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Original Article

Imaging-guided SMART improves survival in locally advanced and borderline resectable pancreatic cancer: a comparative study

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Abstract: Pancreatic cancer remains notoriously challenging to treat due to its aggressive nature and complex anatomic location. Late-stage diagnoses often result in high mortality rates. This study assesses the effectiveness of combining ablative stereotactic MRI-guided intensity-modulated radiation therapy (SMART) with chemotherapy for treating locally advanced and borderline resectable pancreatic cancer. We retrospectively analyzed 235 pancreatic cancer patients treated between 2020 and 2023. Patients were divided into chemoradiation (SMART + chemotherapy, n = 106) and chemotherapy-only (n = 129) groups. Key outcomes included progression-free survival, overall survival, margin-negative resection rates, lymphovascular invasion, and toxicities. The chemoradiation group demonstrated improved PFS (8.30 ± 1.20 vs. 7.90 ± 1.30 months, P = 0.015) and OS (14.30 ± 2.60 vs. 13.50 ± 2.40 months, P = 0.015), with higher rates of margin-negative resections (92.45% vs. 80.62%, P = 0.009) and reduced LVI (37.74% vs. 52.71%, P = 0.022) compared to chemotherapy alone. However, acute toxicities, including fatigue and abdominal pain, were more frequent in the chemoradiation group. Locoregional control and distant metastasis-free survival showed no significant group differences (P > 0.05). Overall, SMART enhances local tumor control and survival outcomes in severe pancreatic cancer, albeit with increased acute toxicity.

Keywords: Pancreatic cancer, ablative radiation therapy, chemotherapy, stereotactic MRI, survival outcomes, toxicity

Introduction

Pancreatic cancer remains to be one of the most challenging malignancies to manage, owing to its aggressive biological behavior and complex anatomically complex location [1, 2]. Despite global advances in surgical techniques and systemic therapies, pancreatic cancer continues to carry a high mortality rate, with a 5-year survival rate ranging from only 3 to 15% [3]. This dismal prognosis stems from two interrelated factors: the tumor's inherently aggressive nature characterized by early micrometastatic spread, and its retroperitoneal location surrounded by radiosensitive organs (e.g., duodenum, stomach), which historically limited the feasibility of definitive local therapy options [4]. Consequently, a significant proportion of patients are diagnosed at a locally advanced or borderline resectable stage, underscoring the demand for advanced therapeutic strategies that can enhance both locoregional control (LRC) and overall survival (OS) [5, 6].

Surgical resection has long been the cornerstone of curative treatment for pancreatic cancer. However, in cases of locally advanced pancreatic cancer (LAPC), surgical resectability is often compromised by the tumor's encasement or invasion of major vasculature structures such as the superior mesenteric artery [7] or vein. Borderline resectable pancreatic cancer (BRPC) represents a distinct subset in which surgical intervention may be feasible, yet achieving negative margins remains challenging due to the tumor's proximity to or limited involvement of critical vasculature. Conventional radiotherapy, while modestly improving local control, is constrained by motion management uncertainties and dose-limiting gastrointestinal

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toxicity, necessitating the exploration of more effective locoregional interventions [8-10].

Ablative stereotactic MRI-guided simultaneous integrated boost intensity-modulated radiation therapy (SMART) represents an innovative approach in the radiotherapeutic landscape, enabling highly precise dose delivery while dynamically adapting to physiological tumor motion throughout treatment. Unlike conventional radiation techniques, SMART allows for escalated radiation doses directly to the tumor while sparing surrounding healthy tissues - a critical advantage when addressing the anatomical complexity of pancreatic cancer. The integration of real-time MRI guidance further enhances tumor visualization, enabling adaptive radiation delivery during treatment sessions - a particularly valuable feature given the substantial motion variability the pancreas and adjacent structures [11-13]. Early phase I/II studies suggest promising local control rates with SMART; however, several critical gaps persist [14]: (1) most trials are single-arm with limited comparative data against chemotherapy alone; (2) long-term survival benefits have yet to be established; (3) toxicity profiles, particularly in combination with modern chemotherapy, remains insufficiently characterized.

While the application of SMART has generated interest due to its theoretical advantages, robust clinical evidence supporting its use in LAPC and BRPC remains limited. We hypothesize that SMART-enhanced locoregional control will translate into improved survival outcomes and higher surgical conversion rates without prohibitive toxicity. Our study aims to inform optimal sequencing of local and systemic therapies in this high-risk population and to evaluate the efficacy of SMART in treating LAPC and BRPC.

Materials and methods

Case selection and ethics statement

Between January 2020 and December 2023, a retrospective analysis was conducted on 235 patients with pancreatic cancer treated at People's Hospital Affiliated to Shandong First Medical University. Clinical data were extracted from the hospital's medical record system, encompassing the participants' demographic characteristics, treatment modalities, surgical procedures, histopathological evaluations, postoperative therapies, and follow-up outcomes.

This study was approved by the Ethics Committee of People's Hospital Affiliated to Shandong First Medical University. As a retrospective analysis using only de-identified patient data, with no impact on patient care, the requirement for informed consent was waived. This waiver was granted in accordance with the regulatory and ethical guidelines governing retrospective research.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age ≥ 18 years; (2) Definitive diagnosis of pancreatic cancer confirmed by enhanced CT, enhanced MRI, or PET/CT [15]; (3) Classification as BRPC or LAPC according to arterial and venous involvement [16]; (4) Completion of at least 3 months of prior induction chemotherapy or radiotherapy [17]; (5) Availability of complete baseline and follow-up medical records.

Exclusion criteria: (1) Pregnancy or breastfeeding; (2) Imaging-confirmed distant metastases or concurrent malignant tumors; (3) Voluntary discontinuation of chemotherapy or radiotherapy during treatment; (4) Presence of cognitive or mental disorders; (5) Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 prior to treatment (as documented at the initial visit).

Data collection

Patient data were collected via the medical record system, including demographic characteristics. Additional information on educational level, marital status, tumor size, and tumor location was also recorded. Patients' overall health and treatment tolerance were assessed using the ECOG performance status scale, which measures physical activity levels [18].

The extent of tumor advancement was evaluated using the internationally recognized TNM staging system [19], which classifies tumors based on stage, with higher stages signifying more advanced disease. The "T" (Tumor) component describes the size and extent of the primary tumor and is subdivided into four categories: T1, T2, T3, and T4. A higher T number

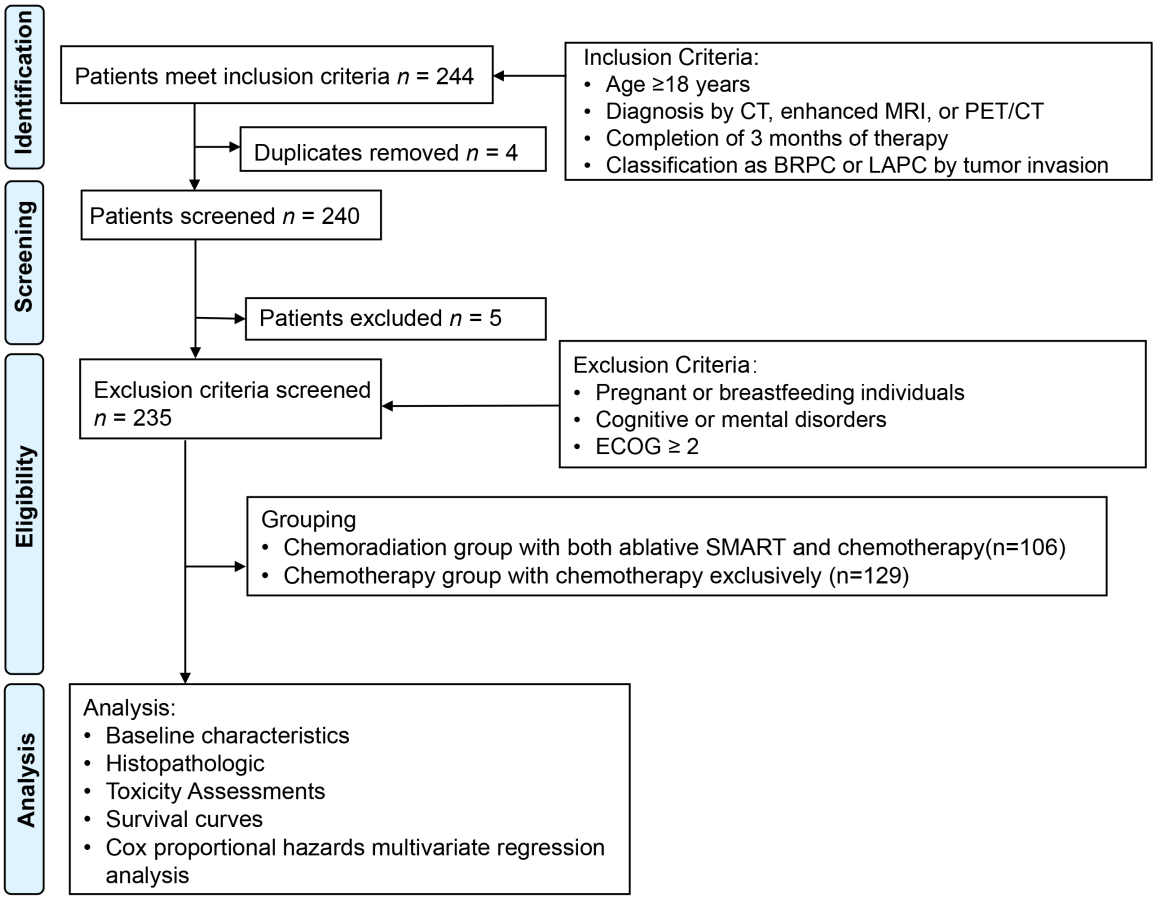

Figure 1. Study design. CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET/CT: Positron Emission Tomography/Computed Tomography; BRPC: Borderline Resectable Pancreatic Cancer; LAPC: Locally Advanced Pancreatic Cancer; ECOG: Eastern Cooperative Oncology Group; SMART: simultaneous integrated boost intensity-modulated radiation therapy.

indicates a larger tumor with greater local invasion. The "N" (Node) component reflects the involvement of regional lymph nodes (LNs) and is categorized into N0, N1, N2, and N3, where a higher number corresponds to more extensive LN involvement. The "M" (Metastasis) component indicates the presence or absence of distant metastases, with M0 representing no metastasis and M1 indicating the presence of metastasis.

Study design

The patients were divided into two distinct groups according to their preoperative treatments. The chemoradiation group (n = 106) underwent both ablative SMART and chemotherapy, while the chemotherapy group (n = 129) received chemotherapy alone.

Post-treatment, surgical timing and approach were determined based on each patient's clinical status. Detailed records of surgical procedures and postoperative pathological outcomes were meticulously maintained for statistical analysis.

Decisions regarding adjuvant chemotherapy were contingent on the patient's recovery and overall condition. Follow-up examinations were conducted every three months to monitor their health status and treatment response (**Figure 1**).

Preoperative treatment

All patients in both groups were treated the FOLFIRINOX regimen, consisting of oxaliplatin, irinotecan, folinic acid (leucovorin), and 5-fluorouracil. This regimen was administered as follows: Oxaliplatin at 85 mg/m^2 administered via intravenous infusion on day 1; Irinotecan at 180 mg/m^2 via intravenous infusion on day 1;

Leucovorin at 400 mg/m^2 via intravenous infusion on day 1; and 5-fluorouracil at 400 mg/m^2 delivered by rapid intravenous injection on day 1, followed by a continuous infusion of 2400 mg/m^2 over 46 hours [20]. This treatment cycle was repeated every two weeks.

Patients in the chemoradiation group underwent ablative SMART after completing chemotherapy. During treatment preparation, patients were positioned supine, typically with both arms alongside their body to enhance comfort, while ensuring that adiation beam paths did not intersect the arms. Simulation involved mid-inspiration breath-hold planning using a 0.35 T balanced steady-state free precession sequence (TrueFISP) MRI sequence on the MRIdian Linac, with each scan lasting 17-25 seconds. This was immediately followed by a planning CT scan for treatment alignment and dose calculation. Constraints on maximum point doses were standardized across protocols as follows: according to institutional protocol A, the bowel was limited to < 39.5 Gy, while the stomach and duodenum were constrained to < 38 Gy; under protocol B, all three structures (bowel, stomach, and duodenum) were restricted to ≤ 39.5 Gy. Mean dose constraints for the bowel and kidneys were determined to be < 25 Gy and < 10 Gy, respectively, under both protocols. Additional constraints for the stomach, duodenum, and bowel included V32 Gy ≤ 2 cc and V35 Gy ≤ 0.5 cc. Continuous intrafraction cine-MRI scans were performed in the sagittal plane during treatment to monitor primary tumor motion using a manually defined "tracking structure". Radiation delivery was automatically paused if more than 5% of the tracking structure exceeded a 3 mm margin from the intended location. Treatment was generally administered using a breath-hold technique but was adjusted to free-breathing respiratory gating as needed.

Surgical technique

One week after completing preoperative therapy, all patients underwent comprehensive restaging. Subsequently, both groups proceeded to surgery, with the surgical approach tailored to each patient's condition. Pancreatoduodenectomy (PD) was performed using a standardized technique, which involved the dissection of the uncinate process by skeletonizing the right lateral aspect of the Superior Mesenteric Artery (SMA) from its origin to the level of the first jejunal branch of the superior mesenteric vein. Depending on the patient's condition, distal pancreatectomy (DP) or total pancreatectomy could also be selected. During the operation, the total number of LNs excised and any vascular resections were meticulously recorded.

Histopathologic analysis

Every surgical specimen was evaluated using a standardized protocol. Immediately following resection, the surgeon and pathologist applied ink to the pancreatic neck, bile duct, and SMA margins. The pancreatic neck and bile duct margins were inked en face, and considered positive if tumor cells were found at the inked surface. Meanwhile, the entire inked SMA margin was sectioned perpendicularly for microscopic evaluation [21].

R1 resection status was defined as the presence of tumor cells at the inked surfaces of the common bile duct, pancreatic neck, or SMA margins, indicating microscopic residual disease. The treatment effect was measured by assessing the percentage of residual viable cancer cells within the resected specimen [22].

Postoperative therapy and follow-up

Postoperative therapy was selectively administered based on individual patient conditions. All patients were followed up every three months until their death or until December 2024 with a median follow-up duration of 24 months (range: 6-48 months). Follow-up assessments included the detection of distant metastasis, patterns of metastatic spread, treatment-related adverse reactions, quality of life, and survival outcomes. Standardized follow-up protocol as follows: (1) Frequency: Imaging and clinical assessments were conducted every 3 months for the first 2 years; (2) Content: Assessments at each follow-up included: disease progression (distant metastasis, metastatic patterns, and locoregional recurrence), treatment-related outcomes (adverse reactions and quality of life), and survival endpoints (mortality, oncologic outcomes); (3) Data collection formats: Most cases involved structured interviews and physical exams conducted at our institution. For patients unable to attend in-person visits, standardized questionnaires were administered via telephone.

Pancreatic tumor status was assessed three months post-surgery using the Response Evaluation Criteria in Solid Tumors (RECIST) [23]. Partial Response (PR) was defined as a reduction of at least 30% in the sum of diameters of target lesions from baseline. Progressive Disease (PD) was characterized by at least a 20% increase in the sum of diameters of target lesions compared to the smallest measurement recorded during the study, with an absolute growth of at least 5 mm, or the appearance of new lesions. Stable Disease (SD) was assigned when the changes did not meet the criteria for PR or PD.

Patients underwent evaluations every three months through cross-sectional imaging and physical examination. Progression-free survival (PFS), Local Recurrence-Free Control (LRC), distant metastasis-free survival (DMFS), and Overall Survival (OS) were calculated from the first post-surgery date. The Kaplan-Meier estimation method was used to analyze censored data. PFS referred to the duration during which patients remained free of disease progression. DMFS measured the time from diagnosis or start of treatment until the occurrence of distant metastasis or death from any cause. LRC was defined as the absence of tumor recurrence in the treated region, encompassing the primary tumor site and the regional LNs. OS was defined as the time span from diagnosis or treatment start to death from any cause.

Outcome measures

The primary outcome measures are clinical endpoints, including PFS and OS. The secondary outcome measures are LRC, DMFS, surgical procedures, postoperative pathological findings, postoperative treatment, tumor status, assessments of acute and late toxicities, and patterns of metastatic spread to organ sites.

Statistical analysis

Data analysis was conducted using SPSS statistical software, version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies (%) and analyzed using χ^2, continuity correction, or Fisher's exact test, as appropriate. For normally distributed data, values are presented as the mean ± standard deviation (X ± SD). For data not normally distributed, the Wilcoxon rank-sum test was applied, with results reported as the median along with the interquartile range [median (IQR), 25th-75th percentiles]. Statistical significance was set at a *p*-value less than 0.05. Screen significant factors associated with PFS and OS using a multivariate Cox regression model. All variables showing significant differences in univariate analysis ($P < 0.05$) were included in the model as independent variables, while PFS and OS were used as dependent variables.

Results

Baseline characteristics of patients

The mean age was 65.35 ± 4.23 years in the chemoradiation group and 65.98 ± 4.58 years in the chemotherapy group ($P = 0.281$) (**Table 1**). BMI was similar between the groups, averaging 23.65 ± 3.19 kg/m^2 and 23.37 ± 3.62 kg/m^2, respectively ($P = 0.534$). Gender distribution was balanced, with the chemoradiation group comprising 52.83% females and the chemotherapy group comprising 48.84% females ($P = 0.542$). Smoking and drinking histories did not differ significantly between the groups ($P = 0.977$ and $P = 0.289$, respectively). Other demographic and clinical parameters, including hypertension, diabetes, ethnicity, educational level, marital status, ECOG performance status, histology, tumor location, largest tumor size, resectability, and clinical T, N, and M stages, were comparable, with no statistically significant differences observed (all $P > 0.05$). Notably, all patients were at the M0 stage, indicating no distant metastasis. The consistency in baseline characteristics confirms the comparability of the two groups for evaluating the efficacy of SMART in treating LAPC and BRPC.

Intraoperative characteristics

The type of surgical procedure performed did not significantly differ between the two groups, with PD performed in 88.68% of the chemoradiation group and 84.5% of the chemotherapy group ($P = 0.352$), and DP/TP in 11.32% and 15.5% of cases, respectively (**Table 2**). However, there was a statistically significant difference in the number of total LNs excised ($P = 0.039$), with more patients in the chemoradiation group having 0-30 LNs removed (79.24% vs. 65.89%) and fewer having more than 30 LNs excised (20.75% vs. 34.11%) compared to the chemotherapy group. The incidence of vascular

Table 1. Comparison of baseline characteristics between the two groups

Parameters	Chemoradiation group (n = 106)	Chemotherapy group (n = 129)	t/χ^2	P
Age (years)	65.35 ± 4.23	65.98 ± 4.58	1.081	0.281
Body Mass Index (kg/m^2)	23.65 ± 3.19	23.37 ± 3.62	0.622	0.534
Female/Male	56 (52.83%)/50 (47.17%)	63 (48.84%)/66 (51.16%)	0.371	0.542
Smoking history (Yes/No)	24 (22.64%)/82 (77.36%)	29 (22.48%)/100 (77.52%)	0.001	0.977
Drinking history (Yes/No)	32 (30.19%)/74 (69.81%)	31 (24.03%)/98 (75.97%)	1.124	0.289
Hypertension (Yes/No)	27 (25.47%)/79 (74.53%)	34 (26.36%)/95 (73.64%)	0.024	0.878
Diabetes (Yes/No)	16 (15.09%)/90 (84.91%)	18 (13.95%)/111 (86.05%)	0.061	0.805
Ethnicity (Han/Other)	86 (81.13%)/20 (18.87%)	114 (88.37%)/15 (11.63%)	2.406	0.121
Educational level (Junior college graduate/College graduate or higher)	59 (55.66%)/47 (44.34%)	71 (55.04%)/58 (44.96%)	0.009	0.924
Marital Status (Married/Unmarried)	85 (80.19%)/21 (19.81%)	109 (84.5%)/20 (15.5%)	0.75	0.387
ECOG performance status			0.079	0.779
0	49 (46.23%)	62 (48.06%)		
1	57 (53.77%)	69 (51.94%)		
Histology			0.029	0.864
Adenocarcinoma	104 (98.11%)	128 (99.22%)		
Adenosquamous carcinoma	2 (1.89%)	1 (0.78%)		
Tumor location			None	0.967
Head/neck	82 (77.36%)	95 (73.64%)/		
Body	16 (15.09%)	23 (17.83%)		
Head/body	3 (2.83%)	4 (3.1%)		
Body/tail	4 (3.77%)	6 (4.65%)		
Tail	1 (0.94%)	1 (0.78%)		
Largest tumor size (cm)	3.24 ± 0.65	3.21 ± 0.52	0.407	0.684
Resectability			0.005	0.945
Locally advanced	58 (54.72%)	70 (54.26%)		
Borderline resectable	42 (45.28%)	59 (45.74%)		
Clinical T stage			2.305	0.512
T1	4 (3.77%)	5 (3.88%)		
T2	21 (19.81%)	29 (22.48%)		
T3	7 (6.6%)/	15 (11.63%)		
T4	74 (69.81%)	80 (62.02%)		
Clinical N stage			0.21	0.9
N0	76 (71.7%)	89 (68.99%		
N1	23 (21.7%)	31 (24.03%)		
NX	7 (6.6%)	9 (6.98%)		
Clinical M stage				1
M0	106 (100%)	129 (100%)		

ECOG: Eastern Cooperative Oncology Group.

resection was similar between groups, occurring in 33.02% of the chemoradiation group and 38.76% of the chemotherapy group (P = 0.362). These results indicate that, although the surgical approach was consistent across the groups, lymphadenectomy was more extensive in the chemotherapy group.

Histopathologic outcomes: margin clearance and invasion patterns

Margin-negative resections were more common in the chemoradiation group, with 92.45% achieving negative margins compared to 80.62% in the chemotherapy group (P = 0.009) (**Table 3**). LN status also varied significantly, with 53.77% of patients in the chemoradiation group having negative LN status, compared to 37.21% in the chemotherapy group (P = 0.011). The incidence of lymphovascular invasion (LVI) was lower in the chemoradiation group than in the chemotherapy group (37.74% vs. 52.71%, P = 0.022). Additionally, perineural invasion (PNI) was less frequent in the chemoradiation group, with 24.53% showing no PNI versus 13.95% in the chemotherapy group (P = 0.039). These results suggest that SMART

Table 2. Comparison of during operation between the two groups

Parameters	Chemoradiation group (n = 106)	Chemotherapy group (n = 129)	χ^2	P
Operation			0.866	0.352
PD	94 (88.68%)	109 (84.5%)		
DP/TP	12 (11.32%)	20 (15.5%)		
Total LNs excised			6.513	0.039
0-15	21 (19.81%)	15 (11.63%)		
16-30	63 (59.43%)	70 (54.26%)		
> 30	22 (20.75%)	44 (34.11%)		
Vascular resection			0.831	0.362
No	71 (66.98%)	79 (61.24%)		
Yes	35 (33.02%)	50 (38.76%)		

DP: Distal pancreatectomy; TP: total pancreatectomy; PD: Pancreatoduodenectomy; LNs: lymph nodes.

Table 3. Comparison of histopathologic between the two groups

Parameters	Chemoradiation group (n = 106)	Chemotherapy group (n = 129)	χ^2	P
Margin negative			6.749	0.009
Yes	98 (92.45%)	104 (80.62%)		
No	8 (7.55%)	25 (19.38%)		
LN status			6.459	0.011
Negative	57 (53.77%)	48 (37.21%)		
Positive	49 (46.23%)	81 (62.79%)		
LVI			5.255	0.022
No	66 (62.26%)	61 (47.29%)		
Yes	40 (37.74%)	68 (52.71%)		
PNI			4.276	0.039
No	26 (24.53%)	18 (13.95%)		
Yes	80 (75.47%)	111 (86.05%)		

LN: lymph nodes; LVI, lympho vascular invasion; PNI, perineural invasion.

may offer histopathologic advantages, including improved margin clearance and reduced incidence of nodal positivity, LVI, and PNI, in patients with severe pancreatic cancer. Histopathological images show normal tissue is differentiated from the tumor tissue (**Figure 2**).

Post-Surgical tumor response at 3 months, postoperative treatment and adjuvant therapy utilization

At three months post-surgery, the pancreatic tumor status showed no statistically significant difference between the two groups ($P = 0.635$) (**Table 4**). The proportions of SD, PR, and PD were similar between chemoradiation and chemotherapy groups: SD occurred in 71.7% vs. 65.89%, PR in 12.26% vs. 14.73%, and PD in 16.04% vs. 19.38%, respectively. These findings suggest that the tumor response at this time point was largely consistent between the two treatment modalities.

There was no statistically significant difference in the administration of adjuvant chemotherapy between the two groups ($P = 0.149$) (**Figure 3**). In the chemoradiation group, 38.68% of patients received adjuvant chemotherapy compared to 48.06% in the chemotherapy group. Conversely, 61.32% of patients in the chemoradiation group and 51.94% in the chemotherapy group did not receive adjuvant chemotherapy. These results indicate that the treatment regimens regarding the use of adjuvant chemotherapy were similar between the two groups.

Acute and late toxicity profiles associated with chemoradiation

In the assessment of acute toxicity (≤ 3 months), fatigue (15.09% vs. 6.98%, $P = 0.045$), Nausea/anorexia (13.21% vs. 4.65%, $P = 0.019$) and abdominal pain (14.15% vs. 5.43%, $P = 0.022$) were significantly more common in the chemoradiation group than in the chemotherapy group, as shown in **Table 5**. No significant differences were observed for diarrhea, duodenal stricture, or biliary obstruction, all of which had very low incidences ($P = 1$ for diarrhea and biliary obstruction). These results indicate that the chemoradiation group experienced higher rates of certain acute toxicities compared to the chemotherapy group.

In the assessment of late (> 3 months) toxicity, fatigue was significantly more frequent in the chemoradiation group (8.49%) than in the chemotherapy group (1.55%) ($P = 0.028$). Although nausea/anorexia (5.66% vs. 0.78%) and abdominal pain (7.55% vs. 1.55%) were more preva-

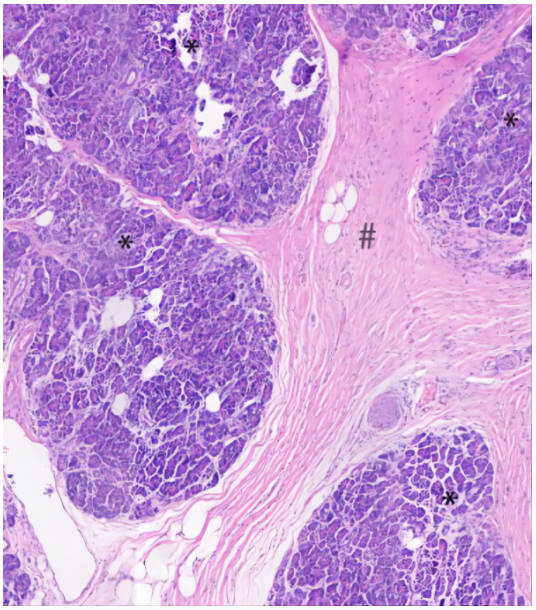

Figure 2. Section of the pancreas. (#) Normal tissue, (*) Tumor tissue. Scale bar = 50 μm. Magnification: 400×.

lent in the chemoradiation group than in the chemotherapy group, these differences did not reach statistical significance ($P = 0.071$ and $P = 0.052$, respectively). There were no notable differences in the rates of diarrhea, duodenal stricture, or biliary obstruction, with negligible to no incidences observed in either group. These results suggest that, among late toxicities, fatigue occurred more frequently in the chemoradiation group, while other adverse effects remained minimal and comparable.

Patterns of metastatic spread at 1-year follow-up

At 1 year post-surgery, rates of hepatic, pulmonary, peritoneal, and out-of-field nodal metastases did not differ significantly between the chemoradiation and chemotherapy groups ($P > 0.05$), indicating comparable metastatic spread patterns. See **Table 6** for more details.

Survival outcomes: progression-free and overall survival benefits of SMART

PFS and OS were significantly longer in the chemoradiation group, with averages of 8.30 ± 1.20 vs. 7.90 ± 1.30 months ($P = 0.015$) and 14.30 ± 2.60 vs. 13.50 ± 2.40 months ($P = 0.015$), respectively (**Figure 3**). However, LRC and DMFS did not differ significantly between the groups, with LRC at 16.20 ± 1.20 months for chemoradiation versus 16.10 ± 1.40 months for chemotherapy ($P = 0.547$), and DMFS at 13.10 ± 1.50 months versus 12.80 ± 1.60 months ($P = 0.139$). These results suggest that while LRC and DMFS were comparable, SMART offers a significant advantage in PFS and OS for patients with LAPC and BRPC, as further demonstrated by the survival curves.

Multivariate cox regression analysis of prognostic factors for survival

Cox regression analysis identified negative surgical margins (HR 0.48 [0.33-0.69], $P < 0.001$), absence of lymphovascular invasion (LVI: HR 0.65 [0.47-0.89], $P = 0.008$), and excision of over 30 lymph nodes (HR 2.08 [1.06-4.08], $P = 0.034$) as significant predictors of improved survival (**Tables 7**, **8**). Conversely, acute toxicities such as nausea/anorexia (HR 1.55 [1.10-2.19], $P = 0.012$) and abdominal pain (HR 1.48 [1.04-2.10], $P = 0.029$) correlated with increased mortality risk. These results underscore the interplay between treatment modality, surgical quality, and toxicity burden in determining outcomes.

Logistic regression model for predictors of long-term survival

Logistic regression identified several independent predictors of favorable survival: higher lymph node yield (OR = 1.703, $P = 0.011$), margin-negative resection (OR = 0.228, $P = 0.002$), and negative nodal status (OR = 0.524, $P = 0.032$) (**Table 9**). Conversely, perineural invasion (PNI: OR = 2.360, $P = 0.023$) and acute abdominal pain (OR = 3.303, $P = 0.048$) predicted poor survival. These results highlight the prognostic importance of histopathological clearance and treatment-related toxicities.

Discussion

Pancreatic cancer remains one of the most lethal malignancies, with a 5-year survival rate of less than 10%, primarily due to late-stage diagnoses and the anatomical complexity of the pancreas, which limits surgical resectability and complicates conventional radiotherapy [24, 25]. Traditional chemoradiation approaches are often constrained by dose-limiting toxici-

Table 4. Comparison of pancreatic tumor status at 3 months after surgery and postoperative treatment between the two groups

Parameters	Chemoradiation group (n = 106)	Chemotherapy group (n = 129)	χ^2	P
Stable disease	76 (71.7%)	85 (65.89%)	0.910	0.635
Partial response	13 (12.26%)	19 (14.73%)		
Progressive disease	17 (16.04%)	25 (19.38%)		
Adjuvant chemotherapy			2.081	0.149
No	65 (61.32%)	67 (51.94%)		
Yes	41 (38.68%)	62 (48.06%)		

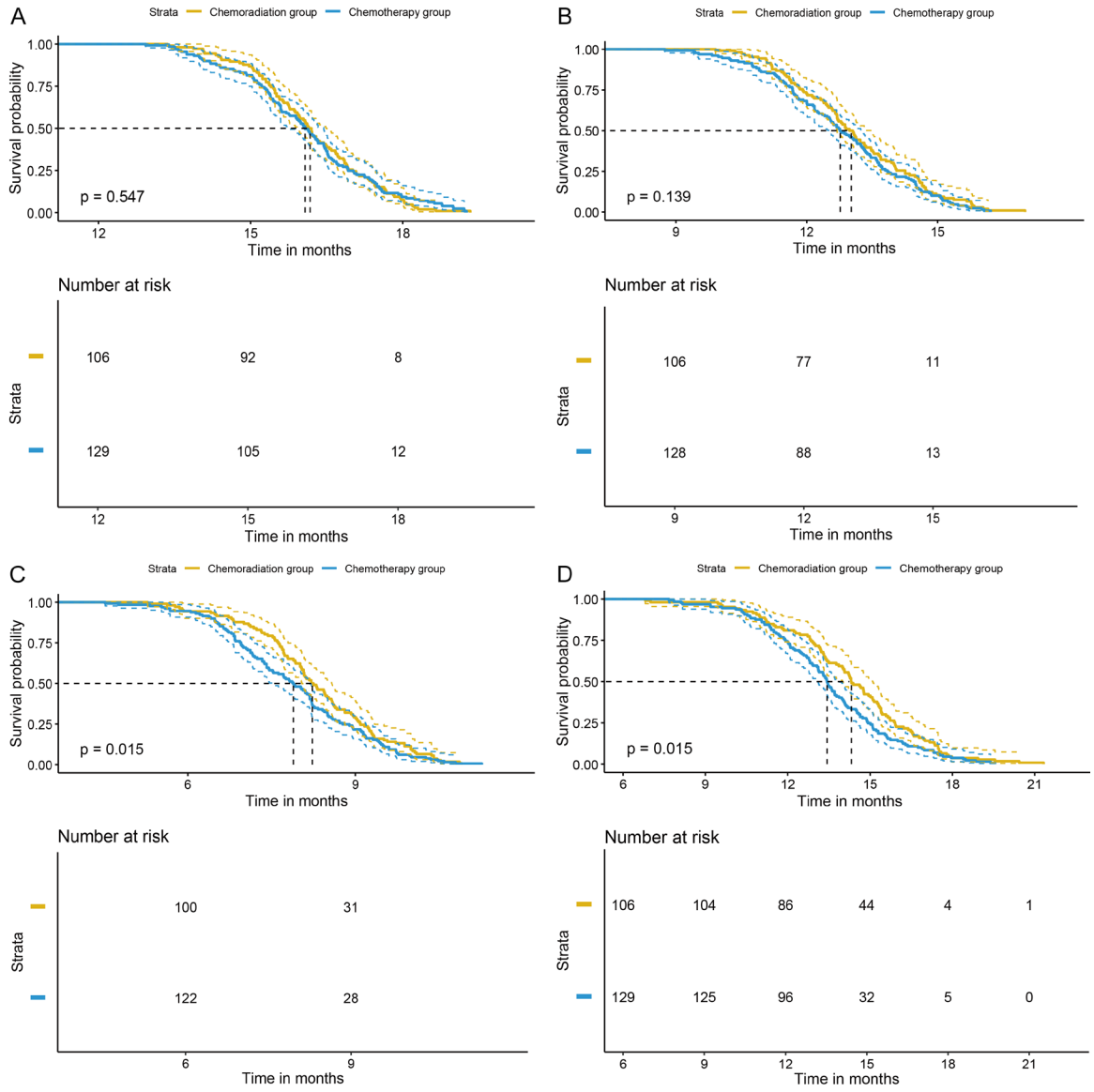

Figure 3. Comparison of survival curve between the two groups. A. LRC; B. DMFS; C. PFS; D. OS. LRC: locoregional control; OS: overall survival; PFS: progression-free survival; DMFS: distant metastasis free survival.

ties to adjacent radiosensitive organs such as duodenum and stomach, resulting in suboptimal locoregional control [25]. Against this backdrop, the present study focuses on evaluating

Table 5. Comparison of toxicity assessments between the two groups

Parameters	Chemoradiation group (n = 106)	Chemotherapy group (n = 129)	χ^2	P
Fatigue				
≤ 3 months	16 (15.09%)	9 (6.98%)	4.033	0.045
> 3 months	9 (8.49%)	2 (1.55%)	4.822	0.028
Nausea/Anorexia				
≤ 3 months	14 (13.21%)	6 (4.65%)	5.471	0.019
> 3 months	6 (5.66%)	1 (0.78%)	3.263	0.071
Abdominal pain				
≤ 3 months	15 (14.15%)	7 (5.43%)	5.22	0.022
> 3 months	8 (7.55%)	2 (1.55%)	3.769	0.052
Diarrhoea				
≤ 3 months	2 (1.89%)	3 (2.33%)	0	1
> 3 months	1 (0.94%)	0 (0%)		0.451
Duodenal stricture				
≤ 3 months	1 (0.94%)	0 (0%)		0.451
> 3 months	0 (0%)	0 (0%)		1
Biliary obstruction				
≤ 3 months	1 (0.94%)	1 (0.78%)	0	1
> 3 months	1 (0.94%)	0 (0%)		0.451

Table 6. Comparison of metastatic spread to organ sites at 1 year post surgery between the two groups

Parameters	Chemoradiation group (n = 106)	Chemotherapy group (n = 129)	χ^2	P
Liver	18 (16.98%)	33 (25.58%)	2.533	0.112
Lung	13 (12.26%)	19 (14.73%)	0.3	0.584
Peritoneum	15 (14.15%)	17 (13.18%)	0.047	0.829
Out of field node	2 (1.89%)	3 (2.33%)	0	1
Widespread	1 (0.94%)	1 (0.78%)	0	1

the efficacy of ablative SMART for treating LAPC and BRPC, offering key insights into the potential advantages and limitations of SMART compared to traditional chemotherapy.

One of the notable outcomes of this study was the observed improvement in PFS and OS in the chemoradiation group compared to the chemotherapy group. This supports the hypothesis that integrating advanced radiation techniques, like SMART, can enhance local tumor control and subsequently improve survival metrics. As reported by Mineur and Maulik et al., the effectiveness of SMART likely derives from its ability to deliver high doses of radiation with precision, facilitated by real-time imaging and adaptive planning [26, 27]. However, their studies were limited to common cancers, whereas the present analysis addresses more severe cases. This precision of SMART reduces the exposure of surrounding healthy tissues to radiation, potentially minimizing treatment-related side effects while delivering a therapeutic dose sufficient to overcome radioresistance often observed in pancreatic tumors [28, 29].

The histopathological findings further support the efficacy of SMART. The higher rate of margin-negative resections and lower incidence of lymphovascular and perineural invasion in the chemoradiation group suggest that SMART may more effectively eradicate microscopic disease at tumor margins, which was critical in preventing locoregional recurrence. These results underscore the role of precise radiotherapy in addressing the challenging anatomy and dense stromal environment characteristic of pancreatic cancer, which often impedes effective drug delivery and therapeutic responses. This is consistent with the findings of Carbonara et al. and Yokota et al. [30, 31], with our study addressing limitations in their research by including a larger number of cases.

Despite these benefits, the study identified higher rates of acute toxicities, such as fatigue, nausea, anorexia, and abdominal pain, in the chemoradiation group. These adverse effects highlight a critical consideration when opting for aggressive therapies like SMART. The increased acute toxicity could be associated with the ablative doses of radiation and their impact on surrounding gastrointestinal structures, which, despite precise targeting, remain vulnerable due to their proximity to pancreatic tumors. This underscores the need for enhanced supportive care and patient monitoring to manage these acute toxicities effectively, a point also

Table 7. Multivariate cox proportional hazards regression analysis - PFS

Variable	Hazard Ratio (HR) [95% CI]	*P*-value
Treatment (Chemotherapy vs. Chemoradiotherapy)	0.82 [0.68-1.00]	0.051
Total LNs excised (0-15 vs. > 30)	2.14 [1.10-4.17]	0.025
Total LNs excised (16-30 vs. > 30)	1.48 [0.91-2.41]	0.118
Margin status (Negative vs. Positive)	0.51 [0.36-0.72]	< 0.001
LN status (Negative vs. Positive)	0.59 [0.43-0.82]	0.001
Lymphovascular invasion (Absent vs. Present)	0.67 [0.49-0.92]	0.013
Perineural invasion (Absent vs. Present)	0.70 [0.51-0.96]	0.027
Nausea/Anorexia (≤ 3 months)	1.50 [1.07-2.10]	0.018
Abdominal pain (≤ 3 months)	1.45 [1.03-2.04]	0.032
Fatigue (> 3 months)	1.85 [1.10-3.12]	0.020

LN: Lymph Nodes.

Table 8. Multivariate cox proportional hazards regression analysis - OS

Variable	Hazard Ratio (HR) [95% CI]	*P*-value
Treatment (Chemotherapy vs. Chemoradiotherapy)	0.80 [0.65-0.98]	0.034
Total LNs excised (0-15 vs. > 30)	2.08 [1.06-4.08]	0.034
Total LNs excised (16-30 vs. > 30)	1.41 [0.86-2.31]	0.171
Margin status (Negative vs. Positive)	0.48 [0.33-0.69]	< 0.001
LN status (Negative vs. Positive)	0.56 [0.40-0.78]	0.001
Lymphovascular invasion (Absent vs. Present)	0.65 [0.47-0.89]	0.008
Perineural invasion (Absent vs. Present)	0.67 [0.48-0.94]	0.020
Nausea/Anorexia (≤ 3 months)	1.55 [1.10-2.19]	0.012
Abdominal pain (≤ 3 months)	1.48 [1.04-2.10]	0.029
Fatigue (> 3 months)	1.90 [1.12-3.22]	0.017

LN: Lymph Nodes.

Table 9. Multivariate logistic regression for survival outcomes

Variable	Coefficient	SE	Wald	P	OR	95% CI
Total LNs excised	0.533	0.209	2.545	0.011	1.703	1.130-2.568
With Margin negative	-1.476	0.475	-3.110	0.002	0.228	0.090-0.579
Negative LN status	-0.647	0.302	-2.142	0.032	0.524	0.290-0.947
With LVI	0.587	0.305	1.925	0.054	1.799	0.989-3.272
With PNI	0.859	0.378	2.273	0.023	2.360	1.125-4.949
Acute Nausea/Anorexia	1.143	0.667	1.714	0.087	3.135	0.849-11.579
Acute Abdominal pain	1.195	0.603	1.981	0.048	3.303	1.013-10.773

LN: Lymph Nodes; LVI: Lymphovascular Invasion; PNI: Perineural Invasion.

emphasized by the conclusions of Yokota et al. and Ristau et al. [32, 33].

Moreover, the study did not find significant differences in LRC and DMFS between the groups. This suggests that while SMART offers superior local control and can achieve more frequent margin-negative resections, it have limited impact on systemic disease progression. Given pancreatic cancer's tendency for early dissemination and distant metastases, advances in local therapies must be complemented by effective systemic treatments to address microscopic metastatic spread.

Interestingly, the number of LNs excised was higher in the chemotherapy group, possibly indicating a more extensive surgical intervention. While this may seem counterintuitive, it could result from the differences in surgical

planning and intraoperative decisions based on preoperative imaging and tumor characteristics identified during chemoradiation versus chemotherapy. It further emphasizes the necessity for a multidisciplinary approach integrating radiologists, surgeons, and oncologists to tailor treatment strategies that optimize both local control and surgical feasibility.

In the late toxicity assessment, fatigue remained notably higher in the chemoradiation group. The persistence of fatigue as a late effect may be attributable to the cumulative impact of high-dose radiation on patients' overall energy and physiological function. Although the incidence of other late toxicities was similar between groups, continued monitoring for long-term side effects is crucial to preserve quality of life for patients undergoing intensive therapies like SMART.

This study's findings emphasize the persistent challenge of treating pancreatic cancer, where local control and systemic management must be seamlessly integrated. While SMART represents a promising advancement in local therapy, future protocols may achieve better outcomes by combining it with novel systemic treatments, such as targeted agents or immunotherapies, to more effectively address the systemic nature of pancreatic cancer.

This study acknowledges several limitations that must be considered when interpreting the findings. Firstly, the retrospective nature of the analysis may introduce selection bias and limits the ability to infer causality. The sample size, although sufficient for preliminary insights, may not fully capture the heterogeneity of pancreatic cancer presentations and responses to treatment. Additionally, the lack of standardized criteria for selecting patients and treatment protocols across participating centers may have led to variability in outcomes. Particularly, while chemotherapy cycles and the radiation doses were based on the same protocol, variations in the dose intensity could have influenced the results. Furthermore, the study predominantly focuses on short-term treatment outcomes with limited long-term follow-up to assess durability of SMART's therapeutic benefits and late-onset toxicities. Finally, the absence of comprehensive biomarker analysis limits insights into patient-specific factors that might predict treatment efficacy, underscoring the need for future prospective trials to validate and expand upon these findings.

Conclusion

In conclusion, the integration of SMART in the treatment regimen for LAPC and BRPC demonstrates promising improvements in local control and survival, albeit with certain increased toxicities. These findings advocate for the ongoing advancement of radiotherapy techniques and their incorporation into multidisciplinary treatment frameworks, striving for enhanced both local and systemic management of pancreatic cancer. Ongoing clinical research and technological innovation are essential to refining these strategies and ultimately improving survival and quality of life for affected patients.

Disclosure of conflict of interest

None.

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