RESEARCH ARTICLE

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Survival Outcomes in Nonmetastatic pT4 Pancreatic Ductal Adenocarcinoma: A SEER Database Analysis Comparing Neoadjuvant Therapy and Upfront Surgery with Propensity Score Matching

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Abstract

Background: Given the increasing use of neoadjuvant therapy (NAT) for localized pancreatic ductal adenocarcinoma (PDAC), this study aimed to evaluate the survival outcomes of patients with pathological T4 (pT4) PDAC who received NAT followed by resection versus those who underwent upfront surgery. **Methods:** We conducted a retrospective analysis using the Surveillance, Epidemiology, and End Results (SEER) database (2004-2015) to compare survival outcomes of T4N0-XM0 PDAC patients in NAT and upfront surgery groups. Propensity score matching (PSM) was used to balance baseline characteristics. Kaplan-Meier curves and Cox regression analyses were employed to assess overall survival (OS) and identify prognostic factors. Subgroup analyses were conducted within the NAT cohort to determine the impact of different NAT modalities, adjuvant therapy (AT), lymph node yield (LNY), and lymph node ratio (LNR) on OS in this cohort. **Results:** Of 8950 pT4 PDAC patients identified, 654 met the inclusion criteria (241 NAT vs. 413 upfront surgery). After PSM, 152 well-matched pairs remained. The median survival times were 26 months for NAT and 12 months for upfront surgery ($P < 0.001$). NAT was associated with significantly improved OS at all time points. Multivariate analysis identified NAT ($P < 0.001$) and AT ($P = 0.002$) as independent prognostic factors of improved OS. No significant OS difference was observed between neoadjuvant chemotherapy and chemoradiotherapy or between NAT with and without AT. Subgroup analysis revealed no significant difference in OS based on LNY cutoff values in either node-negative or node-positive cohorts but worse OS in node-positive patients with LNR ≥ 0.1 ($P = 0.003$). **Conclusions:** NAT followed by resection significantly improves OS in patients with pT4 PDAC, even in the absence of complete pathological downstaging.

Keywords: Pancreatic ductal adenocarcinoma- neoadjuvant therapy- propensity score matching- overall survival

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) presents a formidable challenge in surgical oncology, characterized by its highly lethal nature and rising global incidence [1]. In the United States alone, PDAC tragically claims over 50,000 lives annually and is projected to become the second leading cause of cancer-related deaths by 2030 [2, 3]. Despite significant advancements in oncological care, long-term survival for PDAC patients remains poor, with a five-year survival rate of approximately 10-12% [4].

Pancreatectomy remains the only curative option for localized PDAC. However, its success depends on the complex interplay between clinical staging and surgical resectability. While the 8th edition of the American Joint Committee on Cancer (AJCC) [5] utilizes the TNM system for pathological staging, surgical resectability is assessed using empirical criteria established by the Americas Hepato-Pancreato-Biliary Association, the Society of Surgical Oncology and the Society of Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) [6], The University of Texas MD Anderson Cancer Center [7], the Alliance for Clinical Trials in Oncology [8], or the US National Comprehensive Cancer Network (NCCN) [9]. At initial presentation, 50-55% of PDAC patients have metastatic disease [10], precluding curative resection. In comparison, 15-20% present with resectable disease, and 25-30% are diagnosed with borderline resectable (BR-

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PDAC) or locally advanced (LA-PDAC) disease based on radiological imaging [11, 12]. However, radiological assessment may underestimate the true extent of the disease due to limitations in detecting subtle local invasion or vascular involvement [13]. Consequently, tumors initially classified as resectable (radiological T1-T3) may be upstaged to T4 upon pathological examination, reflecting the aggressive growth patterns often seen in BR-PDAC and LA-PDAC.

This discrepancy underscores the importance of focusing on pathological T4 (pT4) PDAC, encompassing a significant proportion of patients with advanced disease at the time of surgery, regardless of initial radiological staging. The extensive local invasion characteristic of pT4 tumor, often encasing vital structures such as the celiac axis, superior mesenteric artery, superior mesenteric vein, and portal vein [14, 15], poses significant challenges for surgical resection, necessitating high-risk procedures with potential for morbidity and mortality. Therefore, refining treatment strategies specifically for pT4 PDAC is crucial to improving outcomes for this patient population, who often face a challenging prognosis due to the aggressive nature of their disease.

Neoadjuvant therapy (NAT), including chemotherapy and/or chemoradiotherapy administered before surgery, has emerged as a paradigm shift in the management of PDAC, particularly for BR-PDAC and LA-PDAC cases [16]. NAT has demonstrated efficacy in downstaging tumors, enabling resection in approximately 20% of patients with initially unresectable, nonmetastatic PDAC following 4-6 months of treatment [17]. Furthermore, NAT has consistently shown improvements in resectability rates and the achievement of margin-negative (R0) resections for BR-PDAC and LA-PDAC [18]. Despite this growing body of evidence supporting the benefits of NAT in advanced PDAC, the comparative effectiveness of NAT followed by resection versus upfront surgery, specifically in pT4 PDAC patients, remains a critical area of ongoing research.

Recognizing this critical knowledge gap, we conducted a retrospective analysis using the Surveillance, Epidemiology, and End Results (SEER) database. By employing propensity score matching (PSM) to minimize potential confounding biases inherent in observational data, we aimed to rigorously evaluate the comparative effectiveness of NAT followed by resection versus upfront surgery regarding long-term survival outcomes for patients with pT4 PDAC.

Materials and Methods

Patient selection and eligibility criteria

Our study adhered to the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline. Data for patients with pT4 PDAC were extracted from the SEER database (17 registries) using SEER*Stat software (version 8.4.3). This study utilized de-identified data from publicly available sources within the SEER database, so it was exempt from the requirement for informed consent and ethical approval.

Inclusion criteria, adapted from a prior study [19], were confirmed pancreatic cancer based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) anatomical (C25.0-C25.4, C25.7-C25.9) and histological codes, and AJCC staging of T4N0-XM0. Exclusion criteria were no curative surgery or surgery status unknown, not the first malignant primary according to the SEER indicator, site not PDAC as per ICD-O-3 codes, chemotherapy was given without timing information (unclear if before or after surgery), or survival less than three months after surgery to ensure adequate follow-up.

Data collection

The following variables were extracted from the SEER database for analysis: age at diagnosis, sex, and median household income; year of diagnosis, primary tumor site, and differentiation grade; RX Summ-Surg Prim Site (Surgery of Primary Site) indicating whether surgery was performed on the primary tumor site; RX Summ-Surg/Rad Seq (Sequencing of Radiation and Surgery) specifying the sequence of radiation therapy and surgery; RX Summ-Systemic/Sur Seq (Sequencing of Systemic Therapy and Surgery) detailing the sequence of systemic therapy and surgery; chemotherapy recode indicating whether the patient received chemotherapy; derived T stage, derived N stage, and derived M stage; total lymph nodes examined and positive lymph nodes; survival time in months; and vital status (alive or deceased) at the end of follow-up.

Propensity score matching

PSM was employed to mitigate potential selection bias and balance baseline characteristics between the NAT and upfront surgery groups. A 1:1 nearest-neighbor PSM without replacement was implemented, utilizing a caliper width of 0.05 (recommended $\leq$ 0.2 standard deviations) [20]. The propensity score was estimated for each patient using a multivariate logistic regression model. This model incorporated the following covariates: age, sex, year of diagnosis, median household income, tumor site, differentiation grade, N stage, and adjuvant therapy (AT). The balance of baseline covariates between the matched groups was assessed using the standardized mean difference (SMD). A covariate was considered adequately balanced if SMD was less than 0.1 after matching.

Survival analysis

Overall survival (OS) for the entire cohort, both before and after PSM, and for subgroups, were estimated using Kaplan-Meier curves. The log-rank test was employed to assess the statistical significance of differences in survival between groups. Univariate and multivariate Cox proportional hazards regression analyses were conducted to identify independent prognostic factors, with hazard ratios (HR) and 95% confidence intervals (CI) presented. Survival functions were stratified by receiving NAT prior to resection in pT4 PDAC patients. Subgroup analyses were conducted to investigate the impact of different NAT modalities (chemotherapy [NAC] alone vs. chemoradiotherapy [NACRT]) and the use of AT on OS within the NAT cohort. Additionally, the NAT cohort was stratified by nodal status (N0: node-negative vs. N1:

node-positive) to assess the influence of lymph node yield (LNY: the total number of lymph nodes removed during surgery) and lymph node ratio (LNR: the ratio of positive lymph nodes to total lymph nodes removed) on OS. Patients with unknown information on total lymph nodes examined or unknown positive lymph nodes were excluded from this nodal status subgroup analysis.

Statistical analysis

All statistical analyses were conducted using R software (version 4.4.1). Categorical variables were presented as counts and percentages. Median survival duration was reported as median and range. The $\chi 2$ test or Fisher's exact test, as appropriate, was used to compare categorical variables between groups. Statistical significance was defined as a P-value < 0.05.

Results

Study population and baseline characteristics

The flow diagram for patient selection from the SEER database is shown in Figure 1. We identified 8950 patients in the SEER database with T4N0-XM0 PDAC between 2004 and 2015. The study period was specifically chosen to ensure all patients had sufficient follow-up time to assess 5-year OS, a critical endpoint for evaluating long-term outcomes in pancreatic cancer. By ending the inclusion period in 2015, we allowed for at least five years of follow-up for all patients, enabling a complete and robust OS analysis. After applying our inclusion and exclusion criteria, the final study cohort consisted of 654 T4 PDAC patients, of which 241 received NAT before resection and 413 underwent upfront surgery.

Baseline characteristics of the study cohort are presented in Table 1. The majority of pT4 PDAC patients had tumors located in the head of the pancreas (69.2% in the upfront surgery group and 61.8% in the NAT group). Before PSM, significant differences were observed between the NAT and upfront surgery groups in terms of age (P = 0.018), year of diagnosis (P < 0.001), differentiation grade (P < 0.001), N stage (P = 0.003), and receipt of AT (P < 0.001). Notably, 81.3% of patients

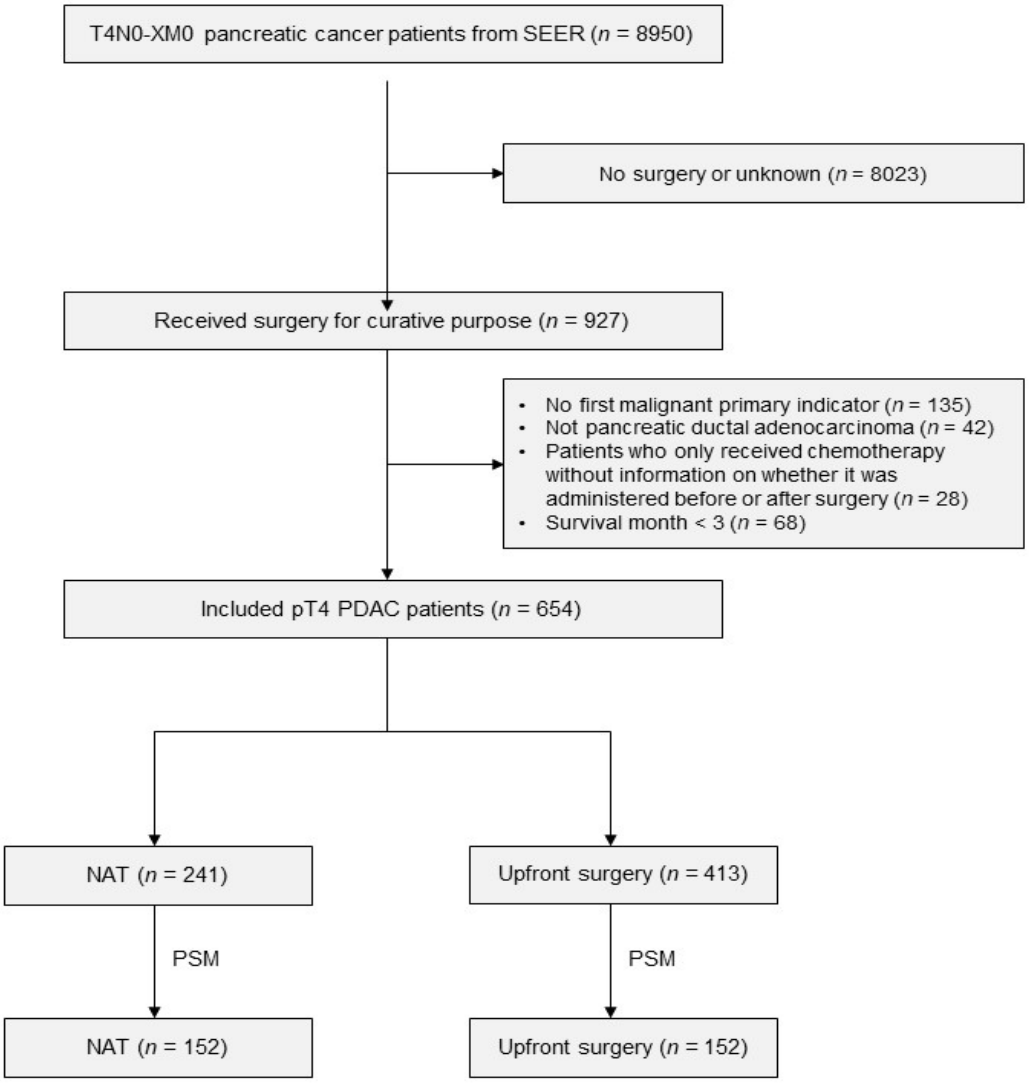

Figure 1. Flow Diagram for Patient Selection from SEER Database (PDAC, pancreatic ductal adenocarcinoma; NAT, neoadjuvant therapy; PSM, propensity score matching; SEER, Surveillance, Epidemiology, and End Results).

Table 1. Comparison of Baseline Characteristics and Survival Probabilities between Upfront Surgery and Neoadjuvant Therapy for pT4 Pancreatic Ductal Adenocarcinoma Patients before and after Propensity Score Matching

Variable	Before PSM			After PSM		
	Upfront surgery n = 413 (%)	NAT n = 241 (%)	P value	Upfront surgery n = 152 (%)	NAT n = 152 (%)	P value
Age						
< 50 years	42 (10.2)	26 (10.8)	0.018	15 (9.9)	16 (10.5)	0.827
50 - 64 years	164 (39.7)	116 (48.1)		67 (44.1)	65 (42.8)	
65 - 74 years	137 (33.2)	78 (32.4)		54 (35.5)	50 (32.9)	
≥ 75 years	70 (16.9)	21 (8.7)		16 (10.5)	21 (13.8)	
Sex						
Female	197 (47.7)	115 (47.7)	1.000	72 (47.4)	76 (50.0)	0.731
Male	216 (52.3)	126 (52.3)		80 (52.6)	76 (50.0)	
Year of diagnosis						
2004 - 2009	211 (51.1)	45 (18.7)	< 0.001	50 (32.9)	43 (28.3)	0.455
2010 - 2015	202 (48.9)	196 (81.3)		102 (67.1)	109 (71.7)	
Median household income (inflation-adjusted to 2022)						
< $40,000 - $59,999	72 (17.4)	38 (15.8)	0.432	26 (17.1)	26 (17.1)	0.740
$60,000 - $89,999	235 (56.9)	130 (53.9)		74 (48.7)	80 (52.6)	
≥ $90,000	106 (25.7)	73 (30.3)		52 (34.2)	46 (30.3)	
Tumor site						
Head	286 (69.2)	149 (61.8)	0.062	97 (63.8)	94 (61.8)	0.839
Body/Tail	59 (14.3)	51 (21.2)		29 (19.1)	28 (18.4)	
Overlapping/Other	68 (16.5)	41 (17.0)		26 (17.1)	30 (19.7)	
Grade						
I: Well differentiated	48 (11.6)	21 (8.7)	< 0.001	15 (9.9)	14 (9.2)	0.893
II: Moderately differentiated	165 (40.0)	72 (29.9)		57 (37.5)	56 (36.8)	
III: Poorly differentiated	140 (33.9)	42 (17.4)		36 (23.7)	38 (25.0)	
IV: Undifferentiated	2 (0.5)	1 (0.4)		1 (0.7)	0 (0.0)	
Unknown	58 (14.0)	105 (43.6)		43 (28.3)	44 (28.9)	
N stage						
N0	137 (33.2)	112 (46.5)	0.003	68 (44.7)	58 (38.2)	0.295
N1	274 (66.3)	128 (53.1)		84 (55.3)	94 (61.8)	
NX	2 (0.5)	1 (0.4)		0 (0.0)	0 (0.0)	
AT	296 (71.7)	100 (41.5)	< 0.001	90 (59.2)	89 (58.6)	1.000
Median survival duration (month, range)	12 [3, 145]	27 [3, 117]	< 0.001	12 [3, 96]	26 [3, 117]	< 0.001
1-year survival probability (95% CI)	0.490 (0.444, 0.541)	0.854 (0.811, 0.900)	-	0.487 (0.413, 0.573)	0.809 (0.749, 0.874)	-
2-year survival probability (95% CI)	0.200 (0.165, 0.242)	0.570 (0.511, 0.637)	-	0.197 (0.143, 0.272)	0.539 (0.465, 0.624)	-
3-year survival probability (95% CI)	0.096 (0.071, 0.130)	0.386 (0.329, 0.453)	-	0.112 (0.071, 0.175)	0.339 (0.271, 0.424)	-
4-year survival probability (95% CI)	0.057 (0.038, 0.084)	0.281 (0.229, 0.344)	-	0.059 (0.031, 0.112)	0.253 (0.192, 0.333)	-
5-year survival probability (95% CI)	0.042 (0.026, 0.067)	0.197 (0.153, 0.255)	-	0.046 (0.022, 0.095)	0.173 (0.122, 0.245)	-

Continuous variables were presented as median [range]; Categorical variables were presented as n (%); Survival probabilities were presented with 95% CI. P values of categorical variables were calculated by χ^2 or Fisher's exact test; P values of median follow-up duration were calculated by Log-rank test. Bold values indicate statistical significance at the P < 0.05 level. NAT, neoadjuvant therapy; AT, adjuvant therapy; PSM, propensity score matching; CI, confidence interval

who received NAT were diagnosed between 2010 and 2015. The annual trends and statistics in the surgical management of pT4 PDAC patients are illustrated in Figure 2. A steady increase in the number of patients undergoing surgical resection was observed from 2004 to 2015. This was accompanied by a significant rise in the utilization of NAT after 2010. PSM balanced the baseline characteristics between the two groups, resulting in 152 well-matched pairs. The SMDs for all covariates after PSM, as shown in Supplementary Table 1, were within the acceptable range, indicating successful balancing of the two groups.

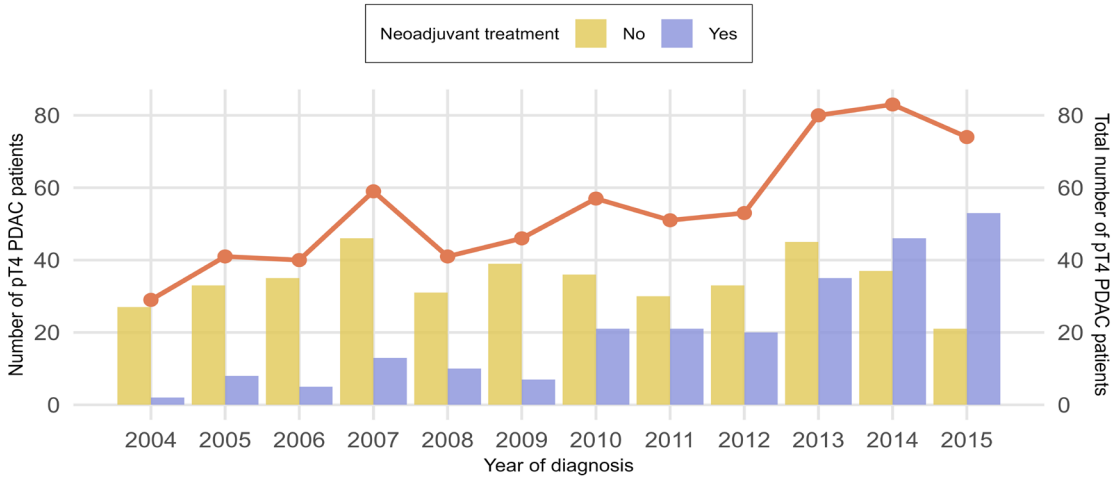

Figure 2. Annual Trends in the Surgical Management of Patients with pT4 Pancreatic Ductal Adenocarcinoma (PDAC), comparing neoadjuvant therapy with upfront surgery and showing overall case volume. There was a steady increase in pT4 PDAC patients undergoing resection from 2004 to 2015. This growth was accompanied by a significant rise in the utilization of neoadjuvant therapy, particularly after 2010.

Survival outcomes in T4 PDAC

The median survival duration differed significantly between the two groups before and after PSM. Prior to PSM, the median survival times were 12 months for the upfront surgery group and 27 months for the NAT group ($P < 0.001$). This difference persisted after PSM, with the median survival times of 12 months for upfront surgery and 26 months for NAT ($P < 0.001$). Kaplan-Meier plots revealed a significant OS advantage for pT4 PDAC patients receiving NAT compared to those undergoing upfront surgery before and after PSM (Figure 3).

After PSM, the 1-year survival probability of pT4 PDAC patients was 48.7% for the upfront surgery group and 80.9% for the NAT group. This significant difference persisted over time, with 2-year survival probabilities of 19.7% and 53.9%, 3-year survival probabilities of 11.2% and 33.9%, 4-year survival probabilities of 5.9% and 25.3%, and 5-year survival probabilities of 4.6% and 17.3% for the upfront surgery and NAT groups, respectively.

A multivariate Cox regression analysis of the entire cohort before PSM, which identified several prognostic factors for OS in pT4 PDAC patients, is shown in Table 2. The forest plot illustrating the association between covariates and OS is presented in Supplementary Figure 1. Male gender (HR: 1.21, 95% CI: 1.03-1.43, $P = 0.021$) and poorly differentiated and undifferentiated tumors Grade III/IV (HR: 1.34, 95% CI: 1.11-1.63, $P = 0.003$) were associated with worse OS, while receipt of NAT (HR: 0.36, 95% CI: 0.29-0.44, $P < 0.001$) and AT (HR: 0.73, 95% CI: 0.61-0.88, $P < 0.001$) were associated with improved OS. After PSM, the multivariate regression

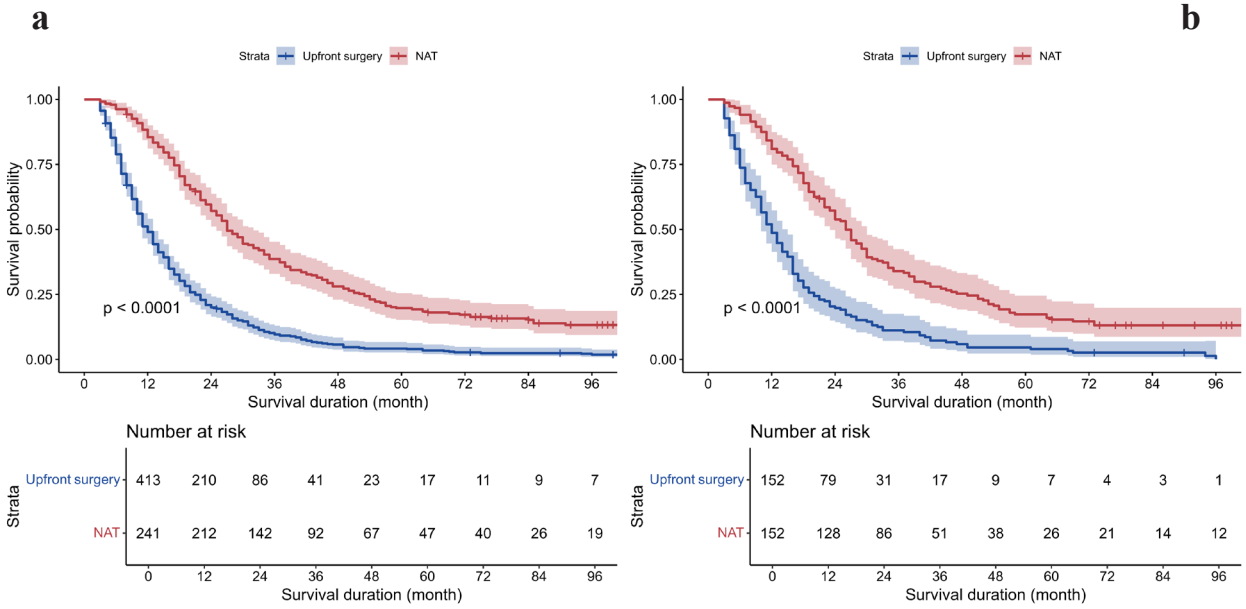

Figure 3. Kaplan-Meier Curves Illustrate the Overall Survival of Patients with pT4 Pancreatic Ductal Adenocarcinoma in Upfront Surgery and Neoadjuvant Therapy (NAT) Groups, both before (a) and after (b) propensity score matching. Log-rank tests were used to assess differences in survival between the groups, with p-values presented on each panel.

Table 2. Prognostic Factors for Overall Survival in pT4 Pancreatic Ductal Adenocarcinoma Patients Undergoing Resection before and after Propensity Score Matching

Variable	Before PSM				After PSM			
	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age								
< 50 years	Ref.				Ref.			
50 - 64 years	0.91 (0.69, 1.20)	0.500			1.17 (0.77, 1.76)	0.500		
65 - 74 years	1.00 (0.76, 1.33)	0.900			1.06 (0.70, 1.62)	0.800		
≥ 75 years	1.33 (0.96, 1.83)	0.084			1.22 (0.74, 2.01)	0.400		
Sex								
Female	Ref.		Ref.		Ref.		Ref.	
Male	1.14 (0.97, 1.33)	0.110	1.21 (1.03, 1.43)	0.021	1.14 (0.90, 1.44)	0.300	1.14 (0.90, 1.44)	0.300
Year of diagnosis								
2004 - 2009	Ref.		Ref.		Ref.		Ref.	
2010 - 2015	0.65 (0.56, 0.77)	< 0.001	0.91 (0.76, 1.08)	0.300	0.81 (0.63, 1.05)	0.110	0.88 (0.68, 1.15)	0.300
Median household income								
< $40,000 - $59,999	Ref.				Ref.			
$60,000 - $89,999	1.02 (0.82, 1.27)	0.900			1.02 (0.74, 1.42)	0.900		
≥ $90,000	0.91 (0.71, 1.16)	0.500			0.91 (0.64, 1.28)	0.600		
Tumor site								
Head	Ref.				Ref.		Ref.	
Body/Tail	0.88 (0.71, 1.10)	0.300			1.03 (0.76, 1.39)	0.900	1.04 (0.76, 1.41)	0.800
Overlapping/Other	0.98 (0.79, 1.22)	0.900			0.79 (0.57, 1.08)	0.140	0.79 (0.57, 1.09)	0.150
Grade								
I/II	Ref.		Ref.		Ref.		Ref.	
III/IV	1.40 (1.16, 1.69)	< 0.001	1.34 (1.11, 1.63)	0.003	1.27 (0.95, 1.69)	0.110	1.30 (0.96, 1.75)	0.088
Unknown	0.81 (0.66, 0.98)	0.034	1.17 (0.94, 1.45)	0.150	1.15 (0.87, 1.52)	0.300	1.32 (1.00, 1.75)	0.052
N stage								
N0	Ref.		Ref.		Ref.			
N1	1.19 (1.01, 1.40)	0.042	1.07 (0.90, 1.26)	0.400	1.00 (0.79, 1.27)	0.900		
NX	0.58 (0.14, 2.34)	0.400	0.67 (0.16, 2.71)	0.600	-	-		
NAT								
No	Ref.		Ref.		Ref.		Ref.	
Yes	0.40 (0.33, 0.47)	< 0.001	0.36 (0.29, 0.44)	< 0.001	0.42 (0.33, 0.53)	< 0.001	0.37 (0.29, 0.48)	< 0.001
AT								
No	Ref.		Ref.		Ref.		Ref.	
Yes	1.13 (0.96, 1.33)	0.140	0.73 (0.61, 0.88)	< 0.001	0.80 (0.63, 1.01)	0.062	0.67 (0.52, 0.87)	0.002

Univariate and multivariate Cox proportional hazard models were employed to calculate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for overall survival. Bold values indicate statistical significance at the P < 0.05 level. NAT, neoadjuvant therapy; AT, adjuvant therapy; PSM, propensity score matching

analysis revealed that NAT (HR: 0.37, 95% CI: 0.29-0.48, P < 0.001) and AT (HR: 0.67, 95% CI: 0.52-0.87, P = 0.002) remained independent predictors of improved OS.

Impact of NAT modality, AT, LNY and LNR on OS

Within the NAT group, 34% (n = 83) received NAC alone, while 66% (n = 158) received NACRT. Baseline characteristics and survival probabilities for the NAC and NACRT subgroups are detailed in Supplementary Table 2. The median survival times were 26 months for NAC and 27 months for NACRT (P = 0.579). There was no significant difference in OS between the NAC and NACRT groups (Figure 4a). Furthermore, 58.5% of patients within the NAT group did not receive AT after resection, while 41.5% did. Baseline characteristics and survival probabilities for these two subgroups are shown in Supplementary Table 3. Both groups who received NAT, with or without AT, had a similar median survival duration of 27 months (P = 0.524). No significant differences were observed in OS between the two groups (Figure 4b).

Within the NAT cohort, subgroup analysis based on nodal status used an LNY cutoff of 15, corresponding to the median LNY. In the N0 (node-negative) subgroup, there was no significant difference in OS between patients with LNY < 15 and LNY ≥ 15, as all patients had an LNR of 0 (Figure 5a). In the N1 (node-positive) subgroup, LNY did not significantly impact OS (Figure 5b). A significant difference in OS was observed based on LNR. Patients with LNR ≥ 0.1 (indicating a higher proportion of positive lymph nodes) experienced worse OS (P = 0.002) compared

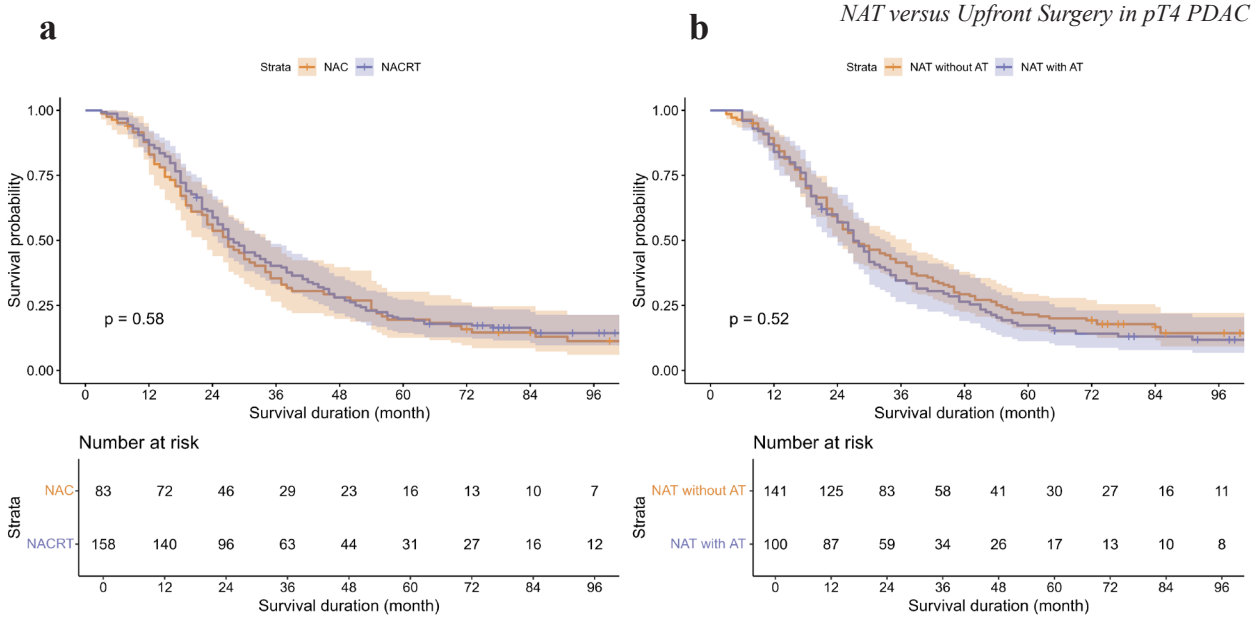

Figure 4. Kaplan-Meier Curves Illustrate the Overall Survival of pT4 Pancreatic Ductal Adenocarcinoma Patients Undergoing Resection who Received Neoadjuvant Therapy (NAT). The curves compare survival in subgroups based on (a) neoadjuvant chemotherapy (NAC) versus neoadjuvant chemoradiotherapy (NACRT) and (b) NAT with adjuvant therapy (AT) versus NAT without AT. Log-rank tests were employed to assess differences in survival, and p-values are indicated on each panel.

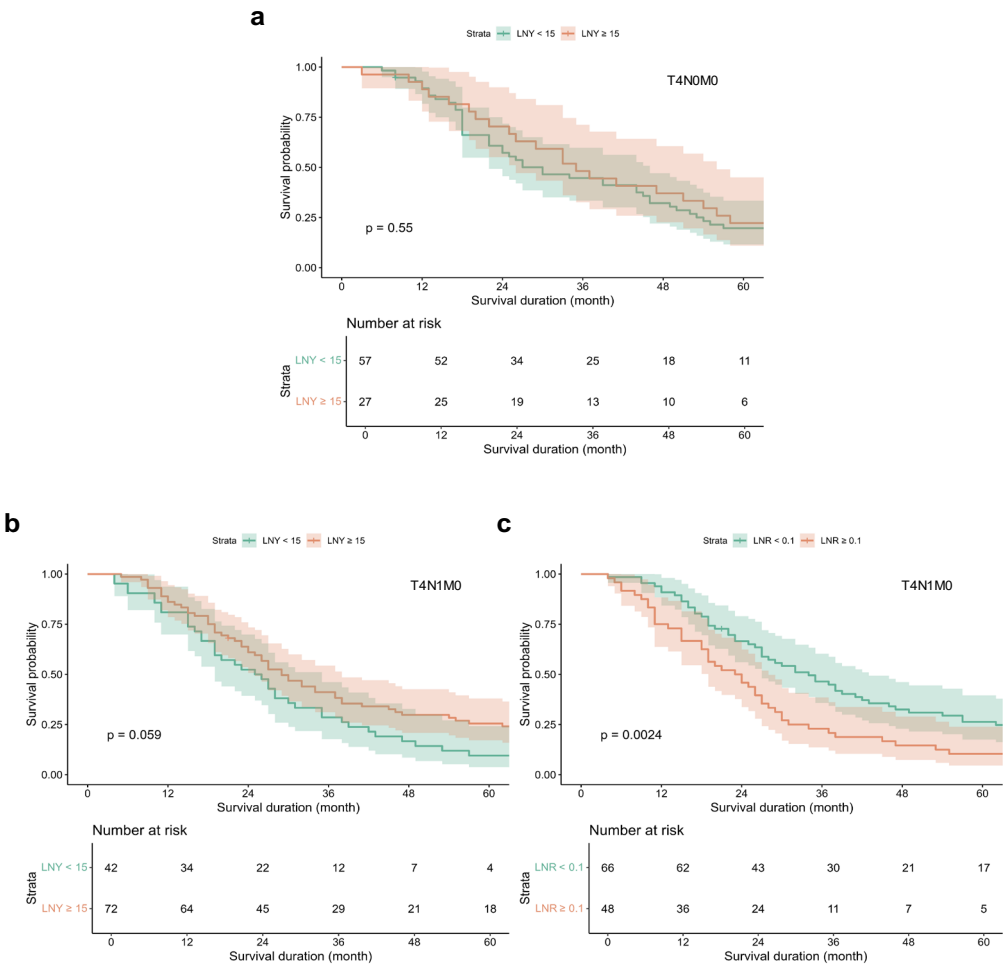

Figure 5. Kaplan-Meier Curves Depict the Overall Survival of Patients with pT4 Pancreatic Ductal Adenocarcinoma Undergoing Resection after Neoadjuvant Therapy. The curves are stratified into subgroups based on nodal status and cutoff values for different prognostic indices: (a) Node-negative cohort (T4N0M0) with lymph node yield (LNY) cutoff value; (b) Node-positive cohort (T4N1M0) with the LNY cutoff value; (c) Node-positive cohort (T4N1M0) with the lymph node ratio (LNR) cutoff value. Log-rank tests were used to assess differences in survival between subgroups within each panel, and corresponding p-values are indicated.

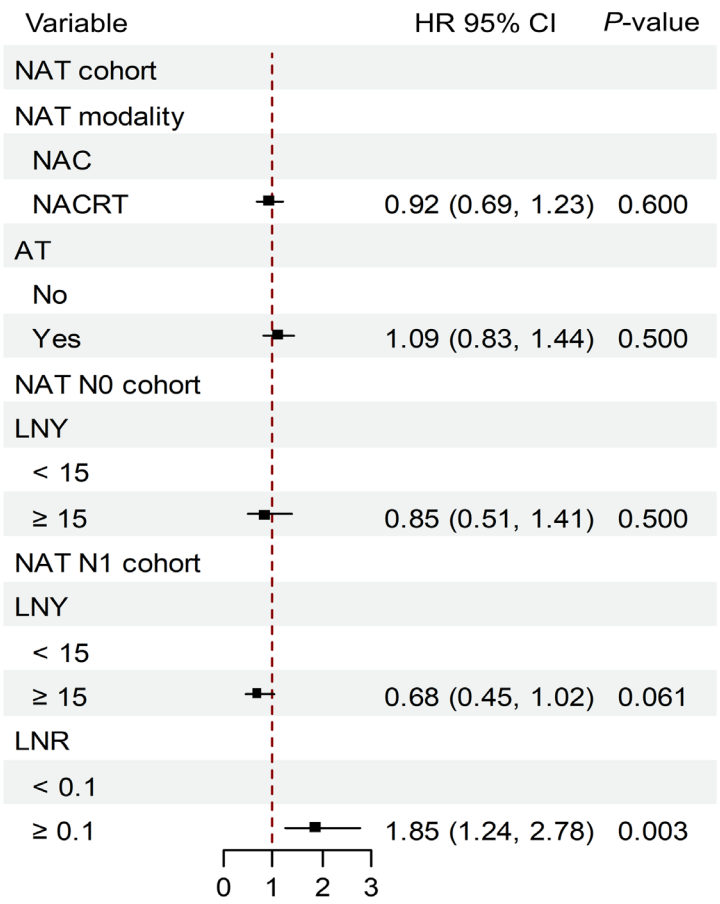

Figure 6. Forest Plot Illustrating the Univariate association between Various Covariates (NAT modality, AT, LNY, and LNR) and overall survival in pT4 PDAC patients (AT, adjuvant therapy; NAT, neoadjuvant therapy; LNY, lymph node yield; LNR, lymph node ratio; HR, hazard ratio; CI, confidence interval).

to those with LNR < 0.1 (Figure 5c). The univariate association between various covariates (NAT modality, AT, LNY, and LNR) and OS in T4 PDAC patients is shown in Figure 6. Patients who received NAT and had a node-positive (N1) status with LNR ≥ 0.1 demonstrated a significantly worse OS (HR: 1.85, 95% CI: 1.24-2.78, P = 0.003).

Discussion

This study, focused on patients with potentially resectable PDAC classified as T4N0-XM0, demonstrates a compelling survival benefit associated with NAT compared to upfront surgery. Leveraging the SEER database and employing PSM to minimize confounding factors, our findings underscore the significant improvement in OS conferred by NAT in this challenging patient population. NAT and AT emerged as independent prognostic factors for improved OS, emphasizing the importance of a multimodal approach in managing advanced pT4 PDAC.

The management of PDAC has evolved considerably, with the current standard of care embracing a multimodal approach incorporating surgery, chemotherapy, and occasionally radiation therapy aimed at maximizing long-term survival [21]. Within this paradigm, NAT has emerged as a transformative strategy, particularly for patients presenting with BR-PDAC or LA-PDAC disease [18]. Although its role in potentially resectable PDAC remains somewhat controversial, the remarkable advances in surgical techniques and the increasing confidence in utilizing NAC and NACRT regimens have led to the emergence of resection for initially unresectable PDAC as an important development for selected patients [22, 23]. The rationale for NAT in these advanced stages is multifaceted. Firstly, NAT has shown promise in downstaging tumors, with approximately 20% of initially unresectable, nonmetastatic PDAC cases becoming eligible for resection after 4-6 months of induction chemotherapy [24]. Secondly, it has consistently demonstrated improved resectability and margin-negative (R0) resection rates in BR-PDAC and LA-PDAC [25]. Pioneering institutions have paved the way for integrating NAT into clinical practice [18, 26-28], and the development of refined anatomical staging systems has enabled more precise identification of potential beneficiaries [16, 29]. This is reflected in our analysis of the SEER database, which revealed a significant increase in NAT utilization after 2010, likely driven by accumulating evidence from clinical trials and real-world experience supporting its benefits.

The value of NAT lies in its ability to address several critical challenges in PDAC management. By ensuring early delivery of systemic chemotherapy, NAT mitigates the risk of patients being unable to tolerate or complete adjuvant chemotherapy due to postoperative complications,

poor performance status, or disease progression [17, 30]. Moreover, NAT consistently improves R0 resection rates across all PDAC stages [31-33]. Furthermore, NAT offers a unique opportunity for personalized therapy, allowing in vivo assessment of treatment response in this aggressive and heterogeneous malignancy [34]. The effectiveness of NAT might be attributed to its ability to target not only the primary tumor but also microscopic metastatic deposits that may not be readily detectable at initial staging [35]. By eradicating these micrometastases and shrinking the primary tumor, NAT can downstage the disease, potentially converting unresectable or borderline resectable cases into operable ones [35]. Importantly, our study focused on pathologically confirmed T4 PDAC, a group representing the most advanced local disease. This group likely includes a subset of patients initially classified as radiologically resectable, even as early as T1, but found to have extensive local invasion or vascular involvement during surgery, leading to a final pT4 designation. Despite the lack of complete downstaging to ypT0-3 in these patients, we observed a significant survival benefit with NAT, suggesting additional mechanisms beyond tumor shrinkage may be at play. These findings underscore the potential value of NAT, particularly in patients with aggressive PDAC who may not achieve complete pathological downstaging but still derive significant survival benefit from this approach.

Compared to most types of cancer, PDAC is relatively resistant to chemotherapy [36]. Despite this challenge, several NAC regimens have been investigated as first-line therapy for advanced PDAC [37-41]. While our study, constrained by the limitations of the SEER database, could not distinguish specific NAC regimens, it is important to recognize that gemcitabine-based regimens and FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin) remain the predominant choices in clinical practice. While FOLFIRINOX is often considered the preferred regimen due to its higher response rates, gemcitabine plus nab-paclitaxel offers a viable alternative, particularly for patients who may not tolerate the more aggressive FOLFIRINOX regimen [17]. This combination has demonstrated a response rate of 23% in stage IV PDAC, with only 20% of patients experiencing disease progression as their best response [39]. Within the NAT setting, NACRT can be utilized either as an alternative to chemotherapy alone or as an additional administration. Within our NAT cohort, 83 (34.4%) patients received NAC alone, while 158 (65.6%) received NACRT. We observed no significant difference in OS between these two subgroups, aligning with the findings of randomized controlled trials (RCTs) evaluating NACRT in LA-PDAC, which have not demonstrated a significant survival benefit over NAC alone [23, 24, 42]. The rationale behind NACRT stems from the observation that approximately 30% of PDAC patients succumb to local progression despite the absence of distant metastases [43]. Therefore, for advanced PDAC patients who do not experience metastatic spread during systemic therapy, NACRT may offer potential benefits in terms of local tumor control. However, the precise role of NACRT in these settings remains unclear due to inconsistencies in the reporting of radiation details and conflicting results across studies [18, 43]. While not directly addressing the NAC versus NACRT question, our findings contribute to the ongoing debate on optimal NAT strategies for pT4 PDAC, suggesting that adding radiation therapy may not universally improve survival. This underscores the need for further research to identify patient subgroups who may benefit from NACRT and to standardize treatment protocols for improved comparability across studies.

Our results also confirmed the prognostic value of AT in improving OS for pT4 PDAC patients after surgery, consistent with several RCTs demonstrating its role in reducing recurrence and improving survival [44-47]. However, within the subset of patients receiving NAT, we did not observe a significant OS difference between those receiving AT and those not. Our findings diverged from a previous SEER-based PSM study [48], which found a survival benefit for NAT+AT in the T4N1-2M0 subgroup. This discrepancy may be attributed to our study design, which focused on the overall pT4 PDAC NAT cohort without subgroup PSM for AT, potentially obscuring any subgroup-specific effects. The inability of some pT4 PDAC patients to complete or even initiate AT due to postoperative complications could also have influenced the results. Moreover, recent evidence suggests that the survival benefit of AT may be primarily observed in patients with positive (R1) resection margins [49], a subgroup not explicitly analyzed in our study. This observation and the potential influence of tumor biology and individual patient characteristics highlight the need for a personalized approach to AT decision-making in pT4 PDAC patients following NAT. In cases where complete pathological downstaging is not achieved with NAT, AT may still be considered based on individual risk factors and potential benefits.

We further conducted a stratified analysis within the NAT cohort to investigate the impact of LNY and LNR on OS. The AJCC staging manual recommends harvesting at least 12 lymph nodes for optimal disease staging [24], and several studies have demonstrated a positive correlation between LNY and OS in PDAC patients undergoing upfront surgery [50-52]. A recent study found that an LNY cutoff of 22 was associated with significantly better OS in T1-3N0M0 patients treated with NAT and pancreatoduodenectomy across two independent datasets [53]. Other studies have suggested an LNY cutoff of 20 nodes as a predictor of improved OS in node-negative and node-positive disease [54, 55]. However, our analysis of the pT4 PDAC cohort, using a median LNY of 15 as the cutoff point, did not reveal a significant association between increased LNY and improved survival in either node-negative or node-positive patients. Even when exploring higher LNY cutoffs ranging from 15 to 25, no significant survival benefit was observed in patients with greater LNY. This may be due to the limited sample size and insufficient ability to demonstrate statistical significance. In contrast, LNR emerged as a significant prognostic factor in the node-positive subgroup, with LNR ≥ 0.1 associated with worse OS in the NAT group. This finding aligns with previous studies demonstrating the prognostic value of LNR in PDAC, where higher LNR

has been consistently associated with poorer survival outcomes [25]. This seemingly paradoxical relationship between LNY and LNR can be explained by their inherent mathematical connection. LNY is the denominator in the LNR calculation, meaning that a higher LNY could lead to a lower LNR if the number of positive lymph nodes remains constant. However, in aggressive pT4 PDAC, even with extensive lymphadenectomy resulting in higher LNY, the number of positive lymph nodes may also be disproportionately higher, leading to an LNR ≥ 0.1.

Our study, while providing some insights into the potential benefits of NAT in pT4 PDAC, is not without limitations inherent to its retrospective design and reliance on the SEER database. Despite employing PSM to minimize selection bias, the possibility of residual confounding due to unmeasured variables cannot be entirely excluded. Furthermore, the SEER database lacks granular details for a comprehensive analysis, including resection margin status (R0/R1), specific NAC regimens, and preoperative radiological T stage. The absence of information on initial resectability status may also introduce bias in patient selection. Additionally, the study's focus on surgically resected patients inherently excludes those who progressed or deteriorated during NAT, or those found unresectable intraoperatively. This selection bias, common in database studies, may limit the generalizability of our findings to the broader pT4 PDAC population. Finally, it is important to recognize that pT4 staging in the SEER database represents a heterogeneous group, encompassing both BR-PDAC and LA-PDAC. This heterogeneity makes it challenging to discern the specific impact of NAT on each subgroup. Moreover, our focus on pT4 PDAC may not fully capture the downstaging effect of NAT, as some patients may have been downstaged to ypT1-3 at the time of surgery. Despite these limitations, our study explored some potential benefits of NAT in pT4 PDAC, providing a more accurate reflection of real-world survival outcomes in this challenging patient population. By focusing specifically on pT4 disease, we have highlighted the significant survival advantage conferred by NAT, even in the absence of complete downstaging.

Author Contribution Statement

Conceptualization and design: Yun Zhao, Ye Xin Koh. Administrative support: Brian Kim Poh Goh, Aik Yong Chok, Ye Xin Koh. Provision of study materials or patients: All authors. Collection and assembly of data: Yun Zhao, Aik Yong Chok, Ye Xin Koh. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Reporting Checklist

The authors have completed the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist.

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. This study utilized de-identified data from publicly available sources within the SEER database, so it was exempt from the requirement for informed consent and ethical approval.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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