Retrospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Examining neoadjuvant treatment candidates in resectable pancreatic cancer based on tumor-vessel interactions and CA 19-9 levels: a retrospective cohort study

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Introduction: The applicability of neoadjuvant treatment (NAT) for resectable pancreatic ductal adenocarcinoma (PDAC) has arisen, however, high-level evidence is lacking. This study aimed to explore patient subgroups with high-risk resectable PDAC for selecting candidates who may benefit from NAT.

Methods: The 1132 patients with resectable or borderline resectable PDAC who underwent surgery between 2007 and 2021 were retrospectively reviewed. Patients with resectable PDAC without contact of major vessels (R-no contact) ($n=651$), with contact of portal vein or superior mesenteric vein (PV/SMV) $\leq 180°$ (R-contact) ($n=306$), and borderline resectable PDAC without arterial involvement (BR-V) ($n=175$) were analyzed.

Results: The mean age was 64.3 ± 9.8 years, and 647 patients (57.2%) were male. The median follow-up was 26 months in the entire cohort. Patients with resectable PDAC without vascular contact had the most improved overall survival (OS) (median; 31.5 months). OS did not significantly differ between NAT and upfront surgery in the entire resectable PDAC cohort. However, in R-contact group, NAT showed significantly improved OS compared to upfront surgery (33 vs. 23 months). Neoadjuvant FOLFIRINOX was showed a better OS than gemcitabine-based regimens in patients who underwent NAT (34 vs. 24 months). NAT was associated with a better survival in the patients with CA 19-9 level ≥ 150 U/ml, only when the tumor has PV/SMV contact in resectable disease (40 vs. 19 months, $P=0.001$).

Conclusions: NAT can be considered as an effective treatment in patients with resectable PDAC, particularly when the tumor is in contact with PV/SMV and CA 19-9 ≥ 150 U/ml.

Keywords: neoadjuvant, outcome, pancreatic cancer, resectable, survival

Introduction

Pancreatic cancer is the seventh most prevalent cancer globally and is expected to become the second leading cause of cancer-related deaths worldwide by 2030[1]. Although patients undergo surgery, the prognosis is very poor with a 5-year survival rate of ~15–20%[2–4].

According to the National Comprehensive Cancer Network (NCCN) guidelines, resectable pancreatic cancer is defined as a tumor that has no contact with a major artery and no contact with superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180°$ contact without irregularity of the vein contour[5]. This is evaluated by pancreatic protocol CT (computed tomography) or MRI.

The standard treatment for resectable pancreatic cancer is radical surgery followed by adjuvant chemotherapy. Adjuvant chemotherapy has been shown to substantially enhance survival rates in patients with pancreatic cancer. Nonetheless, due to the advanced age of a significant proportion of patients and the high

HIGHLIGHTS

- The effectiveness of neoadjuvant treatment (NAT) in resectable pancreatic ductal adenocarcinoma (RPDAC) is controversial.
- NAT showed better survival in each group with tumor-vascular contact or CA 19-9 ≥ 150 U/ml in RPDAC.
- Considering the two factors together, we propose that patients with both factors can be candidates to benefit from NAT.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:2883–2893

Received 17 November 2023; Accepted 29 January 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 19 February 2024

http://dx.doi.org/10.1097/JS9.0000000000001184

complication rates and prolonged recovery periods following pancreatectomy, only about 50% of patients initiate adjuvant chemotherapy subsequent to the surgical procedure[6,7].

Neoadjuvant treatment (NAT) using chemotherapy with or without additional radiation is the current accepted standard of care for patients with borderline resectable and locally advanced pancreatic ductal adenocarcinoma (PDAC) since it holds promise for downstaging PDAC and enhancing the rate of R0 resection[8,9].

Conversely, the effectiveness of preoperative chemotherapy in resectable pancreatic cancer remains uncertain, despite several retrospective studies reporting improved survival outcomes[10,11]. A Dutch group recently reported that neoadjuvant chemoradiation with gemcitabine in resectable/borderline resectable pancreatic cancer was associated with better survival compared to upfront surgery (5-year survival rate; 16.5 vs 6.5%, hazard ratio; 0.73, 95% CI: 0.56–0.96, $P=0.025$) (PREOPANC trial)[9]. However, this trial did not show a significant survival difference between NAT and upfront surgery in the resectable patients only (HR 0.79, 95% CI: 0.54–1.16, $P=0.23$). A recent NORPACT trial including 140 patients with resectable pancreatic cancer reported that neoadjuvant FOLFIRINOX did not improve overall survival (OS) (median OS; NAT vs. upfront surgery, 25.1 vs. 34.9 months, $P=0.096$)[12]. NEONAX trial reported that the disease-free survival rate, the primary endpoint of the trial examining perioperative gemcitabine plus nab-paclitaxel in resectable PDAC, was not reached in either arm of neoadjuvant or upfront surgery[13].

There is still a lack of evidence regarding a standard neoadjuvant protocol and in which patient subgroups it improves survival, given that the definition of resectable disease does not consider the biochemical activity of the tumor and encompasses a broad anatomical range.

Therefore, we aimed to explore the treatment outcomes of preoperative chemotherapy in patients with resectable pancreatic cancer and to provide optimal treatment for resectable disease, particularly according to vascular invasion and carbohydrate antigen (CA) 19-9 levels.

Material and methods

Patients

A total of 1271 consecutive patients with resectable or borderline resectable PDAC diagnosed between January 2007 and June 2021 at a tertiary hospital in South Korea were retrospectively reviewed. Patients were included if they met the following criteria: 1) patients without distant metastasis 2) patients with pathologically confirmed PDAC 3) patients who were evaluated with pancreatic protocol CT or MRI before and after NAT 4) patients who have both initial and post-NAT CA 19-9 levels. Patients who had borderline resectable PDAC with arterial invasion ($n=76$), who showed disease progression during neoadjuvant chemotherapy ($n=45$), and incomplete follow-up data for analysis ($n=18$) were excluded. Finally, 1123 patients were included (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JS9/B951).

This study was conducted in compliance with the Declaration of Helsinki. This retrospective study has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[14] (Supplemental Digital Content 4, http://links.lww.com/JS9/B954). The study was registered in the ClinicalTrials.gov database.

Preoperative radiological evaluation

The resectability at initial diagnosis was reassessed based on the NCCN 2021 guidelines, which defines resectable and borderline resectable PDAC as[1]: tumor contact of $\leq 180°$ with PV or SMV were determined resectable[2]; tumor contact with the PV or SMV of $>180°$ or contact of $\leq 180°$ with contour irregularity were determined borderline resectable with PV/SMV contact[3]; tumor contact of $\leq 180°$ with common hepatic artery, superior mesenteric artery, or proper hepatic artery was determined borderline resectable with arterial contact[5]. The evaluation and measurement of contact angle between tumors and vessels based on the thin-section (2–3 mm) CT or MRI with pancreatic protocol and multiplanar reconstruction of surrounding vessels were conducted by an experienced pancreatic surgeon and radiologist in multidisciplinary conference. The multidisciplinary team in our hospital include pancreatic surgeons practicing pancreatic surgery for at least 5 years and radiologists specializing in pancreatobiliary images. For the evaluation of tumor-vascular contact, both axial and coronal reformatted images were carefully reviewed. A hepatobiliary-pancreas-specialized radiologist who had more than 15 years of experience on pancreatobiliary protocol images helped with defining resectability in several ambiguous cases (L.D.H.).

Patients were categorized into three groups according to resectability. The study divided the patients into three subgroups to compare outcomes based on the extent of tumor-vessel contact[1]: resectable PDAC with no contact to major vessels (R-no contact) ($n=651$)[2] resectable PDAC with contact PV/SMV of $\leq 180°$ (R-contact) ($n=306$) and[3] borderline resectable PDAC with PV/SMV contact $>180°$ (BR-V) ($n=175$) (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JS9/B951).

Neoadjuvant and adjuvant treatment

Intravenous gemcitabine-based combination regimens or FOLFIRINOX were included in NAC. The combination of gemcitabine plus nab-paclitaxel was not included in this study. Concurrent chemoradiation therapy with gemcitabine (400 mg/m^2 body surface area) included intravenous gemcitabine administered weekly for 6 weeks. In some patients who received chemotherapy only, gemcitabine was administered as a 30 min intravenous infusion once weekly for 3 of every 4 weeks at a dose of 1000 mg/m^2. One FOLFIRINOX cycle was defined as 2 weeks. FOLFIRINOX consisted of 85 mg/m^2 oxaliplatin, followed by 400 mg/m^2 leucovorin both which are administered as a 2 h intravenous infusion, with the addition of 180 mg/m^2 irinotecan after 30 min, administered over 90 min as an intravenous infusion. This treatment was followed by 5-FU at a dose of 400 mg/m^2 administered as an intravenous bolus, followed by a continuous infusion of 2400 mg/m^2 for a 46 h period[15]. Neoadjuvant radiotherapy consisted of 44–58 Gy in 28 fractions administered with intravenous gemcitabine or 5-FU. Some patients received stereotactic body radiation therapy consisting of 50 Gy in five fractions. If there was a change in regimen during neoadjuvant chemotherapy, patients were considered to have been treated with the main treatment regimen.

Gemcitabine, 5-FU based chemoradiation, and FOLFIRINOX were used as adjuvant therapy. The cycle and dose of the adjuvant chemotherapy was the same as the neoadjuvant chemotherapy protocol. Recently, our hospital has used FOLFIRINOX as a first-line agent for adjuvant chemotherapy. Adjuvant therapy was recommended for all patients who underwent resection; however, some patients did not receive adjuvant treatment because of their performance status or recovery after pancreatectomy.

Outcome measures

Clinical information for this study was collected prospectively. Clinical factors such as age, sex, ECOG (Eastern Cooperative Oncology Group) performance status, initial serum CA 19-9 level, tumor location and size on radiologic findings, angle of tumor-vessel contact, type of operation, vascular resection, stage according to the 8th edition of the American Joint Committee on Cancer staging, T stage, N stage, number of harvested lymph node (LN) and positive LN, resection margin status, NAT, regimen of neoadjuvant chemotherapy, and adjuvant treatment were collected. The upfront surgery included pancreatoduodenectomy, pylorus-preserving pancreatoduodenectomy, distal or total pancreatectomy, open biopsy (only exploration), and bypass surgery with palliative intent. The tumor size was measured as the longest diameter on the axial images of the baseline computed tomography scans. The presence of microscopic residual tumor (R1) was defined as the presence of tumor deposits on the resection margin. OS was defined as the time from diagnosis to death from any cause or the date of the last visit.

Statistical analysis

Statistical analysis was performed using SPSS version 27.0 for Windows (IBM Corporation) and R software, version 4.2.2 (The R Foundation for Statistical Computing). Continuous variables were compared using the Mann–Whitney *U* test or Student's *t*-test. Categorical variables were analyzed using χ^2 or Fisher's exact tests. Multivariate analysis was performed using the Cox regression model to analyze prognostic factors. The Kaplan–Meier method was used to analyze the survival outcomes. Survival curves were compared using the log-rank test. Statistical significance was determined when the *P* value <0.05.

Results

Clinicopathological characteristics

The mean age was 64.3 ± 9.8 years, and 647 patients (57.2%) were male. The numbers of patients with R-no contact, R-contact, and BR-V were 651 (57.5%), 306 (27.0%), and 175 (15.5%), respectively (Table 1). Vascular resection was performed in 31 (4.8%), 109 (35.6%), and 48 (27.4%) patients in each group, respectively. Patients in the BR-V group were the most likely to receive NAT, followed by the R-contact and R-no contact groups (R-no contact, R-contact, BR-V; 2.6%, 21.6%, 66.3%). FOLFIRINOX was administered to nine (52.9%), 47 (74.6%), and 80 (69.0%) patients, and adjuvant treatment was administered to 557 (85.6%), 259 (84.6%), and 168 (96.0%) patients in each group (Table 1).

Characteristics of NAT group

The median duration of receiving neoadjuvant chemotherapy was 3[1–14] months. The median CA 19-9 level before and after neoadjuvant chemotherapy was 213 (IQR 21–845) U/ml, 33 (IQR, 10.4–134.5) U/ml in patients who underwent neoadjuvant chemotherapy. When resectability was reassessed after NAT for the 199 patients who underwent NAT, 157 (78.9%) had resectable and 42 (21.1%) had borderline resectable PDAC, respectively (not shown in the Table 1).

A comparison of the clinicopathological characteristics between NAT and upfront surgery in patients with R-contact is shown in Supplementary Table 1 (Supplemental Digital Content 3, http://links.lww.com/JS9/B953).

Survival according to tumor-vessel contact

The median follow-up period was 26 months in the entire cohort. Patients with R-no contact showed the best OS after surgery among three patient groups (median survival; 31.5 months). There was no significant difference in survival between patients with R-contact and those with BR-V (26 vs. 24 months, $P = 0.354$), respectively (Fig. 1A).

According to the degree of tumor-vessel contact, patients with tumors touching a PV/SMV of 91°–180° (24 months) had worse survival rate compared to patients with contact degree of ≤ 90° (29 months, $P = 0.039$) (Fig. 1B).

Survival difference according to the NAT versus upfront surgery

Survival analyses were performed according to treatment (Fig. 2). OS did not differ between NAT and upfront surgery in the entire resectable cohort (NAT vs. upfront surgery; 33 vs. 28 months, $P = 0.088$) and in patients with R-no contact (31 vs. 32 months, $P = 0.693$). However, patients who underwent NAT had significantly improved OS compared to those who underwent upfront surgery in the R-contact group (33 vs. 23 months, $P = 0.003$).

Among the patients with R-contact and BR-V, a subgroup survival analysis was conducted (Fig. 3). Patients who underwent NAT with either R-contact (median survival, 33 months; 5-year survival rate, 30.0%) or BR-V (26 months, 30.5%) survived longer than those who underwent upfront surgery (R-contact, 23 months, 17.5%; BR-V, 20 months, 12.7%). Patients with BR-V who underwent NAT showed better survival than patients with R-contact undergoing upfront surgery ($P = 0.021$).

When analyzing serum CA 19-9 levels at diagnosis in resectable disease, survival did not significantly differ between NAT and upfront surgery when initial CA 19-9 was <150 U/ml according to vessel contact. However, in the CA 19-9 ≥ 150 U/ml group, patients who underwent NAT had better OS compared to upfront surgery, only when the tumor contacts with PV/SMV (40 vs. 19 months, $P = 0.001$) (Fig. 4).

Prognostic factors for OS

Factors associated with OS in the entire cohort ($n = 1132$), R-contact group ($n = 306$), and patients who received neoadjuvant chemotherapy followed by surgery ($n = 196$) are shown in Table 2. In the overall cohort, age ≥ 70 (1.286), initial CA 19-9 ≥ 150 U/ml (HR 1.387), pancreatoduodenectomy (HR 1.309), stage III/IV (HR 1.286), LN metastasis (HR 1.423), LN ratio (HR

Table 1

Demographic, clinicopathologic characteristics of 1132 patients according to the initial resectablility.

Variables	Total ($n=1132$)	R-No contact ($n=651$)	R-Contact ($n=306$)	BR-V ($n=175$)	*P*
Age, mean ± SD	64.3 ± 9.8	65.1 ± 9.9	64.2 ± 9.5	61.5 ± 9.3	< 0.001
Sex, *n* (%)					
Male	647 (57.2)	374 (57.5)	180 (58.8)	93 (53.1)	0.072
Female	485 (42.8)	277 (42.5)	126 (41.2)	82 (46.9)	
ECOG					
0	559 (49.4)	310 (47.6)	135 (44.1)	114 (65.1)	< 0.001
1	443 (39.1)	269 (41.3)	127 (41.5)	47 (26.9)	
2	127 (11.2)	70 (10.8)	43 (14.1)	14 (8.0)	
3	3 (0.3)	2 (0.3)	1 (0.3)	0 (0)	
Initial CA 19-9 U/ml, median (IQR)	147.0 (25.4–708.5)	118.0 (23.7–614.5)	144.0 (26.1–709.5)	245.0 (36.6–1170.0)	< 0.001
Tumor location, *n* (%)					
Head	729 (64.4)	311 (47.8)	266 (86.9)	152 (86.9)	< 0.001
Body/Tail	403 (35.6)	340 (52.2)	40 (13.1)	23 (13.1)	
Initial tumor size, mean ± SD	2.7 ± 0.9	2.6 ± 1.0	2.7 ± 0.8	2.9 ± 0.9	< 0.001
Degree of tumor-vessel contact, *n* (%)					
< 90°			59 (51.9)		
90–180°	N/A	N/A	1 147 (48.1)	N/A	—
Operation type, *n* (%)					
PD/PPPD	687 (60.7)	315 (48.3)	251 (82.0)	121 (69.1)	< 0.001
DP/STP	367 (32.4)	316 (48.6)	33 (10.8)	18 (10.3)	
TP	60 (5.3)	18 (2.8)	21 (6.9)	21 (12.0)	
Open biopsy or Bypass	18 (1.6)	2 (0.3)	1 (0.3)	15 (8.6)	
Vascular resection, *n* (%)					
Yes	188 (16.6)	31 (4.8)	109 (35.6)	48 (27.4)	< 0.001
T stage, *n* (%)					
pT0/1	5 (0.4)/186 (16.4)	1 (0.1)/101 (15.5)	1 (0.3)/55 (18.0)	3 (1.7)/30 (17.1)	< 0.001
pT2	677 (59.8)	425 (65.2)	198 (64.7)	54 (30.9)	
pT3	219 (19.3)	117 (18.0)	45 (14.7)	57 (32.6)	
pT4	24 (2.1)	4 (0.6)	7 (2.3)	13 (7.4)	
N/A	21 (1.9)	3 (0.4)	0 (0)	18 (10.3)	
N stage, *n* (%)					
pN0	464 (41.0)	266 (40.9)	120 (39.2)	78 (49.4)	0.008
pN1	475 (42.0)	276 (41.8)	129 (42.2)	70 (39.4)	
pN2	175 (15.5)	108 (16.9)	57 (18.6)	10 (6.3)	
N/A	18 (1.5)	1 (0.4)	0 (0)	17 (4.9)	
Harvested LNs, mean ± SD	18.4 ± 10.9	16.7 ± 10.3	20.4 ± 11.7	20.7 ± 10.7	< 0.001
Positive LNs, mean ± SD	1.7 ± 2.5	1.8 ± 2.6	1.9 ± 2.6	1.2 ± 1.9	< 0.001
Lymph node ratio	0.11 ± 0.16	0.12 ± 0.17	0.10 ± 0.14	0.07 ± 0.11	< 0.001
Margin status, *n* (%)					
R0	947 (83.7)	569 (87.5)	242 (79.1)	136 (77.7)	< 0.001
R1	145 (12.8)	65 (10.0)	56 (18.3)	24 (13.7)	
R2	39 (3.5)	16 (2.5)	8 (2.6)	15 (8.6)	
Neoadjuvant treatment, *n* (%)					
Yes	199 (17.6)	17 (2.6)	66 (21.6)	116 (66.3)	< 0.001
Neoadjuvant CTx, *n* (%)					
Yes	196 (17.3)	17 (2.6)	63 (20.6)	116 (66.3)	< 0.001
Neoadjuvant RTx, *n* (%)					
Yes	102 (9.0)	8 (1.2)	32 (10.5)	62 (35.4)	< 0.001
Neoadjuvant					
FOLFIRINOX	136 (69.4[a])	9 (52.9[b])	47 (74.6[c])	80 (69.0[d])	0.058
CTx regimen, *n* (%)					
Gemcitabine-based	60 (30.6[a])	8 (47.1)	16 (25.4[c])	36 (31.0[d])	
Adjuvant treatment, *n* (%)					
Yes	984 (86.9)	557 (85.6)	259 (84.6)	168 (96.0)	< 0.001

[a]Of 196 patients who received neoadjuvant chemotherapy.
[b]Of 17 patients,
[c] Of 63 patients,
[d]Of 116 patients.
N/A, not evaluated due to incomplete resection or missing.
CTx, chemotherapy; CA 19-9, carbohydrate antigen 19-9; DP, distal pancreatectomy; ECOG, Eastern cooperative oncology group; IQR, interquartile range; N/A, not applicable; PPPD, pylorus-preserving pancreaticoduodenectomy; PV, portal vein; RTx, radiotherapy; SMV, superior mesenteric vein.

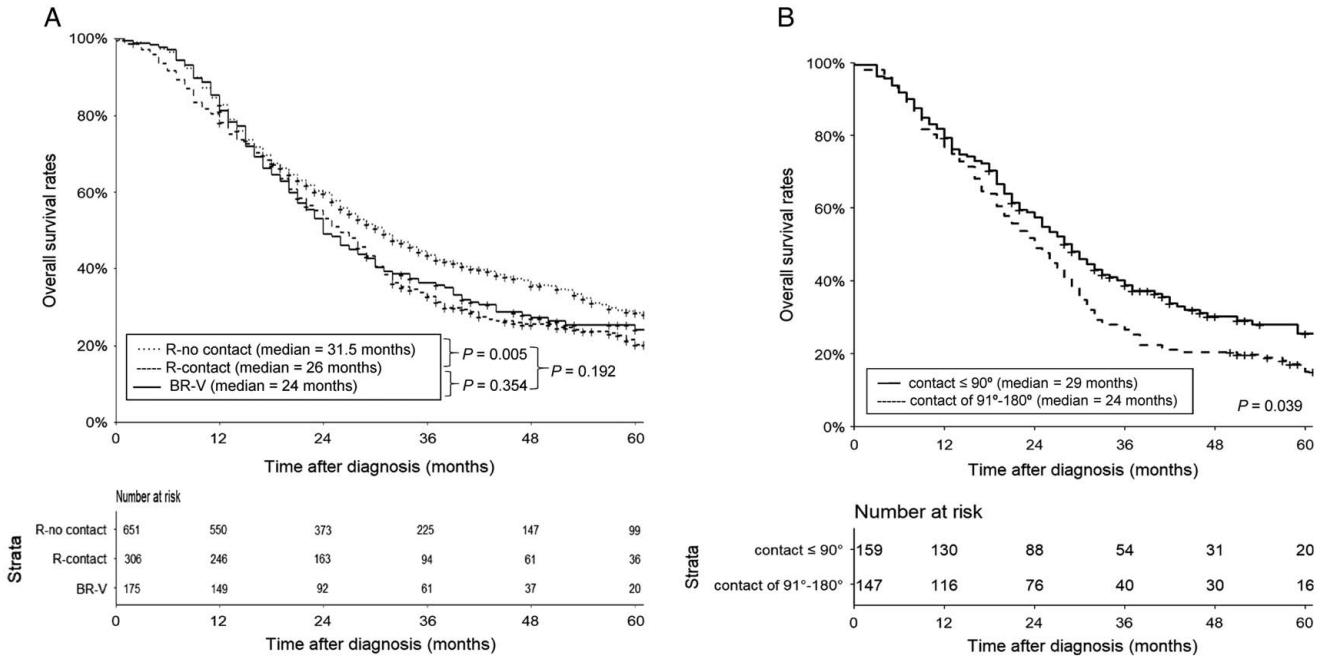

Figure 1. Overall survival according to (A) tumor-vessel relationship; tumor that has no contact with major vessels (R-no contact), that has contact with portal or superior mesenteric vein (PV/SMV) within 180° (R-contact), and that has contact with greater than 180° (BR-V), and (B) contact degree (≤ 90° vs 91–180°).

1.309), R1 resection (HR 1.355), and adjuvant treatment (HR 0.586) were associated with OS. In patients undergoing neoadjuvant chemotherapy, age ≥70 (HR 1.418, 95% CI: 1.079–1.863, $P=0.012$), LN ratio greater than 0.1 (HR 1.863, 95% CI: 1.126–3.080, $P=0.015$) and Gemcitabine-based chemotherapy regimen (HR 1.539, 95% CI: 1.062–2.229, $P=0.023$) were associated with worse survival. The median OS for patients undergoing neoadjuvant FOLFIRINOX was 34 months, respectively (gemcitabine-based; 24 months) (Supplementary Fig. 2, Supplemental Digital Content 2, http://links.lww.com/JS9/B952).

Discussion

Recent randomized controlled trials regarding the effectiveness of NAT in resectable PDAC did not support NAT as an applicable therapeutic option. However, these studies are limited by the fact that they do not differentiate resectable PDAC anatomically or biologically. In the PREOPANC trial, resectable pancreatic cancer was defined as tumor contact with the SMV or PV was ≤90° without any arterial contact[9]. There are few studies on the tumors in contact with PV/SMV with 91–180°, which is also defined as resectable PDAC according to the NCCN guidelines. Additionally, there are reports that prognosis varies by tumor marker level even in resectable disease, suggesting that NAT may have a role in resectable PDAC presenting systemic features[16,17]. Therefore, we explored candidates who may benefit from NAT in resectable PDAC based on anatomical and biological aspects.

In this study, patients with resectable PDAC without vascular contact had the improved OS compared to those with vascular contact (31.5 vs 26 months, $P=0.005$). It is assumed that even if a tumor in contact with PV/SMV is technically resectable, its behavior is already similar to a borderline resectable tumor. Furthermore, even within resectable PDAC with vascular contact, survival varied by contact angle (≤90 vs 91–180; 29 vs 24 months, $P=0.039$). A recent multicenter international study including 42 hepato-biliary pancreatic surgeons and 54 radiologists reported interobserver variability in assessing the tumor-vessel relationship in pancreatic cancer is highest when the tumor is in contact with PV/SMV within 180°[18]. Therefore, it is possible that patients with tumors within 91–180° of contact were clinically underestimated and did not receive the NAT they needed.

In this study, patients were divided into three groups based on the angle of contact between the tumor and the PV/SMV. Patients in R-contact group were more likely to undergo vascular resection than those in R-contact groups (35.6 vs 27.4%) (Table 1). More patients in the BR-V group underwent NAT (66.3 vs 21.6%), which is believed to increase the likelihood of R0 resection, therefore, surgeons tried to preserve vessels to avoid vascular complications. On the other hand, patients who did not receive NAT and whose tumors were attached to vessels were treated more aggressively, resulting in a higher frequency of vessel resection. Meanwhile, in the R-no contact group, 31 patients (4.8%) underwent vascular resection, because of the suspicious focal invasion of PV/SMV, pancreatitis, or anatomic variation of hepatic artery during the operation.

NAT is associated with downstaging of the tumor. In this study, 83 patients with resectable and 116 patients with borderline resectable disease underwent NAT, and after NAT, 157 were reevaluated as resectable and 42 as borderline resectable. Among the 116 patients, 84 (72.4%) patients were clinically downgraded to resectable disease. Meanwhile, 10 resectable patients were evaluated as borderline resectable after NAT. The contact angle between the tumor and PV/SMV at the time of diagnosis in these patients was all greater than 150 and lesser than

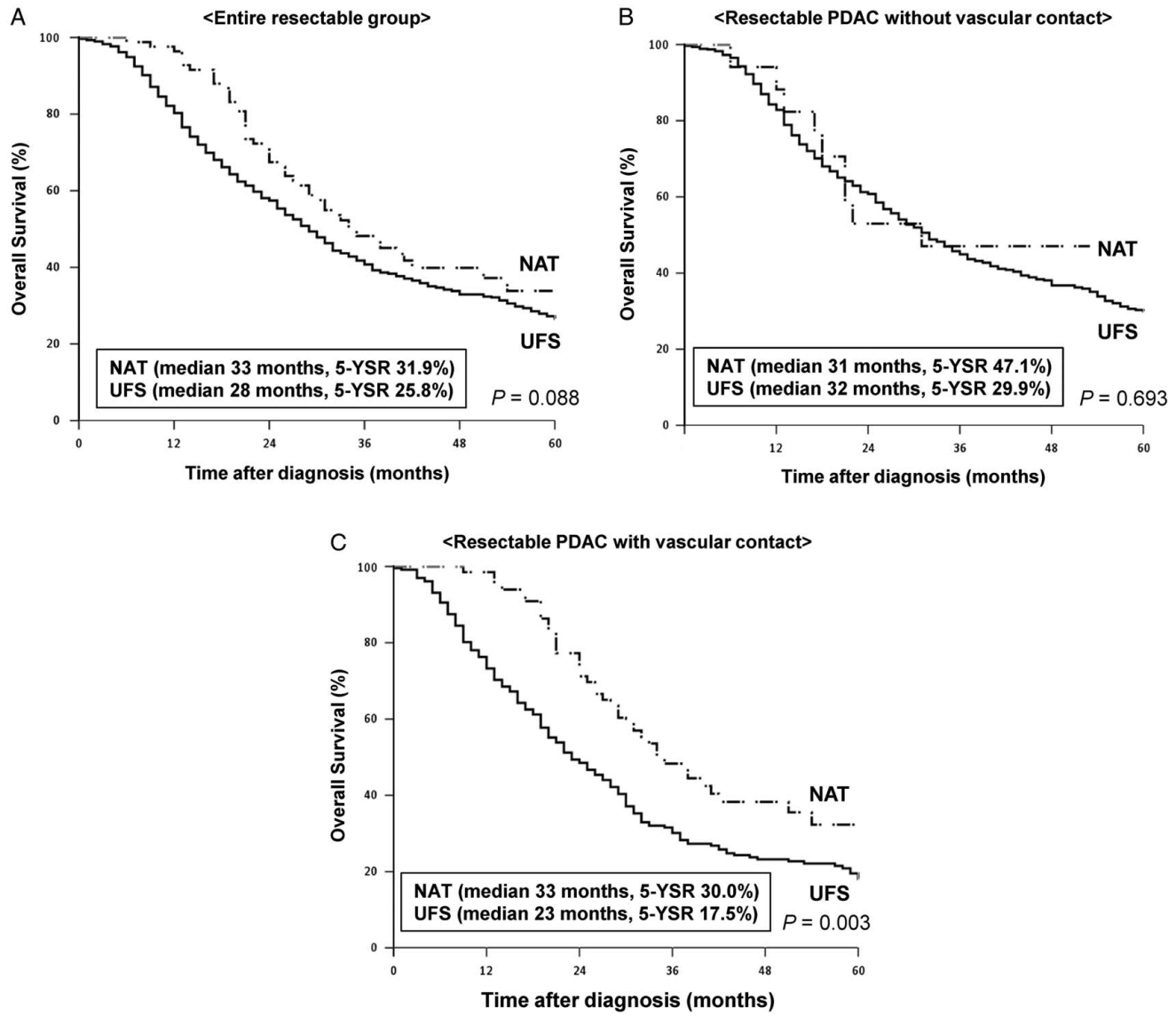

Figure 2. Survival according to treatment in patients with resectable PDAC. (A) Entire group, (B) without vessel contact, (C) with vessel contact.

180°, which may have caused the different assessment results due to interobserver variability[19,20]. Giannone *et al.*[19] reported the lowest interobserver agreement in assessing resectability when the tumor-vessel contact angle was less than 180°.

The difference in survival was not statistically significant when comparing NAT with upfront surgery in patients with resectable disease. Whether NAT improves OS in patients with resectable disease remains controversial. Reni *et al.*[21] reported a prolonged median OS in the NAT arm in the PACT-15 trial (NAT vs two upfront surgery groups; 38.2 vs. 20.4 and 26.4 months). The recent meta-analysis including only randomized controlled trials reported gemcitabine-based NAT resulted in favorable OS compared to upfront surgery in resectable PDAC (HR 0.73, 95% CI: 0.59–0.91)[22]. The ongoing randomized trial reported better survival of NAT using gemcitabine and S1 versus upfront surgery (median OS; 36.7 vs. 26.6 months) (Prep-02/JSAP-05)[23]. On the other hand, a meta-analysis including only resectable disease reported the survival gain of NAT was not demonstrated in intention-to-treat analysis (HR 0.96, 95% CI: 0.82–1.12)[24]. The PREOPANC trial did not demonstrate significant difference in survival in resectable disease (HR 0.79, 95% CI: 0.54–1.16, $P = 0.23$)[9].

Interestingly, when analyzing subgroups according to anatomy, NAT was associated with longer survival in patients whose tumors were in contact with PV/SMV (33 vs. 23 months). In the group with PV/SMV contact, R0 resection (86.3 vs. 77.1%, $P = 0.004$) and LN negativity rates (57.6 vs. 34.2%, $P = 0.002$) were improved in NAT compared with upfront surgery. The NORPACT trial also reported that neoadjuvant FOLFIRINOX was associated with a higher rate of N0 and R0 resection[12]. A meta-analysis including 17 studies reported a higher R0 resection rate (Effect size; 1.95, 95% CI: 1.40–2.71) and lower LN metastasis rate (Effect size; 0.28, 95% CI: 0.21–0.38) were achieved in NAT[25]. This suggests that resectable tumors with

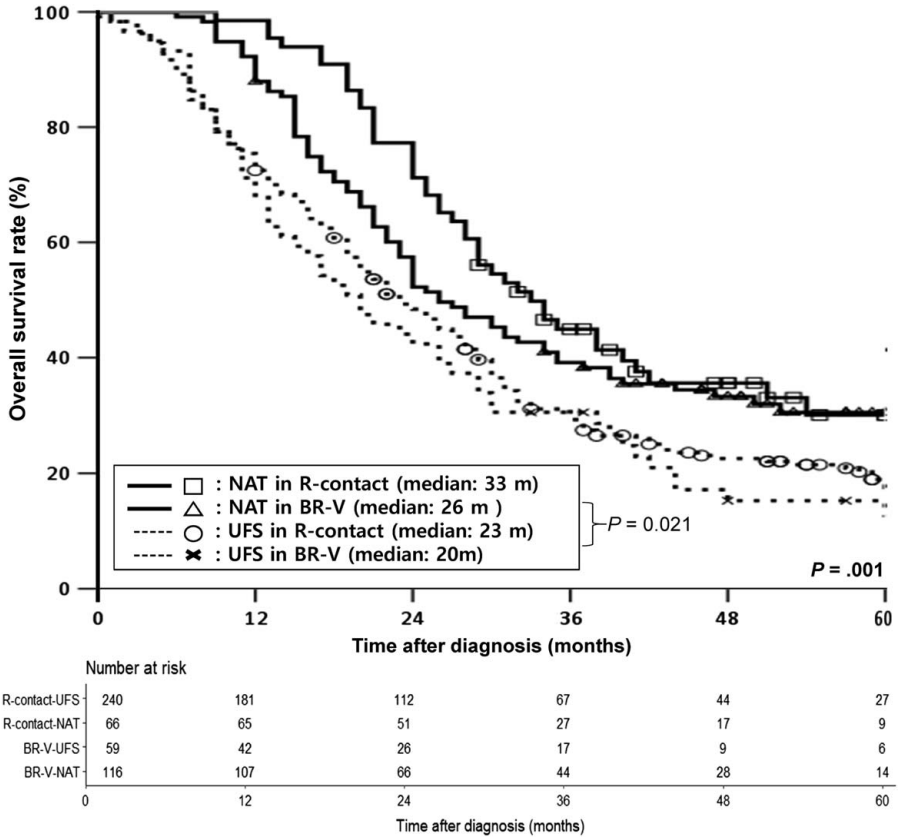

Figure 3. Survival according to the treatment (NAT versus upfront surgery) in patients with resectable tumor in contact with PV/SMV ≤180° (R-contact) and in patients with borderline resectable tumor in contact with PV/SMV of >180° (BR-V).

vascular involvement have a different biological meaning compared to those without it. In addition, given the significant interobserver variability in the CT-based assessment of resectability for pancreatic cancer[20], some patients with underestimated resectability may benefit from NAT, which has the advantage of improving the R0 resection rate and preventing tumor spread to the regional LN.

In our study, patients with BR-V who underwent NAT had better survival rates than those who underwent upfront surgery with R-contact (31 vs. 23 months, $P=0.003$). This may have resulted from advances in chemotherapeutic regimens such as FOLFIRINOX for borderline resectable diseases in this cohort. In addition, the higher proportion of patients receiving adjuvant treatment in the BR-V group than in the resectable group may have resulted in favorable outcomes. Marchegiani *et al.*[26] reported reduced incidence of pancreatic fistula and postpancreatectomy hemorrhage in patients undergoing NAT. The lower complication rate in patients undergoing NAT may lead to an increased delivery of adjuvant treatment.

The NCCN 2021 guidelines state that large primary tumors can be classified as high-risk resectable PDAC and considered for NAT[5]. This is consistent with our results in that there are selective patients with anatomically high-risk PDAC despite being judged as resectable and may have potential advantages with NAT. The high-risk resectable PDAC also includes CA 19-9 >500 U/ml[5]. The International Study Group of Pancreatic Surgery and the International Association of Pancreatology proposed the concept of biological resectability, considering the prognostic impact of CA 19-9 levels, which suggests CA 19-9 levels >500 U/ml as a biological borderline resectable[27,28].

In our study, CA 19-9 ≥150 U/ml was a worse prognostic factor (HR 1.372), and patients with CA 19-9 ≥150 U/ml who underwent NAT had improved survival compared to upfront surgery in resectable disease (35 vs. 23 months, $P=0.011$). Takahashi *et al.*[17] reported survival of patients with anatomically resectable disease was similar to that of borderline resectable patients when their preoperative CA 19-9 ≥120 U/ml (5-year survival rate; 44l% vs. 34%, $P=0.082$). Kim *et al.*[29] reported that patients with CA19-9 >150 U/ml undergoing NAT showed better survival compared with upfront surgery in resectable PDAC (34.0 vs. 18.0 months, $P=0.004$). Previous studies have also reported that elevated CA 19-9 levels are associated with a higher LN metastasis[30,31], margin positive[31,32], and recurrence rate[33] in resectable PDAC.

NAT controls biological activity of the tumor. The CA 19-9 levels in patients who received NAT decreased from a median of 213 U/ml at diagnosis to 33 U/ml after NAT. However, there is still a lack of evidence on whether all patients with high CA 19-9 levels in resectable PDAC may benefit from receiving NAT. This study found that NAT was associated with better survival in the group with CA 19-9 level ≥150 U/ml, only when the tumor has PV/SMV contact in resectable disease (40 vs. 19 months, $P=0.001$). Tumors in contact with the vessels have a higher risk of micrometastasis, which may result in early disease control

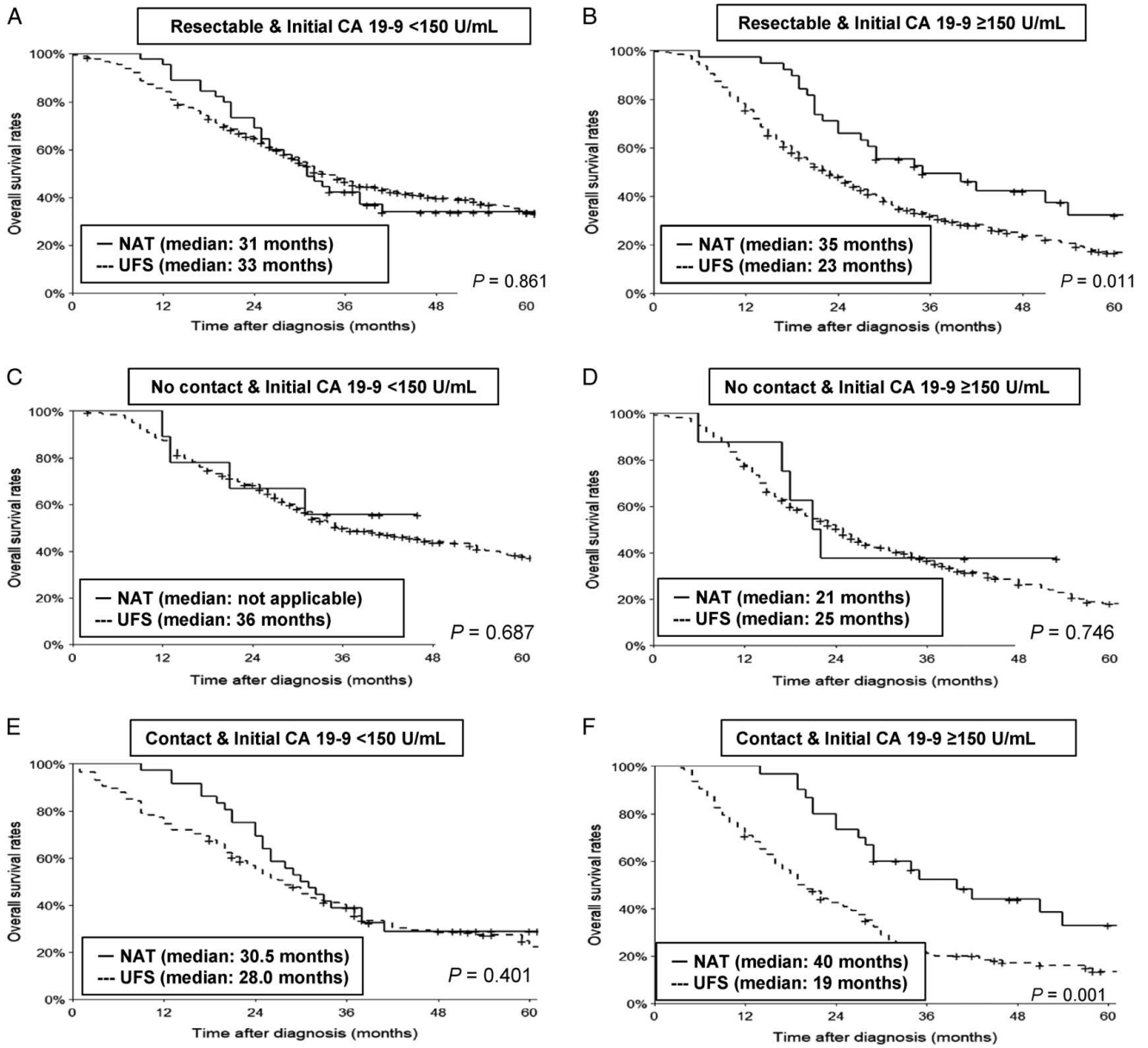

Figure 4. Survival comparison of NAT versus upfront surgery in resectable PDAC. (A) Patients with initial CA 19-9 <150 U/ml, (B) Patients with initial CA 19-9 ≥ 150 U/ml, (C) Patients with no PV/SMV contact with initial CA 19-9 <150 U/ml, (D) Patients with no PV/SMV contact with initial CA 19-9 ≥ 150 U/ml, (E) Patients with PV/SMV contact with initial CA 19-9 <150 U/ml, (F) Patients with PV/SMV contact with initial CA 19-9 ≥ 150 U/ml.

using NAT. In this study, when analyzed using a CA 19-9 level of 500 U/ml, no survival difference was observed between the NAT and upfront surgery groups. Moon *et al.*[16] reported a C-tree statistical method to predict the prognostic cutoff level of CA 19-9, and a value of 150 U/ml was recommended. Further investigation to establish a reliable cutoff level to select patients who may benefit from more aggressive treatment is needed.

In this study, neoadjuvant FOLFIRINOX was associated with a better OS than gemcitabine-based regimens in patients who underwent NAT (34 vs. 24 months, $P = 0.008$). Few studies have reported on the efficacy of FOLFIRINOX as a neoadjuvant chemotherapeutic agent for resectable PDAC. A recent NORPACT trial using FOLFIRINOX as a neoadjuvant chemotherapy regimen did not show a survival difference between NAT and upfront surgery. However, four neoadjuvant cycles of this trial's protocol may not be sufficient for disease control and the completion rate of NAT was 60%, too low to analyze the effectiveness of NAT[12]. The ongoing trials investigating neoadjuvant FOLFIRINOX for resectable PDAC are expected to provide high-level evidence (NCT02959879, NCT05529940)[34].

This study had several limitations. First, this was a retrospective, single-center study, and selection bias could not be avoided. Second, comorbidities, comalignancies, and perioperative performance status were not controlled for in the patients included in this study. Third, the number of patients receiving

Table 2

Factors associated with overall survival in entire cohort ($n = 1132$), resectable pancreatic cancer with vessel contact group ($n = 306$) and in patients who received neoadjuvant chemotherapy from baseline cohort ($n = 196$).

		Univariate analysis		Multivariate analysis	
Variables		**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Entire group (n = 1132)					
Age (year)	≥ 70 vs <70	1.234 (1.068–1.426)	0.004[a]	1.286 (1.099–1.505)	0.002[a]
Sex	Male vs Female	0.856 (0.741–0.988)	0.034[a]	0.865 (0.744–1.006)	0.060
ECOG	0,1 vs 2,3	1.097 (0.878–1.371)	0.416		
Initial CA 19-9, U/ml	< 150 vs ≥ 150	1.409 (1.228–1.617)	< 0.001[a]	1.387 (1.198–1.607)	< 0.001[a]
Operation type	DP vs PD	1.252 (1.072–1.462)	0.005	1.309 (1.116–1.536)	< 0.001[a]
Stage	I, II vs III, IV	2.016 (1.713–2.372)	< 0.001	1.286 (1.044–1.584)	0.018[a]
T stage	T1,2 vs T3,4	1.393 (1.185–1.637)	< 0.001[a]	1.114 (0.936–1.325)	0.225
N stage	N0 vs N1,2	1.819 (1.572–2.104)	< 0.001[a]	1.423 (1.172–1.728)	< 0.001[a]
LNR	< 0.1 vs ≥ 0.1	1.850 (1.604–2.134)	< 0.001	1.309 (1.064–1.611)	0.011[a]
Resection margin	R0 vs R1	1.605 (1.345–1.914)	< 0.001[a]	1.355 (1.116–1.646)	0.002[a]
Neoadjuvant treatment	No vs Yes	0.852 (0.708–1.026)	0.091	—	—
Adjuvant treatment	No vs Yes	0.575 (0.477–0.694)	< 0.001[a]	0.586 (0.479–0.716)	< 0.001[a]
R-contact group (n = 306)					
Age (year)	≥ 70 vs <70	1.436 (1.100–1.875)	0.008[a]	1.418 (1.079–1.863)	0.012[a]
Sex	Male vs Female	0.959 (0.741–1.240)	0.748	—	—
Initial CA 19-9, U/ml	< 150 vs ≥ 150	1.252 (0.971–1.613)	0.083	—	—
Operation type	DP vs PD	0.894 (0.591–1.354)	0.598	—	—
Stage	I,II vs III,IV	1.647 (1.220–2.223)	0.001[a]	1.132 (0.749–1.709)	0.557
T stage	T1,2 vs T3,4	1.411 (1.025–1.941)	0.035[a]	1.123 (0.789–1.598)	0.521
N stage	N0 vs N1,2	1.497 (1.148–1.953)	0.003[a]	1.132 (0.802–1.597)	0.482
LNR	< 0.1 vs ≥ 0.1	1.767 (1.360–2.296)	< 0.001[a]	0.681 (0.454–1.022)	0.063
Resection margin	R0 vs R1	1.244 (0.916–1.688)	0.173	—	—
Neoadjuvant CTx	No vs Yes	0.611 (0.437–0.853)	0.004[a]	0.757 (0.535–1.070)	0.115
Neoadjuvant RTx	No vs Yes	0.832 (0.540–1.280)	0.402	—	—
Adjuvant treatment	No vs Yes	0.478 (0.344–0.664)	< 0.001[a]	0.595 (0.414–0.854)	0.005[a]
Patients who received NAT followed by surgery ($n = 196$)					
Age (year)	≥ 70 vs <70	1.167 (0.764–1.784)	0.475	—	—
Sex	Male vs Female	0.632 (0.295–1.357)	0.239	—	—
Initial CA 19-9, U/ml	< 150 vs ≥ 150	0.892 (0.632–1.257)	0.513	—	—
Operation type	DP vs PD	1.094 (0.678–1.765)	0.713		
Stage	I,II vs III,IV	1.400 (0.872–2.247)	0.164		
Tumor-vessel	R-no contact	1 (Ref)		—	—
relationship	R-contact	0.992 (0.482–2.044)	0.983		
	BR-V	1.113 (0.555–2.231)	0.763		
T stage	T1,2 vs T3,4	1.526 (0.945–2.462)	0.084	—	—
N stage	N0 vs N1,2	1.643 (1.136–2.377)	0.008[a]	1.217 (0.784–1.891)	0.382
LNR	< 0.1 vs ≥ 0.1	2.133 (1.423–3.197)	< 0.001[a]	1.863 (1.126–3.080)	0.015[a]
Resection margin	R0 vs R1	1.887 (1.220–2.917)	0.004[a]	1.329 (0.815–2.168)	0.255
Neoadjuvant radiation	No vs Yes	1.587 (0.853–2.955)	0.145	—	—
Neoadjuvant chemo regimen	FOLFIRINOX vs Gemcitabine-based	1.719 (1.191–2.480)	0.004[a]	1.539 (1.062–2.229)	0.023[a]

CA 19-9, carbohydrate antigen 19-9; CTx, chemotherapy; DP, distal pancreatectomy; LNR, lymph node ratio; PD, pancreatoduodenectomy; RTx, radiotherapy.
[a]statistically significant.

NAT in this study was small. This is because resectable PDAC represents a small percentage of all PDAC patients and upfront surgery is still the standard of care in the NCCN and Korean guidelines. Therefore, high-level evidence of the effectiveness of NAT in patients with resectable PDAC is still needed. In addition, it is unclear whether the initial CA 19-9 levels presented in this study were measured while the patient had obstructive jaundice or when it resolved. If the serum bilirubin value at the time the CA 19-9 level was measured could have been presented, the CA 19-9 level presented in this study was more correlated with the biological behavior of the tumor. Lastly, the patients received various combinations of chemotherapy and radiotherapy, with differences in the dosages and number of cycles administered, making it difficult to interpret the impact of NAT on survival.

In conclusion, NAT can be considered as an effective treatment in patients with resectable PDAC, particularly when the tumor is in contact with PV/SMV and CA 19-9 ≥ 150 U/ml at diagnosis.

Ethical approval

Ethical approval for this study was provided (No. H 2304-125-1426) by the Institutional Ethics Review Board of Seoul National University Hospital, Seoul, South Korea on 26 May 2023.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2022R1A2C2011122).
※ MSIT: Ministry of Science and ICT.

Author contribution

H.-S.J. and Y.H.: had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; J.-Y.J.: concept and design; H.-S.J., Y.H., W.-G. Y., Y.J.C., M.L, and D.H.L.: acquisition, analysis, or interpretation of data; H.-S.J.: drafting of the manuscript; D.H.L., W.K., and J.-Y.J.: critical revision of the manuscript for important intellectual content; H.-S.J.: statistical analysis; Y.H., W.-G.Y., Y.J.C., D.H.L., W.K., and J.-Y.J.: administrative, technical, or material support; J.-Y.J.: study supervision.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

The study was registered in the ClinicalTrials.gov database (NCT06129812).

Guarantor

Hye-Sol Jung and Jin-Young Jang.

Data availability statement

Data sharing is not applicable to this article.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

Assistance with the study: None.

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