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Emerging molecular biomarkers and treatment strategies in resectable pancreatic cancer

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Chapter 10

Reappraisal of the American Joint Commission on Cancer (8th Edition) Changes in Patients with Pancreatic Adenocarcinoma who Underwent Neoadjuvant Therapy

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Submitted

ABSTRACT

Purpose: This study aimed to compare and validate the seventh and eighth edition American Joint Commission on Cancer (AJCC) staging criteria in pancreatic cancer patient who underwent neoadjuvant therapy followed by pancreaticoduodenectomy.

Methods: The National Cancer Data Base was queried for pancreatic adenocarcinoma patients who underwent neoadjuvant therapy followed by pancreaticoduodenectomy. Patients were staged according to the seventh and eighth edition AJCC staging criteria. Prognostic performance was assessed using multivariable Cox proportional hazards analyses and concordance statistics.

Results: A total of 2,019 patients were identified. The median survival was 24.2 months. The seventh edition staging significantly discriminate survival between stage IIB vs. IIA (HR, 1.143; $p=0.0299$), but not between stage IB vs. IA (HR, 1.189; $p=0.2278$), stage IIA vs. IB (HR, 1.134; $p=0.2532$), and stage III vs. IIB (HR, 0.955; $p=0.7560$). The eighth edition staging was able to distinguish survival between stage III vs. IIB (HR, 1.173; $p=0.0278$), but not between stage IA vs. IB (HR, 1.138; $p=0.2458$), stage IIA vs. IB (HR, 1.063; $p=0.5759$), and stage IIB vs. IIA (HR, 1.072; $p=0.5146$). A simplified eighth edition staging significantly distinguished survival for all stages (II vs. I: HR, 1.157; $p=0.0168$; III vs. II: HR, 1.187; $p=0.0142$). The C-statistics for the group staging improved from 0.54 for the seventh to 0.56 for the eighth edition.

Conclusions: Neoadjuvant therapy is known to induce fibrosis in pancreatic adenocarcinoma, hampering accuracy and granularity of pathologic assessment. Therefore, a simplified eighth edition staging system might be more clinically applicable after neoadjuvant therapy.

INTRODUCTION

Pancreatic adenocarcinoma ranks the third leading cause of cancer-related death in the United States and is expected to become the second leading cause by 2030.¹⁻³ To date, surgical resection remains at the nexus of pancreatic cancer care, providing the sole – albeit rare – prospect of cure, and the best chance at prolonged survival.⁴ Neoadjuvant therapy is a relatively recent treatment strategy, which is gaining traction with the increasing availability of more effective chemotherapeutic agents, such as FOLFIRINOX and gemcitabine/nab-paclitaxel.⁵⁻⁷ The advantages of neoadjuvant therapy, include early treatment of micro-metastatic disease, optimized selection of surgical candidates, and increased likelihood of negative resection margins, and multimodality therapy completion.⁸

In pancreatic adenocarcinoma patients, neoadjuvant therapy frequently induces pronounced fibrosis involving both the tumor and the adjacent non-neoplastic parenchyma, which may hamper the accurate pathological staging of the surgical specimen.⁹ The American Joint Committee on Cancer (AJCC) has recently introduces the eighth edition staging manual for pancreatic cancer.^{10,11} To reduce the substantial inter-observer bias reported for preceding iterations of the AJCC pancreatic cancer staging system, the eighth edition has introduced a size-based staging paradigm.¹⁰⁻¹⁷ Furthermore, lymph node staging was adjusted to take into account the number of positive lymph nodes.^{10,11} Previous studies in upfront resected pancreatic cancer patients have shown that the eighth edition TNM staging may be able to more equally distribute patients among stages and increase prognostic accuracy.^{11,18} However, data regarding the performance of the eighth edition staging system in patients who underwent neoadjuvant therapy remain scarce.⁹

A single-institution study at a high-volume tertiary center has suggested that the new AJCC eighth edition ypT stage grouping performs better than the AJCC seventh edition ypT stage in patients who underwent neoadjuvant therapy.⁹ The present study aims to compare and validate the seventh and eighth edition AJCC staging criteria in pancreatic cancer patient who underwent neoadjuvant therapy followed by pancreaticoduodenectomy using a large nationwide dataset.

METHODS

Data Source

Patient data were obtained from the National Cancer Data Base (NCDB), a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This database contains more than 30 million records of individual cancer cases collected from over 1,500 Commission on Cancer approved facilities across the United States.¹⁹ Enhancing this data beyond mere numbers, the Commission on Cancer requires centers to maintain a 90% follow-up rate for patients diagnosed within 5 years to remain accredited, improving long-term survival analyses.¹⁹

All NCDB data are de-identified, and hence this study was deemed exempt from institutional review board review.

Inclusion/Exclusion Criteria

Patients with pancreatic adenocarcinoma who underwent neoadjuvant chemotherapy or chemoradiation followed by pancreaticoduodenectomy between 2006 to 2015 were identified using Facility Oncology Registry Data Standard (FORDS) procedure (35, 36, 37, 70), International Classification of Disease for Oncology, 3rd edition (ICD-O-3), morphology (8140 and 8500) and topography (C25.0, C25.1, C25.2, C25.3, C25.7, C25.9, and C25.9) codes, as well as the NCDB systemic treatment and surgical procedure sequence variable.²⁰ Patients who did not undergo surgery at the reporting facility (n=166), had malignancies other than pancreatic cancer (n=862), clinical or pathologic metastatic disease (n=139), or pathologic tumor stage p0, pIS, or pX (n=591) were excluded, as well as patients with missing for any of the following variables: age, sex, race, tumor size, comorbidities, insurance status, facility type, number of positive lymph nodes, number of lymph nodes examined, resection margin status, tumor grade, pathologic primary tumor stage, pathologic lymph node stage, radiation and surgery treatment sequence, and vital status (n=1,529).

Covariates

Patient demographics included: age (<65 years, ≥ 65 years), gender (male, female), race (white, black, other), insurance (private insurance, Medicare, Medicaid/uninsured/other Governmental), treatment facility (community, academic center, Integral cancer network), tumor differentiation (well/moderately differentiated, poorly/undifferentiated), type of neoadjuvant therapy (chemotherapy, chemoradiation), and receipt of any adjuvant therapy. Type of neoadjuvant therapy and receipt of any adjuvant therapy were identified based on the surgery and systemic therapy treatment sequence variable, as well as the surgery and radiation therapy treatment sequence variable provided by the NCDB. Comorbidities were reported as previously described by Charlson/Deyo based on ten comorbidities.²¹ For the purpose of this study patients were grouped as no comorbidities, 1 comorbidity, and more than 1 comorbidity. Hospital volume was calculated based on the number of pancreaticoduodenectomies per year, and dichotomized in low- and high volume centers based on the median hospital volume (23 cases per year). Resection margin status was recorded as it appeared in the pathology report, and dichotomized as negative (all margins are grossly and microscopically negative) or positive (microscopic residual tumor, margin involvement is indicated, but not otherwise specified). The total number of pathologically assessed lymph nodes was recorded from the final pathology report for each surgical specimen.

Patients were staged according to the seventh and eighth edition AJCC staging manuals, as shown in Supplementary Table 1.^{22,23} For the purpose of this study solely

pathology stage was assessed. The T-, and overall stage according to the seventh edition staging criteria were readily provided by the NCDB.¹² For both staging criteria N0 was defined as all nodes examined are negative. The seventh edition stage N1 included patients with any or an unspecified number of positive regional lymph nodes. The eighth edition staging variables were created based on tumor size and number of positive lymph nodes reported by the NCDB. Stage T1 was coded in the eighth edition as tumor size ≥ 0.01 cm ≤ 2.0 cm. The eighth edition stage T4 was substituted by the seventh edition stage T4, as they are defined the same. The eighth edition stage N2 was defined as 4-89 nodes. For both staging criteria, the M0 group was defined as absence of pathological distant metastases. Previous studies have suggested that in patients who underwent neoadjuvant therapy a simplified group stage may be more appropriate, grouping stage as I (IA and IB), II (IIA and IIB), and III.²⁴

Statistical analysis

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Descriptive statistics were summarized with frequencies and percentages for categorical variables and as medians with interquartile range (IQR) for continuous variables. Categorical and continuous variables were compared using the Chi-square test and Kruskal-Wallis test, respectively. The primary outcome was overall survival, which was calculated from the date of diagnosis to the patient's death or last known follow-up. Survival curves and median survival estimated were obtained using the Kaplan-Meier method and compared using the log-rank test. Univariate Cox proportional hazard analyses for seventh and eighth edition group stage, simplified group stage, T- and N-stage, stratified for resection margin status and tumor differentiation, were performed. Chatterjee et al (2017) identified resection margin status and tumor differentiation as the most important prognosticators in pancreatic cancer patients who received neoadjuvant therapy.⁹

Prognostic accuracy for overall survival of the seventh and eighth edition of the TNM staging system was assessed using concordance statistics (Uno C statistics), the traditional receiver operating characteristics (ROC) curve, and the time-dependent area under the curve (AUC).^{18,25,26} The Uno C statistic is comparable with a routinely used C statistic, but it accounts for a covariate- dependent censoring distribution; in addition, 95% CIs were calculated based on 100 perturbation samples.²⁵ The time- dependent AUC can be appreciated as the predictive accuracy over time, as derived from each ROC curve.²⁶

RESULTS

Patient population

In total, the study cohort comprised of 2,019 patients. Baseline characteristics are shown in table 1. The median age was 64 (IQR, 57 – 70) years, and 1,058 patients (52.4%) were male. The median tumor size was 30 (IQR, 25 – 40) mm and the median number of

lymph nodes retrieved was 17 (IQR, 11 -24) nodes. A total of 381 patients (18.9%) had positive resection margins and 959 patients (47.5%) underwent neoadjuvant chemoradiation.

Table 1. Clinicopathologic features of patients with pancreatic adenocarcinoma who underwent neoadjuvant therapy and pancreaticoduodenectomy.

Characteristics	Total (n=2,019)
Age at diagnosis, n (%)	
≤ 65 years	1,186 (58.7%)
> 65 years	833 (41.3%)
Sex, n (%)	
Male	1,058 (52.4%)
Female	961 (47.6%)
Race, n (%)	
White	1,671 (82.8%)
Black	211 (10.4%)
Other	137 (6.8%)
Charles/Deyo score, n (%)	
0	1,344 (66.6%)
1	536 (26.5%)
≥2	139 (6.9%)
Tumor differentiation, n (%)	
Well differentiated	235 (11.6%)
Moderately differentiated	1,139 (56.4%)
Poor/undifferentiated	645 (32.0%)
Insurance status, n (%)	
Private insurance	988 (48.9%)
Medicare	881 (43.7%)
Medicaid/uninsured	150 (7.4%)
Facility type, n (%)	
Community	375 (18.6%)
Academic	1,405 (69.6%)
Integrated Network Cancer Network	239 (11.8%)
Hospital volume, n (%)	
Low	990 (49.0%)
High	1,029 (51.0%)
No. of lymph nodes resected, n (%)	
< 15 nodes	788 (39.0%)
≥ 15 nodes	1,231 (61.0%)
Resection margin status, n (%)	
Negative	1,638 (81.1%)
Positive	381 (18.9%)
Neoadjuvant therapy, n (%)	
Chemotherapy	1,060 (52.5%)
Chemoradiation	959 (47.5%)
Adjuvant therapy, n (%)	
No	1,208 (59.8%)
Yes	811 (40.2%)

Via the seventh edition AJCC TNM staging system, stage IA was found in 165 patients (8.2%), stage IB in 157 patients (7.8%), stage IIA in 593 patients (29.4%), stage

IIB in 1,039 patients (51.5%), and stage III in 65 patients (3.2%), and via the eighth edition, stage IA was found in 163 patients (8.1%), stage IB in 597 patients (29.6%), stage IIA in 155 patients (7.7%), stage IIB in 692 patients (34.3%), and stage III in 412 patients (20.4%) (Figure 1). Using the eighth-edition classification, 967 patients (47.9%) migrated to a different stage, of who 496 patients (24.6%) were assigned to a lower stage and 471 patients (23.3%) to a higher stage.

Table 2. Univariable cox regression analysis of the overall survival effect by tumor stage according to the seventh and eighth edition AJCC staging criteria.

	Seventh edition		Eighth edition	
	Hazard Ratio (95% CI)*	P	Hazard Ratio (95 CI)*	P
Group stage				
Stage IB (vs. IA)	1.189 (0.897 – 1.576)	0.2278	1.138 (0.915 – 1.417)	0.2458
Stage IIA (vs. IB)	1.134 (0.914 – 1.406)	0.2532	1.063 (0.857 – 1.319)	0.5759
Stage IIB (vs. IIA)	1.143 (1.013 – 1.290)	0.0299	1.072 (0.868 – 1.325)	0.5146
Stage III (vs. IIB)	0.955 (0.716 – 1.275)	0.7560	1.173 (1.018 – 1.352)	0.0278
Simplified group stage				
Stage II (vs. I)	1.339 (1.150 – 1.560)	0.0002	1.157 (1.027 – 1.304)	0.0168
Stage III (vs. II)	0.998 (0.750 – 1.329)	0.9910	1.187 (1.035 – 1.362)	0.0142
Primary Tumor Stage				
ypT2 (vs. ypT1)	1.275 (1.015 – 1.601)	0.0370	1.160 (0.993 – 1.355)	0.0621
ypT3 (vs. ypT2)	1.088 (0.931 – 1.271)	0.2906	1.039 (0.906 – 1.191)	0.5868
ypT4 (vs. ypT3)	1.002 (0.752 – 1.334)	0.9912	0.996 (0.727 – 1.336)	0.9253
Lymph Node Stage				
ypN1 (vs. ypN0)	1.204 (1.083 – 1.339)	0.0006	1.134 (1.009 – 1.276)	0.0356
ypN2 (vs. ypN1)	-		1.202 (1.037 – 1.392)	0.0144

Abbreviations: CI, Confidence Interval

*Stratified by resection margin status and tumor differentiation

Via the seventh edition staging system, 220 patients (10.9%) were stage ypT1, 266 patients (13.2%) were stage ypT2, 1,468 patients (72.7%) were stage ypT3, and 65 (3.2%) were stage ypT4 (Figure 1). According to the eight edition AJCC staging, 300 patients (14.9%) were stage ypT1, 1,272 patients (63.0%) were stage ypT2, 382 patients (18.9%) were stage ypT3, and 65 patients (3.2%) were stage ypT4 (Figure 1). Overall, 33.0% of ypT1 according to the eighth edition corresponded with the seventh edition ypT1 stage, 16.0% of eighth edition ypT2 stage corresponded with the seventh edition ypT2 stage, and 80.9% of eighth edition ypT3 stage corresponded with the seventh edition ypT3 (Supplementary Table 2).

Via the seventh edition staging system, 945 patients (46.8%) were staged as ypN0, and 1,074 patients (53.2%) as ypN1 (Figure 1). In agreement with the eighth edition, 945 patients (46.8%) were staged as ypN0, 716 patients (35.5%) were staged as ypN1, and 358 patients (17.7%) were staged as ypN2 (Figure 1).

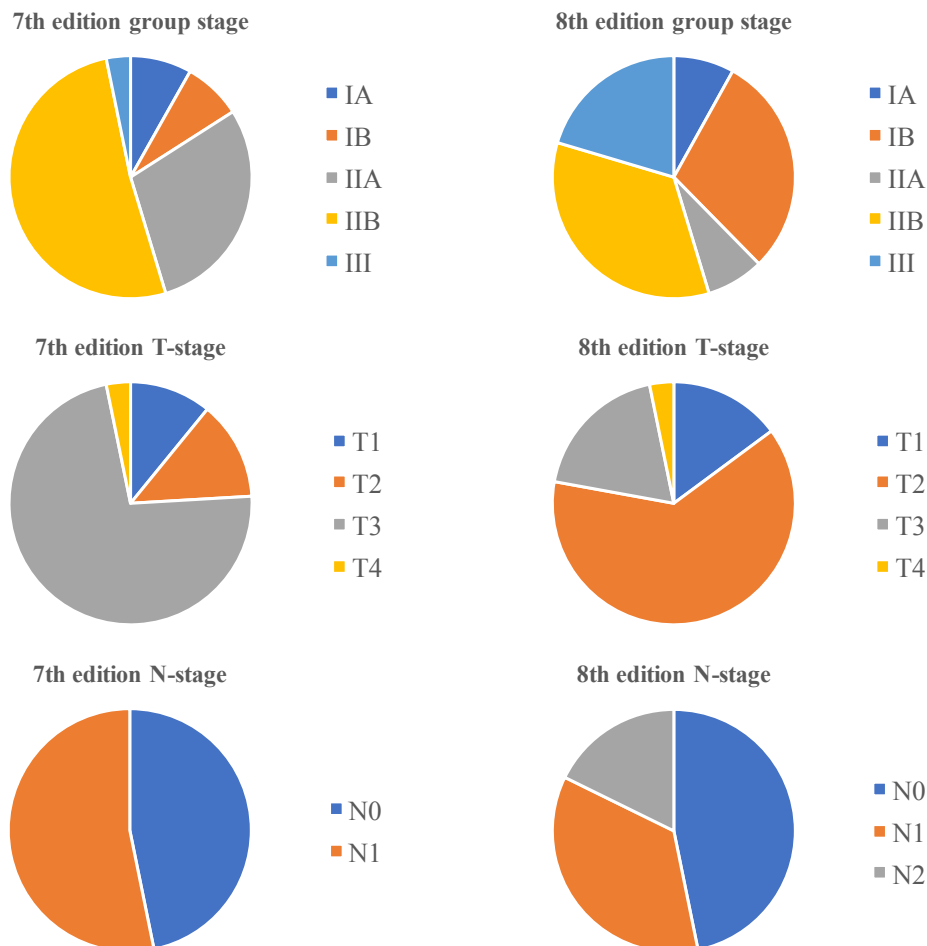


Figure 1. Distribution of TNM classification in the seventh and eighth edition AJCC staging system.

Survival by TNM Stage

At the time of last follow-up, 597 patients (29.6%) were alive, median overall survival for the entire cohort was 24.2 months, and the 5-year survival rate was 17.3%. Median overall survival changed from 34.5 months for patients in stage IA, 27.0 months for patients in stage IB, 25.0 months for patients in stage IIA, 22.1 months for patients in stage IIB, 22.8 months for those in stage III (Figure 2a; log-rank $p < 0.0001$) under seventh-edition classification to 30.9 months for patients in stage IA, 25.7 months for those in stage IB, 24.6 months for those in stage IIA, 23.0 months for those in stage IIB, and 21.1 months for those in stage III (Figure 2b; log-rank $p < 0.0001$) under eighth-edition classifications. On multivariable Cox proportional hazard analyses, the seventh edition AJCC staging was able to significantly distinguish survival between stage IIB vs. IIA (HR, 1.143; $p = 0.0299$), but not for any of the successive stages (Table 2). The eighth edition TNM stage was able to

discriminate survival between stage III vs. IIB (HR, 1.173; $p=0.0278$), but not between the other subsequent stages (Table 2).

Via the seventh edition staging, the median survival was 30.9 months for the simplified stage I (IA + IB), 23.4 months for stage II (IIA + IIB), and 22.8 months for stage III (Figure 3a; $p<0.0001$). For the eighth edition simplified group stage, patients with stage I (IA + IB) disease demonstrated a median survival of 26.8 months, patients with stage II (IIA + IIB) had a median survival of 23.3 months, and patients with stage III disease a median survival of 21.1 months (Figure 3b; $p<0.0001$). The simplified version of seventh edition group stage was able to distinguish survival between stage I vs. II (HR, 1.339; $p=0.0002$). However, not between stage II vs. III (HR, 0.998; $p=0.9910$; Table 2). The simplified eighth edition group stage was able to discriminate survival between stage I vs. II (HR, 1.157; $p=0.0168$) and stage II vs. III (HR, 1.187; $p=0.0142$; Table 2).

For the seventh edition TNM stage, median survival was 33.7 months for patients with stage ypT1, 25.9 months for stage ypT2, 23.3 months for stage ypT3, and 22.8 months for stage ypT4 (Figure 4a). Via the eighth edition, the median survival was 27.3 months for stage ypT1, 24.1 months for stage ypT2, 22.8 months for stage ypT3, and 22.8 months for stage ypT4 (Figure 4b). On multivariable Cox proportional hazard analyses, the seventh edition was able to distinguish survival between stage ypT2 vs. ypT1 (HR, 1.275; $p=0.0370$), but not between ypT3 vs. ypT2 (HR, 1.088; $p=0.2906$) and ypT4 vs. ypT3 (HR, 1.002; $p=0.9912$; Table 2). The eighth edition distinguished survival between stage ypT2 vs. ypT1 (HR, 1.160; $p=0.0621$), but not between ypT3 vs. ypT2 (HR, 1.039; $p=0.5868$), and ypT4 vs. ypT3 (HR, 0.996; $p=0.9253$; Table 2).

The median survival for patients with negative and positive lymph nodes was 26.1 and 22.5 months, respectively (Figure 5a). The new classification of the ypN-stage in the eighth edition was highly discriminative, with median survival of 26.1 months for stage ypN0, 23.1 months for stage ypN1, and 20.9 months for stage ypN2 (Figure 5b). Adjusted for other covariates, multivariable analysis of the seventh (ypN1 vs. ypN0: HR, 1.204; $p=0.0006$) and eighth (ypN1 vs. ypN0: HR, 1.134; $p=0.0356$; ypN2 vs. ypN1: HR, 1.202; $p=0.0144$) edition demonstrated a significant survival difference between all lymph node stage (Table 2).

Prognostic Accuracy

When assessing prognostic accuracy on survival, the Uno C statistics was 0.54 for the seventh edition group stage and 0.55 for the eighth edition of the TNM group stage. The Uno C statistics was 0.53 for the seventh edition simplified group stage and 0.54 for the eighth edition simplified group stage. Furthermore, the Uno C statistics was 0.53 for the seventh edition T-stage and dropped to 0.52 for the eighth edition T-stage. In addition, the Uno C statistic was 0.53 for the seventh edition N-stage and 0.54 for the eighth edition N-stage.

The ROC curve at 5-year survival demonstrated a time-dependent area under the curve (AUC) of 0.57 with the seventh edition group stage compared to 0.57 with the eighth edition group stage. For the seventh edition simplified group stage the AUC was 0.54 and 0.56 for the eighth edition simplified group stage. The AUC was 0.54 and 0.54 for respectively the seventh and eighth T-stage. For the seventh edition N-stage the AUC was 0.55 and 0.56 for the eighth edition N-stage.

DISCUSSION

Neoadjuvant therapy for pancreatic adenocarcinoma is on the rise.⁵ To the best of our knowledge, this study is the first to validate the eighth edition AJCC staging system in a nationwide cohort of pancreatic cancer patients who underwent neoadjuvant therapy. This study demonstrated that neither the seventh nor the eighth edition staging system was able to significantly distinguish survival between all subsequent group stages. However, a simplified group stage, collapsing stage IA with IB and stage IIA with IIB, was able to distinguish survival for all stages defined according to the eighth edition staging system (II vs. I: HR, 1.157; $p=0.0168$; III vs. II: HR, 1.187; $p=0.0142$). The simplified seventh edition group stage was only able to distinguish survival between stage II vs. I (HR, 1.339; $p=0.0002$), but not between stage III vs. II (HR, 0.998; $p=0.9910$). The Uno C-statistics for the modified group stage improved from 0.54 for the seventh to 0.56 for the eighth edition. In conclusion, a novel simplified staging system might be more practicable for pancreatic cancer patients who received neoadjuvant therapy.

Previous studies validating the value of the recently introduced eighth edition AJCC staging in patients who underwent upfront surgery for pancreatic adenocarcinoma have shown improved prognostic accuracy with the eighth edition staging system.^{11,18} The Uno C-statistics for both the seventh and eighth edition staging systems reported by these studies were slightly higher than found in our study, indicating that the prognostic accuracy of pathologic staging decreases after neoadjuvant therapy.^{11,18} These findings may be ascribed to the impeding effect of neoadjuvant therapy on pathologic examination. After neoadjuvant therapy the tumor and the adjacent non-neoplastic pancreatic parenchyma become fibrotic, which makes it challenging to delineate the boundaries of the tumor. In addition, pancreatic adenocarcinomas often have a heterogeneous response to neoadjuvant therapy, resulting in islands and nests of surviving tumor, with stretched of tumor-free fibrotic tumor bed in between, further complicating pathologic examination.⁹

A single-center study performed at the MD Anderson Cancer Center in 398 patients with pancreatic ductal adenocarcinoma who underwent neoadjuvant therapy followed by pancreaticoduodenectomy demonstrated that the eighth edition ypT stage better stratified survival than the seventh edition ypT AJCC stage.

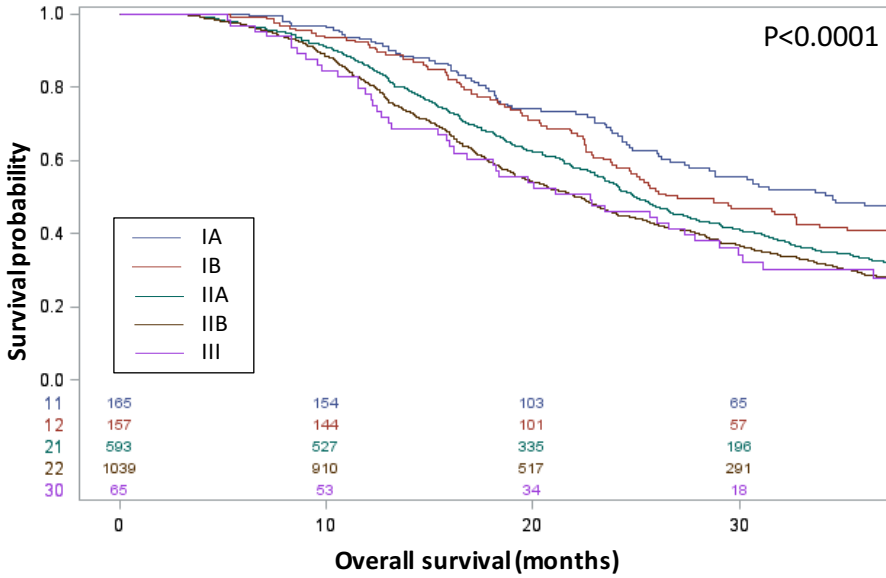


Figure 2a. Kaplan-Meier survival curves for pancreatic cancer patients staged according to the seventh edition AJCC group stage.

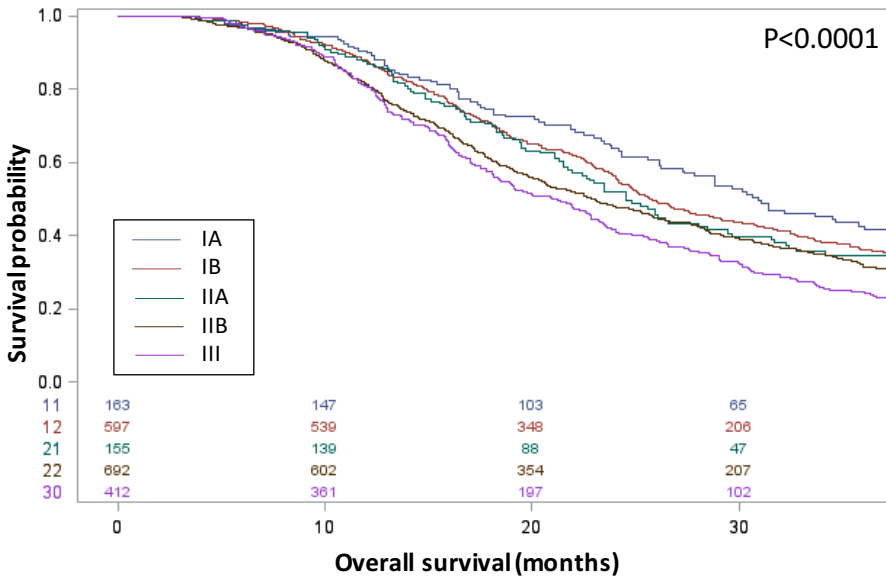


Figure 2b. Kaplan-Meier survival curves for pancreatic cancer patients staged according to the eighth edition AJCC group stage.

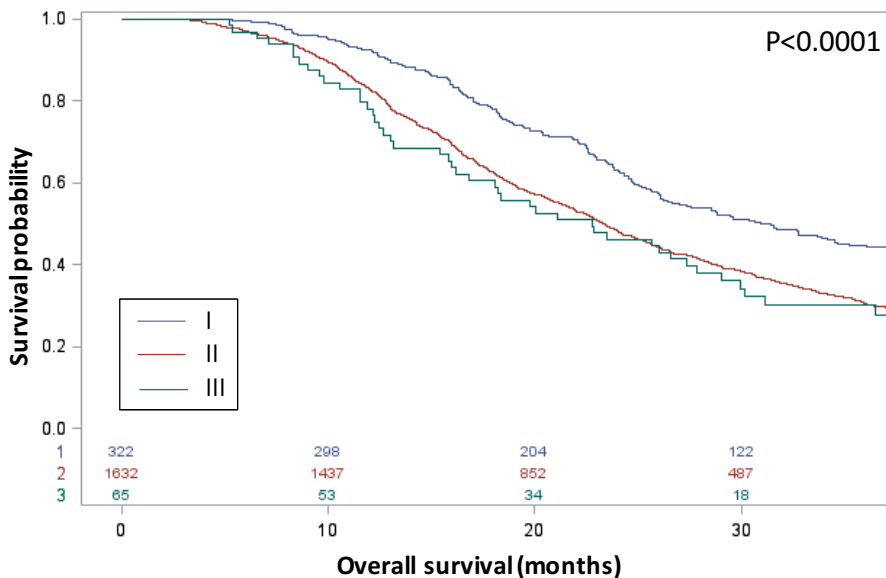


Figure 3a. Kaplan-Meier curves for pancreatic cancer patients staged according to the seventh edition AJCC modified group stage.

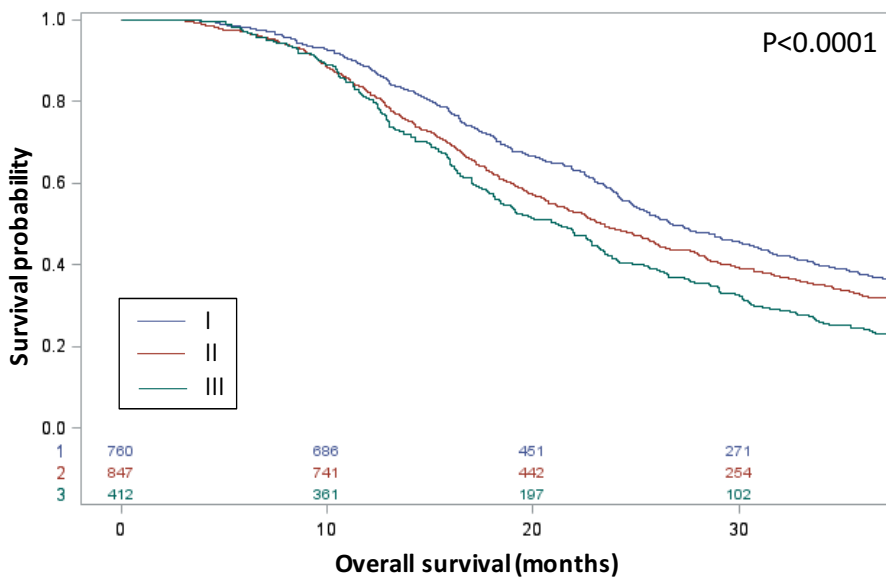


Figure 3b. Kaplan-Meier curves for pancreatic cancer patients staged according to the eighth edition AJCC modified group stage.

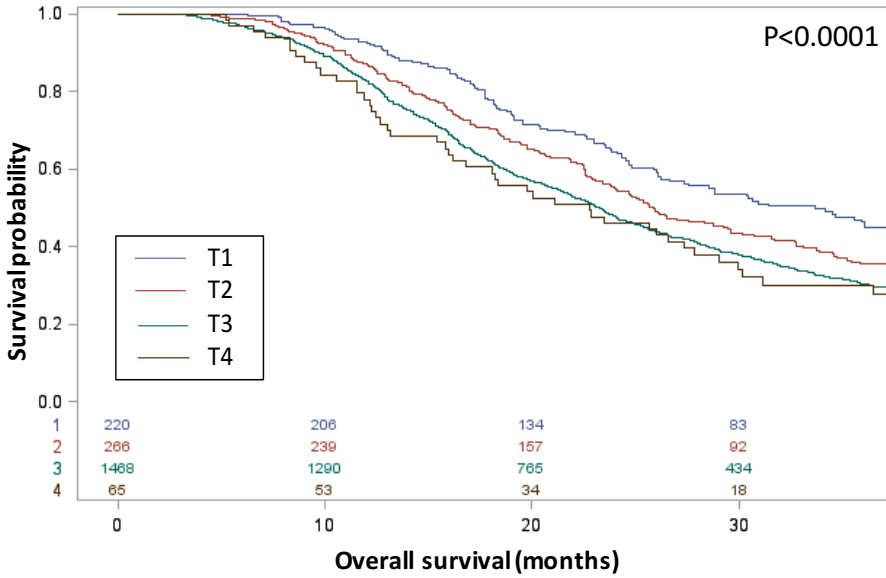


Figure 4a. Kaplan-Meier curves for pancreatic cancer patients staged according to the seventh edition AJCC T-stage.

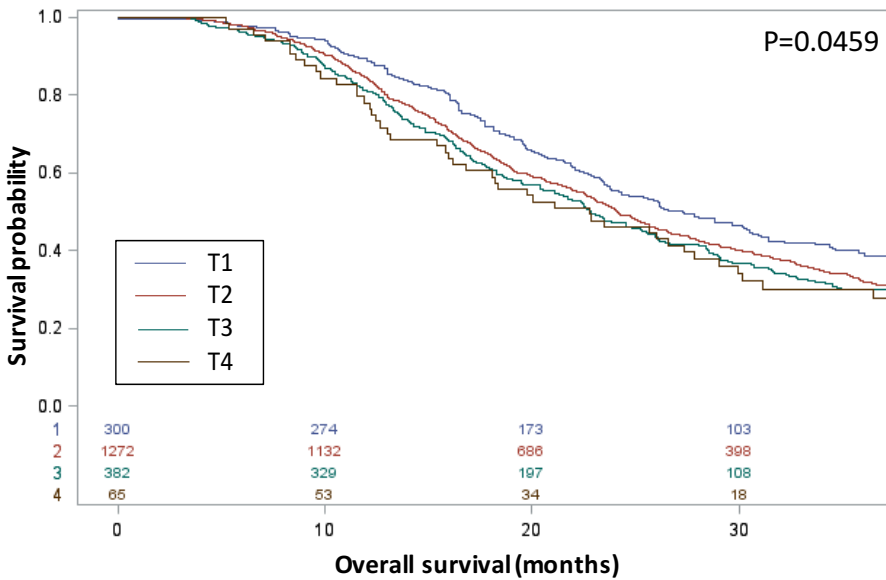


Figure 4b. Kaplan-Meier curves for pancreatic cancer patients staged according to the eighth edition AJCC T-stage.

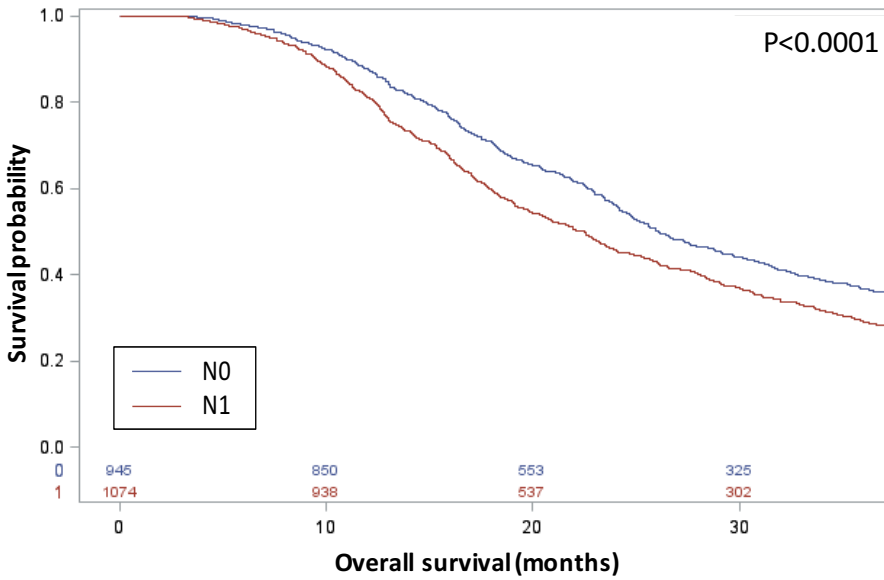


Figure 5a. Kaplan-Meier curves for pancreatic cancer patients staged according to the seventh edition AJCC N-stage.

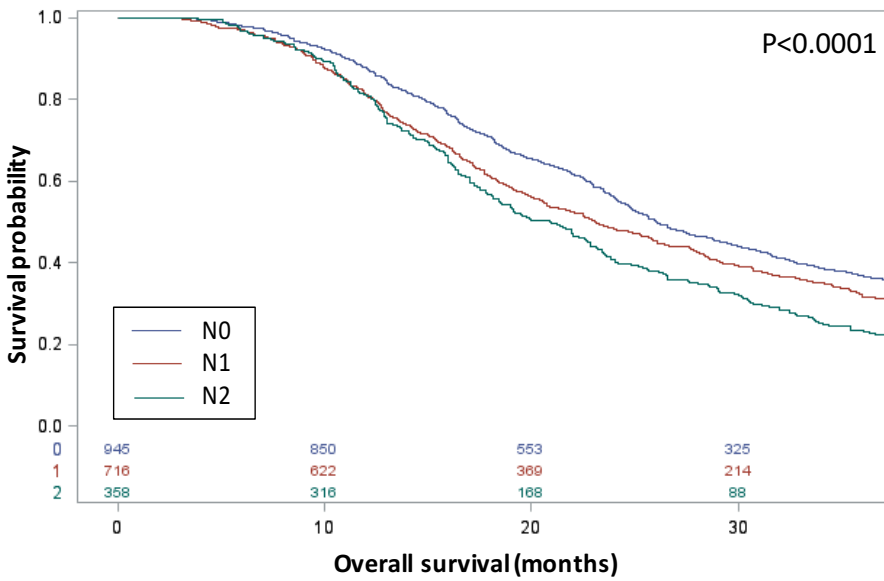


Figure 5b. Kaplan-Meier curves for pancreatic cancer patients staged according to the eighth edition AJCC N-stage.

In absence of pancreatic cancer specific guidelines, their study applied the standardized post-neoadjuvant therapy pathologic evaluation guidelines recommended for breast cancer by the international working group. Despite the stringent pathologic examination, they were not able to find a significant survival difference between the eighth edition ypT2 vs. ypT1 and ypT1 vs. ypT3 stage, similar to our results. Their study did not assess grouped stage.⁹ These findings confirm that even when using a standardized pathology approach, assessment of tumor size after neoadjuvant therapy remains challenging.

The results of this study should be interpreted with respect to its limitations. First, the NCDB is subject to coding errors and does not report on various covariates, including the specific neoadjuvant chemotherapeutic regimen used, postoperative carbohydrate antigen 19-9 (CA 19-9) lab values, and the presence of perineural and/or vascular invasion.^{27,28} The second limitation is the lack of standardization of the pathological examination guidelines, in particular for the pathologic assessment of pancreatic cancer specimen after neoadjuvant therapy, resulting in considerable variability in tumor size and lymph node yield. This variability may further comprise the relationship between pathology stage and clinical outcomes after pancreatic cancer surgery.¹⁸ Finally, the NCDB does only collect data from commission on cancer approved hospitals. Although these centers capture 74% of all newly diagnosed pancreatic cancer cases in the United States, these findings may not be entirely generalizable to all centers.²⁹

Despite these limitations, the present is to the best of our knowledge the first to validate the prognostic accuracy of the new eighth edition AJCC staging in pancreatic adenocarcinoma patients who underwent neoadjuvant therapy at a nationwide level. As neoadjuvant therapy is becoming more common, these findings will become more important over time. In addition, the present study possesses adequate statistical power to warrant its negative findings. Furthermore, the results of this study reflect the value of the eighth edition staging system beyond the high-volume specialized pancreatic cancer clinics where this staging system originated.^{9,11}

In conclusion, the results of this study suggest that neither the seventh nor the eighth edition AJCC staging criteria are able to significantly discriminate survival between subsequent tumor stages. Neoadjuvant therapy has been well known to induce fibrosis in pancreatic adenocarcinoma and its surrounding non-neoplastic pancreatic parenchyma. These changes hamper the accuracy and granularity of the pathologic assessment of the tumor extent and therefore the prognostic value of the primary tumor stage. Although evidence-based consensus guidelines regarding the pathologic examination of post-neoadjuvant therapy surgical pancreatic cancer specimen are pivotal, previous work suggests this may not be sufficient to give the eighth edition staging system clinical relevance in patients who underwent neoadjuvant therapy.⁹ In this study, a simplified eighth edition group stage, collapsing stage IA with IB, and IIA with IIB, was able to significantly discriminate survival between all subsequent stages. This simplified group stage may

provide a more practicable clinically relevant alternative to the original eighth edition group stage.

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SUPPLEMENTARY TABLES

Supplementary table 1. Pancreatic cancer staging according to the seventh and eighth edition AJCC staging criteria.

	Seventh edition			Eighth edition		
Primary Tumor (T)						
ypT1	Tumor limited to the pancreas, ≤ 2 cm in greatest dimension			Maximum tumor diameter ≤ 2 cm		
ypT2	Tumor limited to the pancreas, > 2 cm in greatest dimension			Maximum tumor diameter > 2 ≤ 4 cm		
ypT3	Tumor extend beyond the pancreatic without involvement of the celiac axis or the superior mesenteric artery			Maximum tumor diameter > 4 cm		
ypT4	Tumor involves the celiac axis or the superior mesenteric artery			Tumor involves the celiac axis or the superior mesenteric artery		
Regional Lymph Nodes (N)						
ypN0	No regional lymph node metastasis			No regional lymph node metastasis		
ypN1	Regional lymph node metastasis			Metastasis in 1-3 regional lymph nodes		
ypN2	-			Metastasis in ≥ 4 regional lymph nodes		
Distant Metastases (M)						
ypM0	No distant metastases			No distant metastases		
ypM1	Distant metastases			Distant metastases		
Overall stage						
Stage IA	ypT1	ypN0	ypM0	ypT1	ypN0	ypM0
Stage IB	ypT2	ypN0	ypM0	ypT2	ypN0	ypM0
Stage IIA	ypT3	ypN0	ypM0	ypT3	ypN0	ypM0
Stage IIB	ypT1-T3	ypN1	ypM0	ypT1-T3	ypN1	ypM0
Stage III	ypT4	ypN0-N1	ypM0	ypT4	ypN0-N1	ypM0
	-	-	-	ypT1-T4	ypN2	ypM0

Supplementary Table 2. Correlation between primary tumor stage by the American Journal Committee of Cancer (AJCC) 8th Edition and clinicopathologic factors in pancreatic cancer patients who underwent neoadjuvant therapy and resection.

Characteristics	Primary Tumor Stage, Eighth Edition				<i>p</i>
	T1 (n=300)	T2 (n=1,272)	T3 (n=382)	T4 (n=65)	
Primary Tumor Stage, Seventh Edition, n (%)					
T1	99 (33.0%)	98 (7.7%)	23 (6.0%)	0 (0.0%)	<0.0001
T2	12 (4.0%)	204 (16.0%)	50 (13.1%)	0 (0.0%)	
T3	189 (63.0%)	970 (76.3%)	309 (80.9%)	0 (0.0%)	
T4	0 (0.0%)	0 (0.0%)	0 (0.0%)	65 (100.0%)	

Supplementary table 3. 5-year survival for the seventh and eighth edition AJCC staging.

	Seventh edition	Eighth edition
Group stage		
Stage IA	26.4%	23.2%
Stage IB	21.2%	21.0%
Stage IIA	18.7%	15.0%
Stage IIB	14.9%	16.0%
Stage III	11.1%	12.5%
Simplified group stage		
Stage I	23.7%	21.5%
Stage II	16.3%	15.7%
Stage III	11.1%	12.5%
Primary Tumor Stage		
T1	24.2%	20.6%
T2	17.2%	17.5%
T3	16.6%	15.1%
T4	11.1%	11.1%
Lymph Node Stage		
N0	19.9%	19.9%
N1	15.0%	15.9%
N2	-	13.5%