Original Article

Long-term outcomes by response to neoadjuvant chemotherapy or chemoradiation in patients with resected pancreatic adenocarcinoma

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Background: Response of pancreatic adenocarcinoma to neoadjuvant chemotherapy (nCT) or chemoradiotherapy (nCRT) may be associated with prognosis, but long-term outcomes based on response to neoadjuvant therapy have not been well evaluated to date.

Methods: The National Cancer Database was queried for patients with pancreatic adenocarcinoma receiving nCT/nCRT. To evaluate response to nCT/nCRT, comparisons were made from cT and cN stage to the respective post-neoadjuvant therapy ypT and ypN stages. Based on these comparisons, patients were classified as responders, progressors, or non-responders. Statistical analyses included estimation of survival using Kaplan-Meier analysis, as well as multivariable Cox proportional hazards modeling.

Results: Of 2,028 patients, 30% had a response, 32% progressed, and 38% had no response; 1% of patients experienced pathologic complete response (pCR). Responders were more likely to have received multi-agent chemotherapy (P=0.0001) as well as radiotherapy (RT) (P=0.02) in the neoadjuvant setting. Response to nCT/nCRT was also associated with a higher R0 resection rate (P=0.02). At a median follow-up of 49 months, median overall survival (OS) was higher in responders than non-responders or progressors (29.9 *vs.* 24.3 *vs.* 22.2 months, P<0.001). The mean OS for patients experiencing pCR was 55.5 months. On multivariable analysis, treatment response was independently associated with OS (P=0.02).

Conclusions: Response to nCT/nCRT independently predicts long-term outcomes following resection of pancreatic adenocarcinoma; higher rates of treatment response were observed for patients receiving neoadjuvant RT as well as neoadjuvant multi-agent chemotherapy. These results may have implications on strategies to improve response rates.

Keywords: Neoadjuvant chemotherapy (nCT); neoadjuvant chemoradiotherapy (nCRT); pancreatic adenocarcinoma

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a lethal, yet relatively common malignancy, with over 55,000 patients diagnosed annually (1). Surgical resection is the only potential curative treatment option; however, only 15–20% of patients are considered acceptable candidates for surgery (2). Even following complete resection, prognosis remains poor, with 5-year estimated survival rates of 10% and 30% in cases of node-positive and node-negative disease, respectively (3,4).

While multiple prospective studies have supported adjuvant systemic therapy for these patients, the data regarding neoadjuvant therapy are comparatively sparse (5-12). Current guidelines recommend consideration of neoadjuvant therapy in patients with borderline resectable (BR) disease. For patients with BR disease, neoadjuvant therapy may increase the rate of R0 resection (10). This is particularly important in the context of PDAC since survival following R1/2 resection is comparable to that of unresected disease (13,14). Additionally, roughly 30% of patients with initially unresectable disease can be converted to resectable disease after neoadjuvant therapy (15,16).

An additional advantage to neoadjuvant therapy relates to the assessment of clinical response (tumor biology) and individualizing subsequent therapy accordingly. Following neoadjuvant chemotherapy (nCT) or chemoradiotherapy (nCRT), a meta-analysis using the response evaluation criteria in solid tumors (RECIST) showed that a partial response was achieved in 29%, stable disease in 46%, progression in 17%, and a complete response in 3% (17). Despite these data, long-term outcomes based on response to neoadjuvant therapy in PDAC have not been well evaluated thus far. Analogous investigations of other neoplasms have proven highly useful to quantitatively describe expected outcomes based on clinical response to neoadjuvant therapy (18,19). Given this knowledge gap, our aim was to evaluate PDAC outcomes based on response to neoadjuvant therapy (and predictive factors thereof) through analysis of a large contemporary database.

Methods

The National Cancer Database (NCDB) is a tumor registry overseen by the American Cancer Society and the American College of Surgeons. It contains de-identified data involving approximately 70% of cancer cases in the United States from over 1,500 hospitals accredited by the Commission on Cancer (CoC) and is thus exempt from institutional review board supervision. We queried the database [2004–2015] to identify patients with newly diagnosed PDAC who had received nCT or nCRT. Patients were excluded from the study if any of the following criteria were met: non-adenocarcinoma histology, unknown clinical or pathological stage (in order to allow for response assessment), stage IV disease, clinical T0 or TX (evidence of a primary tumor was needed to assess for response), lack of pancreatectomy, and receipt of immunotherapy or palliative treatment (as characterized by the NCDB, this includes therapy intended to control symptoms, alleviate pain and make the patient more comfortable). Patients with follow-up less than one month were also excluded to account for immortal time bias. Patients who had received adjuvant therapy were included in this study as this does not impact pathologic response. A complete CONSORT diagram depicting this selection process is outlined in *Figure S1*.

To evaluate response to neoadjuvant therapy, clinical T and N stage was compared to post-nCT/nCRT pathologic T and N stage (American Joint Cancer Committee, 7th edition); this was done by means of evaluating cT (designated as "*a*") to ypT ("*b*") disease, and cN ("*c*") to ypN ("*d*") disease, similar to prior investigations in other disease sites (18,19). Based on these comparisons, patients were categorized into three cohorts. Responders referred to $a \geq b$ (primary tumor response) and/or $c \geq d$ (nodal response) (with the exception of $a=b$ & $c=d$). Progressors were defined by $a<b$ & $c=d$ (tumor progression), $a=b$ & $c<d$ (nodal progression), or $a<b$ & $c<d$ (tumor and nodal progression). Non-responders encompassed both a lack of response ($a=b$ & $c=d$) and mixed response ($a>b$ & $c<d$, or $a<b$ & $c>d$). In the context of the above response schema, it is noteworthy that the NCDB does not code for imaging-based response criteria, such as RECIST.

Data were analyzed using Medcalc Version 18 (Ostend, Belgium). Overall survival (OS) was calculated in months from time of diagnosis to time of death (or censored at last contact). The Kaplan-Meier method was utilized to estimate survival over time; reverse Kaplan-Meier survival analysis was used to estimate median follow-up time. Cox proportional hazards model was used for multivariable survival analysis. Adjusted hazard ratios and 95% confidence intervals were reported, using an α-level of 0.05 to indicate statistical significance.

Results

Patient and disease characteristics

We identified 2,028 patients meeting the above eligibility criteria, with 30% of patients (n=611) having a response to nCT/nCRT, 32% (n=640) progressing, and 38% (n=777) having no response. Twenty-two patients (1%) experienced pathologic complete response (pCR). *Table 1* provides baseline characteristics for the entire cohort. The majority of patients were cT3 (52%) and cN0 (70%). Nearly two-thirds of the cohort (65%) received multiagent nCT, while approximately half (51%) received neoadjuvant radiation therapy. Following surgery, more than 80% of patients had negative margins (R0 resection). *Table 2* compares the clinical and pathologic staging of both the primary tumor and lymph nodes for the entire cohort.

Differences in demographic and disease-related characteristics between those patients who responded to nCR/nCRT and those who did not are outlined in *Table 3*. Of note, receipt of multiagent nCT [P<0.001; hazard ratio (HR): 0.55; 95% confidence interval (CI): 0.40–0.74] and neoadjuvant radiation therapy (P=0.02; HR: 0.72; 95% CI: 0.55–0.94) were associated with higher likelihood of pathologic response. Additionally, responding patients were more likely to have negative surgical margins (P=0.02; HR: 0.65; 95% CI: 0.45–0.94). Examining the 22 pCR patients, only receipt of neoadjuvant radiation therapy predicted for pCR (P=0.05).

Survival

Median follow-up for the full cohort was 49 months (95% CI: 44–49 months). Median OS was assessed by treatment response (29.9 months for responders, 24.3 months for non-responders, and 22.2 months for progressors); OS was higher among responders compared to either non-responders (P<0.001; HR: 0.63; 95% CI: 0.57–0.71) or progressors (P<0.001; HR: 0.52; 95% CI: 0.46–0.59) (*Figure 1A*). Additionally, the average OS for patients with pCR versus all non-pCR responders, non-responders and progressors was 55.5 *vs.* 26.6 months (median OS of the pCR cohort was not reached) (P=0.001) (*Figure 1B*). To evaluate the comparative effect of primary tumor versus nodal response, responders were further subdivided into those experiencing a T response, an N response, or both. This revealed similar OS between each subgroup (29.5 *vs.* 28.6 *vs.* 35.4 months, respectively) (P=0.28) (*Figure 1C*). When comparing OS between those patients receiving

Table 1 Patient and treatment characteristics (n=2,028)

Characteristic	No. (% or range)
Demographics	
Sex	
Male	1,050 (51.8)
Female	998 (49.2)
Age	
≤65	1,118 (55.1)
>65	910 (44.9)
Race	
Caucasian	1,793 (88.4)
African American	168 (8.3)
Other/unknown	66 (3.3)
Comorbidity score	
0	1,366 (67.4)
1	522 (25.7)
2+	140 (6.9)
Insurance	
Not insured	37 (1.8)
Private	910 (44.9)
Government	1,050 (51.8)
Unknown	51 (2.5)
Education	
≥21%	260 (12.8)
13% to 20.9%	489 (24.1)
7% to 12.9%	694 (34.2)
<7%	565 (27.9)
Unknown	40 (2.0)
Income, US dollars	
<38,000	301 (14.8)
38,000 to 48,000	480 (23.7)
48,000 to 63,999	573 (28.3)
≥63,000	674 (33.2)
Treatment facility type	
Community cancer program	425 (21.0)
Academic/research program	1,225 (60.4)
Integrated network	351 (17.3)
Unknown	27 (1.3)
Distance to treatment facility, miles	
≤20	1,021 (50.3)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	No. (% or range)
>20	987 (48.7)
Unknown	20 (1.0)
Treatment facility location	
Eastern	959 (47.3)
Central	880 (43.4)
Western	189 (9.3)
Patient residence	
Metro	1,567 (77.3)
Urban	350 (17.3)
Rural	35 (1.7)
Unknown	96 (4.7)
Year of diagnosis	
Before 2012	1,143 (56.4)
After 2012	885 (43.6)
Disease characteristics	
CA 19-9 Level	
>98	664 (32.7)
≤98	552 (27.2)
Unknown	812 (40.0)
Surgical margins	
Positive margin	331 (16.3)
R0	1,645 (81.1)
Unknown	52 (2.6)
Multiagent CT	
Yes	1,256 (61.9)
No	685 (33.8)
Unknown	87 (4.3)
Grade	
Well differentiated	153 (7.5)
Moderately differentiated	656 (32.3)
Poorly differentiated	444 (21.9)
Unknown	775 (38.2)
nCRT	
Yes	1,041 (51.3)
No	987 (48.7)

Education refers to the percent of the patient's zip code without a high school diploma. Income is median household income in the patients' residence census tract. CT, chemotherapy; nCRT, neoadjuvant chemoradiotherapy.

Table 2 Relationship between clinical and pathologic staging in primary tumor and lymph nodes

Variable	No. [%]
Primary tumor	pT0/pT1/pT2/pT3/pT4
cT1	0 [0]/50 [42]/10 [9]/57 [48]/1 [1]
cT2	4 [1]/78 [14]/121 [22]/328 [61]/8 [2]
cT3	14 [1]/127 [12]/132 [13]/754 [72]/26 [2]
cT4	5 [2]/43 [13]/30 [9]/184 [58]/57 [18]
Nodal	pN0/pN+
cN0	889 [63]/531 [37]
cN+	355 [58]/253 [42]

nCRT *vs.* nCT, there was no significant difference in OS (*Figure 2*).

On multivariable analysis, treatment response was independently associated with OS. Progression following treatment was independently associated with decreased OS (P<0.05 for both; *Table 4*). Additionally, R0 resection, receipt of multiagent chemotherapy, and lower CA 19-9 level also predicted for better OS (P<0.05 for all). Although limited by the small sample sizes, pCR showed a trend toward increased OS (HR 0.41 with non-pCR as a reference, P=0.08).

Discussion

Response of PDAC to neoadjuvant therapy influences prognosis, but to date high-volume data of long-term outcomes based on treatment response have been lacking. Our results have shown that following nCT/nCRT, T/N response was achieved in 30% of patients, compared to progression in 32% and non-response in 38%. The pCR rate is this study was 1%. Treatment response significantly influenced OS, including a strong trend for pCR (P=0.08) (*Table 4*).

Several studies have assessed the impact of nCT regimens on oncologic outcomes in the resectable or BR populations (12,20,21). A recent phase II trial evaluated R0 resection rates in patients with previously untreated, BR PDAC following neoadjuvant FOLFIRINOX. R0 resection was achieved in 65% of patients, and median progression free survival (PFS) and OS were found to be prolonged (20). The current PREOPANC trial has shown similar results, with preoperative chemoradiotherapy significantly

Table 3 Comparative analysis of baseline characteristics in patients with PDAC who responded to nCT/nCRT

Characteristic	Odds ratio	95% CI	P
Sex			
Male	1	Ref	
Female	1.28	0.99–1.64	0.06
Race			
Caucasian	1	Ref	
African American	1.09	0.68–1.77	0.71
Other	0.98	0.50–1.93	0.96
Age			
≤65	1	Ref	
>65	0.89	0.64–1.23	0.48
Year of diagnosis			
Before 2012	1	Ref	
After 2012	1.06	0.79–1.41	0.71
Insurance			
None	1	Ref	
Private payer	0.68	0.29–1.54	0.35
Government	0.82	0.35–1.92	0.65
Unknown	0.87	0.58–4.11	0.38
Facility type			
Community cancer program	1	Ref	
Academic cancer program	0.88	0.63–1.22	0.45
Integrated cancer program	1.05	0.70–1.56	0.82
Patient residence			
Metro	1	Ref	
Urban	1.05	0.72–1.54	0.79
Rural	1.15	0.47–2.82	0.76
Unknown	1.51	0.92–2.49	0.11
Facility location			
Eastern region	1	Ref	
Central region	1.06	0.81–1.40	0.68
Western region	1.30	0.84–2.0	0.24
Distance to facility			
≤20 miles	1	Ref	
>20 miles	0.90	0.67–1.19	0.45
Unknown	0.77	0.31–1.87	0.56
Income, USD			
<38,000	1	Ref	
38,000–48,000	1.23	0.78–1.94	0.38
48,000–62,999	1.26	0.78–2.03	0.34
>63,000	1.11	0.63–1.96	0.71
Education			
≥21%	1	Ref	
13% to 20.9%	1.42	0.90–2.26	0.14
7% to 12.9%	1.13	0.70–1.85	0.61
<7%	1.44	0.82–2.54	0.21
Unknown	0.56	0.22–1.41	0.22
Comorbidity score			
0	1	Ref	
1	0.82	0.62–1.10	0.19
>2	0.42	0.24–0.73	0.002
Grade			
Well differentiated	1	Ref	
Moderately differentiated	0.79	0.44–1.37	0.38
Poorly differentiated	0.92	0.52–1.65	0.79
Unknown	1.07	0.61–1.85	0.82
CA 19-9 level			
≥98	1	Ref	
<98	0.94	0.73–1.21	0.64
Unknown	0.95	0.76	0.61
Surgical margins			
Positive margin	1	Ref	
Negative margin	0.65	0.45–0.94	0.02
Unknown	0.96	0.51–1.81	0.89
Multiagent CT			
No	1	Ref	
Yes	0.55	0.40–0.74	0.0001
Unknown	0.95	0.61–1.47	0.83
nCRT			
Yes	1	Ref	
No	0.72	0.55–0.94	0.02

Education refers to the percent of the patient's zip code without a high school diploma. Income is median household income in the patients' residence census tract. PDAC, pancreatic ductal adenocarcinoma; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy; CT, chemotherapy.

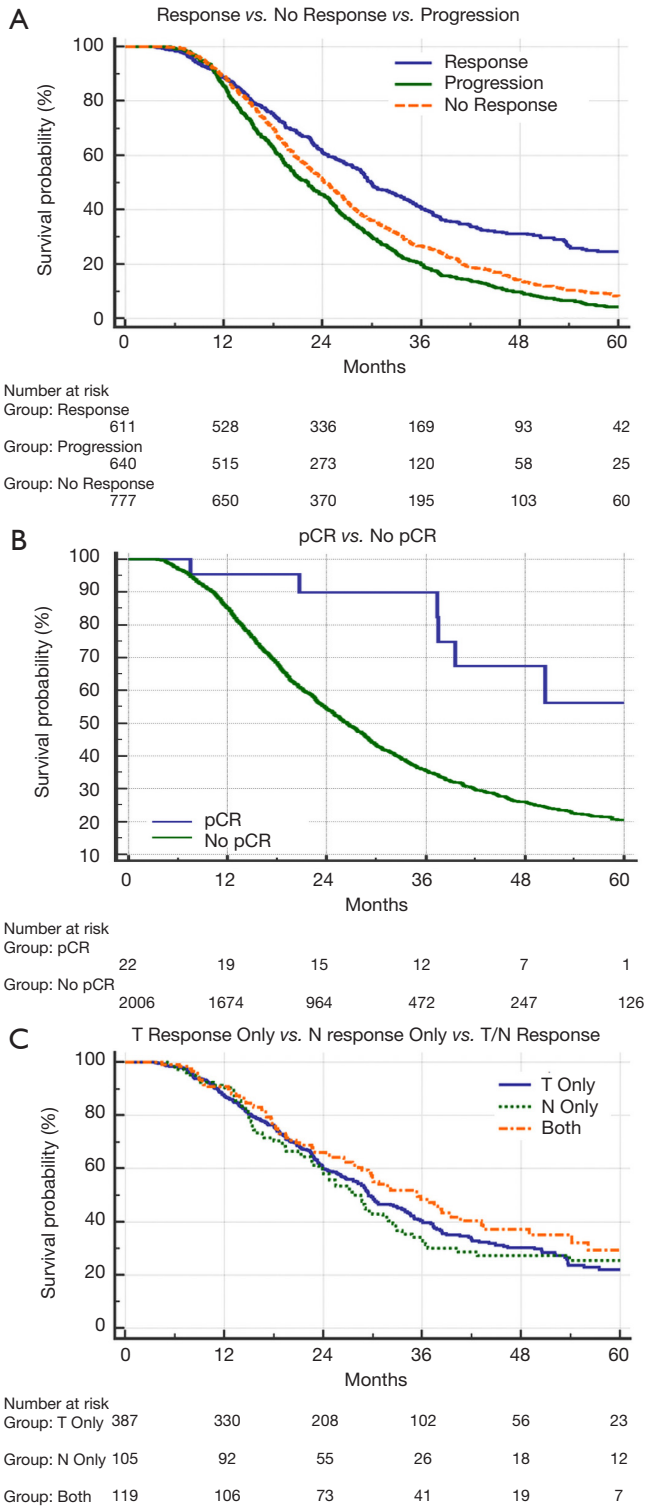

Figure 1 Kaplan-Meier curves comparing OS in responders *vs.* non-responders *vs.* progressors (A) patients achieving pCR *vs.* no pCR (B) and patients with T downstaging *vs.* N downstaging *vs.* both (C). OS, overall survival; pCR, pathologic complete response.

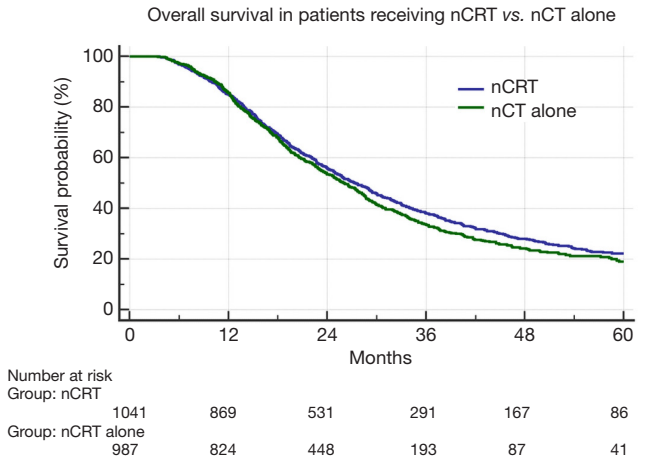

Figure 2 Kaplan-Meier curve comparing OS in patients receiving nCRT *vs.* nCT alone. OS, overall survival; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy.

prolonging OS in patients with BR PDAC when compared with immediate surgery (12). A recent meta-analysis aimed to clarify the effectiveness of FOLFIRINOX as part of a neoadjuvant regimen when compared with single-agent gemcitabine. The median OS ranged from 16–38 months; previous studies of single-agent gemcitabine had observed a median OS of only 6–13 months, indicating that FOLFIRINOX may be more efficacious as a neoadjuvant regimen (21). Taken together, these results support a multiagent neoadjuvant regimen in these patients, as it could increase R0 resection rates and lengthen OS. Our results support these findings, as receipt of multiagent chemotherapy was associated with improved survival. While combination chemotherapy may be more effective in killing tumor cells, the toxicity associated with multiple agents remains a potentially inhibitory risk. Clinical trials are ongoing to determine whether FOLFIRINOX is more effective than gemcitabine/nab-paclitaxel as neoadjuvant therapy (NCT02562716) (22).

The addition of RT to nCT remains controversial. Our data demonstrate an association between nCRT and a higher rate of downstaging (including nodal sterilization), potentially impacting OS indirectly. This concept parallels data from non-small cell lung cancer (23,24). Among PDAC patients, recent retrospective data showed that when used as part of a neoadjuvant regimen with either single agent or multiagent chemotherapy, use of nRT resulted in a significantly higher likelihood of nodal downstaging. Moreover, patients with node-negative status following

Table 4 Multivariable cox proportional hazards models for overall survival in patients with pancreatic adenocarcinoma receiving neoadjuvant ChT or CRT

Significant characteristic	Hazard of death (95% CI), cox model without propensity score	P
Age		
≤65	Reference	
>65	0.97 (0.81–1.18)	0.78
Sex		
Male	Reference	
Female	0.92 (0.79–1.07)	0.28
CA 19-9 level		
≥98	Reference	
<98	1.18 (1.01–1.38)	0.03
Comorbidity score		
0	Reference	
1	1.05 (0.88–1.25)	0.58
>2	0.85 (0.63–1.14)	0.27
cN stage		
0	Reference	
1	1.35 (1.13–1.61)	0.01
cT stage		
1	Reference	
2	1.07 (0.74–1.54)	0.71
3	1.19 (0.83–1.71)	0.33
4	1.68 (1.11–2.57)	0.01
Race		
White	Reference	
African American	0.82 (0.61–1.1)	0.19
Other	1.07 (0.69–1.65)	0.75
Year of treatment		
After 2012	Reference	
Before 2012	1.02 (0.86–1.21)	0.86
Facility location		
Eastern region	Reference	
Central region	1.19 (1.02–1.38)	0.03
Western region	0.89 (0.68–1.18)	0.43
Distance to facility		
≤20 miles	Reference	
>20 miles	1.08 (0.91–1.3)	0.36
Education		
≥21%	Reference	
13% to 20.9%	1.04 (0.80–1.36)	0.75
7% to 12.9%	0.98 (0.76–1.26)	0.86
<7%	0.92 (0.70–1.21)	0.57
Insurance		
Uninsured	Reference	
Private	1.04 (0.60–1.80)	0.88
Government	1.34 (1.15–1.56)	<0.01
Facility type		
Community cancer program	Reference	
Academic program	0.91 (0.75–1.11)	0.35
Integrated program	1.15 (0.90–1.46)	0.27
Patient residence		
Metro	Reference	
Urban	0.99 (0.80–1.24)	0.99
Rural	0.79 (0.46–1.34)	0.34
Grade		
Well-differentiated	Reference	
Moderately-differentiated	1.45 (1.03–2.04)	0.03
Poorly-differentiated	1.80 (1.26–2.56)	<0.01
Response to nCT/nCRT		
No response	Reference	
Response	0.76 (0.61–0.95)	0.02
Progression	1.56 (1.25–1.95)	<0.01
Receipt of nCRT		
No	Reference	
Yes	1.11 (0.94–1.32)	0.21
Surgical margins		
Positive margin	Reference	
Negative margin	0.57 (0.47–0.69)	<0.01
Multiagent chemotherapy		
Yes	Reference	
No	1.5 (1.25–1.76)	<0.01
Pathologic complete response		
Yes	Reference	
No	2.44 (0.90–6.62)	0.08

Education refers to the percent of the patient's zip code without a high school diploma. Income is median household income in the patients' residence census tract. nCT, neoadjuvant | chemotherapy; nCRT, neoadjuvant chemoradiotherapy.

neoadjuvant therapy had a significantly lower risk of death as compared to node-positive cases (25). Our results demonstrate that patients with a response to neoadjuvant therapy are more likely to have R0 resection. Taken together, these results suggest that while neoadjuvant CRT may not directly play a role in increasing OS, it could increase the likelihood of developing a tumor response and make surgery more effective. Lastly, the improved distant control from new multi-agent chemotherapy regimens may shift patterns of failure, implying a greater necessity for local control, which can be better addressed with RT (26).

pCR in PDAC is an extremely rare occurrence, seen in only 3–11% of patients who have undergone resection after receiving neoadjuvant treatment (27), consistent with our results. It should be noted that the rarity of pCR makes interpreting results related to OS difficult. Notably, when multi-agent chemotherapeutic regimens such as FOLFIRINOX are used, however, the rate of pCR has been reported as high as 13% (28). When pCR is achieved, the recurrence risk is sharply lower than expected, thus resulting in improved survival (27). A retrospective study from Johns Hopkins University attempted to clarify the relationship between OS and pCR in 186 patients with PDAC who received neoadjuvant chemoradiation (nCRT) followed by pancreatectomy. The median disease-free survival and OS were found to be significantly increased in patients with pCR when compared to those with near complete response (defined as a primary tumor less than 1cm without nodal metastasis) at 26 *vs.* 12 months and 60 *vs.* 26 months, respectively (29).

Regarding the limitations of this study, there are factors inherent to the NCDB which must be considered when interpreting these results (30-44), in addition to inevitable retrospective selection biases. Most importantly, the results of our study depend on the accuracy of preoperative clinical staging, which is not specified in the NCDB. If cT and cN staging was inaccurate in the NCDB, our grouping of responders, non-responders, and progressors (and survival results thereof) could be affected. The NCDB does not code for RECIST response, necessitating comparison of cT/N to ypT/N to evaluate clinical response [similar to existing studies (18,19)], which may be less clinically significant in some instances (e.g., a 2.1 cm cT2 tumor to a 1.9 cm pT1 tumor). Similarly, as ycN staging is not coded for in the NCDB, our comparison depends on radiologic diagnosis of lymph node metastases, which may not always be accurate. Furthermore, it is unknown if patients underwent pancreatic protocol CT evaluation, which theoretically may yield higher diagnostic accuracy in evaluating the local extent of disease. However, the rates of response (or lack thereof) were roughly similar to studies using RECIST (17). Second, the NCDB lacks data regarding specific chemotherapeutic agents and number of cycles completed, characteristics of RT regimens (e.g., target volumes), tumor biology, performance status, and salvage therapies. Third, the NCDB does not provide data on whether patients are resectable, BR or locally advanced, meaning that translating our results to these specific subgroups of patients is challenging. Fourth, the NCDB also does not code for the time from nC(R)T completion to surgery. Fifth, CA 19-9 and tumor grade were not reported in approximately 40% of patients, limiting robust assessment thereof. As noted above, with such a small sample size, interpreting our results related to pCR is challenging. Furthermore, patients receiving adjuvant therapy were included in the study such that some patients may have received both neoadjuvant and adjuvant therapy which may have affected survival data. Additionally, the NCDB does not provide detailed information regarding surgical resection or vascular invasion, so this data could not be included in our analysis. Lastly, although the NCDB includes data for 70% of the United States population, only CoC-accredited facilities contribute data; as such, these findings may not necessarily be representative of the entire United States population.

In summary, we have shown that receipt of multiagent nCT and nCRT predicts for a downstaging response, and in patients with a response, there is a significant increase in OS. Our novel data thus suggests that more aggressive neoadjuvant therapy can lead to improved outcomes in PDAC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

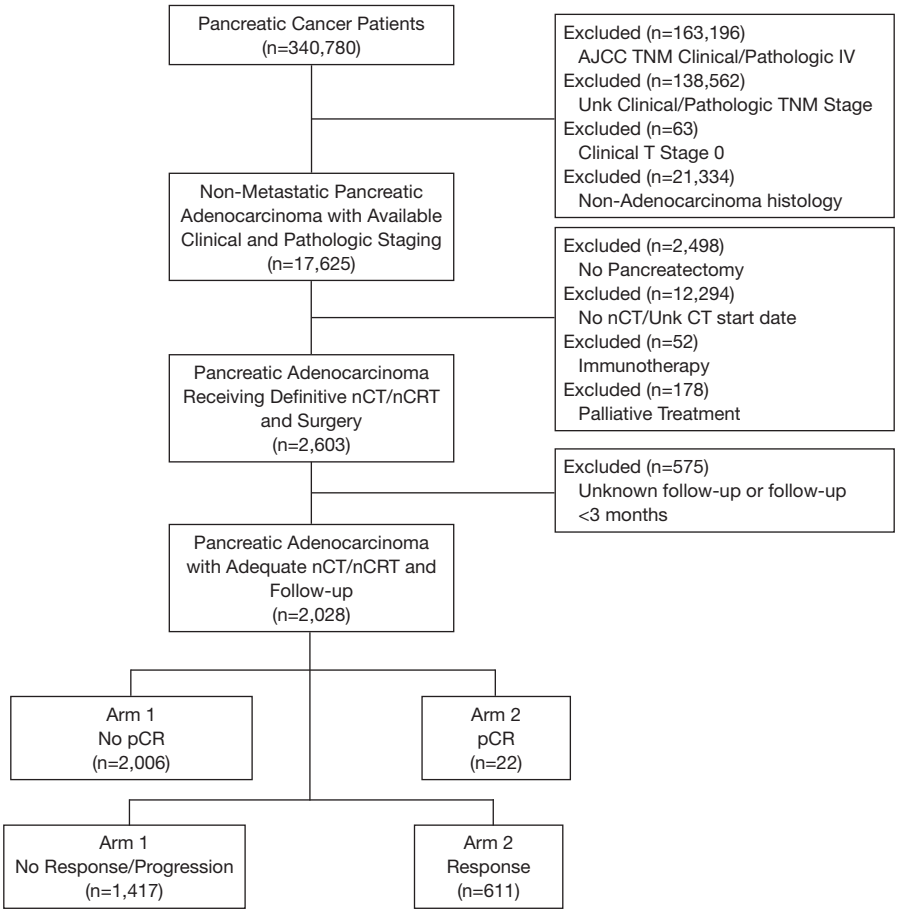

Figure S1 CONSORT diagram, pancreatic cancer patients treated with neoadjuvant chemotherapy or CRT +/– pCR. CRT, chemoradiotherapy; pCR, pathologic complete response; Unk, unknown; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy.