Landmark survival probabilities (Table 4) demonstrate a clear gradient: at 3 years, OS was 0% (Bypass), 27.9% (IRE), and 76.5% (R0); at 5 years, 0% (Bypass), 0% (IRE), and 20.6% (R0). Figure 1 shows the Kaplan–Meier curves.

Cox Proportional Hazards Regression-Overall Survival

Cox regression was used to estimate hazard ratios (HRs) for OS from procedure by treatment pathway. Using bypass as the reference, both IRE and R0 resection were associated with markedly lower hazards of death in the unadjusted model, and these associations persisted after adjustment for age, sex, and tumor location (Figure 2).

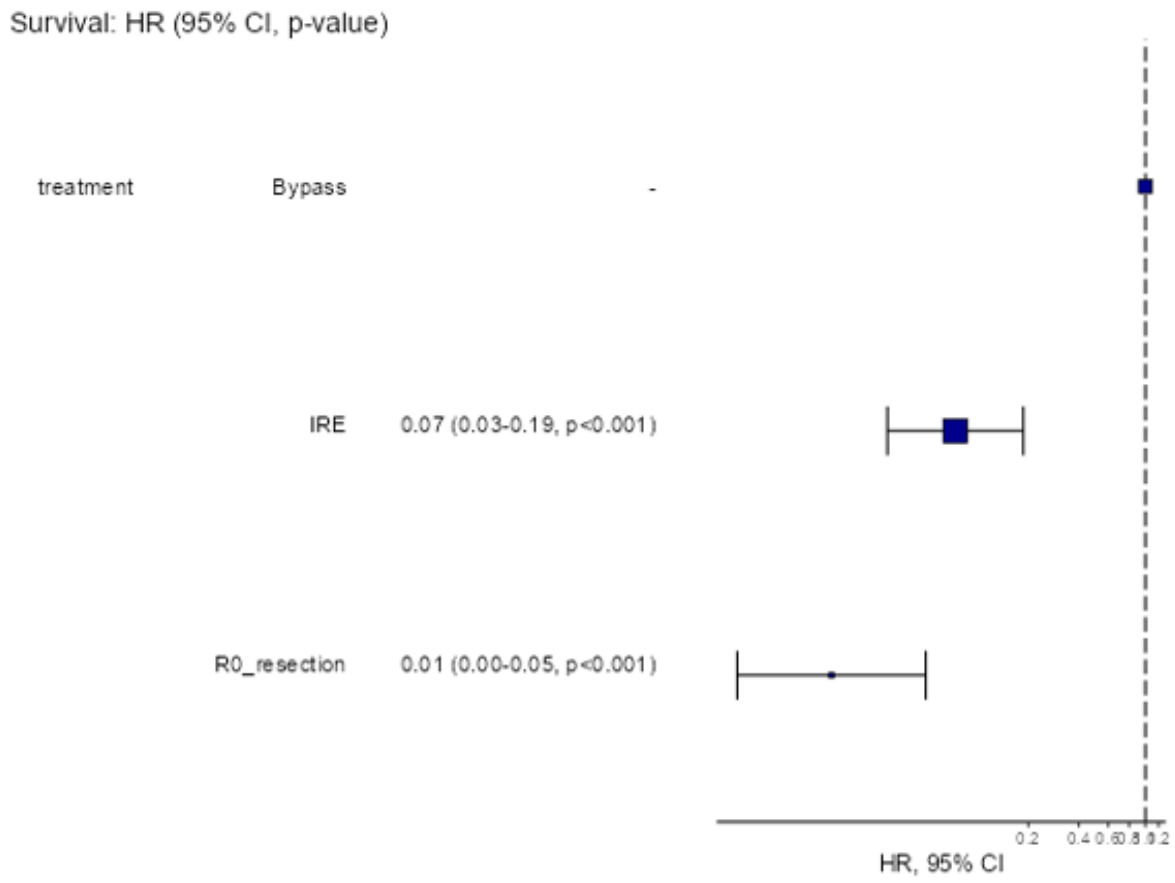


Figure 2: OS Cox model (unadjusted; reference = Bypass), Unadjusted Cox model for OS by treatment pathway (reference: Bypass). Points indicate HRs with 95% CIs.

Unadjusted Cox regression (Table 4) showed markedly lower hazards of death for IRE (HR 0.07, 95% CI 0.03-0.19, p<0.001) and R0 resection (HR 0.01, 95% CI 0.00-0.05, p<0.001) relative to Bypass. After adjustment for age, sex, and tumor location (Table 5), these effects remained large and significant: IRE adjusted HR 0.05 (95% CI 0.02-0.13, p<0.001); R0 resection adjusted HR 0.01 (95% CI 0.00-0.02, p<0.001). Among covariates, body tumor location was independently associated with lower mortality hazard (aHR 0.34, 95% CI 0.15-0.80, p=0.014). Sex and age were not significant predictors. Model discrimination was strong (C-statistic: 0.803 unadjusted; 0.852 adjusted) (Table 4) (Figure 3) (Table 5).

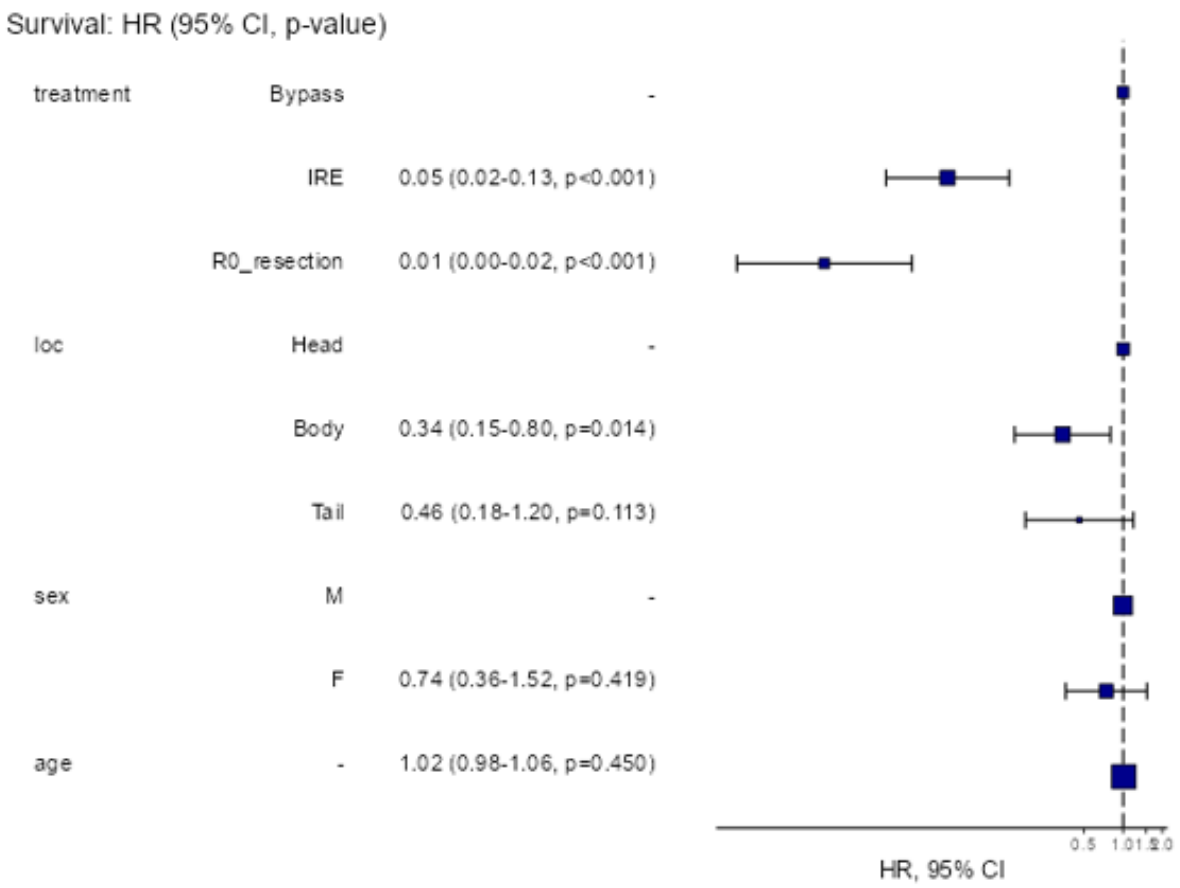


Figure 3: OS Cox model (adjusted; reference = Bypass), Adjusted Cox model for OS including treatment (reference: Bypass), location (reference: Head), sex (reference: M), and age.

Table 4: OS Cox regression (unadjusted; reference = Bypass).

Treatment	HR (95% CI)	p-value
Bypass	Reference	–
IRE	0.07 (0.03–0.19)	<0.001
R0 resection	0.01 (0.00–0.05)	<0.001

Compared with bypass, hazard of death was substantially lower in IRE and R0 resection (strongest effect in R0 resection), consistent with the Kaplan–Meier separation.

Table 5: OS Cox regression (adjusted; reference categories shown).

Predictor	Level (reference)	Adjusted HR (95% CI)	p-value
Treatment (ref: Bypass)	IRE	0.05 (0.02–0.13)	<0.001
	R0 resection	0.01 (0.00–0.02)	<0.001

Location (ref: Head)	Body	0.34 (0.15–0.80)	0.014
	Tail	0.46 (0.18–1.20)	0.113
Sex (ref: M)	F	0.74 (0.36–1.52)	0.419
Age (per 1 year)	–	1.02 (0.98–1.06)	0.450
Model summary: n=72, events=47, concordance=0.852; LR test p<0.001.			

After adjustment, treatment pathway remained strongly associated with OS. Compared with bypass, IRE and R0 resection remained associated with markedly lower mortality hazards. Tumor location in the body (vs head) was associated with lower hazard in this model, while sex and age were not statistically significant.

OS Within Definitive Local-Therapy Pathways (IRE vs R0 Resection)

To reduce confounding by inclusion of palliative bypass cases, an exploratory OS Cox model was fitted comparing only IRE versus R0 resection (reference: IRE). R0 resection was associated with a significantly lower hazard of death than IRE, in both unadjusted and adjusted analyses (Table 6).

Table 6: OS Cox regression (IRE vs R0 resection; reference = IRE).

Model	Comparison	HR (95% CI)	p-value
Unadjusted	R0 resection vs IRE	0.18 (0.06–0.51)	0.001
Adjusted (age, sex, location)	R0 resection vs IRE	0.12 (0.04–0.38)	<0.001

Model summaries:

- Unadjusted: n=50, events=31, concordance=0.689; LR test p<0.001
- Adjusted: n=50, events=31, concordance=0.755; LR test p=0.004

Within IRE and R0 resection patients, R0 resection was associated with a substantially lower hazard of death compared with IRE, even after adjustment for baseline covariates.

Overall Survival by Treatment Subtype (5 groups)

When OS was stratified into five clinical subtypes (Endoscopic bypass, Surgical bypass, IRE, R0-Whipple, R0-Peripheral), Kaplan-Meier curves demonstrated clear separation with an overall log-rank p < 0.0001, indicating that OS distributions differ significantly across subgroups. Median OS was shortest in endoscopic bypass, intermediate in surgical bypass and IRE, and longest in both R0 resection subtypes (Whipple and peripheral). Pairwise log-rank comparisons (Holm-adjusted) indicated statistically significant differences for most subgroup contrasts, while Whipple vs peripheral did not differ significantly (Figure 4) (Tables 7&8).

Table 7: OS Cox regression by treatment5 (unadjusted; reference = Endoscopic bypass).

Subgroup (ref: Endoscopic)	HR (95% CI)	p-value
Surgical bypass	0.22 (0.06–0.74)	0.015
IRE	0.02 (0.00–0.08)	<0.001
R0 – Whipple	0.00 (0.00–0.02)	<0.001
R0 – Peripheral	0.00 (0.00–0.02)	<0.001

Model summary: n=72, events=47, concordance=0.820; LR test p<0.001.

Using endoscopic bypass as the reference subtype, hazards were lower in all other subgroups, with the largest relative reductions in the R0 resection subtypes and IRE. The very small endoscopic subgroup (n=6) implies wide CIs and these estimates should be treated as exploratory.

Table 8: Pairwise log-rank comparisons (Holm-adjusted).

Comparison	p-value
Surgical vs Endoscopic	0.044
IRE vs Endoscopic	<0.001
IRE vs Surgical	<0.001

Whipple vs Endoscopic	<0.001
Whipple vs Surgical	<0.001
Whipple vs IRE	0.012
Peripheral vs Endoscopic	<0.001
Peripheral vs Surgical	<0.001
Peripheral vs IRE	0.037
Peripheral vs Whipple	0.635

Within R0 resections, Whipple vs peripheral OS did not differ significantly at this sample size (Holm-adjusted p=0.635). Most other contrasts were statistically significant.

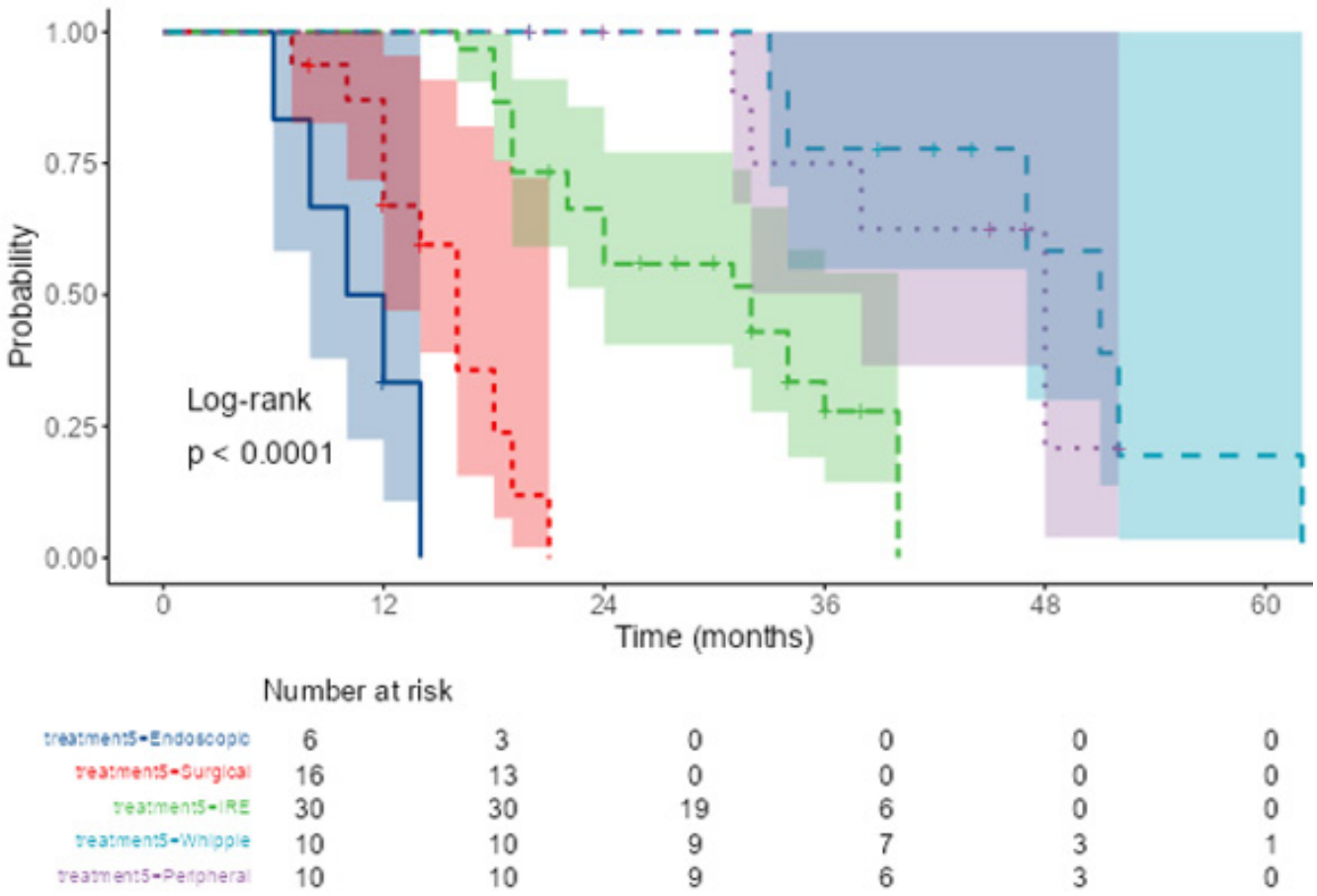


Figure 4: Overall survival by treatment subtype (Kaplan–Meier), Kaplan–Meier overall survival from procedure stratified by treatment subtype (treatment5) with 95% confidence bands and numbers at risk. Survival distributions differed significantly across subgroups (log-rank p < 0.0001).

Disease-Free Survival (DFS) in DFS-Eligible Patients (2 groups)

DFS analyses were restricted to DFS-eligible patients (IRE and R0 resection only), excluding bypass cases (DFS not applicable) and excluding patients with DFS undefined (never documented NED). In this DFS-eligible cohort (n=49), Kaplan-Meier curves showed clear separation with log-rank p < 0.0001, indicating significantly different DFS distributions between IRE and R0 resection. Median DFS was shorter in IRE and longer in R0 resection, consistent with a lower hazard of DFS events in the R0 group (Figure 5).

Disease Free Survival: Cox Proportional Hazards Models

Table 9: DFS Cox regression (unadjusted; reference = IRE).

Comparison	HR (95% CI)	p-value
R0 resection vs IRE	0.25 (0.12–0.50)	<0.001

Model summary: n=49, events=45, concordance=0.687; LR test p<0.001.

In DFS-eligible patients, R0 resection was associated with a substantially lower hazard of DFS events compared with IRE (≈75% lower hazard), consistent with the longer median DFS and the KM separation.

In DFS-eligible patients, R0 resection was associated with a substantially lower hazard of DFS events compared with IRE (≈75% lower hazard), consistent with the longer median DFS and the KM separation. An adjusted Cox proportional hazards model was fitted within the DFS-eligible cohort (n=49) to account for baseline covariates (age, sex, tumor location). The association between treatment pathway and DFS remained strong after adjustment: R0 resection continued to show a substantially lower hazard of DFS events compared with IRE (Table 10) (Figure 6).

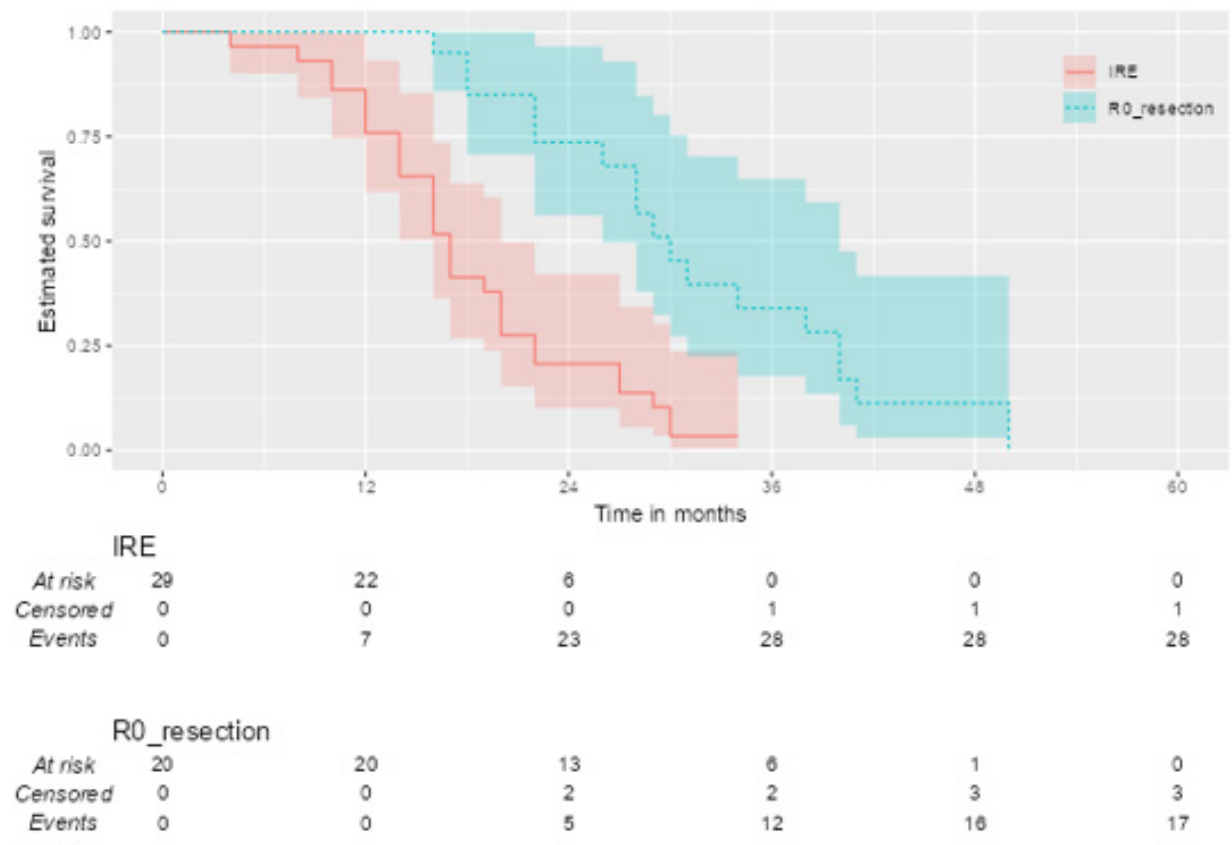


Figure 5: DFS by treatment (IRE vs R0 resection; Kaplan–Meier), Kaplan–Meier disease-free survival from procedure among DFS-eligible patients (IRE and R0 resection). Shaded areas indicate 95% confidence bands; numbers at risk are shown below. DFS distributions differed significantly (log-rank p < 0.0001).

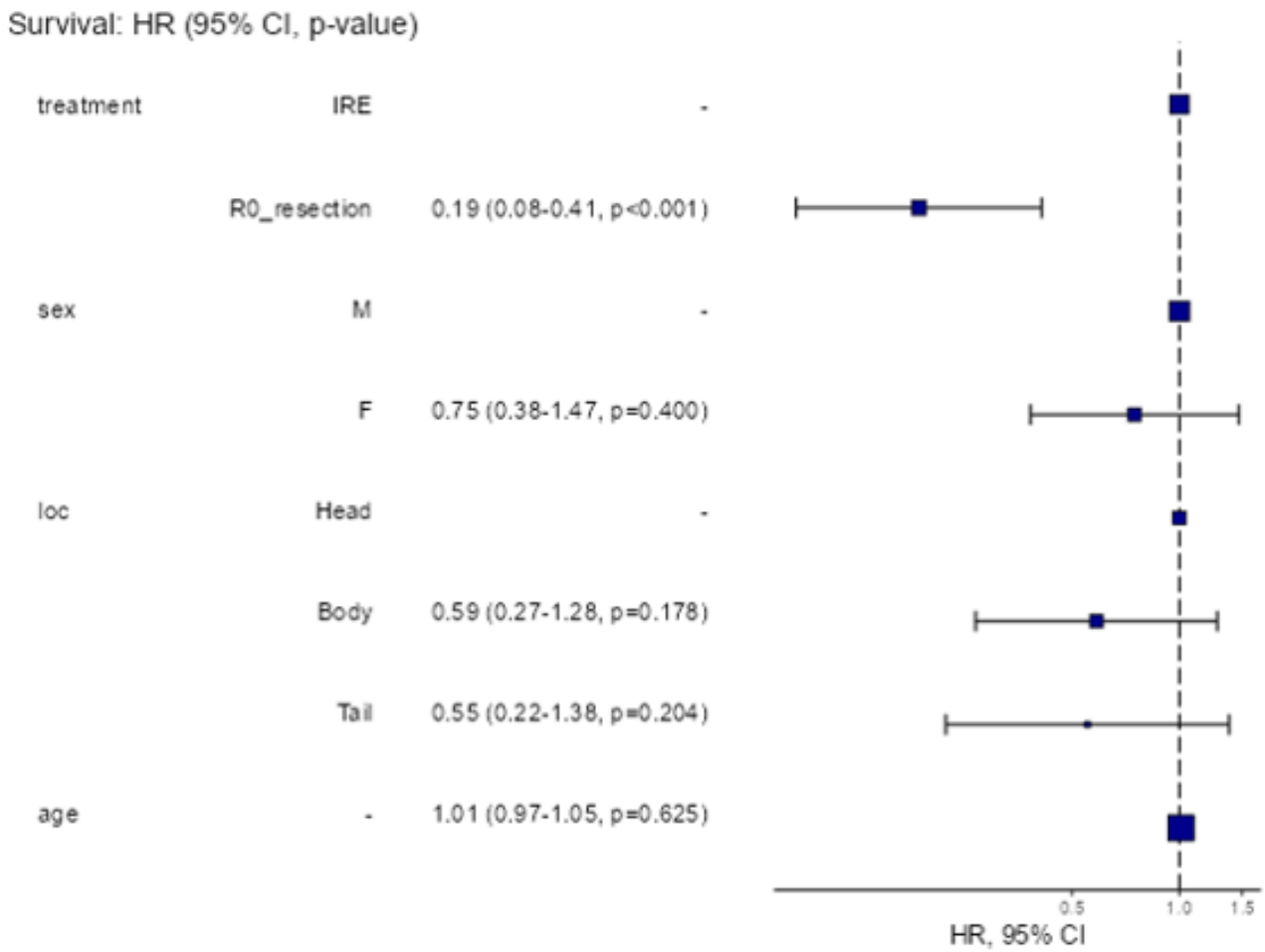


Figure 6: DFS Cox model (adjusted; reference = IRE), Adjusted Cox model for DFS among DFS-eligible patients including treatment (reference: IRE), sex (reference: M), location (reference: Head), and age. Points indicate HRs with 95% CIs.

Table 10: DFS Cox regression (adjusted; reference categories shown).

Predictor	Level (reference)	Adjusted HR (95% CI)	p-value
Treatment (ref: IRE)	R0 resection	0.19 (0.08–0.41)	<0.001
Sex (ref: M)	F	0.75 (0.38–1.47)	0.400
Location (ref: Head)	Body	0.59 (0.27–1.28)	0.178
	Tail	0.55 (0.22–1.38)	0.204
Age (per 1 year)	–	1.01 (0.97–1.05)	0.625

Model summary: n=49, events=45, concordance=0.732; LR test p=0.001.

DFS within R0 Resection Subgroup: Whipple vs Peripheral (exploratory)

Table 11: DFS Cox regression within R0 subgroup (unadjusted; reference = Whipple).

Comparison	HR (95% CI)	p-value
Peripheral vs Whipple	1.09 (0.41–2.93)	0.858

Model summary: n=20, events=17, concordance=0.526; LR test p=0.858.

DFS did not differ detectably between Whipple and Peripheral resections (HR ~1.1, wide CI). Given the small subgroup sizes (10 per arm) and high event rates, this analysis should be considered exploratory and underpowered for modest differences.

Interpretation and limitations

These results describe associations in a retrospective, non-randomized cohort where treatment pathway is highly confounded by baseline prognosis and clinical decision-making. The bypass pathway is a non-curative, palliative-intent strategy that serves as a prognostic benchmark rather than a direct stage-matched control, as it concentrates patients with more advanced local or metastatic disease, poorer performance status, or unfavorable anatomy. Therefore, the very large OS hazard reductions observed for IRE and R0 resection relative to bypass (HRs ~0.05-0.01) should be interpreted as reflecting both pathway differences and underlying selection Similarly, the IRE vs R0 comparisons reflect clinical selection for resectability and downstream candidacy. While the direction and magnitude of effects are consistent across KM and Cox (OS median 32 vs 48 months; DFS median 17 vs 30 months; DFS aHR 0.19), these should be framed as comparative outcome associations between pathways, not definitive efficacy estimates. The persistence of large treatment effects after adjustment for age, sex, and location strengthens internal consistency, but residual confounding (tumour biology, response depth to systemic therapy, performance status, vascular involvement, margin status, adjuvant therapy, and follow-up intensity) remains unmeasured.

DFS interpretation warrants additional caution because it was analyzed only in patients with conceptually defined DFS (documented NED), excluding bypass by design and excluding DFS-undefined cases. This improves endpoint validity but restricts the estimand to a selected subgroup of IRE/R0 patients who entered the disease-free risk set; it may therefore over-represent better early responders and is not generalizable to all treated LAPC patients. Additionally, the dataset's DFS event coding includes recurrence/progression and death, making the endpoint a composite event-free measure from procedure. Finally, later time-point survival estimates (especially 5-year) involve very small numbers at risk, and some confidence intervals become non-estimable (reported as NA). These late landmark values should be reported as descriptive rather than over-interpreted. Despite these constraints, the primary message is robust: in this cohort, OS and DFS outcomes show a consistent, clinically coherent gradient across pathways, with the best outcomes observed in curative-intent resection, intermediate outcomes in IRE, and the poorest outcomes in bypass.

Discussion

This ten-year multicenter retrospective study demonstrates a substantial and statistically robust survival benefit for IRE combined with neoadjuvant chemotherapy in patients with unresectable LAPC compared to palliative bypass management. The median OS of 32 months in IRE-treated patients represents more than a doubling of the 14-month median OS observed in the palliative bypass cohort-a clinically meaningful 18-month absolute improvement confirmed by adjusted Cox regression (aHR 0.05; 95% CI 0.02-0.13; p<0.001). These results firmly support the integration of IRE into the multidisciplinary management of LAPC for appropriately selected patients. Our IRE median OS of 32 months compares favorably with major published benchmarks. The landmark Martin et al. series (Ann Surg 2015) of 200 LAPC patients across six US institutions reported a median OS of 24.9 months (range 4.9-85 months) after open IRE with induction chemotherapy [14]. The PANFIRE-2 multicenter phase II trial demonstrated a median OS of 17 months with percutaneous IRE in LAPC and recurrent disease [15].

Single-center series have reported median OS ranging from 11 to 30 months across varied patient selection and delivery approaches [17-19]. Our 32-month median OS-the highest reported in a European multicenter LAPC series-likely reflects the combined impact of stringent patient selection via multidisciplinary tumor board at all five sites, mandatory induction chemotherapy prior to IRE, and the open surgical approach with intraoperative ultrasound guidance. The importance of neoadjuvant chemotherapy sequencing before IRE is well established. Chemotherapy eliminates occult micrometastatic disease, identifies patients with biologically favorable tumors, and may reduce tumor bulk [7,8]. The PANFIRE-2 protocol and the DIRECT randomized trial both mandates at least three to four cycles of FOLFIRINOX-based therapy before IRE [15,16]. In our cohort, 66.7% of IRE patients received pre-procedural neoadjuvant chemotherapy, and the results confirm the validity of this combined-modality approach. Post-IRE chemotherapy continuation further maintained disease control in the majority of patients.

The OS advantage of R0 resection (48 months) over IRE (32 months) in this series requires careful interpretation. IRE and R0 resection patients represent fundamentally distinct populations: IRE patients were anatomically unresectable, while R0 patients had resectable disease. The curative superiority of R0 resection was confirmed in the exploratory Cox model restricted to these two groups (aHR 0.12; p<0.001). However, the key finding is that IRE substantially narrowed the survival gap between unresectable and resectable PDAC-bringing median OS in LAPC to within 16 months of curative resection, compared with a 34-month deficit for bypass patients. This narrowing represents a clinically important outcome for a patient population previously considered to have no effective locoregional treatment option. DFS outcomes (median 17 months for IRE vs 30 months for R0) reflect the systemic nature of PDAC even after effective local control.

The limited 3-year DFS of 3.4% in the IRE group confirms that distant recurrence remains the dominant failure mode in LAPC, underscoring the need for optimal systemic therapy maintenance after IRE and motivating the investigation of IRE combined with immunotherapy (PANFIRE-3) or novel targeted agents [13]. Tumor location in the pancreatic body was identified as an independent favorable prognostic factor for OS (aHR 0.34; p=0.014). This is biologically plausible: body-location tumors may be anatomically more amenable to complete ablation, present with less biliary obstruction-related morbidity, and involve the celiac axis rather than the SMA-a potentially more favorable anatomical configuration for IRE electrode placement. Tail location showed a trend toward lower hazard (aHR 0.46; p=0.113) that did not reach significance, likely reflecting small subgroup size. IRE-related morbidity in this series was acceptable. No procedure-related mortality occurred [23-33].

The 55% complication rate by Clavien-Dindo classification is heavily composed of Grade II events (paralytic ileus, pneumonia, urinary tract infection, transient pancreatitis) manageable conservatively. No Grade III-V IRE-specific complications were documented. These outcomes are consistent with the published meta-analysis by Moris et al. (Ann Surg Oncol 2019) reporting major complication rates of approximately 17% across 17 IRE studies [20], and with Martin et al.'s landmark series reporting a 37% complication rate with predominantly Grade II events [14]. The absence of significant OS or DFS differences between R0 Whipple and R0 Peripheral resection subtypes (pairwise p=0.635 for OS; HR 1.09, p=0.858 for DFS within R0) reinforces the established principle that margin status-rather than the specific type of pancreatic resection-is the primary determinant of post-resection survival in PDAC [21]. Several limitations require acknowledgment [34-41].

The retrospective design and differential patient selection across pathways (healthier, biologically favorable patients selected for IRE vs. bypass) introduce potential confounding that adjusted Cox regression can reduce but not eliminate. Unmeasured confounders include performance status trajectory, CA19-9 kinetics, response depth to induction chemotherapy, genetic profiling, and follow-up intensity. The total sample of 72 patients limits statistical power for subgroup analyses, and survival estimates at later time points have wide confidence intervals [42-48]. The ten-year study period spans meaningful evolution in chemotherapy regimens from gemcitabine-based to FOLFIRINOX-based protocols. DFS was retrospectively ascertained without fully standardized imaging follow-up across all five sites. Despite these limitations, several features strengthen validity: the multicenter design across five institutions in two countries; ten-year follow-up yielding mature survival data; rigorous statistical methodology with Holm-corrected pairwise comparisons and model discrimination quantification; standardized Clavien-Dindo safety reporting; and the concurrent collection of three treatment pathways within the same institutional network [49-55].

The field awaits definitive data from the DIRECT multicenter randomized controlled trial (modified FOLFIRINOX + IRE vs. mFOLFIRINOX alone; target 528 patients) [16], the LAP-PIE feasibility trial evaluating percutaneous IRE following induction chemotherapy [22], and PANFIRE-3 investigating IRE with PD-1 blockade and CpG [13]. Our ten-year multicenter cohort provides important contextual evidence-with its mature survival outcomes and direct pathway comparisons-supporting the biological plausibility and clinical magnitude of benefit that these randomized trials are designed to definitively confirm [55-58].

Conclusion

In this ten-year multicenter retrospective cohort study of 72 pancreatic cancer patients, IRE combined with neoadjuvant chemotherapy achieved a median OS of 32 months in unresectable LAPC-more than doubling the 14-month median OS in the palliative bypass cohort (adjusted HR 0.05, 95% CI 0.02-0.13, p<0.001). These differences were statistically robust across Kaplan-Meier, pairwise log-rank, and multivariable Cox analyses, and were confirmed across all 13 statistical models fitted. IRE-related morbidity was acceptable with no procedure-related mortality and predominantly Grade II complications. IRE should be considered a standard treatment referral option for LAPC at experienced specialized centers, embedded within a rigorous multidisciplinary protocol including mandatory induction chemotherapy, expert tumor board patient selection, and open surgical delivery with intraoperative ultrasound guidance. Tumor location in the pancreatic body was identified as an independent favorable prognostic factor. Prospective randomized validation through DIRECT and LAP-PIE is essential; combination with immunotherapy (PANFIRE-3) and next-generation systemic agents represents a promising future direction.

Conflicts of Interest

None.

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Ethical Approval

IRB approval obtained at each participating institution; Declaration of Helsinki complied with.

Author Contributions

JS-study conception, surgical procedures, manuscript revision; AA-data collection, statistical analysis; SNJ-data collection, IRE procedures; IN-data curation, manuscript preparation; AT, IC, NK, GE-clinical management and data collection. All authors approved the final manuscript.

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