Published in final edited form as:

Ann Surg Oncol. 2020 October ; 27(10): 3950–3960. doi:10.1245/s10434-020-08468-9.

CA19-9 Change During Neoadjuvant Therapy May Guide the Need for Additional Adjuvant Therapy Following Resected Pancreatic Cancer

Hao Liu, MD PhD¹, Mazen S. Zenati, MD PhD², Caroline J. Rieser, MD¹, Amr Al-Abbas, MD¹, Kenneth K. Lee, MD¹, Aatur D. Singhi, MD PhD³, Nathan Bahary, MD PhD⁴, Melissa E. Hogg, MD⁵, Herbert J. Zeh III, MD⁶, Amer H. Zureikat, MD¹

¹Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA

²Department of Surgery and Epidemiology, University of Pittsburgh Medical Center, Pittsburgh, PA

³Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA

⁴Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA

⁵Department of Surgery, NorthShore University Health System, Chicago, IL

⁶Department of Surgery, University of Texas Southwestern, Dallas, TX

Abstract

Background: Neoadjuvant therapy (NAT) is increasingly utilized for pancreatic cancer, however the added benefit of adjuvant therapy (AT) in this setting is unknown. We hypothesized that the magnitude of CA19-9 response to NAT can guide the need for further AT in resected pancreatic cancer.

Methods: CA19-9 secretors who received NAT for pancreatic cancer during 2008–2016 at a single institution were analyzed and CA19-9 response (difference between pre and post NAT values) was measured. Kaplan-Meier estimators and Cox proportional hazard ratio models were used to determine the optimal CA19-9 response at which AT ceases to confer any additional survival benefit after NAT.

Results: A total of 241 patient (mean age 65.4yrs, 50% female) with complete CA19-9 data who underwent NAT followed by resection were analyzed. In a cohort of patients (n=78) in whom CA19-9 normalized *with* a decrease >50% after NAT (optimal responders), AT was not associated with additional survival benefit (40.6 versus 39.0 months, p=0.815). Conversely, in the cohort of patients (n=163) in whom NAT was not associated with normalization and decrease 50% in CA19-9 (sub-optimal responders), receipt of AT was associated with a survival benefit (34.5 versus 19.1 months, p<0.001) following NAT. Cox proportional hazards model confirmed CA19-9

Corresponding Author: Amer H. Zureikat, M.D., FACS, Associate Professor of Surgery, Chief, Division of Gastrointestinal Surgical Oncology, Co-Director UMPC Pancreatic Cancer Center, University of Pittsburgh Medical Center, 5150 Center Ave., Suite 421, Pittsburgh, PA 15232, Tel: (412) 692-2852, Fax: (412) 692-2520, zureikatah@upmc.edu.

Conflicts of Interest: None

normalization and decrease >50% during NAT to predict no additional survival benefit from adjuvant therapy.

Conclusions: The magnitude of CA19-9 response to NAT may predict the need for further adjuvant therapy in resected pancreatic cancer. Prospective studies are needed to elucidate the optimal interplay of NAT and AT in pancreatic cancer.

Keywords

Neoadjuvant therapy; pancreatic cancer; adjuvant therapy; pancreatic surgery

Introduction

Pancreatic resection followed by adjuvant therapy (AT) is the current standard of care for pancreatic adenocarcinoma (PDAC)^{1–4}. However, a significant proportion of patients are unable to receive or complete AT due to post-operative morbidity, a decline in performance status, or progressive disease^{5–8}. This, coupled to the realization that PDAC is a systemic disease at diagnosis, has led to increasing interest in a neoadjuvant therapy (NAT) approach. NAT can downstage tumors, increase R0 resection rates, treat micrometastatic disease, and allow a greater proportion of patients to complete multimodality treatment^{4,9–12}. Recently, the phase III PREOPANC-1 trial reported that preoperative chemoradiotherapy significantly improved survival in localized pancreatic cancer compared to an upfront surgery approach, although the survival benefit was restricted to resected patients only¹³. Several trials are currently underway to confirm the survival benefit of various neoadjuvant regimens^{14,15}.

Despite the enthusiasm for NAT, consensus on the optimal perioperative chemotherapy strategy in localized pancreatic cancer remains under investigation. Specifically, it is unclear whether patients who receive NAT benefit from additional AT^{16,17}. Ideally, patients could receive all planned chemotherapy preoperatively, obviating the need for adjuvant therapy following a potentially morbid resection. According to one single institutional study, AT was only beneficial in a subset of patients with a low lymph node ratio after NAT¹⁶. However, a more recent NCDB analysis of nearly 1,400 patients found no additional benefit for AT after NAT¹⁷.

Gauging the efficacy of NAT is challenging, since tumors may not exhibit radiographic response and downstaging. The magnitude of CA19-9 change during NAT may serve as a good surrogate for systemic disease response. Previous studies demonstrate CA 19-9 to be a biomarker for chemotherapy response in metastatic disease, whereas in the adjuvant setting, it is associated with recurrence and survival^{18–20}. In localized PDAC, CA19-9 decrease during NAT has shown to correlate with clinical stage, surgical resectability, histologic tumor response and survival^{21–23}. Although the optimal cutoff remains to be identified, several reports have indicated that a minimal decrease of 50% during NAT is associated with improved R0 resection rates and survival, while others report that normalization correlates with optimal survival^{8,24–27}.

Therefore, to investigate whether AT confers any additional benefit following NAT, we used CA19-9 response during NAT to determine the incremental survival benefit gained from

adjuvant therapy. We hypothesized that an optimal CA19-9 response during NAT may identify a cohort of patients for whom AT may be safely omitted.

Patients and Methods

Study design and patient population

Our aim was to use CA19-9 change during NAT to delineate the additional impact of AT on survival of PDAC patients who underwent resection. Using an institutional database, all PDAC patients who underwent NAT followed by surgical resection at the University of Pittsburgh Medical Center between 2008 and 2016 were retrospectively identified. Approval from our institutional review board was obtained.

Neoadjuvant therapy in this study was defined as the receipt of systemic chemotherapy with or without radiation. Regimens used were either gemcitabine or 5FU based. The regimen and duration of NAT at our institution is typically guided by a multidisciplinary board. In general, all PDAC patients who undergo resection are typically offered adjuvant therapy at our institution, in line with NCCN guidelines. However, as is the case with real time patient care, some patients did not receive AT due to physician discretion, patient refusal, decline in performance status, or postoperative complications. Reasons for not receiving AT were difficult to abstract from the electronic medical record in this retrospective study.

Preoperative data abstracted from the electronic medical record included patient age, gender, age-adjusted Charlson Comorbidity Index, NAT regimen, and CA19-9 levels pre-and post-NAT. CA19-9 change during NAT was calculated as percentage decrease or increase based on pre (diagnosis) and post (at time of resection) NAT levels. Pathologic data included tumor size, surgical margin status, lymphovascular invasion (LVI), perineural invasion (PNI), grade (differentiation), and lymph node status and ratio; the latter summarized as 0, between 0 and less than or equal to 0.2, and >0.2, reflecting the importance of its prognostic value^{28,29}. Post-operative data included complications graded according to the Clavien-Dindo score, receipt of adjuvant therapy, and survival³⁰.

Patients were excluded from analysis if they had no pathologic diagnosis of PDAC, were CA19-9 non-secretors (defined as CA19-9 level <37 units/mL at diagnosis), had missing CA19-9 data before or after NAT, had baseline CA19-9 levels with total bilirubin ≥ 2 mg/dL, died within 90 days of surgery, or had missing survival data.

Based on our sample size distribution and prior studies indicating a prognostic significance of a 50% decrease and normalization of CA19-9 during neoadjuvant therapy, CA19-9 response was dichotomized as optimal responders (defined as normalization (≤ 37 units/mL) and a decrease of $\geq 50\%$ between pre and post NAT) and suboptimal responders (defined as no normalization (>37 units/mL) or decrease of $< 50\%$). This definition for optimal CA19-9 response took into consideration the importance of both the absolute value of CA19-9 and its relative change.

Statistical Analysis

Normally distributed variables were compared using the student T-test, while non-normally distributed data were compared using the Mann-Whitney U test. Conditional overall survival (OS) was calculated from the time of diagnosis to the time of death or last contact. Kaplan-Meier estimators were applied to analyze the overall survival based on CA19-9 response and receipt of adjuvant therapy. To account for immortal time bias in patients who received adjuvant therapy, conditional landmark analysis was performed by excluding patients who died within 90 days of surgery.

Cox proportional hazards ratio models were fitted by backwards stepwise methods. First, all available parameters were simultaneously entered into the model. Subsequently, a backward stepwise conditional method was utilized to remove parameters that have an association with survival with significance levels >0.1 . Adjuvant therapy, optimal CA19-9 response to NAT and their interaction item were included in the multivariate model to test the interaction between these two factors and the predictive value of CA19-9 response in needing further AT. All Cox proportional hazards ratio models were examined for the test of proportional-hazard assumption. Statistical software used in this analysis include SPSS (version 24) (Armonk, NY: IBM Corp.) and R (version 3.4.3) (R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). Two-sided p values of 0.05 were used for all tests as the significant threshold.

Results

Characteristics of the Overall Cohort and CA19-9 Optimal and Suboptimal Responders

Of 406 patients who underwent resection following NAT during the study time period, 241 met inclusion criteria and were included in the analysis (Figure 1). Demographics and perioperative characteristics are summarized in Table 1. Mean age was 65.4 and 50% were female. Median pre-NAT CA19-9 level was 317. Gemcitabine based neoadjuvant regimens were used in 70.1%, while 29.9% received 5FU based regimens. Nearly 85% underwent a pancreaticoduodenectomy and 12% a distal pancreatectomy. Mean resected tumor size was 2.8cm, and 80.9% underwent a margin negative resection (R0). Most tumors had LVI and PNI (68.5% and 79.3% respectively). Adjuvant therapy was administered to 74% of the cohort.

A total of 78 patients (32.4%) were optimal responders to NAT (normalization and a decrease of $>50\%$) compared to 163 (67.6%) who were suboptimal responders (no normalization or $\leq 50\%$ decrease) (Table 1 and Figure 2). Optimal responders had lower pre-treatment CA19-9 levels (480 vs 165, $p=0.001$), and received more 5FU-based (versus gemcitabine based) combination regimens compared to suboptimal responders ($p=0.044$). The median number of NAT cycles was similar in both groups (3 vs 3, $P=0.17$). Age, gender and preoperative CCI scores were comparable in both groups (all $p>0.05$). Use of radiation as a component NAT was comparable (17.9% vs 20.9%, $p=0.597$). Optimal responders had lower lymph node positive rate, fewer positive lymph nodes, lower lymph node ratios, lower incidence of PNI and smaller tumor size on final pathologic specimen analysis (all $p<0.05$). Rates of LVI, tumor grade and lymph node yield were not statistically different.

Notably, the incidence of overall and major complications rates was comparable between optimal suboptimal responders, as was receipt of adjuvant chemotherapy (74.2% vs 73.1%, $p=0.848$) and number of adjuvant cycles. Median follow up was also comparable (27.9 vs 27.7 months, $p=0.997$) between both groups.

Predictors of Survival in the Overall Cohort

Multivariable analysis was performed to identify predictors of survival in the overall cohort (Table 2). Backwards stepwise modeling identified increased lymph node ratio, positive surgical margin, perineural invasion, higher tumor grade, optimal CA19-9 response, and receipt of AT as predictors of survival. To test the interaction between optimal CA19-9 response and AT, the interaction variable ‘optimal CA19-9 response *and* receipt of AT’ was also included in this model and was found to significantly predict survival ($p=0.040$), suggesting that the impact of adjuvant therapy varies with CA19-9 neoadjuvant response. Notably, pre-NAT CA19-9 and type of NAT regimen did not reach the univariate threshold to be included in the multivariate analysis.

Determining the Benefit of AT following NAT based on CA19-9 response

In the cohort of optimal responders who received AT ($n=57$), AT was not associated with any survival benefit compared to patients who did not receive AT ($n=21$): median OS was 40.6 months (95% CI: 28.1–53.1) versus 39.0 months (95% CI: 18.9–59.1) ($p=0.815$). Conversely, in patients with a sub-optimal CA19-9 response to NAT, AT ($n=121$) was associated with substantially improved survival compared to those who did not receive AT ($n=42$): median OS 34.5 months (95% CI: 27.6–41.4) versus 19.1 months (95% CI: 12.3–25.9) ($p<0.001$) (Figure 2).

To further examine the impact of AT based on CA19-9 change during NAT, Cox regression was performed separately on the optimal and sub-optimal responders. On multivariable analysis in suboptimal (Table 3) and optimal responders (Table 4), AT was only associated with a significant survival benefit in the cohort of suboptimal CA19-9 response (HR 0.448, 95% CI 0.291–0.689, $p=0.001$). Among the covariates adjusted for, higher lymph node ratio (HR 1.45), positive resection margin (HR 1.86), presence of PNI (HR 2.48), and high tumor grade (HR 1.64) were also independently associated with OS in the suboptimal group. However, AT was not associated with a significant survival difference in patients who had an optimal CA19-9 response during NAT. High tumor grade (HR 3.97) and higher number of positive lymph nodes (HR 1.16) were associated with OS in this cohort of optimal responders.

Discussion

This study suggests that the magnitude of CA19-9 response during neoadjuvant therapy may predict additional survival benefit (or lack thereof) from adjuvant therapy. Our findings suggest that adjuvant therapy may not be associated with additional survival benefit when a large CA19-9 decline was observed after NAT (in this case normalization and decrease of $>50\%$). Conversely, adjuvant therapy may still be associated with a survival benefit in patients with a suboptimal CA19-9 response during NAT.

Adjuvant chemotherapy is the current standard of care for all resected pancreatic cancer³¹. Available options include single agent regimens such as 5FU, gemcitabine, and S1, or the multidrug combinations of gemcitabine plus capecitabine or FOLFIRINOX. Data from the CONKO-001 study coupled with correlative data from the ESPAC-3 trial suggest that 6 cycles of therapy is associated with optimal survival in the adjuvant setting, with fewer cycles being associated with poor survival³². However, due to the significant morbidity and decline in performance status after surgery, a significant percentage of resected patients do not go on to receive post-operative chemotherapy, while others fail to receive the intended 6 cycles of therapy or require dose reductions during therapy. This, in addition to the realization that localized pancreatic cancer is likely a systemic disease at diagnosis, has shifted the paradigm in favor of delivering systemic therapy in the neoadjuvant setting. To date, neoadjuvant therapy has been shown to downstage tumors, increase R0 resection rates, and sterilize regional lymph nodes^{4,9–12}. A more recent phase III trial also reported that neoadjuvant chemoradiotherapy significantly improved survival in localized pancreatic cancer compared to an upfront surgery approach¹³.

Despite its increasing use, data on the optimal sequencing of systemic therapy remains debated. By analyzing a cohort of NAT patients within the National Cancer Database (NCDB), Swords et al. concluded that the benefit of AT was restricted to those with negative nodes or low lymph node ratio (LNR)¹⁶, although de Geus et al. observed no survival benefit of AT after NAT¹⁷. Such contradictory results highlight the significant heterogeneity in NAT response for PDAC. Both studies used national datasets lacking information on treatment details such as CA19-9 response. Utilizing more granular data, and building on evidence that 6 cycles of AT was the optimal treatment for resected pancreatic cancer, a recent single institutional study examined sequencing of chemotherapy for localized pancreatic cancer and suggested 6 cycles of chemotherapy to be associated with optimal survival regardless of sequence (AT, NAT or a combination of both)³³.

The aforementioned studies do not tackle an important question in the sequencing of pancreatic cancer treatment: can a group of patients be identified for whom all systemic therapy can be delivered preoperatively, obviating the need for adjuvant therapy? Ideally, a readily available biomarker (such as CA19-9) could signal maximum treatment effect from NAT, obviating the need for further AT. In this study, we hypothesized that the magnitude of CA19-9 response to NAT would indicate the need for further AT. Although an optimal response (reduction) cutoff has not been validated, a decline of > 50% during NAT has been associated with improved R0 resection rates, less vascular resections, and longer survival in a prior study²⁴. A CA19-9 reduction >50% or normalization was also associated with non-progression in another study²⁵, while normalization correlated with longer survival in others^{8,26}.

Based on the above studies, and our sample size distribution, we defined an optimal CA19-9 response as ‘normalization and greater than 50% reduction’. This definition takes into consideration both the absolute value of CA19-9 and the magnitude of reduction. Our findings indicate that this cutoff predicted no additional benefit from AT. Notably, various cutoffs of CA19-9 response were examined (Supplementary figure 1) revealing a trend indicating that the beneficial impact of AT was incrementally smaller when the magnitude of

CA19-9 reduction was more pronounced. Due to sample size restrictions, however, separate Cox proportional models could not be performed for the various CA19-9 cutoffs. Regardless, our observation that NAT response may predict the efficacy of AT is consistent with the notion that PDAC is a systemic disease at diagnosis and that systemic tumor burden (whether treated by NAT or AT) is an important primary determinant of survival³⁴.

It is worth emphasizing several aspects of this analysis. First, although this study was retrospective and subject to selection bias, both groups of optimal and suboptimal CA19-9 responders had comparable post-operative complication rates (overall and major complications), rate of adjuvant therapy receipt, and total number of neoadjuvant and adjuvant therapy cycles received. Second, although baseline CA19-9 levels were different in both groups, this variable lacked a significant association with overall survival on multivariate analysis. Third, the type of neoadjuvant therapy regimen did not influence survival, again supporting the notion that CA19-9 response is the ultimate arbitrator of survival; it may not matter which regimen (5FU or Gem based) is delivered as long as a substantial CA19-9 reduction is achieved. Finally, nearly three fourths of patients did not achieve optimal CA19-9 response in this study; those patients benefited from adjuvant therapy. This highlights the need for more effective systemic therapy options to expand the pool of optimal responders.

This study has several limitations. First, CA19-9 non-secretors were excluded from analysis. This subgroup represents a substantial percentage of the total NAT cohort (19%, figure 1), and their exclusion may have introduced bias. Histopathologic response may be an alternative surrogate for systemic response in this population. Additionally, novel biomarkers such as liquid biopsy to assess cell-free tumor DNA or circulating tumor cells, could be useful tools to measure systemic treatment response in this cohort. Second, as a conditional landmark, patients who died within 90 days following surgery (n=10) were excluded to account for immortal time bias. Although this could have introduced bias, all 10 patients who died within 90 days had comparable pre and post NAT CA19-9 to those patients who died after 90 days, and none received adjuvant therapy. Third, our sample size was limited since this was a single institutional study. Although the definition of optimal CA19-9 response (normalization and >50% reduction during NAT) was based on prior studies, it was also a consequence of sample size distribution; other cutoffs of CA19-9 response may prove significant in predicting benefit (or lack thereof) of AT. Further validation of this definition of optimal response using larger multicenter database is required. Forth, the optimal responder cohort had lower baseline CA19-9 levels and a higher percentage of neoadjuvant FOLFIRINOX. We included chemotherapy regimen type and length of treatment in our analysis, but due to the small sample size, none of these therapy delivery factors were statistically associated with overall survival, especially after adjusting for therapy effect measured by CA19-9 response. Lastly, histopathological response to NAT may serve as an objective surrogate of systemic response; this was not included in our analysis due to a lack of consistency in reporting this outcome in the literature and our own institution.

In conclusion, this study suggests that the magnitude of CA19-9 response during neoadjuvant therapy may predict additional survival benefit (or lack thereof) from adjuvant

therapy. In our cohort, CA19-9 normalization with a decline of >50% during neoadjuvant therapy was associated with lack of any additional survival benefit from adjuvant therapy. Conversely, adjuvant therapy was found to be beneficial in the subgroup that did not achieve optimal CA19-9 decline during NAT. The optimal sequencing of chemotherapy in localized pancreatic cancer needs to be further investigated in larger prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosure:

Dr. Melissa Hogg has received grant from Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and Intuitive Surgical Inc.

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Synopsis

Although adjuvant therapy confers a survival benefit in resected pancreatic cancer, its impact following neoadjuvant therapy remains to be evaluated. In this analysis, CA19-9 normalization with a decline of >50% during neoadjuvant therapy was associated with lack of additional survival benefit from adjuvant therapy. Conversely, adjuvant therapy was found to improve survival in the subgroup that did not achieve optimal CA19-9 decline during NAT. This study suggests that the magnitude of CA19-9 response to neoadjuvant therapy may predict the need (or lack thereof) for further adjuvant therapy in resected pancreatic cancer.

Figure 1:
CONSORT diagram.

Figure 2:

CA19-9 changes during NAT (panels A and B) and Kaplan Meier analysis (panels C and D).

A: sub-optimal CA19-9 response

B: optimal CA19-9 response

C: Adjuvant therapy conferred additional survival in patients whose CA19-9 did not optimally respond to NAT: median OS 34.5 months (95% CI: 27.6–41.4) versus 19.1 months (95% CI: 12.3–25.9) ($p < 0.001$).

D: Adjuvant therapy did not confer additional survival benefit in patients with optimal CA19-9 response to NAT: median OS 40.6 months (95% CI: 28.1–53.1) versus 39.0 months (95% CI: 18.9–59.1) ($p = 0.815$)

Table 1:Overall cohort demographics, disease and treatment-related characteristics^{*}

Variable	Overall cohort	**Non-optimal CA19-9 response (n=163)	***Optimal CA19-9 response (n=78)	P value
Baseline data				
Age (Years)	65.4 ± 9.5	65.8 ± 9.5	64.6 ± 9.5	0.352
Sex, Male	121 (50.2%)	79 (48.5%)	41 (52.6%)	0.552
CCI (age adjusted)	5 (4 – 6)	5 (4 – 6)	4.5 (4 – 5)	0.277
Pre-NAT CA19-9 (U/mL)	317 (118.7 – 1283.9)	480.1 (158.7 – 1901.7)	165.3 (94.1 – 374.9)	<0.001
Neoadjuvant treatment (NAT) data				
Neoadjuvant regimen				
Gem based combination	169 (70.1%)	121 (74.2%)	48 (61.5%)	0.044
5FU based combination	72 (29.9%)	42 (25.8%)	30 (38.5%)	
No. of neoadjuvant cycles	3 (2 – 4)	3 (2 – 4)	3 (2 – 5)	0.165
Neoadjuvant chemoradiation	48 (19.9%)	34 (20.9%)	14 (17.9%)	0.597
Operation				
Whipple	201 (83.4%)	139 (85.3%)	62 (79.5%)	0.066
Distal	29 (12.0%)	20 (12.3%)	9 (11.5%)	
DPCAR	10 (4.2%)	3 (1.8%)	7 (9%)	
Total pancreatectomy	1 (0.4%)	1 (0.6%)	0 (0%)	
Pathologic data				
Lymph node positive disease	159 (66.0%)	115 (70.6%)	44 (56.4%)	0.030
Number of positive nodes	2.8 ± 0.3	3.2 ± 0.3	2.0 ± 0.4	0.008
Number of lymph nodes examined	30 ± 13	29 ± 12	31± 14	0.210
Lymph Node Ratio				
0	84 (34.9%)	50 (30.7%)	34 (43.6%)	0.066
>0 and 0.2	121 (50.2%)	84 (51.5%)	37 (47.4%)	
>0.2	36 (14.9%)	29 (17.8%)	7 (9%)	
Tumor Size (cm)	2.8 ± 1.2	3.0 ± 1.2	2.5 ± 1.2	<0.001
Margin Positive (R1)	46 (19.1%)	33 (20.3%)	13 (16.7%)	0.508
LVI Positive	165 (68.5%)	117 (71.8%)	48 (61.5%)	0.109
PNI Positive	191 (79.3%)	138 (84.7%)	53 (68.0%)	0.003
Tumor differentiation				
Well/moderate	170 (70.5%)	114 (69.9%)	56 (71.8%)	0.081
Poorly diff	59 (24.5%)	44 (27.0%)	15 (19.2%)	
Unspecified (due to treatment effect)	12 (5%)	5 (3.1%)	7 (9%)	
Post-operative/Adjuvant data				
Any complications	161 (66.8%)	104 (63.8%)	57 (73.1%)	0.153
Clavien-Dindo 3	51 (21.2%)	35 (21.5%)	16 (20.5%)	0.865
Adjuvant chemotherapy receipt	178 (73.9%)	121 (74.2%)	57 (73.1%)	0.848
Number of adjuvant chemotherapy cycle	4 (3–6)	4.5 (3–6)	4 (3–6)	0.689
Adjuvant chemoradiation	19 (7.9%)	12 (7.4%)	7 (9.0%)	0.664

NAT: Neoadjuvant therapy, LVI: lymphovascular invasion, PNI: perineural invasion, DPCAR: Distal pancreatectomy with celiac artery resection,

* Presented as n (%), mean $\pm$ SD, or median (IQR) were appropriate

** CA19-9 sub-optimal responders: post-NAT CA19-9 did not normalize or did not decrease more than 50%

*** CA19-9 optimal responders: post-NAT normalization of CA19-9 by decreasing more than 50%

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Table 2:

Cox Proportional Hazard Model on 241 patients with NAT and CA19-9 measurement

	Univariable		Multivariable*	
	Hazards Ratio (95% CI)	P value	Hazards Ratio (95% CI)	P value
Age	1.007 (0.988 – 1.026)	0.468		
Sex (F)	1.137 (0.804 – 1.608)	0.467		
CCI, age adjusted	1.068 (0.950 – 1.201)	0.268		
Baseline (pre NAT) CA19-9 (log2)	1.022 (0.944 – 1.108)	0.588		
Neoadjuvant Regimen (5FU vs Gem)	0.730 (0.482 – 1.105)	0.137		
Number of neoadjuvant cycles	0.941 (0.858 – 1.032)	0.194		
Neoadjuvant chemoradiation	1.262 (0.854 – 0.867)	0.242		
Operation (vs Whipple)				
Distal pancreatectomy	0.603 (0.316 – 1.152)	0.125		
DPCAR	1.090 (0.444 – 2.675)	0.850		
Others	1.992 (0.277 – 14.337)	0.494		
Lymph node ratio	1.773 (1.369 – 2.296)	<0.001	1.438 (1.096 – 1.887)	0.009
N1 disease	1.650 (1.128 – 2.415)	0.010		
No. of positive LN	1.102 (1.067 – 1.140)	<0.001		
Tumor size	1.136 (0.991 – 1.302)	0.066		
Positive Margin	2.215 (1.476 – 3.325)	<0.001	1.856 (1.215 – 2.835)	0.004
LVI	2.130 (1.425 – 3.185)	<0.001		
PNI	2.602 (1.561 – 4.338)	<0.001	1.737 (0.999 – 3.021)	0.051
Tumor grade (poor vs well/mod)	2.116 (1.443 – 3.103)	<0.001	1.841 (1.248 – 2.716)	0.002
Clavien-Dindo complications 3	1.518 (1.033 – 2.233)	0.034		
Adjuvant chemoradiation	0.824 (0.418 – 1.625)	0.576		
Adjuvant chemotherapy	0.642 (0.443 – 0.931)	0.019	0.437 (0.284 – 0.672)	<0.001
Number of adjuvant chemo cycles	0.889 (0.830 – 0.952)	0.001		
Optimal CA19-9 response (normalization and >50% reduction)	0.665 (0.445 – 0.992)	0.046	0.419 (0.203 – 0.865)	0.019
Interaction between adjuvant therapy and optimal CA19-9 response	0.707 (0.447 – 1.120)	0.139	2.495** (1.043 – 5.968)	0.040

NAT: Neoadjuvant therapy, CCI: Charlson Comorbidity index, LVI: lymphovascular invasion, PNI: perineural invasion, DPCAR: Distal pancreatectomy with celiac artery resection,

* Backwards stepwise multivariate adjusted model. Input model included age, gender, NAT regimen, Charlson Comorbidity index, pre-NAT CA19-9, operation type, lymph node ratio, tumor size, margin status, LVI, PNI, Tumor grade, Calvein-Dindo grade of surgical complication, adjuvant therapy, CA19-9 optimal response as well as adjuvant therapy*CA19-9 interaction term.

Number of observations = 241, LR chi2 (5) = 55.54, P<0.0001

Test of proportional-hazard assumption: P = 0.280, fail to reject and therefore there is not enough evidence to assume that proportional-hazard assumptions have not been met.

*** Independent Hazard Ratio presented in stratified analysis (Table 3 and 4)

Table 3:

Cox proportional hazard model in sub-optimal CA19-9 responders indicating *a benefit* to adjuvant therapy in this cohort.

	Univariable		Multivariable*	
	Hazards Ratio (95% CI)	P value	Hazards Ratio (95% CI)	P value
Age	1.000 (0.979 – 1.022)	0.968		
Sex (F)	1.309 (0.878 – 1.952)	0.186		
CCI, age adjusted	1.027 (0.895 – 1.178)	0.708		
Baseline (pre-NAT) CA19-9 (log2)	0.999 (0.911 – 1.095)	0.982		
Neoadjuvant Regimen (5FU vs Gem)	0.816 (0.501 – 1.329)	0.413		
Number of neoadjuvant cycles	0.957 (0.864 – 1.060)	0.399		
Operation (vs Whipple)				
Distal	0.431 (0.188 – 0.985)	0.046		
DPCAR	1.435 (0.351 – 5.861)	0.615		
Others	1.700 (0.235 – 12.279)	0.599		
Lymph node ratio	1.769 (1.314 – 2.382)	<0.001	1.454 (1.076 – 1.965)	0.015
N1 disease	1.661 (1.045 – 2.640)	0.032		
No. of positive LN	1.088 (1.048 – 1.129)	<0.001		
Tumor size	1.102 (0.933 – 1.302)	0.252		
Positive Margin	2.322 (1.471 – 3.665)	<0.001	1.864 (1.157 – 3.004)	0.011
LVI	2.498 (1.508 – 4.135)	<0.001		
PNI	3.328 (1.594 – 6.948)	0.001	2.481 (1.153 – 5.338)	0.020
Tumor grade (poor vs well/mod)	1.814 (1.176 – 2.798)	0.007	1.641 (1.062 – 2.534)	0.026
Clavien-Dindo complications 3	1.581 (1.013 – 2.465)	0.141		
Adjuvant therapy	0.491 (0.319 – 0.755)	0.001	0.448 (0.291 – 0.689)	<0.001
Number of adjuvant chemo cycles	0.860 (0.795 – 0.931)	<0.001		

NAT: Neoadjuvant Chemotherapy, LVI: lymphovascular invasion, PNI: perineural invasion, DPCAR: Distal pancreatectomy with celiac artery resection

* Backwards stepwise multivariate adjusted model. Input model included age, gender, NAT regimen, Charlson Comorbidity index, pre-NAT CA19-9, operation type, lymph node ratio, tumor size, margin status, LVI, PNI, Tumor grade, Clavien-Dindo grade of surgical complication and adjuvant therapy. Number of observations = 163, LR chi2 (5) = 44.89, P<0.0001

Test of proportional-hazard assumption: P = 0.492, fail to reject and therefore there is not enough evidence to assume that proportional-hazard assumptions have not been met.

Table 4:

Cox proportional hazard model on optimal CA19-9 responders, indicating *lack of benefit* from adjuvant therapy in this cohort

	Univariable		Multivariable*	
	Hazards Ratio (95%CI)	P value	Hazards Ratio (95%CI)	P value
Age	1.020 (0.980 – 1.062)	0.325		
Sex (F)	0.799 (0.397 – 1.606)	0.528		
CCI, age adjusted	1.154 (0.903 – 1.473)	0.252	1.300 (0.989 – 1.708)	0.060
Baseline (pre NAT) CA19-9 (log2)	0.991 (0.808 – 1.216)	0.934		
Neoadjuvant regimen (5FU vs Gem)	0.655 (0.292 – 1.470)	0.305		
No. of neoadjuvant cycles	0.913 (0.746 – 1.117)	0.377		
Operation (vs Whipple)				
Distal	1.583 (0.547 – 4.580)	0.397		
DPCAR	1.337 (0.400 – 4.461)	0.637		
Lymph node ratio	1.575 (0.890 – 2.785)	0.119		
N1 disease	1.422 (0.693 – 2.918)	0.337		
No. of positive LN	1.135 (1.050 – 1.228)	0.002	1.155 (1.063 – 1.255)	0.001
Tumor size	1.076 (0.827 – 1.401)	0.585		
Positive Margin	1.725 (0.693 – 4.297)	0.242		
LVI	1.412 (0.682 – 2.924)	0.353		
PNI	1.601 (0.733 – 3.499)	0.238		
Tumor grade (poor vs well/mod)	3.142 (1.360 – 7.261)	0.007	3.967 (1.627 – 9.670)	0.002
Clavien-Dindo complications 3	1.407 (0.645 – 3.068)	0.391		
Adjuvant therapy	1.094 (0.517 – 2.316)	0.815		
Number of adjuvant chemo cycles	0.941 (0.813 – 1.089)	0.417		

NAT: Neoadjuvant therapy, LVI: lymphovascular invasion, PNI: perineural invasion, DPCAR: Distal pancreatectomy with celiac artery resection

* Backwards stepwise multivariate adjusted model. Input model included age, gender, NAT regimen, Charlson Comorbidity index, pre-NAT CA19-9, operation type, positive LN number, tumor size, margin status, LVI, PNI, Tumor grade, Calvein-Dindo grade of surgical complication and adjuvant therapy.

Number of observations = 78, LR chi2 (3) = 17.25, P=0.0006

Test of proportional-hazard assumption: P=0.901, fail to reject and therefore there is not enough evidence to assume that proportional-hazard assumptions have not been met.