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ORIGINAL ARTICLE

Neoadjuvant therapy affects margins and margins affect all: perioperative and survival outcomes in resected pancreatic adenocarcinoma

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Abstract

Background: Resection margin status is an important prognostic factor in pancreatic cancer; however, the impact of positive resection margins in those who received neoadjuvant therapy remains unclear. The current study investigates the prognostic impact of resection margin status after neoadjuvant therapy and pancreaticoduodenectomy for patients with pancreatic adenocarcinoma.

Methods: Patients who underwent pancreaticoduodenectomy for pancreatic adenocarcinoma between 2006 and 2013 were identified from the National Cancer Database. Multivariable logistic regression analysis was utilized to examine the predictive value of neoadjuvant therapy for resection margin status. Long-term outcomes were compared using a Cox proportional hazards model.

Results: 7917 patients were identified in total: 1077 (13.6%) and 6840 (86.4%) patients received neoadjuvant therapy and upfront surgery, respectively. Upfront surgery was independently predictive of a positive margin (25.7% vs. 17.7%; OR, 1.54) compared to neoadjuvant therapy. After receipt of neoadjuvant therapy, positive margins (median overall survival, 18.5 vs. 25.9 months; HR, 1.58) remained significantly associated with poor survival on multivariable analysis.

Discussion: While neoadjuvant therapy is associated with decreased R1/R2-resection rates after pancreaticoduodenectomy, the poor prognostic impact of positive margins is not abrogated by neoadjuvant therapy, stressing the need for complete tumor clearance and postoperative treatment even after neoadjuvant therapy.

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Introduction

Pancreatic adenocarcinoma currently ranks as the third leading cause of cancer-related death and is estimated to become the second most common cause by 2030.[1] Despite advances in operative techniques, postoperative care, and therapeutic agents, improving the prognosis of pancreatic cancer patients remains a formidable challenge.[2] Complete surgical resection offers the only hope for meaningful survival, yet 50%–86% of patients develop local recurrence following a presumed curative resection.[3–6] The high frequency of local recurrence points to the necessity of multimodal therapy.[7,8] Adjuvant therapy represents the standard of care throughout the United States.[9] While the use of neoadjuvant therapy is recommended in patients with borderline resectable disease and increasingly applied for resectable pancreatic adenocarcinoma, there remains a lack of conclusive results from randomized controlled trials.[10,11]

Over the past decades, pancreatic surgeons have been pushing the boundaries of surgical resection in an effort to attain negative margins. Nonetheless, data from high-volume academic centers show R0-resection rates of only 70%–76% after upfront surgery.[12–14] Previous studies have suggested that neoadjuvant chemoradiation may potentially downstage pancreatic tumors to attain locoregional control and subsequently reducing positive

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margin rates.[15,16] However, controversy continues to exist as to whether neoadjuvant therapy has the ability to abrogate the negative survival impact of positive margins after pancreatic cancer surgery.[17]

As neoadjuvant therapy becomes a more widespread treatment strategy for pancreatic adenocarcinoma, a better understanding of its potential significance for surgical margin clearance is pivotal.[11] Therefore, the aim of this study was to assess the impact of neoadjuvant therapy on resection margin status, and the prognostic impact of incomplete margin clearance after neoadjuvant therapy in resected stage I-III pancreatic adenocarcinoma patients using national cancer registry data.

Methods

Data source

The National Cancer Database is a nationwide hospital-based cancer registry, founded as a joint initiative of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The National Cancer Database comprises more than 30 million patient records collected by over 1500 Commission on Cancer accredited facilities across the United States (US).[18] Furthermore, the National Cancer Database requires centers to maintain a 90% follow-up rate for patients diagnosed within 5 years to remain accredited.[19]

Selection criteria

Using the National Cancer Database, patients diagnosed with pancreatic adenocarcinoma between 2006 and 2013 were identified according to the third edition of the International Classification of Disease for Oncology (ICD-O-3) morphology (8140 and 8500) and topography codes (C25.0, C25.1, C25.2, C25.3, C25.7, C25.8, and C25.9). Patients were excluded if they did not receive pancreaticoduodenectomy (n = 195,674) based on the following Facility Oncology Registry Data Standards (FORDS) site-specific procedure coding: 35, 36, 37, and 70.

The cohort was further limited by sequentially excluding patients diagnosed with clinical M1 disease (n = 748), that did not receive any treatment at the reporting facility (n = 1072), reported other malignancies or received hormone therapy (n = 95), immunotherapy (n = 339), and/or intraoperative chemotherapy and radiation (n = 45). Furthermore, patients were excluded if one of the following variables was unknown or missing: type of surgery, other malignancies (n = 5815), receipt of hormone therapy (n = 1492), receipt of immunotherapy (n = 25), sequence of radiation and surgery (n = 302), sequence of systemic treatment and surgery or receipt of intraoperative systemic therapy (n = 3730), surgical margin status (n = 426), length of inpatient stay (n = 2117), vital status (n = 2421), 90-day mortality (n = 149), age, sex, race (n = 151), comorbidities, insurance status (n = 184), type of treatment facility (n = 2003), clinical stage (n = 4488), tumor differentiation (n = 837), lymph node status (n = 110), and treatment sequence (n = 350).

Predictive variables

Systemic therapy categories were defined using the National Cancer Database PUF's variables for systemic and surgical therapy sequencing. Patients who received any neoadjuvant systemic therapy were grouped together regardless of receipt of adjuvant systemic therapy. Age was dichotomized into <65 years and ≥65 years. Race was grouped as white and other. Comorbid conditions were analyzed using the Deyo modified Charlson comorbidity index and divided into Charlson-Deyo scores of 0 and ≥ 1.[20] Insurance status was dichotomized into private and other. Type of treatment facility was divided in academic and non-academic center. Clinical stage was defined in compliance with the 6th/7th edition staging system proposed by the American Joint Committee on Cancer (AJCC). Whenever clinical tumor stage was missing, the individual clinical T, N and M stages were combined according to AJCC staging guidelines into a group stage.[21] Tumor differentiation was categorized into well, moderately, and poorly or undifferentiated tumors. Receipt of chemotherapy included both single- and multi-agent chemotherapy. Radiotherapy was classified as beam radiation, radioactive implants, and/or radioisotopes. Neoadjuvant therapy was defined as neoadjuvant chemotherapy with or without radiation either before or after surgery. Upfront surgery was defined as either no chemotherapy or chemotherapy administered only after surgical resection, independent of receipt of radiation.

Using the final pathologic report, resection margin status was graded as "negative" (no residual tumor) or "positive" (microscopic residual tumor, macroscopic residual tumor, or residual tumor not otherwise specified). Prolonged hospital stay was defined as over 14 days of hospital admission after date of surgery. 90-day mortality was defined from date of most definitive surgery. Overall survival was calculated as the number of months between the date of diagnosis and the date on which the patient was last contacted or died.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline characteristics were reported as frequencies and distributions. Categorical variables were compared using the chi-square test. The predictors of positive resection margins, prolonged hospital stay, and 90-day mortality were identified using multivariable logistic regression models, including receipt of neoadjuvant therapy, gender, age at diagnosis, race, comorbidities, insurance status, type of treatment center, clinical stage, lymph node status, and tumor differentiation. Since the objective of these multivariable regression models is assessing the association between neoadjuvant therapy and positive resection margins, prolonged hospital stay, and 90-day mortality, these models take into account most confounders and effect modifiers to reduce potential bias at the cost of the discriminative ability of the overall model. This study did not use automated variable selection or resampling.[22–24] The results of the logistic regression models were expressed as odds ratios

(ORs) with 95% confidence intervals (CIs). The c-statistics for the multivariable models were as follows: 0.608 for positive resection margins, 0.576 for prolonged hospital stay, and 0.650 for 90-day mortality.

Survival analysis in all resected pancreatic cancer patients was performed by treatment sequence and by resection margins status using the Kaplan–Meier method. In addition, the prognostic impact of resection margins was assessed separately after neoadjuvant therapy, upfront surgery with or without adjuvant therapy, and upfront surgery succeed by adjuvant chemoradiotherapy using a multivariable Cox proportional hazard model. For patients that received neoadjuvant therapy the model adjusted for: insurance status, type of treatment center, clinical stage and lymph node status, stratified by age group and tumor differentiation grade. For patients that received upfront surgery with or without adjuvant therapy the model adjusted for clinical stage and tumor differentiation, stratified by age group, type of treatment center, insurance status, lymph node status, and receipt of adjuvant therapy. For patients that received upfront surgery succeeded by adjuvant chemoradiotherapy the model adjusted for age group, insurance status, type of treatment center, lymph node status, and clinical stage, stratified by tumor differentiation.

Sensitivity analyses were carried out to assess the robustness of our findings. Multivariable regression analyses predicting positive resection margins (c-statistics, 0.605), prolonged hospital stay (c-statistics, 0.571), and 90-day mortality (c-statistics, 0.645) were performed in patients that underwent neoadjuvant chemoradiotherapy followed by surgery and upfront surgery with or without adjuvant therapy. In addition, multivariable Cox proportional hazard survival analysis adjusted for insurance status, type of treatment center, clinical stage, lymph node status, and margin status, stratified by age and tumor differentiation was performed after excluding patients with macroscopically residual tumor documented. Furthermore, after exclusion of patients treated at non-academic centers, additional multivariable regression analyses for positive resection margins (c-statistics, 0.599), prolonged hospital stay (c-statistics, 0.580), and 90-day mortality (c-statistics, 0.639) were performed. Kaplan–Meier survival analysis was also executed in the afore mentioned subgroup, as the proportional hazard assumption did not hold for margin status in this subgroup. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

7917 patients were identified. In the entire cohort, 1077 (13.6%) patients received neoadjuvant therapy and 6840 (86.4%) patients were resected upfront. The majority of patients were over 65 years old (n = 4427; 55.9%), male (n = 4027; 50.9%), white (n = 6601; 83.4%), had no comorbidities (n = 5265; 66.5%), had non-private insurance (n = 4654; 58.8%), were treated at academic centers (n = 5401; 68.2%), had clinical stage II disease (n = 4576; 57.8%), had positive lymph nodes (n = 5470; 69.1%), and moderately differentiated tumors (n = 4126; 52.1%).

Baseline characteristics are summarized in Table 1. Neoadjuvant therapy was significantly associated with age group, insurance, treatment center, clinical stage, lymph nodes, tumor differentiation, and resection margin status (all $p < 0.0001$).

Surgical outcomes

17.7% (n = 191) and 25.8% (n = 1761) of patients had positive resection margins after neoadjuvant therapy and upfront surgery, respectively. On multivariable analysis, the probability of positive resection margins, male sex, non-white race, non-academic treatment center, upfront surgery, poorly differentiated tumor grade, negative lymph nodes, stage II disease, and stage III disease were predictive for positive resection margins (Table 2). However, age, comorbidities, and insurance were not correlated with resection margin status (Table 2).

17.6% (n = 190) and 21.7% (n = 1481) of patients experiences prolonged hospital stay after surgery following neoadjuvant therapy and upfront surgery, respectively. On multivariable analysis, the probability of experiencing prolonged hospital stay, age ≥65 years at diagnosis, non-white race, any comorbidities, non-private insurance, non-academic treatment center, positive resection margins, upfront surgery, and negative regional lymph nodes were significant predictors of prolonged hospital stay on multivariable analysis (Table 2). However, sex, tumor differentiation, and clinical stage were not significantly associated with prolonged hospital stay (Table 2).

The 90-day mortality rate was 5.7% (n = 61) after neoadjuvant therapy and 7.4% (n = 507) after upfront surgery. On multivariable analysis modeling the probability of dying within 90 days of surgery, age ≥65 years at diagnosis, any comorbidities, non-private insurance, non-academic treatment center, and positive resection margins were associated with 90-day mortality (Table 2). However, sex, race, treatment sequence, tumor differentiation, lymph node status, and tumor stage were not associated with 90-day mortality (Table 2).

Survival

Kaplan–Meier survival curves for resected pancreatic cancer patients by multimodality treatment sequence and resection margin status are shown in Fig. 1. After neoadjuvant therapy, patients with negative resection margins (median overall survival, 25.9 months; 95% CI, 24.7–27.6 months) demonstrated a 7.4 month longer median overall survival compared to patients with positive resection margins (median overall survival, 18.5 months; 95% CI, 15.7–20.8 months). On multivariable survival analysis, positive resection margins, positive lymph node status, and non-academic treatment center were predictive for poor overall survival (Table 3). Insurance status and clinical tumor stage were not significantly associated with overall survival (Table 3).

Table 1 Characteristics and surgical outcomes of resected stage I-III pancreatic adenocarcinoma patients by treatment sequence

Characteristics	No neoadjuvant therapy (n = 6840)	Neoadjuvant therapy (n = 1077)	p-value
Sex, n (%)			
Male	3464 (50.6%)	563 (52.3%)	0.3195
Female	3376 (49.4%)	514 (47.7%)	
Age at diagnosis, n (%)			
< 65 years	2886 (42.2%)	604 (56.1%)	<0.0001
≥ 65 years	3954 (57.8%)	473 (43.9%)	
Race, n (%)			
White	5702 (83.4%)	899 (83.5%)	0.9282
Non-white	1138 (16.6%)	178 (16.5%)	
Comorbidities, n (%)			
No comorbidities	4529 (66.2%)	736 (68.3%)	0.1697
Comorbidities	2311 (33.8%)	341 (31.7%)	
Insurance, n (%)			
Private	2693 (39.4%)	570 (52.9%)	<0.0001
Not private	4147 (60.6%)	507 (47.1%)	
Treatment center, n (%)			
Academic	4532 (66.3%)	869 (80.7%)	<0.0001
Non-academic	2308 (33.7%)	208 (19.3%)	
Clinical stage, n (%)			
Stage I	2778 (40.6%)	246 (22.8%)	<0.0001
Stage II	3905 (57.1%)	671 (62.3%)	
Stage III	157 (2.3%)	160 (14.9%)	
Lymph node status, n (%)			
Negative nodes	1913 (28.0%)	534 (49.6%)	<0.0001
Positive nodes	4927 (72.0%)	543 (50.4%)	
Tumor differentiation, n (%)			
Well	574 (8.4%)	135 (12.5%)	<0.0001
Moderate	3553 (51.9%)	573 (53.2%)	
Poor/undifferentiated	2713 (39.7%)	369 (34.3%)	
Margin status, n (%)			
Negative	5079 (74.3%)	886 (82.3%)	<0.0001
Positive	1761 (25.7%)	191 (17.7%)	
Prolonged inpatient stay, n (%)			
No	5359 (78.4%)	887 (82.4%)	0.0027
Yes	1481 (21.6%)	190 (17.6%)	
90-day mortality, n (%)			
No	6333 (92.6%)	1016 (94.3%)	0.0388
Yes	507 (7.4%)	61 (5.7%)	

In patients that received upfront surgery, negative resection margins (median overall survival, 20.8 months; 95% CI, 20.2–21.4 month) showed improved survival compared to patients with positive margins (median overall survival, 14.7 months; 95% CI, 13.8–15.4 months; $p < 0.0001$). After adjustment for patient characteristics, positive resection margins, clinical stage II/III disease, and tumor differentiation were significantly associated with decreased overall survival (Table 3).

After upfront surgery, 31.9% (n = 2177) of patients did not proceed to receive any adjuvant treatment, 32.6% (n = 2222) received adjuvant chemoradiotherapy, 34.7% (n = 2367) received adjuvant chemotherapy, and 0.8% (n = 54) received adjuvant radiotherapy. For 20 patients, it was unknown whether they received any and/or what type of adjuvant therapy. In patients that received upfront surgery followed by adjuvant chemoradiotherapy, negative resection margins were significantly (log-rank $p < 0.0001$) associated with survival benefit compared to positive resection margin, resulting in a median overall survival of 24.2 months (95% CI, 22.9–25.6 months) versus 19.0 months (95% CI, 17.4–20.5 months). On multivariable analysis, negative margins remained associated with favorable survival in patients that received upfront surgery followed by adjuvant chemoradiotherapy (Table 3).

Sensitivity analysis

Sensitivity analysis was performed in patients that received neoadjuvant chemoradiotherapy succeeded by surgery (n = 617) or upfront surgery (n = 6840). 17.0% (n = 105) and 25.8% (n = 1761) of patients demonstrated positive margins after neoadjuvant chemoradiotherapy and upfront surgery, respectively. After adjustment for differences in patient characteristics and tumor factors, upfront surgery remained predictive for positive resection margins (Supplementary Table 1.) 20.8% (n = 128) of patients experienced prolonged hospital stay after neoadjuvant chemoradiotherapy and 21.7% (n = 1481) after upfront surgery. 6.5% (n = 40) of patients that received neoadjuvant chemoradiotherapy and 7.4% (n = 507) of patients that received upfront died within 90 days of primary surgery. Multivariable logistic regression demonstrated that treatment sequence did not significantly influence 90-day mortality (Supplementary Table 1.).

In patients treated at academic centers (n = 5367), 16.4% (n = 142) and 23.5% (n = 1058) demonstrated positive margins after neoadjuvant therapy and upfront surgery, respectively. On multivariable analysis, upfront surgery significantly increased the likelihood of positive resection margins (Supplementary Table 2). Prolonged hospital stay occurred in 18.0% (n = 156) of the patients that received neoadjuvant therapy and 20.4% (n = 916) of upfront resected patients. Treatments sequence did not significantly impact hospital stay on multivariable analysis (Supplementary Table 2). After adjusting for difference in patient and tumor characteristics, the 90-day mortality rate was 5.4% (n = 47) for the neoadjuvant therapy and 6.7% (n = 300) upfront surgery group (Supplementary Table 2).

In patients that received neoadjuvant therapy followed by surgery without macroscopically residual disease reported, positive resection margin status remained associated with decreased overall survival, as well as positive lymph nodes, and non-

Table 2 Multivariable logistic regression analyses predicting positive resection margins (R1/R2), prolonged hospital stay, and 90-day mortality in resected pancreatic adenocarcinoma patients

	Positive resection margins		Prolonged hospital stay		90-day mortality	
	Odd ratio (95% CI)	p-value	Odd ratio (95% CI)	p-value	Odd ratio (95% CI)	p-value
Sex						
Female	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Male	1.14 (1.03–1.26)	0.0155	0.98 (0.88–1.09)	0.6816	1.02 (0.86–1.21)	0.8335
Age at diagnosis						
< 65 years	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
≥ 65 years	1.00 (0.88–1.14)	0.9858	1.21 (1.05–1.39)	0.0069	1.80 (1.42–2.28)	<0.0001
Race						
White	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Non-white	1.15 (1.00–1.32)	0.0448	1.24 (1.08–1.43)	0.0027	1.10 (0.87–1.38)	0.4186
Comorbidities						
No comorbidities	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Comorbidities	1.05 (0.94–1.17)	0.3726	1.13 (1.01–1.27)	0.0325	1.25 (1.04–1.49)	0.0157
Insurance						
Private	1.000 (Ref)		1.00 (Ref)		1.00 (Ref)	
Not private	1.06 (0.93–1.21)	0.4122	1.19 (1.03–1.37)	0.0171	1.58 (1.24–2.01)	0.0002
Treatment center						
Academic	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Non-academic	1.34 (1.20–1.50)	<0.0001	1.20 (1.07–1.35)	0.0020	1.31 (1.10–1.57)	0.0029
Clinical stage						
Stage I	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Stage II	1.19 (1.07–1.34)	0.0018	0.97 (0.86–1.09)	0.6027	1.16 (0.97–1.40)	0.1132
Stage III	2.44 (1.88–3.17)	<0.0001	1.18 (0.89–1.57)	0.2601	1.54 (1.00–2.38)	0.0498
Lymph node status						
Positive nodes	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Negative nodes	0.53 (0.47–0.60)	<0.0001	1.21 (1.08–1.37)	0.0015	1.07 (0.88–1.29)	0.5188
Differentiation						
Well	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Moderate	1.20 (0.98–1.46)	0.0793	1.00 (0.83–1.22)	0.9684	1.06 (0.77–1.47)	0.7269
Poor/undifferentiated	1.25 (1.02–1.54)	0.0293	1.00 (0.82–1.22)	0.9791	1.12 (0.80–1.56)	0.5170
Treatment						
Neoadjuvant therapy	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Upfront surgery	1.54 (1.29–1.83)	<0.0001	1.25 (1.05–1.49)	0.0130	1.15 (0.86–1.54)	0.3472
Margin status						
Negative	–		1.00 (Ref)		1.00 (Ref)	
Positive	–	–	1.21 (1.07–1.37)	0.0032	1.62 (1.34–1.95)	<0.0001

academic treatment center (Table 4). Insurance status and clinical tumor stage did not significantly impact overall survival (Table 4).

Discussion

This population-level analysis demonstrates that neoadjuvant therapy significantly decreases the likelihood of positive resection margins after pancreaticoduodenectomy. These data provide evidence that a neoadjuvant treatment approach may allow the surgeon to more easily attain a complete resection. Nonetheless, although previously suggested otherwise, positive resection margins remain associated with poor prognosis (median overall survival, 18.5 vs. 25.9 months; HR, 1.58) after neoadjuvant therapy.[17] These findings suggest that, despite neoadjuvant therapy improving the probability of complete tumor clearance, negative resection margins continue to be critical to long-term overall survival, and should remain the goal of curative

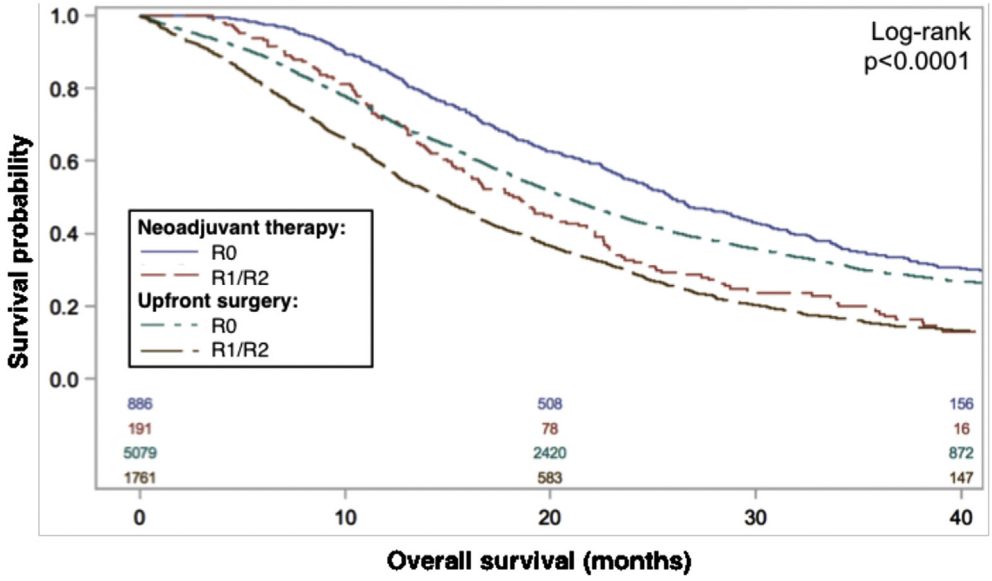

Figure 1 Kaplan–Meier survival curves for resected pancreatic adenocarcinoma patients by treatment sequence and resection margin status

resections. Moreover, these findings highlight the potential for additional postoperative therapy after neoadjuvant therapy and pancreatectomy.

Previous studies have reported varying R0 resection rates, ranging from 15% to 94%.[25,26] This substantial inconsistency in R0 resection rates can partly be explained by intercontinental variability in the definition of R0, which is a 0 mm tumor distance from the resection margin in the US, and ≥1 mm across Europe and Australia.[27–29] In addition, standardized examination has been demonstrated to significantly decrease R0-resection rates.[26] Therefore, the definition of margin involvement wielded in the US and lack of standardization may account for the relatively low R0 resection rates found by this nationwide review in both arms. However, a meta-analysis by Andriulli et al. (2012) demonstrated a pooled proportion R0 resection rate of 89% (95% CI, 83%–94%) after neoadjuvant therapy, which is comparable to our findings.[30] Furthermore, similar to our study, a meta-analysis by Laurence et al. (2011) demonstrated that patients receiving neoadjuvant chemoradiotherapy were significant less likely to have positive margins.[31] Furthermore, this study also revealed that positive margins were associated with increased 90-day mortality, which suggests that positive resection margins are more common in patients that underwent an anatomically challenging resection.

Positive resection margins have been shown to impact outcomes for pancreatic adenocarcinoma, with prior experiences describing a median survival of 10–15 months for patients with positive margins compared to 16–23 months for patients with negative margins after upfront surgery with or without postoperative therapy.[32–37] Raut and colleagues (2007) found no statistically significant difference in survival or recurrence based on resection margin status after the use of neoadjuvant therapy followed by pancreatic surgery with or without postoperative therapy.[17] In their study patients who underwent an R1 resection had a median overall survival of 21.5 months compared with 27.8 months in patients who underwent an R0 resection.[17] Although, the present study was not able to confirm the previously described potential mitigating effect of neoadjuvant therapy on the unfavorable impact of incomplete tumor clearance, it demonstrated a similar survival advantage for patients with negative resection margins.[17]

This study is limited by its retrospective nature and inherent selection bias. In addition, the National Cancer Database has several limitations, including the potential for coding errors, missing data, and the absence of several critical outcomes and variables, including local recurrence rates, specific chemotherapeutic agents, the precise location of margin involvement, vascular invasion, surgeon experience, standardized pathology assessment, and use of frozen section analysis.[28,38,39] Pursuit of negative margins after positive intraoperative frozen-section analysis has been shown to be associated with worse survival than negative margins on initial intraoperative frozen sections.[40,41] In addition, comparability of studies on resection margin status is often plagued by frequent underreporting of microscopic margin involvement due to inconsistent pathologic review practices.[42] Neoadjuvant therapy has also shown to alter the consistency of the pancreas, which may impact pathologic evaluation of tumor cells at the circumferential margin.[43] Furthermore, it should be acknowledged that this study did not take into account intention to treat, and does not account for patients who progressed on chemotherapy and were thus never resected. Patients who undergo resection following neoadjuvant therapy may be considered as a distinct subset of patients with better tumor biology.[15] Therefore, the favorable impact of

Table 3 Multivariate Cox models in stage I-III pancreatic adenocarcinoma that underwent neoadjuvant therapy and surgery, upfront surgery with or without adjuvant therapy, or upfront surgery followed by adjuvant chemoradiotherapy

	Neoadjuvant therapy		Upfront surgery		Upfront surgery and adjuvant chemoradiotherapy	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age at diagnosis						
< 65 years	–		–		1.00 (Ref)	
≥ 65 years	–	–	–	–	1.14 (1.00–1.29)	0.0455
Insurance						
Private	1.00 (Ref)		–		1.00 (Ref)	
Not private	1.14 (0.94–1.37)	0.1752	–	–	1.13 (0.99–1.28)	0.0655
Treatment center						
Academic	1.00 (Ref)		–		1.00 (Ref)	
Non-academic	1.29 (1.08–1.55)	0.0047	–	–	1.18 (1.07–1.31)	0.0009
Clinical stage						
Stage I	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Stage II	1.19 (0.99–1.43)	0.0683	1.08 (1.02–1.14)	0.0109	1.11 (1.00–1.23)	0.0451
Stage III	1.19 (0.93–1.52)	0.1587	1.39 (1.16–1.67)	0.0003	1.51 (1.10–2.08)	0.0107
Lymph node status						
Negative nodes	1.00 (Ref)		–		1.00 (Ref)	
Positive nodes	1.23 (1.06–1.42)	0.0063	–	–	1.46 (1.30–1.65)	<0.0001
Differentiation						
Well	–		1.00 (Ref)		–	
Moderate	–	–	1.29 (1.16–1.44)	<0.0001	–	–
Poor/undifferentiated	–	–	1.65 (1.48–1.85)	<0.0001	–	–
Margin status						
Negative	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Positive	1.58 (1.32–1.89)	<0.0001	1.48 (1.39–1.57)	<0.0001	1.40 (1.27–1.55)	<0.0001

Table 4 Multivariate Cox model or stage I-III pancreatic adenocarcinoma patients that underwent R0/R1-resection

Characteristics	Hazard ratio (95% CI)	p-value
Insurance		
Private	1.00 (Ref)	
Not private	1.14 (0.94–1.37)	0.1821
Treatment center		
Academic	1.00 (Ref)	
Non-academic	1.29 (1.08–1.54)	0.0050
Clinical stage		
Stage I	1.00 (Ref)	
Stage II	1.19 (0.99–1.43)	0.0656
Stage III	1.19 (0.93–1.52)	0.1636
Lymph node status		
Negative nodes	1.00 (Ref)	
Positive nodes	1.22 (1.05–1.41)	0.0092
Margin status, n (%)		
Negative	1.00 (Ref)	
Positive	1.59 (1.33–1.91)	<0.0001

neoadjuvant therapy on R0 resection rates and R0 resection on survival demonstrated by this study suggests, but does not prove that neoadjuvant therapy increases overall survival compared to upfront surgery. Moreover, the c-statistics for the multivariable regression models predicting positive margins, prolonged hospital stay, and 90-day mortality suggest that residual confounding exists; however, this study is limited by the covariates provided by the NCDB.[44]

Despite these limitations, this study is, to the best of our knowledge, the first to investigate the survival impact of positive resection margins after neoadjuvant therapy in pancreatic cancer patients on a population-level. Previous studies have suggested that worse outcomes after R1 resection are associated with advanced disease stage, which is technically more challenging to resect.[33] Therefore, we used a stratified multivariable Cox proportional hazard survival analysis to partially control for these potential confounders. In addition, a sensitivity analysis excluding patients with macroscopically residual disease was performed. Furthermore, neoadjuvant therapy is more often administrated to patients with more advanced disease and in academic centers.[45] To control for selection bias multivariable

logistic regression analyses were performed to investigate the potential predictive value of neoadjuvant therapy for positive resection margins, prolonged hospital stay, and 90-day mortality. This study was not able to distinguish pancreatic adenocarcinoma patients with initially resectable and non-resectable (borderline/locally advanced/unresectable) disease; however, a previous meta-analysis revealed that R0 resection rates were comparable between these groups.[46]

In conclusion, the findings of this population-level analysis emphasize the ability of neoadjuvant therapy to decrease margin positivity rates after pancreaticoduodenectomy, even after controlling for critical confounders. Nevertheless, the poor prognostic impact of incomplete tumor clearance was not abrogated by neoadjuvant therapy, and resection margin status remains a critical prognosticator after neoadjuvant therapy. Therefore, complete margin clearance should continue to be the central aim of pancreatic cancer surgery, even in light of the current increase in the use and efficacy of neoadjuvant therapy.[11] New innovative surgical techniques, methods of intraoperative margin assessment, preoperative imaging for patient selection, and improved neoadjuvant chemotherapy are needed to further decrease the rates of incomplete tumor clearance.

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The National Cancer Database states, "The data used in this study are derived from a de-identified National Cancer Database file. The American College of Surgeons and the CoC have not verified, and are not responsible for the analytic or statistical methodology employed, or the conclusion drawn from these data by the investigator."

Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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