Original Article

Final results of a phase II trial on the role of intraoperative radiotherapy in reducing local recurrence risk in resectable pancreatic cancer with low-energy X-rays

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a high propensity for locoregional recurrence despite curative surgery. We designed a phase II study to evaluate locoregional recurrence and mortality in patients with resectable pancreatic cancer (RPC) treated with intraoperative radiotherapy (IORT) using a 50-kV low-energy X-ray source. This report presents the final results.

Methods: In a prospective single-institution phase II trial, the efficacy of IORT using a 50-kV low-energy X-ray source in resectable PDAC was evaluated. Thirty-eight patients underwent curative pancreatectomy followed by IORT delivering 10 Gy at 5-mm depth (≈16 Gy on the surface). Gemcitabine-based chemotherapy was administered postoperatively in most cases. The primary endpoint was the 2-year local recurrence rate, and the secondary endpoints were recurrence-free survival (RFS) and overall survival (OS). Cox regression was used to identify the prognostic factors.

Results: The 1- and 2-year local recurrence rates were 33.2% and 57.7%, respectively. The median local RFS was 19 months, and the median OS was 43 months. Multivariate analysis identified perineural invasion (PNI) and margin status (R1 *vs.* R0) as significant predictors of local recurrence, whereas lymphovascular invasion (LVI) and tumor-vessel contact ≥90° were associated with poor OS.

Conclusions: Low-energy X-ray IORT was feasible and well tolerated, showing a potential benefit in local control, particularly for patients with microscopic residual disease (R1 resection). PNI, LVI, and tumor-vessel interactions emerged as important prognostic factors. Larger multicenter randomized trials are warranted to confirm these findings.

Keywords: Pancreatic neoplasm; radiotherapy; pancreatectomy; radiotherapy; recurrence

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the seventh most common cancer worldwide and is projected to become the second leading cause of cancer-related deaths globally by 2030 (1). PDAC remains a formidable challenge in oncology, primarily because of its poor prognosis (2). A significant contributor to these poor outcomes is the high disease recurrence rate after surgical resection. Studies have indicated that more than half of the PDAC cases recur within 12 months of curative-intent resection, and early recurrence is associated with poor prognosis (3,4). Consequently, over the years, achieving local control, which refers to the successful elimination or containment of tumor cells within the pancreas and immediate surgical margins to prevent recurrence, has been the primary objective (5-8).

Radiotherapy has emerged as a central approach for achieving local control in pancreatic cancer management (7,9). However, the traditional method, external beam radiation therapy (EBRT), poses challenges. The proximity of the pancreas to vital parts of the body, such as the bone marrow, kidneys, and intestines, makes it difficult to deliver the correct amount of radiation without affecting these areas. Intraoperative radiotherapy (IORT) offers a promising solution and provides a targeted approach to achieve better local control (10,11).

The use of IORT for patients with locally advanced pancreatic cancer (LAPC) was first reported in Japan in the 1980s for patients with LAPC (12-14). IORT has been proposed for LAPC, aiming to provide local control and palliation of pain, and for resectable pancreatic cancer (RPC), with the goal of enhancing local control and survival after pancreaticoduodenectomy. Unlike conventional radiation techniques, IORT is administered directly to the operative bed in a single session, thereby maximizing its therapeutic impact and improving time efficiency. Furthermore, because IORT minimizes radiation exposure to surrounding tissues, it significantly reduces normal tissue toxicity.

In our previous study, we investigated the acute postoperative complications and reviewed the early oncological outcomes of patients with RPC undergoing IORT using a low-energy X-ray source (15). Building on these findings, this follow-up study aimed to evaluate whether IORT effectively reduces long-term local recurrence rates and affects overall mortality in the same patient cohort. We present this article in accordance with the TREND reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2025-337/rc).

Highlight box

Key findings

- In a single-institution prospective phase II trial, intraoperative radiotherapy (IORT) using a low-energy 50-kV X-ray source was applied in 38 patients with resectable pancreatic cancer. The 2-year local recurrence rate was 57.7%, and the median overall survival (OS) was 43 months. Perineural invasion (PNI) and R1 resection margin were independently associated with local recurrence, while lymphovascular invasion and tumor-vessel contact ≥90° predicted poor OS.

What is known and what is new?

- IORT has been explored to improve local control, but evidence for low-energy X-ray-based IORT in resectable pancreatic ductal adenocarcinoma (PDAC) is limited.
- This prospective study suggests that low-energy X-ray-based IORT is feasible and generally well-tolerated, and highlights the prognostic relevance of tumor-vessel contact and certain pathological features for patient stratification.

What is the implication, and what should change now?

- The findings support the selective use of IORT in high-risk resectable PDAC cases, particularly those with R1 resection margins or aggressive histological features such as PNI. Future studies should focus on refining patient selection and integrating IORT into multimodal strategies.

Methods

Study design and patient selection

This single-institution prospective phase II study was registered at ClinicalTrials.gov (NCT 03273374). Patients diagnosed with pancreatic cancer were enrolled between August 1, 2017 and September 30, 2019. All the participants underwent curative pancreatectomy as part of their treatment regimen. The study protocol and early outcomes were published previously (15,16).

The eligibility criteria for this study included patients aged 20 years or older with histologically or clinically confirmed pancreatic carcinoma. Participants were required to have an Eastern Cooperative Oncology Group performance status score of 0–2 and resectable disease, defined by the absence of distant metastases and direct involvement of the inferior vena cava or aorta, along with clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA). Additionally, good bone marrow function was required, as indicated by a hemoglobin level >10.0 g/dL, absolute neutrophil count >1,500/mm^3,

and platelet count >100,000/mm^3. Adequate renal function was also necessary, as demonstrated by a serum creatinine level <1.4 mg/dL and blood urea nitrogen level <20 mg/dL.

The exclusion criteria for this study included: prior radiation therapy to the abdominal area, tumor beds deemed by a radiation oncologist to be unsuitable for adequate IORT coverage, prior neoadjuvant chemotherapy, or the presence of synchronous distant metastases. Additionally, pregnant or nursing women and individuals considered unsuitable for IORT by a physician were excluded. Furthermore, patients who, upon further evaluation, were found ineligible for surgery or whose final pathology did not confirm PDAC were also excluded from the final analysis.

The sample size was determined based on our primary endpoint of 1-year local recurrence. Based on institutional data showing a 36% recurrence rate after surgery alone, we assumed IORT would reduce this to 22%. With α=0.05 and 80% power, 33 patients were needed; accounting for a 20% drop-out rate, the final target was 42. This calculation was previously detailed in our published protocol (15,16).

Treatment scheme and IORT procedure

All patients underwent resection with curative intent, including pylorus-preserving pancreaticoduodenectomy (PPPD), distal pancreatectomy (DP), or total pancreatectomy (TP), depending on tumor location and surgical feasibility. For the IORT component, a mobile 50-kV X-ray source (Intrabeam; Carl Zeiss Meditec AG, Oberkochen, Germany) was used, delivering intraoperative radiation directly to the tumor bed and surrounding high-risk areas, including the celiac and SMAs, the retroperitoneal margin near the SMA, the mesenteric root, and the portal vein (PV). A spherical applicator with a diameter of 3.5 cm, equipped with a shielding device, was selected to ensure precise beam delivery while minimizing radiation exposure to uninvolved tissues. To prevent contamination, a sterile sheath was applied to the IORT device, and additional shielding was placed over the surgical field to protect the operating team.

The prescribed radiation dose was 10 Gy, delivered at a depth of 5 mm into the retroperitoneal margin, which corresponded to a surface dose of approximately 16 Gy, as referenced in the previous literature. The isotropy and output of the IORT system were verified before each procedure, and the pretreatment calibration process was performed in accordance with standard quality assurance protocols. Following surgery and IORT, patients received a standardized adjuvant chemotherapy regimen consisting of six cycles of gemcitabine-based chemotherapy, initiated 8–12 weeks postoperatively or upon adequate wound healing. Each chemotherapy cycle was administered every 4 weeks, with 3 weekly doses of gemcitabine per cycle. All procedures were performed by the attending surgeon and radiation oncologist.

Study endpoints and definitions

The primary endpoint of this trial was the local recurrence rate at 2 years, whereas secondary endpoints included recurrence-free survival (RFS) and overall survival (OS), providing a comprehensive evaluation of both local control and overall patient survival outcomes. Local failure was defined as recurrence occurring around the SMA and celiac trunk, including the tumor bed, remnant pancreas, and regional lymph nodes. Distant failure was defined as recurrence beyond this scope. RFS was defined as the time to local recurrence or distant metastasis, and OS was measured from the date of surgery.

In this study, resection margin status was defined according to the criteria of the Royal College of Pathologists, where R0 resection was classified as a tumor-free margin >1 mm, indicating a lower risk of recurrence, whereas R1 resection, characterized by a tumor-free margin ≤1 mm, was independently associated with a higher likelihood of residual disease and recurrence (17,18). Additionally, for RPC, we stratified the outcomes based on the degree of tumor-vessel contact with the PV or superior mesenteric vein (SMV) into three groups: no contact, <90° contact, and 90°–180° contact. Tumor-vessel contact was assessed preoperatively through consensus in a multidisciplinary team meeting involving surgeons, radiologists, and medical oncologists. All imaging assessments were performed by a radiologist with over 10 years of experience in pancreatic cancer imaging. To enhance consistency, the same imaging protocol and standardized anatomical criteria were applied across all cases, with regular multidisciplinary conferences convened weekly to ensure consistency and minimize interobserver variability.

Statistical analyses

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA), with a

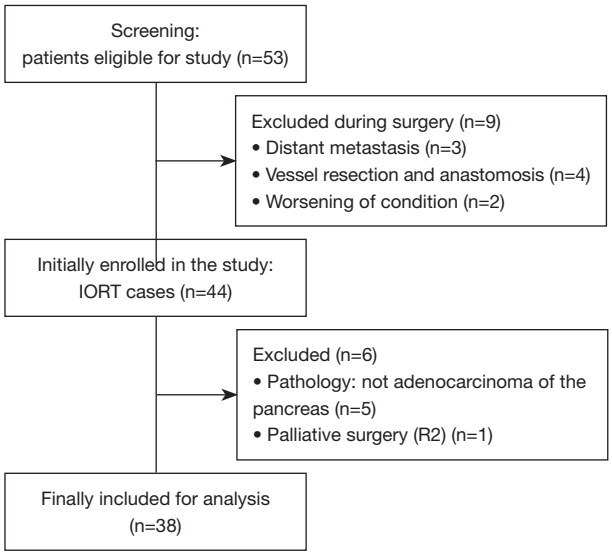

Figure 1 Flow chart of study. IORT, intraoperative radiotherapy.

P<0.05 considered statistically significant. Frequency and descriptive analyses were performed to examine the demographic and clinical characteristics of the study population. Kaplan-Meier survival analysis was used to assess local control and OS, whereas univariate and multivariate analyses were performed using the Cox proportional hazards model to identify factors associated with local control and OS. Variables with P<0.10 in the univariate analysis were included in the multivariate analysis. Additionally, to further explore the prognostic factors, we conducted Cox multivariate analyses and supplementary Kaplan-Meier analyses for local recurrence and OS, incorporating variables that demonstrated statistical significance in the Cox multivariate model.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Institutional Review Board at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (IRB No. 3–2017-0171), and informed consent was obtained from all participants prior to enrollment.

Results

Between November 2017 and August 2019, 53 patients were screened for inclusion in this study, as shown in *Figure 1*. Of these, 9 did not meet the inclusion criteria: three were found to have peritoneal seeding or liver metastasis during surgery, four required SMV or PV resection and reconstruction, and two experienced intraoperative bleeding leading to deterioration of their general condition. Thus, 44 patients were initially enrolled as IORT cases. Of these, five patients were excluded because the final pathology revealed non-adenocarcinoma tumors. While our preliminary report included all pancreatic tumors to describe early outcomes and complications of IORT, the present study focused exclusively on pancreatic adenocarcinoma. One additional patient who underwent SMV resection and grafting for >180° tumor involvement and received IORT as part of palliative (R2) surgery was also excluded. Ultimately, 38 patients were included in the final analysis.

Table 1 presents the demographic and clinical characteristics of the patients. The median age was 66 years (range, 42–84 years), and women comprised 47.4% of the cohort. Most tumors were located in the pancreatic head or uncinate process (63.2%). The median carbohydrate antigen (CA) 19-9 level was 91.90 U/mL (range, 0.08–15,698.30 U/mL). Regarding tumor-vessel contact, 25 patients (65.8%) had no contact, 9 (23.7%) had <90° contact, and 4 (10.5%) had 90–180° contact. Among the surgical procedures, 24 patients (63.2%) underwent PPPD, 12 patients (31.6%) underwent DP, and 2 patients (5.3%) underwent TP. The mean IORT time was 35.49±1.76 minutes. According to American Joint Committee on Cancer 8th edition staging, 44.7% of patients were classified as T3, and 65.8% had regional lymph node metastasis (N1 or N2). Lymphovascular invasion (LVI) and perineural invasion (PNI) were present in 47.4% and 89.5% of the patients, respectively. Regarding resection margin status, 29 patients (76.3%) underwent R0 resection, characterized by a tumor-free margin >1 mm, whereas 9 patients (23.7%) underwent R1 resection, indicating the presence of microscopic tumor cells within 1 mm of the margin.

In *Figure 2*, the local recurrence rate was 33.2% at 1 year and 57.7% at 2 years, with a median local RFS of 19 months [95% confidence interval (CI): 13.2–24.8] and a mean local RFS of 31.5 months. The OS rates were 91.5% at 1 year and 63.1% at 2 years, respectively. The median OS was 43 months, and the mean OS was 43.3 months. The 1-year RFS rate was 40.6%, and the 2-year RFS rate decreased to 13.5%. The median RFS was 11 months (95% CI: 8.0–14.0), and the mean RFS was 16.5 months. In patients with tumors confined to the pancreatic head, the 1- and 2-year local recurrence rates were 27.2% and 58.5%, respectively.

Table 1 Baseline characteristics of patients

Variables	Value
Age (years)	66 [42–84]
<70	22 (57.9)
≥70	16 (42.1)
Sex	
Male	20 (52.6)
Female	18 (47.4)
Location	
Head/uncinated process	24 (63.2)
Body/tail	14 (36.8)
CEA (ng/mL)	3.25 [0.80–144.80]
CA19-9 (U/mL)	91.90 [0.08–15,698.30]
Degree of tumor-vessel contact	
No contact	25 (65.8)
<90°	9 (23.7)
90°–180°	4 (10.5)
Types of surgery	
PPPD	24 (63.2)
Distal pancreatectomy	12 (31.6)
Total pancreatectomy	2 (5.3)
Operation time (min)	355.50±100.04
IORT time (min)	35.49±1.76
Pathological T stage	
T1	1 (2.6)
T2	20 (52.6)
T3	17 (44.7)
Pathological N stage	
N0	13 (34.2)
N1	15 (39.5)
N2	10 (26.3)
Staging groups	
IA	1 (2.6)
IB	6 (15.8)
IIA	6 (15.8)
IIB	15 (39.5)
III	10 (26.3)
LVI	18 (47.4)
PNI	34 (89.5)
Resection margin status	
R0	29 (76.3)
R1	9 (23.7)

Values are presented as median [range], n (%), or mean ± standard deviation. Pathological staging followed the American Joint Committee on Cancer 8th edition. An R0 value with a margin status indicated that no tumor cells were found in the pathology report up to 1 mm from the margin. CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; IORT, intraoperative radiotherapy; LVI, lymphovascular invasion; N, node; PNI, perineural invasion; PPPD, pylorus-preserving pancreaticoduodenectomy; T, tumor.

Cox regression analysis was performed to evaluate the prognostic factors affecting local RFS and OS, as presented in *Table 2*. For local RFS, univariate analysis identified tumor-vessel contact (contact *vs.* no contact) as a significant factor [hazard ratio (HR), 2.870; 95% CI: 1.227–6.716; P=0.02]. In the multivariate analysis, PNI and margin status remained significant independent prognostic factors (PNI: HR, 15.808; 95% CI: 1.699–147.109, P=0.02; margin status: HR, 3.913; 95% CI: 1.101–13.904, P=0.035). Univariate analysis demonstrated that LVI and tumor-vessel contact ≥90° (*vs.* No contact or <90°) were significantly associated with survival (LVI: HR, 3.742; 95% CI: 1.274–10.988, P=0.02; tumor-vessel contact ≥90°: HR, 5.079; 95% CI: 1.359–18.983, P=0.02). In the multivariate analysis, both LVI and tumor-vessel contact ≥90° remained significant independent prognostic factors (LVI: HR, 4.150; 95% CI: 1.431–14.207, P=0.01; tumor-vessel contact ≥90°: HR, 5.841; 95% CI: 1.448–23.565, P=0.01).

Furthermore, a Kaplan-Meier analysis was conducted to assess local RFS and OS, incorporating the significant variables identified in the Cox multivariate regression model (*Figure 3*). In the analysis of local RFS, the PNI and margin status (R1 *vs.* R0) were significantly associated with recurrence risk (P=0.03 and P=0.046, respectively). For OS, LVI and tumor-vessel contact ≥90° showed a statistically significant association with survival (P=0.01 and P=0.007, respectively).

At our institution, 2 patients (4.8%) did not receive adjuvant gemcitabine chemotherapy. One patient

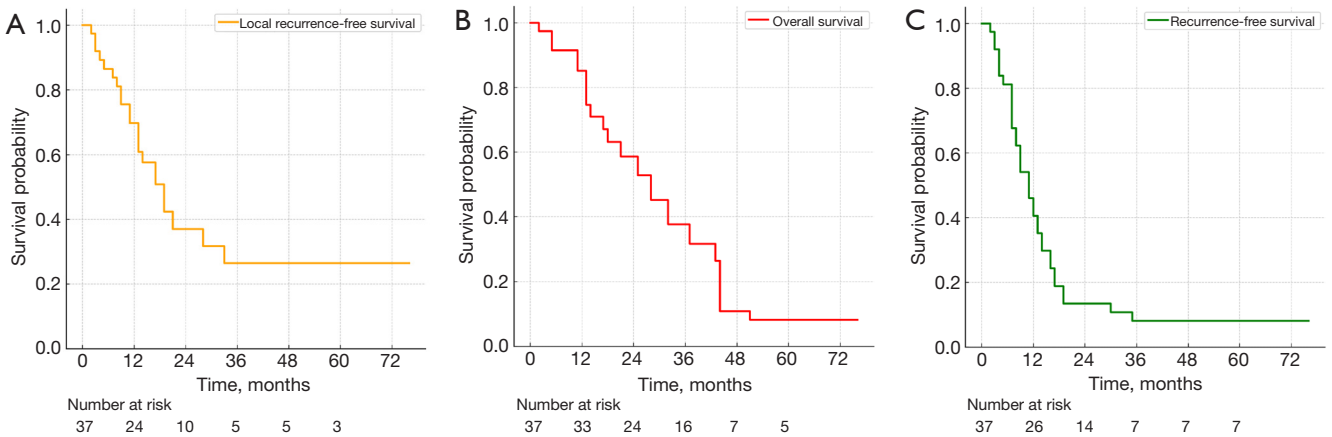

Figure 2 Kaplan-Meier analysis of overall survival and recurrence-free survival. (A) Local recurrence-free survival. (B) Overall survival. (C) Recurrence-free survival.

Table 2 Cox regression analysis of local recurrence

Variables	Category	Local control				Overall survival			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)	≥70 (*vs.* <70)	0.668 (0.282–1.583)	0.36			0.527 (0.178–1.558)	0.25		
Sex	Female (*vs.* male)	0.606 (0.260–1.414)	0.25			0.493 (0.174–1.392)	0.18		
Location	Others (*vs.* head/ uncinated process)	1.319 (0.561–3.097)	0.53			1.638 (0.591–4.536)	0.34		
Initial CA19-9 (U/mL)	≥150 (*vs.* <150)	1.856 (0.788–4.370)	0.16			1.742 (0.622–4.879)	0.29		
pT	T3 (*vs.* T1, 2)	2.072 (0.873–4.917)	0.10	2.296 (0.851–6.195)	0.10	2.552 (0.893–7.294)	0.08	2.347 (0.789–6.983)	0.13
pN	N2 (*vs.* N0, 1)	2.115 (0.851–5.259)	0.11			2.171 (0.722–6.534)	0.17		
LVI	Positive (*vs.* negative)	1.516 (0.628–3.659)	0.36			3.742 (1.274–10.988)	0.02*	4.150 (1.431–14.207)	0.01*
PNI	Positive (*vs.* negative)	7.598 (0.965–59.786)	0.054	15.808 (1.699–147.109)	0.02*	5.583 (0.678–45.987)	0.11		
Tumor-vessel contact	Contact (*vs.* no contact)	2.870 (1.227–6.716)	0.02*	1.934 (0.703–5.318)	0.20	2.761 (0.993–7.675)	0.052		
	≥90° (*vs.* no contact or <90°)	2.727 (0.789–9.433)	0.11			5.079 (1.359–18.983)	0.02*	5.841 (1.448–23.565)	0.01*
Margin status	R1 (*vs.* R0)	2.537 (0.973–6.618)	0.06	3.913 (1.101–13.904)	0.04*	1.320 (0.288–6.052)	0.72		

Multivariate analysis was performed on variables with a P<0.10 for univariate analysis. Variables with a lower univariate analysis P for tumor-vessel contact in OS were used for multivariate analysis. In the margin status, the circumferential margin was not included because it is not a surgical margin. *, P<0.05. CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; PNI, perineural invasion; pN, pathological node; pT, pathological tumor.

experienced early liver metastases, leading to a decline in general condition, whereas another developed a Clavien-Dindo grade IIIb duodenal ulcer perforation, requiring primary repair under general anesthesia. These patients were not excluded in the survival analysis as they underwent pancreatectomy and IORT according to the study protocol. Sensitivity analysis excluding the two patients who did not receive adjuvant gemcitabine (n=36) yielded results consistent with the primary analysis, indicating no material impact on OS (Table S1). Covariates were selected based on the risk factor analysis.

Postoperative complications were consistent with the findings of our previous study (15). Delayed gastric emptying (DGE) occurred in 5 patients, whereas

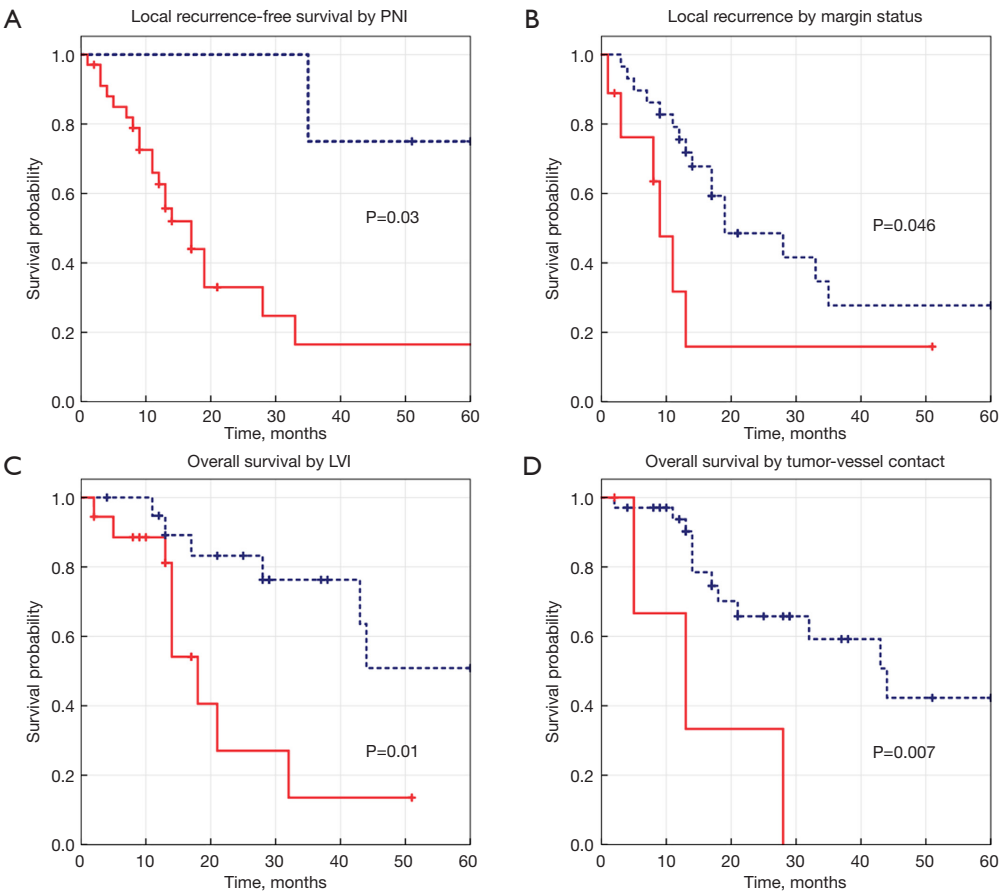

Figure 3 Kaplan-Meier analysis of key prognostic factors in local recurrence. (A) Local recurrence-free survival by PNI. (B) Local recurrence by margin status. (C) Overall survival by LVI. (D) Overall survival by tumor-vessel contact. The red solid line represents patients with the presence of the corresponding adverse prognostic factor (PNI-positive, R1 margin, LVI-positive, or tumor–vessel contact ≥90°), whereas the blue dotted line represents patients without the corresponding factor (PNI-negative, R0 margin, LVI-negative, or tumor–vessel contact <90°). LVI, lymphovascular invasion; PNI, perineural invasion.

postoperative pancreatic fistula (POPF) and chyle leakage were reported in 2 patients each. DGE and POPF were classified according to the International Study Group of Pancreatic Surgery and the International Study Group on Pancreatic Fistula consensus definitions, respectively. Notably, no cases of grade C DGE or POPF were observed, and no additional postoperative complications exceeding Clavien-Dindo classification grade III were reported beyond those mentioned above.

Discussion

Efforts to improve the prognosis of PDAC have increasingly focused on enhancing local control using IORT. In this study, the prescribed dose was set to deliver 10 Gy at a depth of 5 mm from the tumor bed, which corresponds to an approximate surface dose of 16 Gy. This dosing scheme was established based on previous studies using electron-based IORT systems, where doses typically range from 10 to 20 Gy (19-21). Our regimen was selected to balance treatment efficacy with acceptable toxicity, as reported in the existing literature.

Many prior studies on IORT for pancreatic cancer have incorporated EBRT. During the present study period, EBRT was not performed at our institution. In a subgroup analysis of the PREOPANC trial (22) comparing neoadjuvant chemoradiotherapy with upfront surgery, the HR for OS in patients with RPC was 0.79 (95% CI: 0.54–1.16; P=0.56), showing no statistically significant difference. Our study focused on patients with resectable disease, for

whom the departmental standard at that time was upfront surgery. Since 2023, the institutional strategy has shifted to surgery following neoadjuvant chemotherapy in clinical research, however, this approach is not reimbursed under the Korean National Health Insurance system (23). At present, both EBRT and neoadjuvant chemotherapy for RPC remain non-reimbursable in Korea.

To contextualize our rationale and treatment approach, it is essential to review previous studies that have investigated the role of IORT. Zerbi *et al.* (24) conducted comparative analyses between surgical resection alone and surgical resection combined with IORT and demonstrated significantly lower local recurrence rates in the IORT cohort (56.4% *vs.* 26%). Similarly, Reni *et al.* (25) reported a reduction in local failure rates from 60% to 27% among patients with stage I–II disease who underwent IORT.

Our phase II trial offers additional data on the feasibility and effectiveness of IORT in a Korean clinical setting. Although this study did not directly compare IORT-treated patients with those who did not receive IORT, the 2-year local recurrence rate among IORT recipients was 57.7% (*Figure 2*), suggesting a potential benefit to local control. To further assess the impact of our findings, we summarized recent studies investigating curative pancreatectomy with IORT (Table S2). Despite differences in patient selection, particularly in the inclusion of total neoadjuvant therapy, Sekigami *et al.* (19) reported excellent results, with a median OS of 47 months, despite including patients with LAPC. Similarly, our study demonstrated survival outcomes comparable to those of recent studies on IORT for pancreatic cancer (20,21). Although the OS benefits of IORT remain an area of ongoing investigation, our findings align with those of previous reports, emphasizing its role in reducing recurrence and improving local disease control.

In a nationwide questionnaire survey conducted by the Japanese Radiation Oncology Study Group, Ogawa *et al.* (26) reported that among 210 patients with RPC who received IORT, the 2-year local recurrence rate was 16.3%, with a median OS of 19.1 months; 62 of these patients also underwent EBRT. Subgroup analysis indicated that R0 resections were significantly associated with superior local control compared with R1 resections, whereas the addition of EBRT in the R0 subgroup did not provide any discernible benefit. Similarly, Sekigami *et al.* (19) investigated patients with borderline or locally advanced PDAC who underwent a treatment regimen comprising FOLFIRINOX, followed by chemoradiotherapy and subsequent surgical resection. In the non-IORT cohort, R1 resection was significantly correlated with a marked reduction in RFS and OS. In contrast, among patients who received IORT, RFS and OS outcomes did not exhibit a substantial difference between R0 and R1 resections. As shown in *Figure 3B* of this study, patients who underwent R1 resection (n=9) had a 1-year local RFS rate of 15.9%, indicating a poor prognosis, whereas those who underwent R0 resection demonstrated a comparatively favorable outcome, with a 1-year local RFS rate of 75.6%. Furthermore, in our cohort exclusively comprising pancreatic head cancer patients, the median time to local recurrence was 11 weeks following R1 resection (n=16). Previous studies on pancreas head cancer without IORT have reported median times to local recurrence of approximately 8–10 weeks for R1 resections (26-28). Our findings therefore suggest that IORT might contribute to improved locoregional control by potentially reducing microscopic residual disease at the retroperitoneal resection margins adjacent to the SMA. These findings support previous observations that microscopic residual disease (R1 resection) is associated with a higher risk of local recurrence and worse prognosis. Although our results suggest a possible benefit of localized treatments such as IORT, particularly in patients with R1 resection, further randomized controlled trials are necessary to definitively validate the effectiveness of IORT in this setting.

In addition to these clinical findings, IORT offers several advantages and potential developments in the treatment of pancreatic cancer. Investigations conducted at our center suggest that IORT-induced changes in local cytokine profiles may create a hostile microenvironment for residual cancer cells, thereby inhibiting recurrence (27). More recently, the CivaSheet, a low-dose-rate brachytherapy device implanted intraoperatively to target high-risk margins, demonstrated encouraging preliminary results (2-year PFS, 21% *vs.* 0%, P=0.11; 2-year OS, 26% *vs.* 13%, P=0.43) (28). In addition, emerging techniques such as particle therapy (proton and heavy ion therapy), stereotactic body radiotherapy, and online magnetic resonance imaging-guided radiotherapy have shown promise for enhancing radiation precision and therapeutic efficacy (29-31). However, further validation through prospective studies is essential to refine these approaches and to establish their role in pancreatic cancer management.

Jung *et al.* (32) investigated the degree of tumor-vessel contact and its association with vascular invasion and CA19-9 levels to explore the treatment outcomes of neoadjuvant therapy. Their findings suggested that in resectable PDAC, particularly in cases where the tumor was in contact with the

PV/SMV and CA19-9 >150 U/mL, neoadjuvant treatment could be considered an effective therapeutic option. Building on this study, we incorporated tumor-vessel contact stratified at 90° into our Cox hazard regression analysis (*Table 2*). In the univariate analysis, tumor-vessel contact itself showed a significant association with local control, but this significance was not maintained in the multivariate model. In OS, however, tumor-vessel contact ≥90° remained a significant factor, even in the multivariate analysis. Similarly, LVI has emerged as a significant prognostic factor, further reinforcing the critical role of tumor-vessel contact and vascular invasion in patient prognosis.

The high local recurrence rate of PDAC is attributed to microscopic residual disease. Although various methods have been proposed for local control, radiation therapy stands out as a promising option. Conventional EBRT has limitations, particularly when critical structures are in close proximity. Our study demonstrates that IORT can effectively overcome these challenges by providing targeted radiation directly to the operative bed, thereby maximizing the therapeutic effects while minimizing exposure to surrounding tissues. This study aimed to evaluate the efficacy of IORT using 50 kV X-ray (Carl Zeiss Meditec AG) in patients with RPC. The results from our institutional data offer valuable insights into the potential benefits and challenges of this approach. It is worth noting that the Intrabeam system has been validated for other indication in different studies (33,34). Additionally, our institution has prior experience using this device for breast cancer, which facilitated the setting for this study (35).

Our findings suggest a potential reduction in local recurrence rates. Compared with previously published studies on non-IORT cohorts, our observed local recurrence rates of 33.2% at 1 year and 57.7% at 2 years indicated a notably lower recurrence burden, reinforcing the role of enhanced local control strategies. Previous studies have consistently emphasized the importance of local control, and our Cox multivariate regression analysis identified PNI and resection margin status as significant prognostic factors. Given these findings, further investigations of local control approaches are warranted, particularly in patients with microscopic residual disease (R1 resection). Future studies should focus on optimizing the use of IORT, EBRT, and other local control modalities to improve the long-term outcomes in this high-risk population. Additionally, the significant association between tumor-vessel contact and OS suggests that prognostic stratification should extend beyond the conventional concept of borderline RPC. Further research is warranted to refine the tumor-vessel involvement classification, particularly by differentiating PV/SMV contact (no contact *vs.* contact) and angular thresholds, such as 90°, to enhance prognostic modeling and guide treatment decision-making.

Despite these promising findings, our study has several limitations. First, it was a single-institution study with a relatively small sample size, which restricts the generalizability of our results. Second, the study was not designed as a randomized controlled trial, and no contemporary comparison group was available, which limits the ability to draw causal inferences. Third, although tumor-vessel contact was assessed using predefined criteria and consensus review, the absence of a central imaging review may have affected reproducibility. Finally, the lack of adjustment for multiple testing in exploratory subgroup analyses raises the possibility of type I error. Future multicenter randomized trials with larger cohorts, standardized imaging review, and robust statistical validation are warranted to confirm and extend these findings.

Conclusions

The 2-year local recurrence rate after resection was 57.7%. Our findings identified PNI and resection margin status as significant prognostic factors for local recurrence, underscoring the importance of IORT and other local control strategies for high-risk patients. Furthermore, tumor-vessel contact and LVI emerged as key prognostic indicators for OS, highlighting the critical influence of tumor-vascular interactions on patient outcomes and reinforcing the need for further research to refine treatment strategies and enhance long-term survival.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Institutional Review Board at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (IRB No. 3–2017-0171), and informed consent was obtained from all participants prior to enrollment.

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Supplementary

Table S1 Sensitivity analysis for OS excluding patients who did not receive adjuvant gemcitabine

Variable	All patients		Excluding non-gemcitabine patients	
	HR (95% CI)	P value	HR (95% CI)	P value
Tumor-vessel contact ≥90°	7.078 (1.668–30.039)	0.008	7.278 (1.746–30.332)	0.007
Lymphovascular invasion	5.425 (1.623–18.131)	0.006	4.351 (1.323–14.314)	0.016
Tumor location (T_coding)	2.691 (0.874–8.285)	0.085	2.012 (0.648–6.254)	0.227
Gemcitabine (Yes *vs.* No)	0.104 (0.010–1.092)	0.059	–	–

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Table S2 Recent outcomes of curative pancreatectomy with IORT

Study	Nation	Study design	Study period	Patient selection criteria	IORT group sample size	Sex (male/female)	Mean age (years)	Resection status (R0/R1/R2)	RPC/BRPC/LAPC	Recurrence outcomes	Survival outcomes
Yurie *et al.* (2021)	USA	Retrospective study	2011-2019	BRPC/LAPC patients who received total neoadjuvant therapy and underwent resection	88	45/43	65	69/19/0	0/27/61	Median DFS, 24 months	Median OS, 47 months
Sun *et al.* (2024)	China	Retrospective study	2011-2018	RPC patients who underwent surgical resection	28	14/14	62.18	9/12/7	28/0/0	Median PFS, 11.5 months. PFS 1 year, 46.4%. PFS 2 years, 28.6%	Median OS, 16.5 months. OS 1 year, 67.9%. OS 2 years, 39.3%
Chen *et al.* (2025)	China	Prospective phase II study	2021-2023	RPC patients who underwent radical pancreatectomy	35	17/18	67	35/0/0	35/0/0	Median TTF, 11.67 months	Median OS, 22.2 months
Current study	South Korea	Prospective phase II study	2017-2019	BRPC/LAPC patients who underwent radical pancreatectomy	38	20/18	66	29/9/0	25/13/0	Median LRFS, 19 months. LRFS 1 year, 33.2%. LRFS 2 years 57.7%. Median RFS, 11 months. RFS 1 year, 40.6%. LRFS 2 years, 13.5%	Median OS, 43 months. OS 1 year, 91.5%. OS 2 years, 63.1%

IORT, intraoperative radiation therapy; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; RPC, resectable pancreatic cancer; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; TTF, time to treatment failure; LRFS, local recurrence-free survival; RFS, recurrence-free survival.

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