PROGNOSTIC FACTORS FOR BORDERLINE RESECTABLE / LOCALLY ADVANCED PANCREATIC DUCTAL ADENOCARCINOMA UNDERGOING RESECTION

by
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I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

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OVERVIEW:

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a dismal prognosis. Surgical resection remains the only treatment with curative potential. It has been previously suggested that a margin negative(R0) resection is associated with improved overall and progression-free survival for these patients. However, over 50% of the patient present with metastatic disease, and would therefore only be candidate for palliative treatment, while only less than 20% of the patients would be amendable to immediate surgery. The other 30% of the patients present with disease involving the adjacent vasculature that may jeopardize an ontologically complete tumor resection, categorized as borderline resectable (BR) or locally advanced (LA) PDAC.

Neoadjuvant systemic chemotherapy and/or radiation therapy, or neoadjuvant treatment (NT), was initially proposed for patients with LA-PDAC to achieve R0 resection and has also become increasingly popular among patients with less advanced tumors. Current National Comprehensive Cancer Network (NCCN) guidelines recommend receipt of NT for all patients with high risk features, including those with a BR-PDAC. A growing body of evidence suggests that neoadjuvant treatment prior to resection can improve the prognosis of patients with BR/LA-PDAC by facilitating an R0 resection. On the other hand, the term “borderline resectability” was proposed to recognize that, in some of these patients, it is possible to achieve negative margins by upfront resection (UR). For this group, delaying surgery for NT deprives them of the only chance for curative resection. To date, most retrospective studies investigating the prognostic impact of NT vs. UR did not distinguish R0 and R1 resection. It remains

unclear whether there are additional prognostic benefits of NT beyond facilitating R0 resection. In the neoadjuvant setting, specific clinicopathological variables influencing survival may change at different time points. Previous studies tend to merge all variables in to one single model.

In this study, we investigated the prognostic factors of patients with BR-PDAC to clarify whether the benefit of NT were independent of its impact on R status. Furthermore, we set out to identify prognostic factors at diagnosis, restaging and postoperatively of patients with non-metastatic PDAC undergoing NT followed by resection.

Project 1:

Prognostic Factors in Patients with Borderline Resectable Pancreatic Ductal Adenocarcinoma Undergoing Resection

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Running Head: Prognosis of borderline pancreatic cancer

SYNOPSIS

Neoadjuvant treatment is independently associated with improved overall survival and progression-free survival in patients with borderline-resectable pancreatic cancer, however this effect is outweighed by a negative resection. Upfront resection might remain a valid treatment option if negative resection could be accurately predicted.

ABSTRACT

Background: Advancement of neoadjuvant treatment (NT) has alternated the management of borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC), potentially changed the determinant of prognosis.

Methods: Clinicopathological data of patients with BR-PDAC who underwent resection between 01/2008 and 12/2018 at a single institution were retrospectively reviewed. Univariable and multivariate analyses were used to compare survival between patients who received NT vs. those who underwent upfront resection (UR).

Results: A total of 138 patients with BR-PDAC were included in the study, 64 underwent UR and 74 NT. NT resulted in higher R0 resection rate (68.9%) compared with UR (43.8%, p=0.005). NT was associated with improved overall survival (OS, p=0.009) and progression-free survival (PFS, p=0.027). R0 resection was also associated with improved OS (p<0.001) and PFS (p<0.001). On multivariable analysis, when adjusting for clinically relevant variables without considering R status, NT was an independent

predictor for improved OS (p=0.046) and PFS (p=0.040). When additionally accounting for R status, R0 was an independent predictor for improved OS (p<0.001) and PFS (p<0.001) while NT was not. Subgroup analysis, stratified by R status, revealed that NT was not an independent predictor for OS or PFS for either the R0 or R1 subgroups.

Conclusions: NT is independently associated with improved OS and PFS in patients with BR-PDAC, however this effect is outweighed by R status. These results suggest that the primary benefit of NT was the facilitation of R0 resection, UR might remain a valid treatment option if R0 resection could be accurately predicted.

Key words: borderline resectable pancreatic cancer, neoadjuvant therapy, upfront resection, pancreatic surgery, prognostic factors, resection margin

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy, most of the times requiring multimodality treatment .(1-14) Negative margin resection, defined as a 1mm tumor clearance (R0), has been considered the only treatment associated with a potentially sustainable cure.(1, 3-7) Yet, over 30% of patients with localized PDAC present with disease involving the adjacent vasculature that may jeopardize the possibility to achieve an R0 margin. These patients are categorized as having a borderline resectable (BR) or locally advanced (LA) PDAC.(9)

Neoadjuvant systemic chemotherapy and/or radiation therapy, or neoadjuvant treatment (NT), was initially proposed for patients with LA-PDAC to achieve resectablity, and has also become increasingly popular among patients with less advanced tumors.(8-14) NT facilitates an R0 resection in responders, and is believed a possible selection tool for non-responders, sparing some the potential increased undesirable morbidity of a pancreatectomy.(8, 11, 14-17) Current National Comprehensive Cancer Network (NCCN) guidelines recommend receipt of NT for all patients with high risk features, including those with a BR-PDAC(18).However, lack of consensus in the definition of “borderline resectability” and the continuous evolution of guidelines have led to a broad variation in the management of patients with BR-PDAC.(9, 10) Patients with BR-PDAC have been managed by different approaches, with an increasing preference to NT.(10) However, up to approximately 40% of recipients of NT are excluded from surgical treatment, due to either disease progression or a poor

post-treatment performance status. It is conceivable that delaying surgery deprives some patients of the only possibility for curative resection .(8) (12-14)For this reason, upfront resection (UR) may still be a valid choice for selected patients with BR-PDAC. In contrast, several investigators have demonstrated that resection margin (R) status is not an independent risk factor for survival, therefore questioning the necessity to perform an R0 resection, particularly in the setting of NT.(19-23)

With advancement in NT altering management of BR-PDAC, determinants of prognosis may be changing in parallel with better outcomes. To date, most retrospective studies set to identify prognostic factors for patients with resected BR-PDAC have performed conditional survival analyses, excluding patients with residual or unresected disease. (9, 14-16, 21, 24-27) Yet these studies have omitted to clearly distinguish between R0 and R1 resection; thus, it remains unclear whether the impact of NT outweighs that of R status. In this study, we sought to furthermore investigate the prognostic factors of patients with BR-PDAC to clarify whether NT may benefit patients with BR-PDAC independent of its impact on R status.

METHODS

Inclusion Criteria

After Institutional Review Board approval by the Brigham and Women's Hospital, all patients who underwent a pancreatectomy between January 1, 2008, and December 30, 2018, were reviewed. Patients with a diagnosis other than PDAC and those with

metastatic PDAC or residual tumor were excluded. Patients with a BR-PDAC, as defined by the American Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology (AHPBA/SSAO/SSO) Consensus,(9) were identified from reviewing the radiology reports of imaging performed at diagnosis. Inclusion criteria were defined as: abutment (<180°) or encasement (>180°) of the common hepatic artery (CHA) amenable to reconstruction; abutment of the superior mesenteric artery (SMA); or abutment, encasement, and/or occlusion of the superior mesenteric vein (SMV) or portal vein (PV) amenable to surgical reconstruction. AHPBA/SSAO/SSO Consensus is adopted because it is currently mostly used as criteria for administrating NT in USA.(9)

Data collection

All data were retrospectively collected after reviewing electronic medical records. The variables analyzed included gender, age, race, time of diagnosis and resection, American Society of Anesthesiologists (ASA) physical status classification, Eastern Cooperative Oncology Group (ECOG) scale of performance status, body mass index (BMI) at diagnosis, carbohydrate antigen 19–9 levels (CA19–9, U/mL) at diagnosis and resection, tumor location, size of tumor on CT at diagnosis and resection (cm), and venous or arterial involvement. For the patients receiving NT these included: type of therapy received (chemotherapy and/or radiotherapy), the radiological tumor response in accordance to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and the degree of pathological tumor regression. In the absence of a standardized protocol,

NT consisted of a variety of different regimens, however during the study period FOLFIRINOX with/without radiotherapy was predominantly used. Type of surgical procedure performed (pancreaticoduodenectomy, distal, or total/subtotal pancreatectomy), estimated blood loss (EBL, ml), vascular resection, and operative time (hours) were also collected. Tumor histology data assessed included resection margin (R) status, pathological tumor size (cm), number of resected and positive nodes, tumor staging, lymphovascular invasion, and perineural invasion. R status (R0 vs. R1) and tumor staging were defined according to the 8th edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC, 8th revised edition).(28) R0 was defined as a tumor-free margin of >1 mm, which included the pancreatic transection margin, the bile duct margin, the vascular margins, the stomach/duodenal margins, and the circumferential soft tissue margins (medial, anterior surface, superior, posterior).(28-30) Otherwise, it is considered R1. Postoperative data examined included length of hospital stay (LOS in days), in-hospital morbidity according to the Clavien-Dindo (CD) classification, readmission within 30 days, mortality within 90 days, receipt of adjuvant treatment, and time and site of recurrence.

Outcomes

Primary outcomes were overall survival (OS) and progression-free survival (PFS); these were calculated from the date of diagnosis to the date of death or documented recurrence, respectively (event), or to the date of the last follow-up visit (censored). Date of death was obtained either from the Social Security Death Index or from review of medical records. Follow-up data were obtained for all patients until August 1, 2019.

Statistical analysis

Continuous variables are presented as median and dispersion as interquartile range(IQR), and compared using the Wilcoxon signed-rank test. Categorical variables are presented as numbers and percentages and compared using the Chi-square test or Fisher exact test, as appropriate. Median and IQR of OS or PFS were calculated using the Kaplan–Meier (K-M) survival analysis. The log-rank test was used to compare survival. Univariate and multivariable analysis models were built to identify prognostic risk factors for OS and PFS. Variables included in multivariable models were not selected based on p-values on univariate analysis(31-33). But rather, they were predefined based on clinical relevance based on previous reports on the subject. The multivariable model of OS included the following variables: NT vs. UR, age (>70 vs. ≤70), BMI (>30 vs. <=30), ASA (III/IV vs. I/II), ECOG (≥1 vs. 0), venous invasion, arterial invasion, CA19-9 at diagnosis (>100 vs. ≤100), tumor size at diagnosis (>3.0cm vs. ≤3.0cm), tumor location (head/uncinate vs. body/tail) with or without adjusting for R status (R0 vs. R1). Factors such as age, BMI, ASA and ECOG were not included in the multivariable model for PFS due to their lack of clinical relevance for recurrence. All tests performed were two-tailed, and a $p<0.05$ was considered statistically significant. Statistical computations were performed using R Studio.Inc. Version 1.1.456

Subgroup analysis

Interaction between NT and R status was assessed, and a subgroup analysis, stratified by R status, was additionally performed to further assess the impact of NT on OS/PFS.

Patients were divided in R0 vs. R1 subgroups and clinicopathological characteristics were compared between the subgroup patients receiving NT vs. UR. The same statistical models (univariate/multivariable) used for the main analysis were used for the subgroup analysis to identify independent prognostic factors for OS/PFS conditioning on R status.

RESULTS

Overall Cohort and Neoadjuvant Treatment

The flowchart for the study selection cohort is shown in Figure 1. During the study period, 596 patients with pancreatic neoplasm had a pancreatectomy at Brigham and Women's Hospital. According to pathology reports, 277 patients were excluded because they did not have a PDAC, and 12 patients had metastatic or residual disease. Another 169 patients were excluded because they had resectable or locally advanced disease according to the AHPBA/SSAO/SSO consensus. The final cohort consisted of a total of 138 patients with BR-PDAC, among whom 64 underwent UR and 74 received NT prior to operation. At diagnosis, no significant differences were observed between the two groups (NT vs. UR) with respect to age, gender, ECOG, ASA stage, CA19-9, body mass index (BMI), tumor location, and venous involvement (Table 1). Patients undergoing UR were less likely to have arterial involvement (12.5% vs. 33.8%, p=0.006), and had a smaller tumor size (median 2.9cm vs. 3.1cm, p=0.017). Among the 74 patients in the NT

group, 54 (72.9%) received FOLFIRNOX-based treatment (Supplemental Table 1). The median time from diagnosis to resection was 6.6 months in the NT group and 1.0 month in the UR group. At surgery, CA19-9 levels were significantly lower in the NT group (median 43 U/ml vs. 166 U/ml, p<0.001), while tumor size was comparable (median 2.5cm vs. 2.9cm, p=0.152).

Pathologic and Operative Outcomes

Pathologic and operative outcomes are shown in Table 2. For the NT group, the R0 resection rate was 68.9%, which was significantly higher compared to the UR group (43.8%, p=0.005). Final pathology demonstrated prominent tumor down-staging in the NT group: a smaller tumor size (median 2.6cm vs. 3.0cm, p=0.003), fewer positive lymph nodes (median 0 vs. 2, p<0.001), a lower AJCC stage (p<0.001), and lower rates of lymphovascular (p=0.015) and perineural invasion (p=0.004). In terms of perioperative outcomes, no significant differences were observed regarding the type of procedure, length of hospital stay, estimated blood loss, rate of vascular resection, perioperative morbidity or incidence and site of recurrence. Patients receiving NT had longer operations (median 7.5hours vs. 6.5hours, p=0.049), a higher 30-day readmission rate (31.1% vs. 10.9%, p=0.008), a higher 90-day mortality rate (8.1% vs. 0%, p=0.056), and a lower adjuvant treatment delivery rate (50% vs. 78.1%, p=0.001).

Univariate and multivariate analyses of overall survival and progression-free survival

The median follow-up was 42.2 months (IQR 32.9mo-65.0mo) for the entire cohort. Patients receiving NT had longer OS and PFS (Supplemental Table 2).

Patients receiving NT had a median OS of 35.8 months (IQR 16.9mo-78.2mo), with 1, 3, and 5-year survival rates of 93.1%, 48.0%, 31.3%, respectively. In the UR group, the median OS was 27.8 months (IQR 14.8mo-35.9mo) with 1, 3, and 5-year survival rates of 81.0%, 24.3%, 15.5%, respectively (p=0.013). Patients receiving NT exhibited a PFS of 23.3 months (IQR 13.1mo-33.8mo), with a 1 and 3-year disease progression-free rates of 82.4%, and 23.1%, respectively. In the UR group, the median PFS was 17.3 months (IQR 8.1mo-27.4mo), with a 1 and 3-year disease progression-free rate of 58.9% and 14.1%, respectively (p=0.027). The OS and PFS K-M curves stratified by receipt of NT (NT vs. UR) are shown in Figures 2a and b, respectively.

The relationship between relevant clinical variables and OS/PFS is reported in Table 3. Since the assignment of patients in NT vs. UR groups occurred at diagnosis, only R status and clinically relevant variables available at diagnosis were considered. On univariate analysis, NT (HR=0.59, 95%, CI: 0. 0.39-0.90, p=0.013), CA19-9>100 at diagnosis (HR=1.96, 95%CI 1.26-3.07, p=0.003) and R0 (HR=0.41, 95%CI 0.27-0.63, p<0.001) were associated with OS. When R status was not adjusted for, NT (HR=0.59, 95%CI 0.36-0.98, p=0.046), and CA19-9 >100 at diagnosis (HR=2.00, 95%CI 1.26-3.19, p=0.003) were independent prognostic factors of OS. When adjusted for R status, NT

(HR=0.74, 95%CI0.44-1.26, p=0.269) was no longer associated with an improved OS. In contrast, R0 (HR=0.43, 95%CI0.26-0.70, p<0.001) was strongly associated with prolonged OS. CA19-9>100 at diagnosis remained an independent prognostic factor of OS (HR=2.08, 95%CI 1.29-3.36, p=0.003).

With regards to PFS, univariate analysis revealed that NT (HR=0.63, 95%CI 0.42-0.95, p=0.027), CA19-9>100 at diagnosis (HR=1.69, 95%CI 1.10-2.58, p=0.015), and R0 status (HR=0.40, 95%CI 0.27-0.61, p<0.001) were associated with improved PFS. When the model was not adjusted for R status, NT (HR=0.62, 95%CI 0.39-0.98, p=0.040) and CA19-9>100 at diagnosis (HR=1.74, 95%CI 1.14-2.66, p=0.010) were independent prognostic factor for PFS. When adjusted for R status, NT was not independently associated with PFS (HR=0.76, 95%CI 0.47-1.22, p=0.252), while R0 was a strong and independent predictor (HR=0.40, 95%CI 0.26-0.63, p<0.001) for improved PFS. CA19-9>100 at diagnosis (HR= 1.85, 95%CI 1.20-2.86, p=0.005) remained an independent prognostic factor of PFS.

Subgroup analysis stratified by R status

Interaction between NT and R status was assessed for OS (p=0.335) and PFS (p=0.790), indicating absence of an effect modification. To further verify this, patients were stratified according to R status into 2 subgroups: R0 and R1. The clinicopathologic characteristics, OS/PFS of patients stratified by receipt of NT (NT vs. UR) are presented in Supplemental Tables 3-6. In the R0 subgroup, there were 28 patients undergoing UR and 51 who had NT.

For the R0 subgroup patients, no factors were associated with OS/PFS on univariable analysis. On multivariable analysis, CA19-9>100 at diagnosis (HR=2.30, 95%CI 1.10-4.84, p=0.027) was associated with poor OS (Table 4).

The R1 subgroup was composed of 36 patients who had UR and 23 patients who received NT. For this subgroup, CA19-9>100 at diagnosis (HR=2.04, 95%CI 1.12-3.72, p=0.020) was associated with decreased OS on univariable analysis, while ASA III/IV (HR=2.12, 95%CI 1.02-4.42, p=0.044), and CA19-9>100 at diagnosis (HR=2.82, 95%CI 1.29-6.08, p=0.009) were associated with decreased OS on multivariable analysis. No factor was associated with PFS on univariable or multivariable analysis (Table 5). NT was not associated with increased OS/PFS in either subgroup on either univariable or multivariable analysis. The adjusted OS/PFS K-M curves stratified by NT vs. UR for the R0/R1 subgroups are shown in Figures 2c-f.

DISCUSSION

Neoadjuvant treatment has dramatically revolutionized the landscape for the management of BR-PDAC.(9, 11, 14, 24, 27) As confirmed by the results of this study, significantly higher R0 resection rates and tumor down-staging were achieved for patients with BR-PDAC receiving NT as compared to those undergoing UR. NT was also found to be an independent predictor for improved OS and PFS. However, when adjusting for R status, NT was not independently predictive of improved OS or PFS. In a subgroup analysis stratified by R status, NT was also not associated with either a

prolonged OS or PFS. These results suggest that the prognostic impact of R status outweighs that of NT. Based on these findings, achieving tumor-free resection margins should remain the primary goal of the surgical treatment of BR-PDAC irrespective of NT.(1, 3-7, 34)

Previous studies have identified R1 not to be an adverse prognostic indicator, therefore questioning the absolute necessity of performing an R0 resection, especially in the NT setting.(19-23) In our analysis, NT was not independently associated with either a prolonged OS or PFS in R0 or R1 subgroups. These suggested that if an R0 resection can be achieved by UR, they may not further benefit from NT, and that there are no additional benefits of receiving NT if an R1 resection can't be subsequently achieved. The effect of NT was predominately mediated through its ability to facilitate R0 resection. A more careful surgical judgment is necessary to treat patients with BR-PDAC receiving NT if an R0 is deemed difficult to be achieved.

Several hypotheses regarding the potential additional benefits of NT have been previously proposed, including the enhancement of local control of disease and eliminating microscopic systemic disease;(8, 17) however none of these have been conclusively demonstrated. As suggested by our results, NT primarily benefits the patients in whom an R0 resection would be impossible with UR. Therefore our findings question the benefit of extending NT to all patients including those in whom an R0 resection is likely to be achieved with UR. In a review of selected studies of patients with resectable PDAC who received NT, metastatic disease was identified in 14% at restaging, and 18- 42% of patients had unexpected metastases at the time of the

operation.(12-14) Some patients after receiving NT would still be excluded due to poor physical performance, even without having disease progression.(12-14) Therefore, further efforts to accurately identify the patients in whom an R0 resection could be achieved without receiving NT could be beneficial. (9, 14, 15) Unfortunately, the current AHPBA/SSAO/SSO Consensus guidelines fail to identify this group of patients. The current study revealed a 43.8% R0 resection rate with UR, which is comparable with previously reported R0 resection rates in resectable patients.(3, 5) In addition, it must be noted that among patients without vascular involvement on imaging, there is a significant incidence of positive margins that could be reduced by NT.(12-14) These findings likely suggested that factors combined with vascular involvement may better predict an R0 resection(18). A classification system for resectablity based on multiple factors rather than vascular involvement alone is needed to better guide the treatment of PDAC.(8, 9) Nonetheless, it remains a possibility that we were underpowered to detect the additional benefit of NT in patients receiving R0. As in the R0 subgroup analysis, the HR was lower than 1, although insignificant. Further study would be necessary to verify this conclusion.

Our results also demonstrate that R0 status is a robust prognostic factor for improved OS and PFS;(3, 5, 7, 14, 22, 35) whose effect outweighs the impact of NT. Nevertheless, previous reports have demonstrated otherwise, probably due to a different definition of R0 resection, which included a margin smaller than 1mm(20, 22, 23). A more recent study, which adopted R0 margins wider than 1mm, concluded that R status is not an independent risk factor for survival.(21) One possible explanation for this is their

inclusion of patients with metastatic disease(19). If metastases occur prior to resection, the impact of R status is intuitively attenuated. Another potential explanation is that multivariate analysis only included statistically significant factors on univariate variables irrespective of clinical relevance. Clinically relevant factors, as suggested by previous studies, need to be included regardless of their p value to identify indepandent prognotisc factors.(19, 21, 31-33). In this paper, R status was associated with arterial/venous infiltration and N stage, which were independent prognostic factors. It is possile that vascular infiltration and positive lymph nodes predicted R status, which in turn predict prognosis(19).

Also consistently with previous findings,(36-38) CA19-9>100 at diagnosis was an independent predictor for poor OS and PFS in patients with BR-PDAC. In the subgroup analysis of R1 patients, advanced ASA class (III/IV) was an independent prognostic factor for OS. Patients with poor physical performance are more vulnerable to disease progression,(39) which is likely more rapid and frequent in the R1 subgroup. Pertinent literature suggests that up to 38% of patients with PDAC having a UR fail to receive adjuvant therapy due to an increased postoperative morbidity.(14) In our cohort, similarly, adjuvant therapy was not administered in 16 (21.9%) patients undergoing UR. Previous studies demonstrated lower morbidity and mortality rates after NT,(24) while in contrast, others reported increased complications.(40) We found that NT was associated with a significantly increased 30-day readmission rate, but not significantly higher 90-day mortality rates (p=0.056).

The current study has important strengths. First, previous studies investigating the impact of NT have used a mixed cohort of BR and LA patients to compare patients with PDAC receiving NT vs. UR.,(14-16, 24, 25) Our cohort consisted of exclusively BR-PDAC patients, therefore being more homogenous. Second, as aforementioned, instead of establishing a multivariable model based on the statistical significance in univariable analysis(21), the variables included in our models were predefined, accounting for clinical relevance. This method of variable selection is the most recommended to accurately identify independent prognostic factors.(31-33) Third, most retrospective studies investigating prognostic factors in patients with BR-PDAC have violated the intention-to-treat analysis by excluding unresected disease, consequently resulting in analyses that are conditional on tumor removal and still mixed of R1 and R0 patients.(9, 11, 14, 24, 26, 27, 41, 42) In contrast, we have clearly defined R0 as >1mm tumor free margin and performed a subgroup analysis, based on R status.

The limitations of our study include its retrospective nature, small sample sizes, and single-center design. However, this is to date one of the largest cohorts exclusively analyzing the impact of NT for patients with BR-PDAC using comparable groups of patients treated with NT and UR. In addition, there could be bias due to increasing preference for NT to treat patients with BR-PDAC over the past decade, which mirrors national trends. Our study included a cohort of patients with BR-PDAC treated between 2008 and 2018, as defined by the AHPBA/SSAO/SSO consensus guidelines, meticulously by reviewing radiology reports at initial diagnosis.(8) This consensus was adopted because it is currently used as criteria for administrating NT in our institution and also

most of institutions nationally and internationally(9). Therefore, in this cohort, all patients were theoretically candidates for NT, but 64 underwent UR and 74 had NT. This discrepancy was primarily due to the continuous evolution of treatment guidelines, demonstrating an increasing preference trend to use NT.(8, 9, 14) Given that the use of NT depend on various factors including venous or arterial involvement, CA19-9 levels and tumor size, all of these factors were included in our multivariable analysis. Patients with smaller tumors merely abutting the PV/SMV would not usually receive NT under prior guidelines but are considered to be suitable candidates for NT according to the most updated criteria. For these reasons, in this current cohort, patients receiving NT were more likely to have larger tumors and arterial involvement. Although different regimens of NT were adopted, most patients received FOLFIRINOX, which is the treatment currently recommended(14-16, 21, 24, 25). For subgroup analysis, our conclusion may have been limited due to smaller sample size but was consistent with the overall conclusion based on the entire cohort. Further studies would be necessary to verify these results.

CONCLUSIONS

This single-center study is one of the largest analyses identifying prognostic factors, exclusively for patients with a BR-PDAC undergoing resection. It is also the first study to stratify patients based on R status. Our data provide strong evidence that NT is independently associated with improved OS and PFS in patients with BR-PDAC, however this effect is outweighed by R status. R0 and R1 subgroup analyses revealed

that NT is not associated with improved OS or PFS. These results suggest that the benefit of NT is primarily mediated by its ability to facilitate an R0>1mm resection. While UR remains a valid treatment option if R0>1mm resection could be accurately predicted. Future research efforts should aim to address the challenging task to accurately identify such patients preoperatively.

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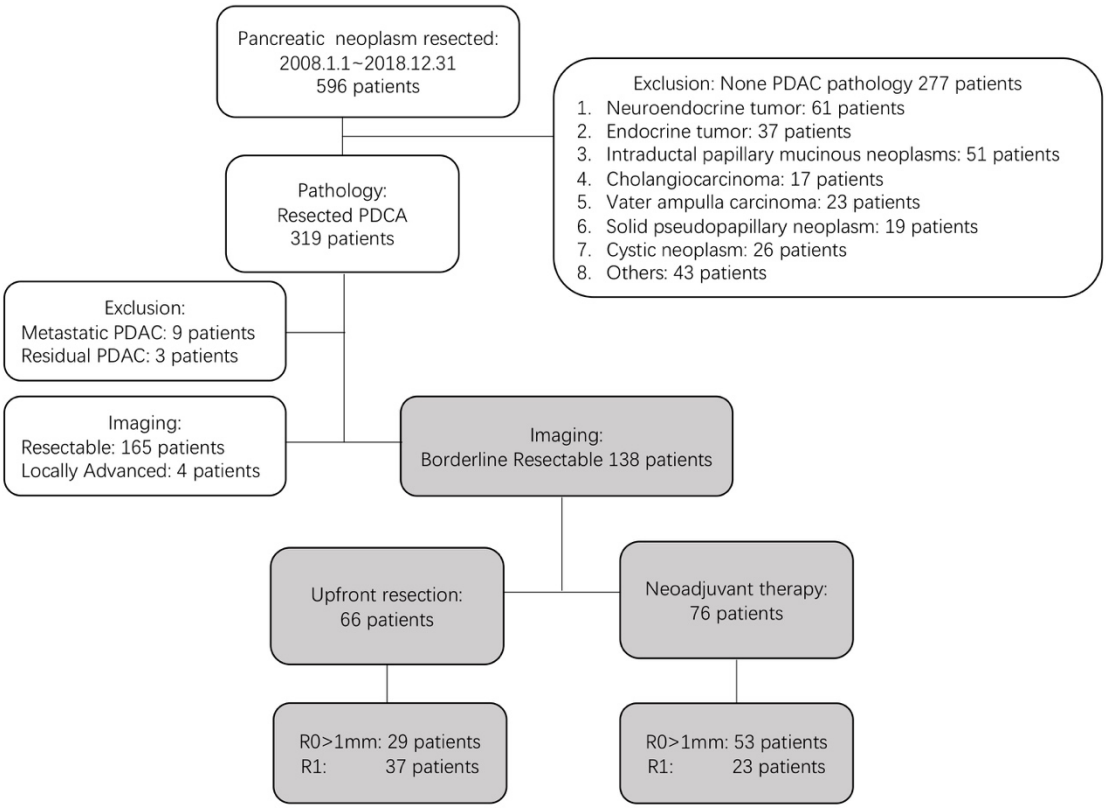

FIGURE 1. Study profile.

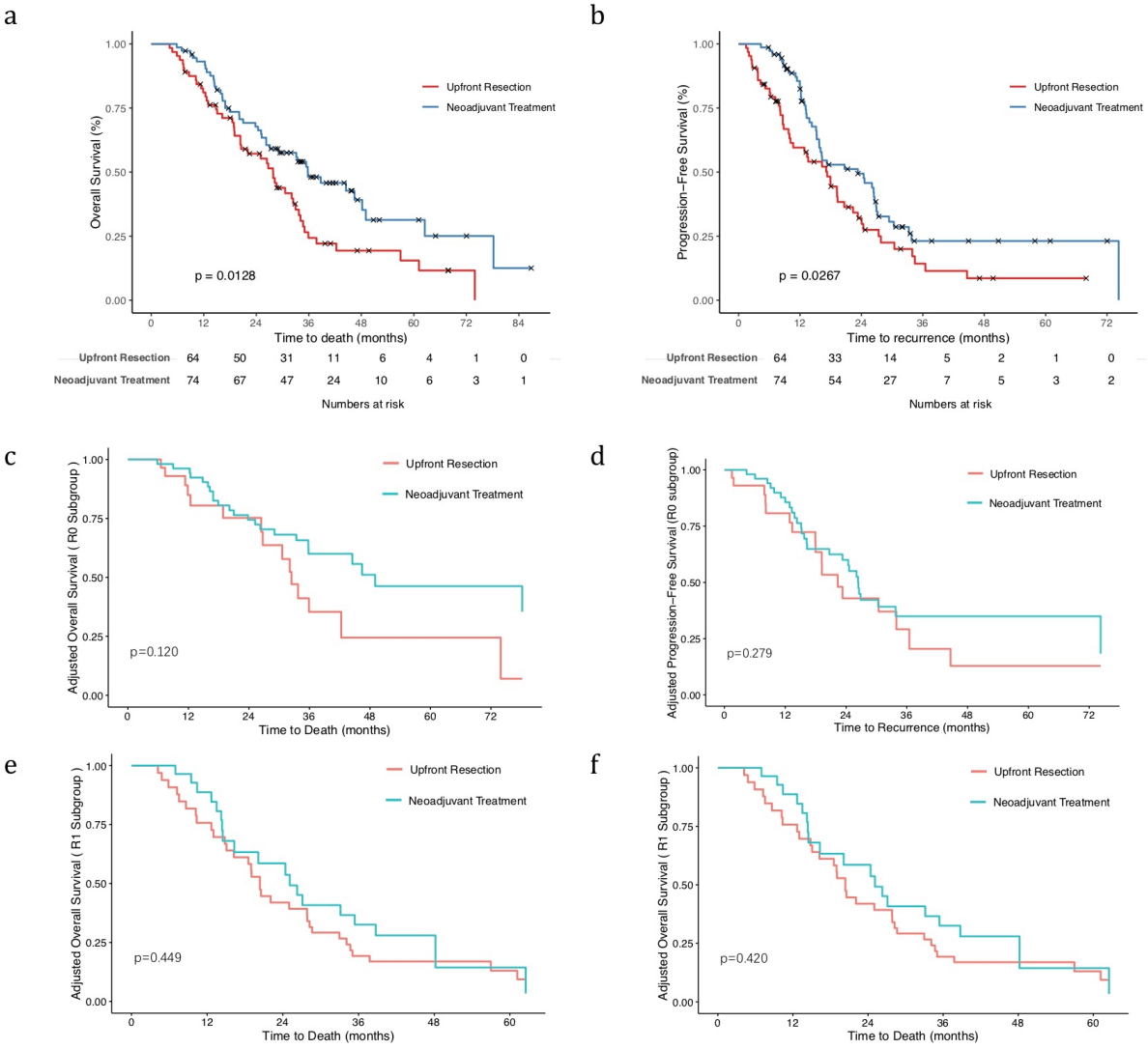

FIGURE2. Survival after diagnosis.(a) Overall survival in the entire cohort ;(b)progression-free survival in the entire cohort; (c) adjusted overall survival in the R0>1mm subgroup ;(d)adjusted progression-free survival in the R0>1mm subgroup; (e) adjusted overall survival in the R1 subgroup ;(f)adjusted progression-free survival in the R1 subgroup;

TABLE 1. Patient Characteristics at diagnosis and reassessment before surgery

		Upfront Resection (64)	Neoadjuvant Treatment(74)	P
Male,N(%)		32 (50.0)	34 (45.9)	0.761
Age in years , median (IQR)		68 (63-75)	66 (60-72)	0.217
Race,N(%)	Caucasian	59 (92.2)	69 (93.2)	0.996
	Others	5 (7.8)	2 (6.8)	
BMI, median (IQR)		24.8 (22.5-29.0)	25.4 (23.2-29.2)	0.547
ASA classification, ,N(%)	I/II	33 (52.6)	29 (39.2)	0.199
	III/IV	31 (48.4)	45 (60.8)	
ECOG≥1, N(%)		35 (54.7)	36 (48.6)	0.591
CA19-9 at diagnosis, u/ml, median (IQR)		164(65-440)	167(30-645)	0.573
CA19-9 at resection, u/ml, median (IQR)		166(66-453)	43(15-138)	<0.001
Tumor location ,N(%)	Head/Uncinate	58 (90.6)	66 (89.2)	1
	Neck/Body/Tail	6 (9.4)	8 (10.9)	
Tumor size: imaging at diagnosis, median (IQR)		2.9 (2.3-3.2)	3.1 (2.5-3.8)	0.017
Tumor size: imaging at resection, median (IQR)		2.9(2.2-3.0)	2.5(1.9-3.2)	0.152
Venous involvement ,N(%)		62 (96.9)	71 (95.9)	1
SMV/PV		60 (93.8)	71 (95.9)	
IVC		2 (3.0)	1 (1.4)	
Arterial involvement ,N(%)		8 (12.5)	25 (33.8)	0.006
SMA		7 (10.9)	20 (27.0)	
CHA		1 (1.6)	5 (6.8)	
Diagnosis to resection, month, median (IQR)		1.0 (0.6-1.6)	6.6 (4.9-8.2)	<0.001

ASA, American Society of Anesthesiologists, ECOG, Eastern Cooperative Oncology Group, BMI, body mass index; CA19–9, carbohydrate antigen 19–9; HA, hepatic artery; IVC, inferior vena cava; PV, portal vein; SD, standard deviation; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

TABLE 2 .Histopathology and Postoperative Data

		Upfront Resection(66)	Neoadjuvant Treatment(76)	P
Negative Resection Margin >1mm		28 (43.8)	51 (68.9)	0.005
Pathological tumor size		3.0 (2.5-4.0)	2.6 (2.0-3.4)	0.003
Total retrieved lymph nodes, median (IQR)		16 (11-22)	15 (11-20)	0.749
Positive lymph nodes, median (IQR)		2 (1-4)	0 (0-1)	<0.001
AJCC stage (8th revised edition), N(%)	0	0 (0.0)	5 (6.8)	<0.001
	Ia	2 (3.1)	15 (20.3)	
	Ib	7 (10.9)	21 (28.4)	
	IIa	5 (7.8)	3 (4.1)	
	IIb	21 (32.8)	11 (14.9)	
	III	29 (45.3)	19 (25.7)	
Lymphovascular invasion, N(%)		33 (51.6)	22 (29.7)	0.015
Perineural invasion, N(%)		54 (84.4)	45 (60.8)	0.004
Type of operation, N (%)	Whipple	56 (87.5)	67 (90.5)	0.907
	Distal	6 (9.4)	5 (6.8)	
	Total/Subtotal	2 (3.1)	2 (2.7)	
Vascular Resection*,N(%)		18 (28.1)	24 (32.4)	0.717
Estimated Blood Loss, Median (IQR)		350 (250-500)	400 (250-700)	0.302
Operative duration, hours, Median (IQR)		6.5 (6-8)	7.5 (6-9.2)	0.049
Length of Stay, days, Median (IQR)		9 (7-11)	8 (7-10)	0.136
In-hospital Clavien-Dindo≥3b Complication		3 (4.7)	5 (6.8)	0.878
Thirty-day readmission, N (%)		7 (10.9)	23 (31.1)	0.008
Ninety-day mortality, N (%)		0 (0.0)	6 (8.1)	0.056
Adjuvant treatment, N(%)		50 (78.1)	37 (50.0)	0.001
Recurrence, N (%)		47 (73.4)	46 (62.2)	0.220
Local		17 (26.6)	27 (36.5)	
Liver		15 (23.4)	12 (16.2)	
Lung		9 (14.1)	9 (12.2)	
Multiple site		2 (3.1)	4 (5.4)	

AJCC, American Joint Committee on Cancer, *Celiac artery, hepatic artery, superior mesenteric artery/vein, portal vein, inferior vena cava.

Table 3 Univariable and multivariable analysis of overall survival and progression-free survival

	Overall Survival						Progression-free Survival					
	Univariate		Model without R		Model with R		Univariate		Model without R		Model with R	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	P	HR(95%CI)	p
Neoadjuvant treatment	0.59(0.39-0.90)	0.013	0.59(0.36-0.98)	0.046	0.74(0.44-1.26)	0.269	0.63(0.42-0.95)	0.027	0.62(0.39-0.98)	0.040	0.76(0.47-1.22)	0.252
Age >70	1.11(0.73-1.76)	0.586	0.99(0.62-1.57)	0.962	1.11(0.69-1.77)	0.669						
BMI >30	0.77(0.42-1.42)	0.403	0.73(0.38-1.37)	0.326	0.77(0.40-1.47)	0.427						
ASA III/IV	0.97(0.64-1.48)	0.901	0.92(0.56-1.49)	0.721	1.21(0.72-2.03)	0.474						
ECOG ≥1	1.14(0.75-1.73)	0.547	1.23(0.75-2.04)	0.415	1.06(0.63-1.77)	0.838						
Venous invasion	1.28(0.40-4.06)	0.674	0.98(0.27-3.60)	0.971	0.83(0.22-3.13)	0.788	0.77(0.28-2.09)	0.604	0.79(0.26-2.43)	0.683	0.60(0.19-1.84)	0.369
Arterial invasion	0.75(0.45-1.27)	0.288	0.88(0.48-1.63)	0.689	0.95(0.50-1.78)	0.866	1.00(0.61-1.63)	0.995	1.22(0.69-2.16)	0.491	1.24(0.69-2.21)	0.474
CA19-9 >100	1.96(1.26-3.07)	0.003	2.00(1.26-3.19)	0.003	2.08(1.29-3.36)	0.003	1.69(1.10-2.58)	0.015	1.74(1.14-2.66)	0.010	1.85(1.20-2.86)	0.005
Tumor size >30mm	0.86(0.55-1.30)	0.445	1.09(0.66-1.79)	0.735	1.12(0.69-1.83)	0.643	0.77(0.50-1.18)	0.237	0.87(0.54-1.41)	0.584	0.93(0.58-1.51)	0.778
Tumor location: Head	1.84(0.85-4.00)	0.122	1.68(0.76-3.70)	0.199	1.44(0.69-3.20)	0.371	1.04(0.55-1.95)	0.906	1.02(0.54-1.93)	0.955	0.86(0.45-1.65)	0.652
R0>1mm	0.41(0.27-0.63)	<0.001			0.43(0.26-0.70)	<0.001	0.40(0.27-0.61)	<0.001			0.40(0.26-0.63)	<0.001

ASA, American Society of Anesthesiologists, ECOG, Eastern Cooperative Oncology Group, BMI, body mass index; CA19–9, carbohydrate antigen 19–9

Table 4 Univariable and multivariable analysis of overall survival and progression-free survival in R0- subgroup

	Overall Survival				Progression-free Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
Neoadjuvant treatment	0.58(0.30-1.12)	0.104	0.52(0.22-1.19)	0.120	0.72(0.39-1.32)	0.288	0.69(0.36-1.35)	0.279
Age >70	0.94(0.46-1.90)	0.859	0.64(0.29-1.43)	0.278				
BMI >30	0.78(0.33-1.89)	0.589	0.80(0.31-2.07)	0.641				
ASA III/IV	0.96(0.50-1.84)	0.900	0.62(0.28-1.35)	0.226				
ECOG ≥1	1.52(0.79-2.92)	0.213	1.97(0.88-4.42)	0.100				
Venous invasion	0.95(0.23-3.96)	0.941	0.74(0.13-4.32)	0.735	0.94(0.23-3.90)	0.930	0.93(0.19-4.65)	0.930
Arterial invasion	0.76(0.36-1.61)	0.468	0.68(0.28-1.66)	0.397	1.05(0.53-2.09)	0.883	1.16(0.53-2.54)	0.712
CA19-9 >100	1.93(0.97-3.86)	0.061	2.30(1.10-4.84)	0.027	1.76(0.95-3.25)	0.073	1.79(0.95-3.35)	0.070
Tumor size >30mm	1.00(0.53-1.94)	0.979	1.25(0.56-2.79)	0.592	0.95(0.52-1.73)	0.861	0.97(0.49-1.93)	0.928
Tumor location: Head	2.19(0.67-7.17)	0.194	1.79(0.52-6.16)	0.354	0.92(041-2.07)	0.841	0.95(0.42-2.19)	0.911

ASA, American Society of Anesthesiologists, ECOG, Eastern Cooperative Oncology Group, BMI, body mass index; CA19–9, carbohydrate antigen 19–9

Table 5 Univariable and multivariable analysis of overall survival and progression-free survival in R1 subgroup

	Overall Survival				Progression-free Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
Neoadjuvant treatment	0.92(0.52-1.63)	0.777	0.76(0.37-1.55)	0.449	0.81(0.44-1.46)	0.474	0.75(0.36-1.52)	0.420
Age >70	1.29(0.72-2.28)	0.393	1.77(0.94-3.35)	0.080				
BMI >30	0.90(0.38-2.11)	0.805	0.73(0.24-2.24)	0.578				
ASA III/IV	1.39(0.80-2.42)	0.244	2.12(1.02-4.42)	0.044				
ECOG ≥1	0.77(0.44-1.35)	0.361	0.64(0.30-1.36)	0.244				
Venous invasion	1.89(0.26-13.81)	0.529	1.44(0.11-18.4)	0.780	0.40(0.09-1.70)	0.215	0.28(0.05-1.44)	0.127
Arterial invasion	0.86(0.42-1.78)	0.682	1.52(0.58-3.99)	0.396	1.12(0.55-2.27)	0.760	1.46(0.59-3.61)	0.408
CA19-9 >100	2.04(1.12-3.72)	0.020	2.82(1.29-6.08)	0.009	1.64(0.91-2.96)	0.099	1.88(0.96-3.68)	0.068
Tumor size >30mm	0.97(0.546-1.76)	0.926	1.21(0.60-2.44)	0.588	0.74(0.39-1.41)	0.361	0.80(0.38-1.71)	0.570
Tumor location: Head	1.22(0.43-3.43)	0.708	0.73(0.24-2.23)	0.585	0.94(0.32-2.68)	0.908	0.74(0.24-2.31)	0.607

ASA, American Society of Anesthesiologists, ECOG, Eastern Cooperative Oncology Group, BMI, body mass index; CA19–9, carbohydrate antigen 19–9

SUPPLEMENTAL TABLES-paper 1

Supplemental Table 1 Neoadjuvant treatment information

		Neoadjuvant treatment before resection(N=74)
Neoadjuvant Chemotherapy, N(%)		69 (93.2)
Neoadjuvant Chemotherapy Regimen, N(%)		
FOLFIRINOX -based		54 (72.9)
Gemcitabine-based		11 (14.9)
Others		4 (5.4)
Neoadjuvant Radiotherapy, N(%)		37 (50.0)
RECIST, N(%)	Stable	31 (41.9)
	Partial	41 (55.4)
	Complete	2 (2.7)
Pathological tumor regression, N(%)	Minimal	46 (62.2)
	Moderate	23 (31.1)
	Complete	5 (6.8)

Supplemental Table 2 Survival by upfront resection and neoadjuvant treatment before resection

	Total (142)	Upfront Resection(66)	Neoadjuvant treatment(76)	P
OS, month [median (IQR)]	32.1(16.3-57.0)	27.8(14.8-35.9)	35.8(16.9-78.2)	0.013
PFS, month [median (IQR)]	18.0(11.1-30.4)	17.3(8.1-27.4)	23.3(13.1-33.8)	0.027

OS, overall survival; PFS, progression-free survival

Supplemental Table 3 Patient Characteristics in the R0>1mm subgroup

		Upfront Resection(28)	Neoadjuvant Treatment(51)	P
Male,N(%)		12 (42.9)	21 (41.2)	1
Age>70		12 (42.9)	13 (25.5)	0.182
Race-whtie,N(%)		24 (85.7)	48 (94.1)	0.399
ASA satge, ,N(%)	I/II	13 (46.2)	17 (33.3)	0.366
	III/IV	15 (53.6)	34 (66.7)	
ECOG≥1, N(%)		15 (53.6)	25 (49.0)	0.879
BMI at diagnosis>30 ,N(%)		5 (17.9)	10 (19.6)	1
CA19-9 >100u/ml at diagnosis, N(%)		16 (57.1)	28 (54.9)	1
Head/Uncinate Tumor		26 (92.9)	44 (86.3)	0.610
Tumor size at diagnosis>3cm,N(%)		9 (32.1)	28 (54.9)	0.088
Vein involvement ,N(%)		27 (96.4)	49 (96.1)	1
Artery involvement ,N(%)		5 (17.9)	16 (31.4)	0.301
In hospital CD≥3b Complication		1 (3.6)	2 (3.9)	1
Thirty-day readmission, N (%)		3 (10.7)	14 (27.5)	0.148
Ninety-day mortality, N (%)		0 (0.0)	2 (3.9)	0.754
Adjuvant treatment, N(%)		22 (78.6)	27 (52.9)	0.045
Recurrecne, N (%)		17 (60.7)	28 (54.9)	0.794

ASA, American Society of Anesthesiologists, ECOG, Eastern Cooperative Oncology Group, BMI, body mass index; CA19–9, carbohydrate antigen 19–9

Supplemental Table 4 Survival by upfront resection and neoadjuvant treatment before resection in R0>1mm subgroup

	Total (82)	Upfront Resection(29)	Neoadjuvant treatment(53)	P
OS, mo [median (IQR)]	42.3(23.8-73.9)	32.4(26.4-42.3)	46.4(23.8-78.2)	0.104
PFS, mo [median (IQR)]	26.1(14.3-44.6)	22.4(13.4-36.5)	26.4(15.1-74.3)	0.288

OS, overall survival; PFS, progression-free survival

Supplemental Table 5 Patient Characteristics in the R1 subgroup

		Upfront Resection(36)	Neoadjuvant Treatment(23)	P
Male,N(%)		20 (55.6)	13 (56.5)	1
Age>70		15 (41.7)	7 (30.4)	0.688
Race-whtie,N(%)		35 (97.2)	21 (91.3)	0.423
ASA satge, ,N(%)	I/II	20 (55.6)	12 (52.2)	1
	III/IV	16 (44.4)	11 (47.8)	
ECOG≥1, N(%)		20 (55.6)	11 (47.8)	0.755
BMI at diagnosis>30 ,N(%)		6 (16.7)	1 (4.3)	0.31
CA19-9 >100u/ml at diagnosis, N(%)		23 (63.9)	13 (56.5)	0.770
Head/Uncinate Tumor site		32 (88.9)	22 (95.7)	0.667
Tumor size at diagnosis>3cm,N(%)		8 (22.2)	12 (52.2)	0.037
Vein involvement ,N(%)		35 (97.2)	22 (95.7)	1
Artery involvement ,N(%)		3 (8.3)	9 (39.1)	0.011
In hospital CD≥3b Complication		2 (5.6)	3 (13.0)	0.598
Thirty-day readmission, N (%)		4 (11.1)	9 (39.1)	0.027
Ninety-day mortality, N (%)		0 (0.0)	4 (17.4)	0.039
Adjuvant treatment, N(%)		28 (77.8)	10 (43.5)	0.016
Recurrecne, N (%)		30 (83.3)	18 (78.3)	0.885

ASA, American Society of Anesthesiologists, ECOG, Eastern Cooperative Oncology Group, BMI, body mass index; CA19–9, carbohydrate antigen 19–9

Supplemental Table 6 Survival by upfront resection and neoadjuvant treatment before resection in R1 subgroup

	Total (60)	Upfront Resection(37)	Neoadjuvant Treatment(23)	P
OS, mo [median (IQR)]	22.1(13.5-35.0)	20.5(12.8-34.1)	25.1(14.2-38.7)	0.777
PFS, mo [median (IQR)]	12.3(8.6-20.6)	9.9(5.2-20.6)	13.2(12.2-26.9)	0.474

OS, overall survival; PFS, progression-free survival

Project 2

Temporal Assessment of Prognostic Factors in Patients with Pancreatic Ductal Adenocarcinoma Undergoing Neoadjuvant Treatment and Resection

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W.R. and D.X. collected, analyzed, interpreted the data prepared the figures, tables and wrote the article. T.C., S.A., and W.R. designed the study. T.C. and S.A. conceptualized the study, supervised the project, and revised the article. All authors vouch for the respective data and analysis and have approved the final version and agreed to publish the article.

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Abbreviated title: neoadjuvant treated pancreatic cancer

ABSTRACT:

Background: The clinicopathologic factors associated with the survival of patients with pancreatic ductal adenocarcinoma (PDAC) during the different phases of neoadjuvant treatment (NT)--at diagnosis, restaging or postoperatively--remain unclear.

Methods: Data of patients with PDAC who underwent pancreatic resection after NT between 2008 and 2018 were retrospectively collected. Clinicopathological characteristics and outcomes were compared stratified by resection margin status. Three multivariable regression models (at diagnosis, restaging, and postoperatively) were constructed to assess the temporal impact of different prognostic factors on all-cause survival (ACS) and disease-free survival (DFS).

Results: All patients were diagnosed with a non-metastatic PDAC and were appropriate candidates for NT according to the current NCCN guidelines. From a total of 83 patients, 57 (68.7%) had a negative resection margin >1 mm (R0>1mm) while 26 (31.3%) patients had a positive resection margin (R1). At diagnosis, tumor location (head, HR=3.84, 95%CI 1.06-13.93, p=0.041) and CA19-9>100u/ml (HR=2.03, 95%CI 1.04-3.97, p=0.039) were independent prognostic factors of decreased ACS. At restaging, FOLFIRINOX (HR=0.45, 95%CI 0.22-0.94,p=0.033) and tumor size>30mm (HR=2.10, 95%CI 1.02-4.32, p=0.044) were independent prognostic factors for increased and decreased ACS, respectively. Postoperatively, R0>1mm was an independent prognostic factor for improved ACS(HR=0.30, 95%CI0.14-0.66, p=0.003) and DFS(HR=0.31, 95%CI 0.14-0.68, p=0.003), while adjuvant therapy (HR=0.35,

95%CI0.16-0.74, p=0.006) was associated with increased ACS. Lymph node involvement (HR=3.14, 95%CI 1.27-7.78, p=0.014) was associated with decreased DFS.

Conclusion: At diagnosis, restaging, and postoperatively, different, relevant clinicopathological factors significantly impact the survival of patients with non-metastatic PDAC undergoing NT and resection. An R0>1mm resection remains the most important prognostic factor and therefore should be the primary goal of surgical treatment in the neoadjuvant setting.

KEY WORDS: neoadjuvant treatment; pancreatic ductal adenocarcinoma; margin negative resection; prognostic factor

INTRODUCTION:

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with high rates of disease-specific mortality.(1, 2)For patients with PDAC, tumor resection remains the only potential curative intervention.(1-3) Approximately half of these patients present with metastases at the time of diagnosis and consequently, they are only candidates for palliative treatment.(3) Among those with non-metastatic disease, risk factors such as involvement of the adjacent vasculature, large tumor size or lymph node involvement, make upfront negative margin resection (R0) challenging.(4-11) Supported by a growing body of evidence, neoadjuvant treatment (NT) has been proven to increase the prospect of achieving an R0 resection with a significant survival benefit.(6, 12-21) NT is now recommended by the National Comprehensive Cancer Network (NCCN) guidelines for patients with PDAC with high-risk features.(11)

Although clinicopathological prognostic factors are well documented for patients with PDAC undergoing upfront resection, they are less well-defined for patients receiving NT.(12, 16) Although a resection margin of at least 1 mm (R0>1mm) is associated with improved survival in patients undergoing upfront resection,(7-10) its significance for those undergoing NT has not been fully validated (6, 22). In our recent work, we compared the survival of patients with borderline resectable PDAC receiving NT followed by surgery versus patients who underwent upfront resection. We found that the impact of R0>1mm resection on survival outweighed that of NT. Given that the treatment choice for these patients, NT vs. upfront resection, is made at diagnosis, our

previous analysis included only factors at that time. Similarly, survival was calculated from the time of diagnosis until the time of death.

In the neoadjuvant setting, it seems possible that specific clinicopathological variables influencing survival may change at different time points, such as restaging and postoperatively. Factors such as tumor size, carbohydrate antigen 19-9 (CA 19–9), and/or vascular involvement could be modified as a result of the NT. A recent study analyzing the prognosis of patients with PDAC undergoing NT, merged pathologic variables at diagnosis, restaging and post-operation and assessed survival from the time of resection.(6) These authors concluded that R0>1mm was not an independent prognostic factor for survival after NT.(6) Similarly, other investigators suggested that pathologic factors such as lymph node involvement may outweigh the impact of resection margin (R) status on survival after NT.(10, 23) If this was verified, it would seem plausible that, as long as NT has been administered, performing an R1 resection is acceptable(24).

To examine the hypothesis that R1 resection is acceptable in the setting of NT, we set out to identify prognostic factors of patients with non-metastatic PDAC undergoing NT followed by surgery. Different factors at diagnosis, restaging and postoperatively may independently impact the survival(11). Clinicopathological factors were incorporated into three different multivariable regression models based on clinical relevance and availability of pertinent data at the different time points of interest i.e. at diagnosis, restaging and postoperatively.(25, 26)

METHODS

Data Acquisition and Study Population

After Brigham and Women's Hospital (BWH) Institutional Review Board approval, the medical records of patients undergoing a pancreatectomy between January 1, 2008, and December 30, 2018, were reviewed. According to pathology reports, diagnoses other than PDAC and patients with metastatic PDAC were excluded from analyses. Among the remaining patients, only recipients of NT were included. These patients were divided into 2 groups according to R status (R0>1mm vs. R1).

Neoadjuvant treatment

Necessity and suitability for NT were assessed at gastrointestinal oncology multidisciplinary conferences (MDC) according to NCCN guidelines(11). This tumor board is composed of a multidisciplinary team, including pancreatic surgeons, gastrointestinal radiologists, medical oncologists, gastrointestinal radiation oncologists. Over the study period, FOLFIRINOX with or without radiotherapy was the predominant NT regimen administered(4). Adjuvant treatment varied depending on the dose, treatment tolerance, and tumor response.

Study Variables

Data available at diagnosis included: age; gender; race; Eastern Cooperative Oncology Group (ECOG) scale of performance status; tumor location, body mass index (BMI); CA

19–9 level; tumor size; vascular involvement including venous, arterial, and degree of portal vein/superior mesenteric vein (PV/SMV) involvement at diagnosis; NT type; and regimen. Additional data acquired at restaging included: NT-related toxicity, American Society of Anesthesiologists (ASA) physical status classification, BMI, CA 19–9, tumor size and vascular involvement , radiological response in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, interval from diagnosis to resection, and the number of FOLFIRINOX cycles received preoperatively. Postoperative data included: pathology, type of procedure, estimated blood loss, vascular resection, operative time, length of hospital stay, Clavien-Dindo≥3b complications, readmission within 30days, mortality within 90days, and adjuvant treatment. Pathology data collected included R status, tumor size and ypT stage, tumor regression, number of resected and positive nodes and ypN stage, and lymphovascular or perineural invasion. Tumor grade was not reported due to the difficulty of interpretation after NT. R status, ypT, and ypN were reported according to the 8th revised edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC).(19) For R status, R0 was defined as a tumor-free margin greater than 1 mm (R0>1mm). Margins included the pancreatic transection margin, the bile duct margin, the vascular margins, the stomach/duodenal margins, and the circumferential soft tissue margins (medial, anterior surface, superior, and posterior).(17-19)

Outcomes

Primary outcomes were all cause survival (ACS) and disease-free survival (DFS). These were calculated from the date of operation to the date of death or documented progression (event), respectively, or to the date of the last follow-up visit (censored). The date of death was obtained either from medical record review or the Social Security Death Index. Follow-up data were obtained for all patients until June 1, 2019.

Statistical analysis

Univariable analyses were performed to compare demographics, clinicopathological variables between RO/ R1 groups. Continuous variables are presented as median and interquartile range (IQR), and compared using the Wilcoxon signed-rank test. Categorical variables are presented as numbers and percentages and compared using the Chi-square test or Fisher exact test, as appropriate. DFS and ACS are presented as median (IQR) and displayed using Kaplan–Meier (K-M) survival curves. The log-rank test was used to compare survival. Univariable and multivariable analysis models were built to identify prognostic risk factors for ACS and DFS, which were assessed by proportional hazards regression analysis. Three pre-defined models were designed, based on temporal availability at the three time points and clinical relevance suggested by previous reports. The model for ACS at diagnosis was adjusted for: ECOG (≥1 vs. 0), age (>70 vs. ≤70), tumor location (head/uncinate vs. body/tail), BMI (>30 vs. ≤30), CA19-9 (>100 vs. ≤100u/ml), tumor size (>30mm vs. ≤30mm), venous invasion, PV/SMV involvement ≥180°, arterial involvement at diagnosis, regimen of neoadjuvant chemotherapy (FOLFIRINOX vs. other) and neoadjuvant radiotherapy. The restaging

model for ACS was adjusted for: ECOG, age, tumor location, BMI, CA19-9, tumor size, venous invasion, PV/SMV involvement ≥180°, arterial invasion at restaging, FOLFIRINOX regimen, neoadjuvant radiotherapy, ASA score (III/IV vs. I/II), and RECIST response (complete/partial vs. stable/progressive). The postoperative model for ACS was adjusted for: R status (R0>1mm vs. R1), ECOG, age, FOLFIRINOX regimen, neoadjuvant radiotherapy, ASA score, BMI, CA19-9 at restaging, type of operation (pancreaticoduodenectomy vs. other), vascular resection, pathology size (>25mm vs. ≤25mm), histopathologic regression (moderate/complete vs. minimal), lymph node involvement (positive lymph node≥1 vs. 0), lymphovascular and perineural invasion, and adjuvant treatment. Due to the lack of clinical relevance for recurrence, ECOG, age, BMI, and ASA were not included in the models of DFS. Hazard ratio (HR), 95% confidence interval (CI) and p-values were presented for all variables included in the models (27). To account for variation in chemotherapy regimens, sensitivity analysis included only patients treated with FOLFIRINOX (n=60). A $p< 0.05$ was considered statistically significant. Statistical computations were performed using R-Studio.Inc. Version 1.1.456.

RESULTS

Patient Cohort and Neoadjuvant Treatment Groups

A flowchart with all patients included in this study is shown in Figure 1. Within the studied period 596 patients received a pancreatectomy. A total of 289 patients were excluded because of pathology other than PDAC, or a diagnosis of metastatic PDAC.

Among the remaining 307 patients with resected PDAC, 83 received NT, and this constituted the final study population. Of these 83 patients, 57(68.7%) had an R0>1mm resection and 26(31.3%) patients had an R1 resection.

At both diagnosis and restaging, no significant differences were found between the R0 and R1 groups with respect to age, gender, ECOG, tumor location, BMI, CA19-9, tumor size, vascular involvement, ASA and diagnosis/resection interval (Table 1). In this cohort, 76 (91.6%) patients had a borderline resectable or locally advanced PDAC according to the AHPBA/SSAO/SSO Consensus.(4) All the remaining 7(8.4%) patients with resectable disease had high-risk tumor features that would warrant NT as recommended by NCCN guidelines(11). In detail, 3 of these patients had confirmed lymph node involvement, 3 had a tumor >3.5cm, and 1 had markedly elevated CA19-9 levels (625U/ml).

In this cohort, 60(72.3%) patients received NT with FOLFIRINOX, for a median of 7 cycles (IQR 4-8). High-grade toxicity was noted in 5(6.6%) patients but this did not disrupt therapy. Paradoxically, more patients in the R1 resection group had a partial response (80.8%), compared to 45.6% in the R0>1mm group. The RECIST response was different between the two groups (p=0.026). **Preoperative and Pathology Results**Preoperative and pathology data were compared between R0>1mm and R1 groups (Table 2). No differences were observed in terms of preoperative data. Patients undergoing an R0>1mm resection had smaller tumors (P=0.019), fewer positive lymph nodes (p=0.008) and consequently had a lower ypT stage (p=0.005), and ypN stage

(p=0.015), as well as lower rates of perineural invasion (p=0.004). No significant differences were found with regard to lymphovascular invasion. Consistent with the RECIST response, pathological regression was different between the two groups (p=0.003). A higher percentage of patients had documented recurrence in the R1 group (p=0.046).

All-Cause and Disease-Free Survival

Median follow-up was 35.4 months (IQR 23.5-52.6 months). Median ACS for the entire cohort was 26.5 months, while the median DFS was 16.1 months (Table3). Compared to R1, patients who had an R0>1mm resection demonstrated significantly improved ACS (median: 44.8 vs. 19.2 months p=0.002) and DFS (median: 21.0 vs. 8.5 months p=0.006). The estimated one- and three-year survival rates were 81.8% and 39.3% for the R0>1mm group and 61.1% and 23.3% for the R1 group, respectively. The estimated recurrence-free survival rates at one and two years were 65.6% and 38.1% for the R0>1mm group, respectively vs. 32.2% and 16.1% for the R1 group. The ACS and DFS K-M curves stratified by R status (R0>1mm vs. R1) are shown in Figures 2A and B, respectively.

Univariable analysis and multivariable prognostic models for All-Cause Survival

Table 4 illustrates the relationship between clinical variables and ACS. On univariable analysis, R0>1mm resection (HR=0.40, 95%CI: 0.22-0.72, p=0.002), CA19-9>100u/ml at diagnosis (HR=2.01, 95%CI 1.09 -3.68, p=0.025) and restaging (HR=1.85, 95%CI 1.03-

3.32, p=0.039), tumor size >30mm at restaging (HR=2.02, 95%CI 1.10-3.70, p=0.024), pancreaticoduodenectomy (HR=4.69, 95%CI 1.14-19.37, p=0.033) and lymph node involvement (HR=2.30, 95%CI 1.28-4.11, p=0.005) were associated with ACS. In the multivariable model at diagnosis, head/uncinate tumor (HR=3.84, 95%CI 1.06-13.93, p=0.041) and CA19-9>100u/ml (HR=2.03, 95%CI 1.04-3.97, p=0.039) were independent prognostic factors for decreased ACS. The restaging multivariable model demonstrated that FOLFIRINOX (HR=0.45, 95%CI 0.22-0.94, p=0.033) and tumor size >30mm (HR=2.10, 95%CI 1.02-4.32, p=0.044) were independent prognostic factors for increased and decreased ACS, respectively. The postoperative model revealed that R0>1mm resection (HR=0.30, 95%CI0.14-0.66, p=0.003) and adjuvant therapy (HR=0.35, 95%CI0.16-0.74, p=0.006) were independent prognostic factors of increased ASC. The adjusted ACS K-M curve stratified by R status (R0>1mm vs. R1) is shown in Figure 2C. Sensitivity analysis revealed that R0>1mm resection remained a potent prognostic factor for improved ACS for patients treated with FOLFIRINOX. (Supplementary Table S1)

Univariable analyses and multivariable prognostic models for DFS

Table 5 illustrates the relationship between clinical variables and DFS. R0>1mm resection (HR=0.44, 95%CI 0.25-0.79, p=0.006) and lymph node involvement (HR=2.19, 95%CI 1.24-3.87, p=0.007) were associated with DFS on univariable analysis. No factors were found to be independently associated with DFS in the diagnosis and restaging multivariable models. In the postoperative model, R0>1mm resection (HR=0.31, 95%CI

0.14-0.68, p=0.003) and lymph node involvement (HR=3.14, 95%CI 1.27-7.78, p=0.014) were independently associated with decreased and increased DFS, respectively. The adjusted DFS K-M curve stratified by R status (R0>1mm vs. R1) is shown in Figure 2D. Sensitivity analysis confirmed the prognostic impact of R0>1mm and lymph node involvement. (Supplementary Table S2)

DISCUSSION:

Neoadjuvant treatment enables a higher rate of R0 resection in patients with PDAC.(4, 14, 16, 28, 29) In this current cohort, an R0>1mm resection was achieved in 68.7% of patients, which is superior to previously reported rates after upfront surgery for PDAC.(7-9) Although an R0>1mm resection has been shown to be an important prognostic factor in the adjuvant setting,(7, 8) its impact is not fully validated in the neoadjuvant setting. This study confirms that an R0>1mm resection remains an important prognostic factor for improved ACS and DFS in patients with non-metastatic PDAC receiving NT.

In our recent study comparing patients with borderline resectable PDAC receiving NT versus upfront resection, we found that the impact of R0>1mm on survival outweighed that of NT. However, relevant factors at restaging and postoperatively could not be included in our analysis models because unavailable for the patients receiving upfront resection or, alternatively, they were modified for patients receiving NT. In the neoadjuvant setting, restaging or postoperative data may compromise the predictability of baseline data. Previous studies identifying prognostic factors for patients receiving

NT adopted analytical plans which included pN, pT, or CA199 after NT, ie restaging and postoperative data using a single multivariable model, which is likely inaccurate.(6, 16, 30, 31) For this reason, built three different multivariable models to identify prognostic factors at different time points of patients' therapeutic iter. R0>1mm remained a potent prognostic factor for both improved ACS and DSF, especially for the patients receiving FOLFIRINOX. This indicates that in the NT setting, achieving R0>1mm resection should remain the primary goal of surgical treatment.

A previous study analyzing the impact of NT on survival of patients with unresectable PDAC demonstrated that R0>1mm is not an independent prognostic factor.(6) Compared to our results, this discrepancy may be attributed to the heterogeneity of their cohort, which also included patients with metastatic PDAC. The prognostic value of R status is likely attenuated due to the inclusion of patients with metastases(24). Our study analyzed a more homogenous cohort of patients with a non-metastatic PDAC receiving NT prior to resection.(11) Likewise, in the study referenced above(6), the selection of variables to assess independent risk factors for survival was based only on the statistical significance of the variables included in univariable analysis.(6) In contrast, our analytical models included clinically relevant variables for survival at diagnosis, restaging and postoperatively with the intent to yield more reliable results .(25, 26, 32)

Previous studies also reported R0 resection rates as high as 97% in patients with PDAC receiving NT prior to pancreatic resection. (30, 31) In our cohort, a lower R0 resection

rates of 68.7%, was demonstrated. This may be due to our adoption of different criteria for an R0 resection. If any margin, including those ≤1mm were classified as R0, our cohort would also have a higher rate of R0 (88.0%). For patients receiving NT, the median ACS was 26.5 months and the median DFS was 16.1 months, which is increased compared to patients who did not undergo a pancreatic resection(33, 34).

Although lymph node involvement is a well-documented prognostic factor in the adjuvant setting(23, 35), its impact for the patients receiving NT has remained controversial. Some investigators concluded that lymph node involvement is not an independent prognostic factor for patients receiving FOLFIRINOX,(16) while others reported that the impact of nodal status on survival outweighed that of the R status in the neoadjuvant setting.(6, 10) In our study, lymph node involvement was identified as an independent prognostic factor for DFS in the postoperative multivariable model as well as the sensitivity analysis. However, the impact of R status was not attenuated by the adjustment for lymph node involvement.

We also found that tumor size on pathology was not an independent risk factor for either decreased ACS or DFS. This is inconsistent with previous analyses that have not adjusted for R status(16) Additionally, when not adjusting for R status, tumor size would likely become a more important prognostic factor for survival. Demonstrating this association, in our restaging model that did not include R status, tumor size was a prognostic factor for poor ACS. In the report by Klaiber et al(6), only ypT4 was found to be an independent prognostic factor for decreased DSF. Given that T4 is defined as a

tumor that involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size,(19) the risk factor most likely associated with DSF was arterial involvement(24).

Adjuvant therapy was identified as a prognostic risk factor for improved ACS. In the neoadjuvant setting, the administration of adjuvant treatment is affected by the dose of NT, treatment tolerance, and tumor response. (12, 16, 36, 37) Therefore, receiving adjuvant therapy could be an indicator of a better NT treatment response or better tolerance. Tumor location was also found to be an independent predictor of poor ACS at diagnosis, likely attributable to the fact that all patients aggravated with a 90-day mortality had tumors located in the head/uncinate process of the pancreas. FOLFIRINOX has dramatically revolutionized the therapeutic landscape for patients with PDAC.(12, 16, 36) In this study, we found that FOLFIRINOX was an independent prognostic factor for increased ACS in the restaging model. The level of CA19-9 at diagnosis, a well-documented prognostic factor for PDCA(38-40), was independently associated with poor ACS.

This study has several limitations predominantly related to its retrospective design and small sample sizes. The sample size of this report is smaller than sizes reported from national databases, but comparable with previous reports. In each model, there were a number of varibles included. According to generally accepted statistical principles, the sample size of the current study allowed us to appropriately adjust for important outcomes such as recurrence and survival (25, 26). Although some bias is unavoidable

by the variation in the regimens of NT due to the absence of standardized evidence and well-established guidelines and protocols,(4, 6, 37) this has been addressed by the sensitivity analysis performed. These limitations are common in all retrospective studies on this topic. In contrast, a major strength of the present study is the inclusion of selected patients with a non-metastatic PDAC receiving NT, which is consistent with current NCCN guidelines. This represents the most common practice observed in national and international centers, and therefore makes our results and conclusions more generalizable. Another strength is the use of 3 predefined multivariable models, which include clinically relevant factors and most importantly account for the impact of different factors during a patient's therapeutic iter.

CONCLUSIONS:

At diagnosis, restaging and postoperatively, R0 resection with at least a 1mm margin remains the most important prognostic factor for increased ACS and DFS in patients with localized PDAC receiving NT. Therefore, an R0>1mm resection should remain the primary goal for the surgical treatment of these patients in the neoadjuvant setting. Furthermore, whereas lymph node involvement was identified to be an adverse prognostic factor for DFS, tumor size on pathology was not a prognostic factor for either ACS or DFS. Head/uncinate tumor and CA19-9>100u/ml at diagnosis and tumor size >30mm at restaging were independently associated with decreased ACS. FOLFIRINOX was an independent prognostic factor for ACS at restaging, supporting its crucial role as the treatment of choice. Although sensitivity analysis confirmed the

validity and reliability of our results, further prospective analyses are necessary to confirm these findings.

Disclosure

Conflict of Interest and Financial Disclosure: Nothing to declare.

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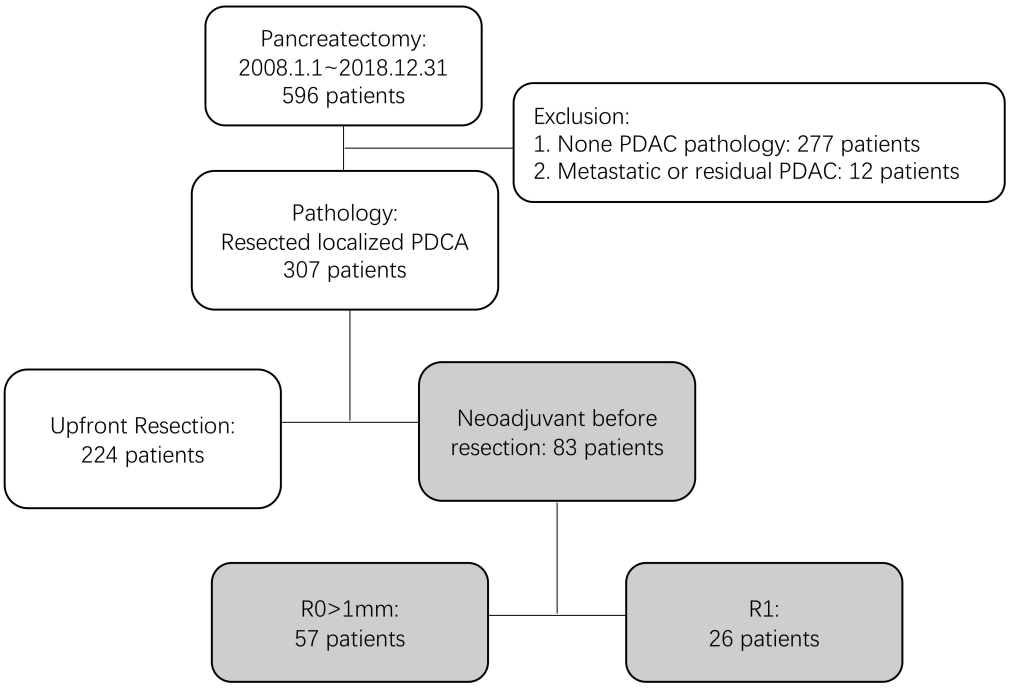

FIGURE 1. Study profile.

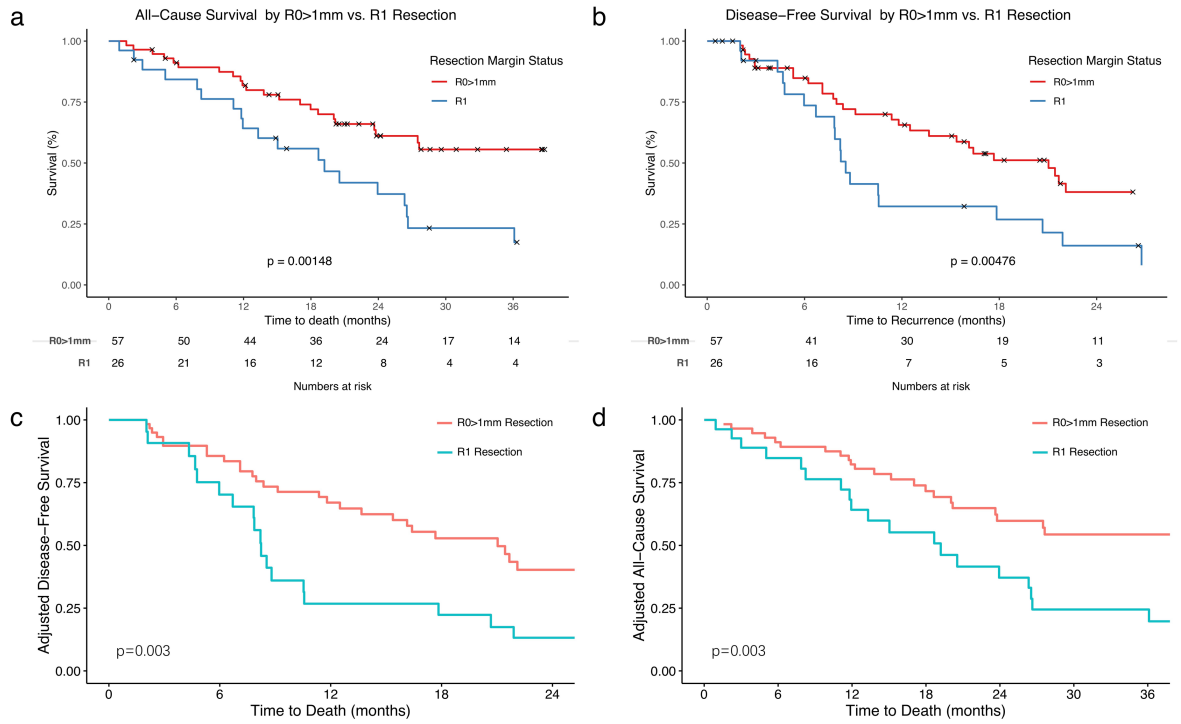

FIGURE2. Survival after surgery by R0>1mm and R1 resection.(A) All-cause survival;(B)disease-free survival; (C) adjusted all-cause survival;(D)adjusted disease-free survival

TABLE 1. Patient Characteristics available at diagnosis and restaging before surgery

		Total (83)	R0>1mm (57) *	R1 (26) †	P
Male,N(%)		41(49.4%)	26 (45.6)	15 (57.7)	0.433
Age, median (IQR)		66(60-72)	66(60-71)	66(58-72)	0.724
Race,N(%)	White	78(94.0)	54 (94.7)	24 (92.3)	1
	Others	5(6.0)	3 (5.3)	2 (7.7)	
ECOG≥1 ,N(%)‡		38(45.8)	27 (47.4)	11 (42.3)	0.848
BMI at diagnosis, median (IQR) §		25.3(23.2-29.2)	25.8(23.2-29.4)	24.9(23.3-27.8)	0.346
CA-199 at diagnosis, u/ml, median (IQR) ||		165(27-610)	168(29-662)	160(22-527)	0.624
Tumor location	Head/Uncinate	72(86.7)	48 (84.2)	24 (92.3)	0.509
	Body/Tail	11(13.3)	9(15.8)	2(7.7)	
Tumor size at diagnosis, median (IQR)		3.1(2.5-3.8)	3.2(2.5-3.8)	3.1(2.6-3.7)	0.941
Vein involvement at diagnosis,N(%)		73(88.0)	51 (89.5)	22 (84.6)	0.789
PV/SMV involvement ≥180° at diagnosis ,N(%)¶		42(50.6)	28(49.1)	14(53.8)	0.690
Artery involvement at diagnosis,N(%)		27(32.5)	18 (31.6)	9 (34.6)	0.983
Neoadjuvant Chemotherapy, N(%)		76(91.6)	53 (93.0)	23 (88.5)	0.794
FOLFIRINOX -based, N(%)#		60(72.3)	43 (75.4)	17 (65.4)	0.493
Neoadjuvant Radiotherapy, N(%)		42(50.6)	26 (45.6)	16 (61.5)	0.267
ASA stage, N(%)**	I/II	32(38.6)	19(33.4)	13(50.0)	0.229
	III/IV	51(61.4)	38 (66.7)	13 (50.0)	
High Grade Toxicity (>3), N(%)		5(6.0)	5 (8.8)	0 (0.0)	0.289
BMI at restaging, median (IQR) §		24.9(22.5-27.3)	25.0(22.4-28.3)	24.8(22.9-26.1)	0.627
CA-199 at restaging, u/ml, median (IQR) ||		43(15-138)	35(15-99)	69(15-173)	0.380
Tumor size at restaging, median (IQR)		2.5(1.9-3.2)	2.4(1.8-3.3)	2.8(2.4-3.2)	0.120
Vein involvement at restaging, N(%)		60(72.3)	39 (68.4)	21 (80.8)	0.367
PV/SMV involvement ≥180° at restaging, N(%)¶		19(22.9)	15 (26.3)	9 (34.6)	0.608
Artery involvement at restaging, N(%)		24(28.9)	11 (19.3)	8 (30.8)	0.383
Diagnosis to resection, mo, median (IQR)		6.5(4.7-8.0)	6.8(4.9-8.2)	6.1(3.7-7.6)	0.336
RECIST, N(%)††	Complete	2(2.4)	2 (3.5)	0 (0.0)	0.026
	Partial	47(56.6)	26 (45.6)	21 (80.8)	
	Stable	33(39.8)	28 (49.1)	5 (19.2)	
	Progressive	1(1.2)	1 (1.8)	0 (0.0)	

* R0>1mm, margin negative resection with 1mm clearance; † R1, margin positive; ‡ECOG, Eastern Cooperative Oncology Group;, §BMI, body mass index; ||CA 19–9 carbohydrate antigen 19–9; ¶PV/SMV, portal vein/superior mesenteric vein; #FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin, ** ASA, American Society of Anesthesiologists; ††RECIST, Response Evaluation Criteria In Solid Tumors

TABLE2. Perioperative Data and Histopathological Findings

			Total(83)	R0>1mm (57) *	R1 (26) †	P
Type of operation, N (%)		Pancreaticoduodenectomy	73(88.0)	48 (84.2)	25 (96.2)	0.452
		Distal pancreatectomy	7(8.4)	6(10.5)	1(3.8)	
		Subtotal/Total pancreatectomy	3(3.6)	3(5.3)	0(0.0)	
Vascular Resection, N(%)‡			26(31.3)	16 (28.1)	10 (38.5)	0.489
Operative time, hours, Median (IQR)			7.5(6-9)	7.5(6.0-9.5)	7.5(6.0-8.5)	0.616
Estimated blood loss, Median (IQR)			400(250-700)	350(250-750)	450(250-600)	0.768
Length of hospital stay, days, Median (IQR)			8(7-10)	8(7-9)	8(7-12)	0.298
In hospital Clavien-Dindo≥3b Complication			5(6.0)	2 (3.5)	3 (11.5)	0.353
Thirty-day readmission, N (%)			23 (27.7)	14 (24.6)	9 (34.6)	0.493
Ninety-day mortality, N (%)			6 (7.2)	2 (3.5)	4 (15.4)	0.139
Adjuvant treatment, N(%)			44(53.0)	31 (54.4)	13 (50.0)	0.893
Pathological tumor size			2.7(2.0-3.5)	2.4(1.8-3.4)	3(2.5-3.5)	0.019
ypT §	0		5(6.0)	5 (8.8)	0 (0.0)	0.005
	1		21(25.3)	19 (33.3)	2 (7.7)	
	2		47(50.6)	29 (50.9)	18 (69.2)	
	3		8(9.6)	4 (7.0)	4 (15.4)	
	4		4(2.4)	0 (0.0)	2 (7.7)	
Pathological tumor regression, N(%)		Minimal	48(57.8)	38 (66.7)	10 (38.5)	0.003
		Moderate	30(36.1)	14 (24.6)	16 (61.5)	
		Complete	5 (6.0)	5 (8.8)	0 (0.0)	
Total retrieved lymph nodes, median (IQR)			15(11-20)	17(12-21)	13(10-17)	0.096
Positive lymph nodes, median (IQR)			0(0-2)	0(0-1)	1(0-2)	0.008
ypN §	0		48(57.8)	39 (68.4)	9 (34.6)	0.015
	1		23(27.7)	12 (21.1)	11 (42.3)	
	2		12(14.5)	6 (10.5)	6 (23.1)	
Lymphovascular invasion, N (%)			27(32.5)	15 (26.3)	12 (46.2)	0.124
Perineural invasion, N (%)			53(63.9)	30 (52.6)	23 (88.5)	0.004
Recurrence, N (%)			49(59.0)	29 (50.9)	20 (76.9)	0.046
Local			13(15.7)	8 (14.0)	5 (19.2)	
Liver			11(13.3)	7 (12.3)	4 (15.4)	
Lung			4(4.8)	3 (5.3)	1 (3.8)	
Multiple sites/ Carcinomatosis			23(26.5)	12 (21.1)	11 (42.3)	

* R0>1mm, margin negative resection with 1mm clearance; † R1, margin positive; ‡Vascular resection: celiac axis, hepatic artery, portal vein, superior mesenteric vein, superior mesenteric artery, inferior vena cava; § ypT, ypN, reported according to the 8th revised edition of the Cancer Staging Manual of the American Joint Committee on Cancer

TABLE3 Survival by R0>1mm and R1 resection

	Total (83)	R0>1mm (57)	R1 (26)	P
All-cause survival, mo [median (IQR)]	26.5(12.2-56.4)	44.8(17.0-NA)	19.2(11.1-26.6)	0.002
Disease-free survival, mo [median (IQR)]	16.1(7.7-32.9)	21.0(8.0-68.7)	8.5(6.0-20.7)	0.006

TABLE4 Univariable and multivariable analysis of all-cause survival

	Univariate		Model 1: Diagnosis		Model2: Restaging		Model3: Post-operation	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
R0>1mm*	0.40(0.22-0.72)	0.002					0.30(0.14-0.66)	0.003
ECOG ≥1†	1.49(0.82-2.69)	0.188	1.38(0.70-2.71)	0.356	1.02(0.46-2.26)	0.958	1.27(0.60-2.70)	0.538
Age >70	1.41(0.74-2.69)	0.303	1.30(0.64-2.63)	0.470	1.46(0.70-3.05)	0.309	1.90(0.92-3.95)	0.084
Head/uncinate process tumor	1.84(0.92-9.54)	0.070	3.84(1.06-13.93)	0.041	2.48(0.71-8.62)	0.153		
BMI >30 at diagnosis‡	0.65(0.26-1.65)	0.364	1.06(0.40-2.83)	0.911				
CA199 >100u/ml at diagnosis §	2.01 (1.09 -3.68)	0.025	2.03(1.04-3.97)	0.039				
Tumor size >30mm at diagnosis	1.26(0.70-2.27)	0.445	1.39(0.73-2.67)	0.316				
Venous invasion at diagnosis	0.86(0.38-1.93)	0.713	0.59(0.22-1.57)	0.289				
PV/SMV involvement ≥180° at diagnosis||	1.20(0.67-2.15)	0.544	1.71(0.77-3.81)	0.187				
Arterial invasion at diagnosis	0.69(0.36-1.33)	0.267	0.64(0.31-1.35)	0.242				
FOLFIRINOX¶	0.60(0.33-1.08)	0.089	0.51(0.25-1.06)	0.072	0.45(0.22-0.94)	0.033	0.58(0.28-1.23)	0.155
Neoadjuvant radiotherapy	1.19(0.67-2.11)	0.560	0.82(0.42-1.58)	0.546	1.00(0.51-1.95)	0.989	0.86(0.40-1.88)	0.709
BMI >30 at restaging‡	0.54(0.19-1.50)	0.237			0.72(0.24-2.14)	0.551	1.14(0.35-3.70)	0.825
CA199 >100u/ml at restaging §	1.85(1.03-3.32)	0.039			1.58(0.82-3.02)	0.170	1.85(0.83-4.09)	0.131
Tumor size >30mm at restaging	2.02(1.10-3.70)	0.024			2.10(1.02-4.32)	0.044		
Venous invasion at restaging	1.12(0.58-2.15)	0.747			0.96(0.45-2.06)	0.925		
PV/SMV involvement ≥180° at restaging||	1.12(0.55-2.25)	0.761			1.95(0.78-4.90)	0.153		
Arterial invasion at restaging	0.62(1.30-1.29)	0.205			0.60(0.25-1.44)	0.256		
RECIST response#	1.29(0.71-2.33)	0.410			0.87(0.42-1.80)	0.707		
ASA III/IV vs. I/II **	1.46(0.80-2.66)	0.213			1.69(0.77-3.72)	0.195	1.78(0.83-3.80)	0.140
Pancreaticoduodenectomy	4.69 (1.14-19.37)	0.033					4.26(0.85-21.29)	0.078
Vascular resection	1.51(0.83-2.75)	0.179					1.07(0.49-2.33)	0.859
Pathological size>25mm	0.97(0.53-1.74)	0.908					0.84(0.39-1.81)	0.656
Histopathologic regression	1.19 (0.66-2.12)	0.562					0.87(0.42-1.78)	0.697
Lymph node involvement	2.30 (1.28-4.11)	0.005					2.06(0.78-5.45)	0.147
Lymphovascular invasion	1.50 (0.81-2.77)	0.197					1.30(0.50-3.37)	0.590
Perineural invasion	1.29 (0.77-2.41)	0.415					0.58(0.24-1.36)	0.211
Adjuvant therapy	0.59(0.33-1.05)	0.074					0.35(0.16-0.74)	0.006

*R0>1mm, margin negative resection with 1mm clearance; †ECOG, Eastern Cooperative Oncology Group; ‡ BMI, body mass index; §CA 19–9, carbohydrate antigen 19–9; || PV/SMV, portal vein/ superior mesenteric vein; # REIST, Response Evaluation Criteria In Solid Tumors; **ASA, American Society of Anesthesiologists.

TABLE5 Univariable and multivariable analysis of disease-free survival

	Univariate		Model 1: Diagnosis		Model2: Restaging		Model3: Post-operation	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
R0>1mm*	0.44(0.25-0.79)	0.006					0.31(0.14-0.68)	0.003
Head/uncinate tumor	1.25(0.56-2.79)	0.589	1.68(0.71-3.97)	0.237	1.20(0.50-2.83)	0.686		
CA199 >100u/ml at diagnosis†	1.79(1.00-3.22)	0.050	1.76(0.94-3.29)	0.075				
Tumor size >30mm at diagnosis	1.17(0.66-2.05)	0.595	1.12(0.60-2.11)	0.723				
Venous invasion at diagnosis	0.85(0.38-1.92)	0.696	0.57(0.22-1.47)	0.245				
PV/SMV involvement ≥180°at diagnosis‡	1.48(0.84-2.62)	0.177	1.92(0.95-3.87)	0.070				
Arterial invasion at diagnosis	1.03(0.57-1.88)	0.924	1.00(0.52-1.96)	0.989				
FOLFIRINOX§	0.80(0.43-1.47)	0.472	0.68(0.35-1.34)	0.262	0.61(0.29-1.30)	0.200	0.91(0.44-1.85)	0.785
Neoadjuvant radiotherapy	0.96 (0.55-1.69)	0.897	0.70(0.37-1.32)	0.272	0.76(0.39-1.47)	0.411	0.84(0.41-1.72)	0.628
CA199 >100u/ml at restaging	1.45(0.81-2.59)	0.214			1.60(0.86-3.00)	0.142	1.10(0.51-2.38)	0.809
Tumor size >30mm at restaging	1.67(0.90-3.08)	0.102			1.68(0.79-3.60)	0.181		
Venous invasion at restaging	0.85(0.47-1.55)	0.596			0.69(0.35-1.38)	0.292		
PV/SMV involvement ≥180°at restaging‡	1.41(0.71-2.78)	0.325			2.00(0.85-4.71)	0.114		
Arterial invasion at restaging	1.08(0.57-2.05)	0.809			1.00(0.45-2.22)	0.994		
RECIST response||	1.27(0.70-2.30)	0.425			0.98(0.48-2.01)	0.952		
Pancreaticoduodenectomy	1.70(0.67-4.29)	0.263					1.06(0.35-3.22)	0.916
Vascular resection	1.46(0.80-2.68)	0.220					1.48(0.69-3.20)	0.315
Pathological size>25mm	0.78(0.44-1.39)	0.407					0.64(0.33-1.25)	0.192
Histopathologic regression	0.95(0.53-1.69)	0.851					0.52(0.23-1.16)	0.110
Lymph node involvement	2.19(1.24-3.87)	0.007					3.14(1.27-7.78)	0.014
Lymphovascular invasion	1.38 (0.74-2.60)	0.314					1.09(0.44-2.72)	0.855
Perineural invasion	1.03 (0.57-1.84)	0.934					0.59(0.29-1.12)	0.088
Adjuvant therapy	0.74(0.41-1.33)	0.315					0.58(0.28-1.22)	0.152

*R0>1mm, margin negative resection with 1mm clearance; † A 19–9, carbohydrate antigen 19–9; ECOG, Eastern Cooperative Oncology Group; ‡ PV/SMV, portal vein/ superior mesenteric vein, §FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin, ||REIST, Response Evaluation Criteria In Solid Tumors

SUPPLEMENTARY TABLES-paper2

Supplementary Table S1 Univariable and multivariable analysis of all-cause survival for patients treated with FOLFIRINOX regimen as neoadjuvant treatment

	Univariate		Model 1: Diagnosis		Model2: Restaging		Model3: Post-operation	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
R0>1mm*	0.31(0.14-0.66)	0.002					0.34(0.13-0.93)	0.035
ECOG ≥1†	1.49(0.70-3.17)	0.295	1.79(0.79-4.08)	0.166	0.55(0.18-1.70)	0.300	0.93(0.31-2.77)	0.891
Age >70	2.11(0.94-4.71)	0.069	2.25(0.87-5.82)	0.094	4.45(1.26-15.77)	0.021	4.05(1.50-10.91)	0.006
Head/uncinate process tumor	2.50 (0.59-10.55)	0.212	2.67(0.59-12.13)	0.202	2.48(0.49-12.69)	0.274		
BMI >30 at diagnosis‡	0.32(0.08-1.36)	0.124	0.62(0.13-2.95)	0.551				
CA199 >100u/ml at diagnosis §	1.88(0.86-4.07)	0.112	2.24(0.82-6.14)	0.118				
Tumor size >30mm at diagnosis	1.49(0.67-3.30)	0.331	1.49(0.65-3.44)	0.351				
Venous invasion at diagnosis	0.60(0.21-1.74)	0.345	0.2(0.05-1.02)	0.053				
PV/SMV involvement ≥180° at diagnosis||	1.52(0.70-3.30)	0.295	1.61(0.48-5.38)	0.440				
Arterial invasion at diagnosis	0.76(0.34-1.67)	0.490	0.88(0.35-2.23)	0.785				
Neoadjuvant radiotherapy	1.46(0.69-3.08)	0.320	1.05(0.40-2.75)	0.928	1.35(0.57-3.20)	0.491	0.95(0.37-2.45)	0.914
BMI >30 at restaging‡	0.33(0.08-1.40)	0.134			0.34(0.07-1.67)	0.185	1.18(0.21-6. 70)	0.852
CA199 >100u/ml at restaging §	1.61(0.75-3.45)	0.217			0.87(0.34-2.25)	0.773	1.13(0.36-3.49)	0.836
Tumor size >30mm at restaging	2.22 (1.05-4.68)	0.037			1.67(0.61-4.58)	0.315		
Venous invasion at restaging	1.14(0.46-2.83)	0.778			0.78(0.25-2.47)	0.671		
PV/SMV involvement ≥180° at restaging||	1.46(0.65-3.24)	0.359			5.23(1.38-19.79)	0.015		
Arterial invasion at restaging	0.62(0.26-1.45)	0.271			0.54(0.16-1.81)	0.320		
RECIST response#	1.47(0.70-3.08)	0.313			1.38(0.54-3.54)	0.505		
ASA III/IV vs. I/II **	1.71(0.75-3.92)	0.203			3.45(0.98-12.07)	0.053	2.71(1.03-7.15)	0.044
Pancreaticoduodenectomy	5.54(0.75-40.79)	0.093					6.89(0.71-66.77)	0.096
Vascular resection	1.85(0.87-3.93)	0.108					1.03(0.37-2.87)	0.952
Pathological size>25mm	1.33(0.62-2.85)	0.469					0.86(0.31-2.38)	0.771
Histopathologic regression	1.40(0.65-3.04)	0.391					1.02(0.35-2.95)	0.965
Lymph node involvement	2.64(1.26-5.55)	0.010					2.38(0.67-8.49)	0.181
Lymphovascular invasion	1.72(0.80-3.67)	0.163					0.96(0.30-3.11)	0.947
Perineural invasion	1.36(0.62-3.01)	0.447					0.88(0.27-2.87)	0.837
Adjuvant therapy	0.64(0.30-1.35)	0.239					0.37(0.12-1.13)	0.080

*R0>1mm, margin negative resection with 1mm clearance; †ECOG, Eastern Cooperative Oncology Group; ‡ BMI, body mass index; §CA 19–9, carbohydrate antigen 19–9; || PV/SMV, portal vein/ superior mesenteric vein; # REIST, Response Evaluation Criteria In Solid Tumors; **ASA, American Society of Anesthesiologists.

Supplementary Table S2 Univariable and multivariable analysis of disease-free survival for patients treated with FOLFIRINOX regimen as neoadjuvant treatment

	Univariate		Model 1: Diagnosis		Model2: Restaging		Model3: Post-operation	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
R0>1mm*	0.40(1.20-0.83)	0.014					0.25(0.10-0.65)	0.005
Head/uncinate tumor	1.19(0.46-3.09)	0.720	1.49(0.54-4.05)	0.439	1.26(0.44-3.60)	0.661		
CA199 >100u/ml at diagnosis†	1.91(0.94-3.90)	0.740	1.93(0.88-4.25)	0.102				
Tumor size >30mm at diagnosis	1.11(0.55-2.21)	0.775	1.16(0.57-2.36)	0.685				
Venous invasion at diagnosis	0.68(0.24-1.94)	0.470	0.32(0.09-1.13)	0.078				
PV/SMV involvement ≥180°at diagnosis‡	1.61(0.79-3.27)	0.186	2.20(0.83-5.88)	0.115				
Arterial invasion at diagnosis	0.90(0.43-1.86)	0.772	0.90(0.41-1.98)	0.792				
Neoadjuvant radiotherapy	1.20(0.60-2.41)	0.600	0.80(0.33-1.92)	0.614	1.07(0.49-2.33)	0.860	0.85(0.36-2.02)	0.711
CA199 >100u/ml at restaging	1.45(0.71-2.96)	0.303			1.75(0.80-3.85)	0.162	1.03(0.41-2.60)	0.944
Tumor size >30mm at restaging	1.53(0.74-3.14)	0.249			1.55(0.61-3.93)	0.355		
Venous invasion at restaging	0.83(0.39-1.74)	0.619			0.56(0.23-1.36)	0.197		
PV/SMV involvement ≥180°at restaging‡	1.60(0.75-3.41)	0.223			2.26(0.85-5.96)	0.100		
Arterial invasion at restaging	1.04(0.49-2.19)	0.922			0.93(0.36-2.40)	0.875		
RECIST response||	1.08(0.54-2.16)	0.826			0.85(0.35-2.05)	0.712		
Pancreaticoduodenectomy	1.94(0.59-6.38)	0.274					1.06(0.27-4.16)	0.938
Vascular resection	1.81(0.88-3.70)	0.107					1.86(0.71-4.87)	0.204
Pathological size>25mm	0.95(0.48-1.88)	0.876					0.73(0.31-1.72)	0.478
Histopathologic regression	0.88(0.41-1.91)	0.749					0.41(0.14-1.17)	0.095
Lymph node involvement	2.41(1.21-4.79)	0.013					3.11(1.01-9.55)	0.048
Lymphovascular invasion	1.56(0.73-3.32)	0.248					1.07(0.38-3.03)	0.896
Perineural invasion	0.85(0.43-1.71)	0.655					0.54(0.22-1.14)	0.098
Adjuvant therapy	0.87(0.42-1.77)	0.693					0.67(0.27-1.66)	0.382

*R0>1mm, margin negative resection with 1mm clearance; † A 19–9, carbohydrate antigen 19–9; ECOG, Eastern Cooperative Oncology Group; ‡ PV/SMV, portal vein/ superior mesenteric vein, §FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin, ||REIST, Response Evaluation Criteria In Solid Tumors

SUMMARY and CONCLUSIONS:

This single-center study is one of the largest analyses identifying prognostic factors. The first part of the study included exclusively patients with a BR-PDAC undergoing resection. It is also the first study to stratify patients based on R status. Our data provide strong evidence that NT is independently associated with improved OS and PFS in patients with BR-PDAC, however this effect is outweighed by R status. R0 and R1 subgroup analyses revealed that NT is not associated with improved OS or PFS. These results suggest that the benefit of NT is primarily mediated by its ability to facilitate an R0>1mm resection. While UR remains a valid treatment option if R0>1mm resection could be accurately predicted.

The second part of the study found that in the neoadjuvant setting, R0 resection with at least a 1mm margin remains the most important prognostic factor for increased ACS and DFS in patients with localized PDAC receiving NT. Therefore, an R0>1mm resection should remain the primary goal for the surgical treatment of these patients in the neoadjuvant setting. Furthermore, whereas lymph node involvement was identified to be an adverse prognostic factor for DFS, tumor size on pathology was not a prognostic factor for either ACS or DFS. Head/uncinate tumor and CA19-9>100u/ml at diagnosis and tumor size >30mm at restaging were independently associated with decreased ACS. FOLFIRINOX was an independent prognostic factor for ACS at restaging, supporting its crucial role as the treatment of choice.

DISCUSSION and PERSPECTIVES

The current studies have important strengths. For the first project, our cohort consisted of exclusively BR-PDAC patients, therefore being more homogenous. Second, the variables included in our models were predefined, accounting for clinical relevance. This method of variable selection is the most recommended to accurately identify independent prognostic factors. Third, we have clearly defined R0 as >1mm tumor free margin and performed a subgroup analysis, based on R status. For the second project, homogeneity was achieved by including patients appropriate for NT according to the current NCCN guidelines, and predefined models were used to identify temporal prognostic factors. This represents the most common practice observed in national and international centers, and therefore makes our results and conclusions more generalizable.

The limitations of these study include its retrospective nature, small sample sizes, and single-center design. However, according to generally accepted statistical principles, the sample size of the current study allowed us to appropriately adjust for important outcomes such as recurrence and survival. These limitations are common in all retrospective studies on this topic.

Future research efforts should aim to address the challenging task to accurately identify such patients preoperatively. Further prospective analyses are necessary to confirm these findings. We have already finished one third paper on predicting R1 resection for patients with BR/LA-PDAC.