Ann Surg Oncol (2017) 24:2023–2030
DOI 10.1245/s10434-017-5810-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: A Surveillance, Epidemiology and End Results (SEER) Analysis

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ABSTRACT

Background. The 8th edition of the AJCC staging system for pancreatic cancer incorporated several significant changes. This study sought to evaluate this staging system and assess its strengths and weaknesses relative to the 7th edition AJCC staging system.

Methods. Using the Surveillance, Epidemiology and End Results (SEER) database (2004–2013), 8960 patients undergoing surgical resection for non-metastatic pancreatic adenocarcinoma were identified. Overall survival was estimated using the Kaplan–Meier method and compared using log-rank tests. Concordance indices (c-index) were calculated to evaluate the discriminatory power of both staging systems. The Cox proportional hazards model was used to determine the impact of *T* and *N* classification on overall survival.

Results. The c-index for the AJCC 8th staging system [0.60; 95% confidence interval (CI), 0.59–0.61] was comparable with that for the 7th edition AJCC staging system (0.59; 95% CI, 0.58–0.60). Stratified analyses for each *N* classification system demonstrated a diminishing impact of *T* classification on overall survival with increasing nodal involvement. The corresponding c-indices were 0.58 (95% CI, 0.55–0.60) for *N*0, 0.53 (95% CI, 0.51–0.55) for *N*1, and 0.53 (95% CI, 0.50–0.56) for *N*2 classification.

Conclusion. This is the first large-scale validation of the AJCC 8th edition staging system for pancreatic cancer. The revised system provides discrimination similar to that of the 7th-edition system. However, the 8th-edition system allows for finer stratification of patients with resected tumors according to extent of nodal involvement.

Pancreatic cancer is the second most common gastrointestinal malignancy and the fourth most common cause of cancer death in the United States.[1] The incidence of pancreatic cancer rose from 11 in 100,000 cases in 2000 to 13.1 in 100,000 cases in 2013. More than 53,000 incident cases occur annually, and pancreatic cancer continues to cause 41,000 deaths every year.

Despite advances in multimodality treatment, long-term survival is achieved for only 5% of patients. Surgical resection remains the only potentially curative therapy for patients with pancreatic cancer. However, only 20% of patients are candidates for surgical resection, and even in this subset of patients who undergo successful resection and adjuvant therapy, the 5-year survival rate is only 20%, with the median survival time ranging from 25 to 30 months.[2–5]

Clinical trials to evaluate novel therapeutic strategies are needed to improve patient outcomes. Physicians also need tools to counsel patients appropriately regarding prognosis. Accurate staging systems are therefore essential.

The American Joint Committee on Cancer (AJCC) incorporated several changes into the 8th-edition staging system of pancreatic adenocarcinoma (Table 1). Two

Electronic supplementary material The online version of this article (doi:10.1245/s10434-017-5810-x) contains supplementary material, which is available to authorized users.

First Received: 23 December 2016;
Published Online: 17 February 2017

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TABLE 1 American Joint Committee on Cancer (AJCC) 8th edition staging system for pancreatic cancer

Primary tumor (*T*)		Regional lymph nodes (*N*)		Distant metastases (M)	
*T*1	Maximum tumor diameter ≤2 cm	*N*0	No regional lymph node metastasis	M0	No distant metástasis
*T*2	Maximum tumor diameter >2 cm but ≤4 cm	*N*1	Metastasis in 1–3 regional lymph nodes	M1	Distant metastasis
*T*3	Maximum tumor diameter >4 cm	*N*2	Metastasis in ≥4 regional lymph nodes		
*T*4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)				
Stage					
Stage 1A		*T*1	*N*0	M0	
Stage 1B		*T*2	*N*0	M0	
Stage 2A		*T*3	*N*0	M0	
Stage 2B		*T*1–*T*3	*N*1	M0	
Stage 3		Any *T*	*N*2	M0	
		*T*4	Any *N*		
Stage 4		Any *T*	Any *N*	M1	

TABLE 2 AJCC 7th edition staging system for pancreatic cancer

Primary tumor (T)		Regional lymph nodes (*N*)		Distant metastases (M)	
*T*1	Tumor limited to the pancreas, <2 cm in greatest dimension	*N*0	No regional lymph node metastasis	M0	No distant metastasis
*T*2	Tumor limited to the pancreas, >2 cm in greatest dimension	*N*1	Regional lymph node metastasis	M1	Distant metastasis
*T*3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery				
*T*4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)				
Stage					
Stage 1A		*T*1	*N*0	M0	
Stage 1B		*T*2	*N*0	M0	
Stage 2A		*T*3	*N*0	M0	
Stage 2B		*T*1–*T*3	*N*1	M0	
Stage 3		*T*4	Any *N*	M0	
Stage 4		Any *T*	Any *N*	M1	

major modifications were made from the 7th edition staging system (Table 2), resulting in new definitions for *T* and *N* classifications.[6] Instead of denoting extrapancreatic invasion, which can be difficult to predict accurately before surgery[7] and may be inconsistently assessed by pathologists, *T*3 tumors are now defined as those larger than 4 cm. Furthermore, nodal involvement has been revised from a binary system to one based on extent of nodal involvement as follows: *N*0, *N*1 (1–3 positive regional lymph nodes), or *N*2 (≥4 positive regional lymph nodes).

A recent multi-institutional study from three centers in the United States evaluated these changes and suggested that it improved discrimination of survival for patients with resected pancreatic cancer.[8] The data used in this study from three East Coast tertiary centers may be subject to referral bias and treatment selection bias. Validation using a nationally representative data set is needed. We sought to evaluate the discriminative ability of the AJCC 8th edition staging system and to study the impact of *T* and *N* classification changes on stratification of survival using nationally representative registry data.

METHODS

Data Source and Study Cohort

This study analyzed prospectively collected data from the Surveillance, Epidemiology, and End Results (SEER) database maintained by the National Cancer Institute. The SEER database began in 1973 with seven cancer registries and has grown to include 21 cancer registries, representing 28% of the U.S. population. Compared with the general

U.S. population, the SEER population is slightly more urban and has a slightly higher percentage of foreign-born individuals. Available data include patient demographics (e.g., age, gender, race), tumor data (histology, grade), SEER stage of disease, details of cancer-directed surgery, use of radiation therapy, and attributes of the patient's county of residence (e.g., urban–rural continuum code). Some data elements (e.g., AJCC staging, details of surgical therapy, tumor size, lymph node involvement) are consistently available only for more recent periods.

Using SEER data from 2004–2013, we identified patients older than 18 years with resected, histologically confirmed, non-metastatic pancreatic adenocarcinoma. The International Classification of Disease 3rd edition (ICD-O3) was used to identify pancreatic cancer using site codes C250–4 and C257–9. For specific identification of patients with pancreatic adenocarcinoma, histology codes 8140, 8141, 8142, 8143, 8144, 8145, 8146, and 8147 were used. Other variants of pancreatic cancers such as mucinous and neuroendocrine tumors and nonspecific histologies [e.g., neoplasm or carcinoma, not otherwise specified (NOS)] were excluded from the analysis. Likewise, cases with vague histology codes for neoplasm (8000–8003), carcinoma, NOS (8010–8013), and carcinoma undifferentiated, NOS (8120–8122) were excluded. We derived the AJCC 7th- and 8th-edition staging using data on tumor size, lymph node (LN) involvement, and extension into extra-pancreatic tissue or adjacent organs, all of which are provided by the SEER database. Cases with missing data for these variables were excluded from the study.

Statistical Analysis

Categorical variables were compared using the chi-square test. Non-normally distributed data were analyzed using the Mann–Whitney *U* test. Survival was estimated using Kaplan–Meier survival curves and compared using the log-rank test. A concordance index (c-index) was calculated to evaluate the discriminatory power of each staging system.[9] A value of 0.5 indicates that chance alone is as predictive as the staging system, whereas a level of 1.0 signifies perfect concordance. A Cox proportional hazards model was used, with stage coded as indicator variables to obtain hazard ratios (HR), and the c-index was calculated from this Cox model.[10] Cox proportional hazards modeling was used to assess the relative impacts of *T* and *N* classifications on survival. A separate model adjusting for potential confounding variables including sex, age, and race also was assessed. A p value lower than 0.05 was considered to be statistically significant. Data were analyzed using SPSS v22.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

We analyzed data on 8960 patients who underwent surgical resection for pancreatic adenocarcinoma from 2004 to 2013. Of these patients, 6701 (75%) underwent pancreaticoduodenectomy, and 2259 (25%) underwent distal or total pancreatectomy. The median follow-up period was 15 months. The patient characteristics are presented in Table 3 for the entire cohort. The more recent period (2009–2013) had significantly older patients undergoing resection for pancreatic adenocarcinoma, with no difference in sex or type of pancreatic surgery. Compared with 2009–2013, significantly greater numbers of LNs were examined in patients with a diagnosis determined from 2004 to 2008 (median, 15 vs. 12; $p < 0.001$).

AJCC Stage Groupings

Reclassification of patients between the 7th and 8th edition staging systems is depicted in Table 4. The 1983 stage 2A tumors in the AJCC 7th-edition staging system were reclassified into stages 1A ($n = 364$), 1B ($n = 1206$), and 2A ($n = 450$) in the AJCC 8th edition staging system. Conversely, 160 patients with stage 1B disease according to the 7th edition staging were upstaged to 2A disease under the 8th edition system.

According to the AJCC 8th edition staging system, the median overall survival was 38 months for stage 1A, 24 months for stage 1B, 18 months for stage 2A, 17 months for stage 2B, and 14 months for stage 3 ($p < 0.0001$; Fig. 1a). The overall survival difference between stages 2A and 2B was not significant ($p = 0.4$). As shown in Fig. 1a, survival for stage 2A and 2B tumors was similar until about 20 months, after which survival for stage 2A was better.

The c-index for the 8th edition staging system was 0.60 [95% confidence interval (CI), 0.59–0.61]. This was comparable with the c-index for the 7th edition (c-index, 0.59; 95 % CI, 0.58–0.60; Fig. 1b).

Overall Survival for T and N Classifications

The median survival period was 27 months for *T*1 tumors, 19 months for *T*2 tumors, and 14 months for *T*3 tumors according to the AJCC 8th edition staging system (Fig. 2a). When stratified by nodal classification (*N*0 vs. *N*1 vs. *N*2), survival did not differ significantly between *N*1 and *N*2 nodal status in the patients with T1 tumors ($p = 0.2$) (Fig. 2b). In cases with *T*2 and *T*3 tumors, the overall survival periods for the patients with *N*2 classification were respectively 15 months (95% CI, 14–16 months) and 11 months (95% CI, 10–12 months). The median survival period was 26 months for *N*0 tumors, 17

TABLE 3 Clinicopathologic variables for the entire cohort

	All patients ($n = 8960$) n (%)
Age (years)	
18–59	2574 (29)
60–79	5589 (62)
>80	797 (9)
Sex	
Male	4527 (51)
Grade	
Well/moderately differentiated	5506 (62)
Poorly differentiated/anaplastic	3454 (39)
Median tumor size (cm)	4 (3.0–4.0)
Type of surgery	
Pancreaticoduodenectomy	6701 (75)
Distal pancreatectomy	1056 (12)
Total pancreatectomy	1203 (13)
Lymph node examined	
1–5	1131 (13)
6–10	1916 (21)
11–15	2088 (23)
16–20	1623 (18)
21+	2161 (24)
Lymph node ratio	
0	2970 (33)
0.01–0.20	3171 (35)
0.21–0.40	1679 (19)
AJCC 8th *T* classification	
*T*1	1537 (17)
*T*2	5218 (58)
*T*3	2205 (25)
AJCC 8th *N* classification	
*N*0	2970 (33)
*N*1	3793 (42)
*N*2	2197 (25)

AJCC American Joint Committee on Cancer

months for *N*1 tumors, and 14 months for *N*2 tumors according to the AJCC 8th-edition staging system (Supplement 1A).

Stratified analyses were performed to demonstrate the prognostic impact of the AJCC 8th edition *T* classification system by *N* classification (*N*0 vs. *N*1 vs. *N*2) (Table 5). In *N*0 disease, the risk of death was significantly higher for both *T*2 tumors [hazard ratio (HR), 1.43; 95% CI, 1.26–1.61; $p < 0.0001$] and T3 tumors (HR, 1.84; 95% CI, 1.60–2.12; $p < 0.0001$) than for T1 tumors. However, the impact of *T* classification diminished as nodal involvement increased. For example, the c-index for the *T* classification of the patients with *N*0 disease was 0.58 (95% CI, 0.55–0.60; $p = 0.011$) compared with 0.53 (95% CI, 0.51–0.55; $p = 0.01$) for *N*1 tumors and 0.53 (95% CI, 0.50–0.56; $p = 0.014$) for *N*2 tumors.

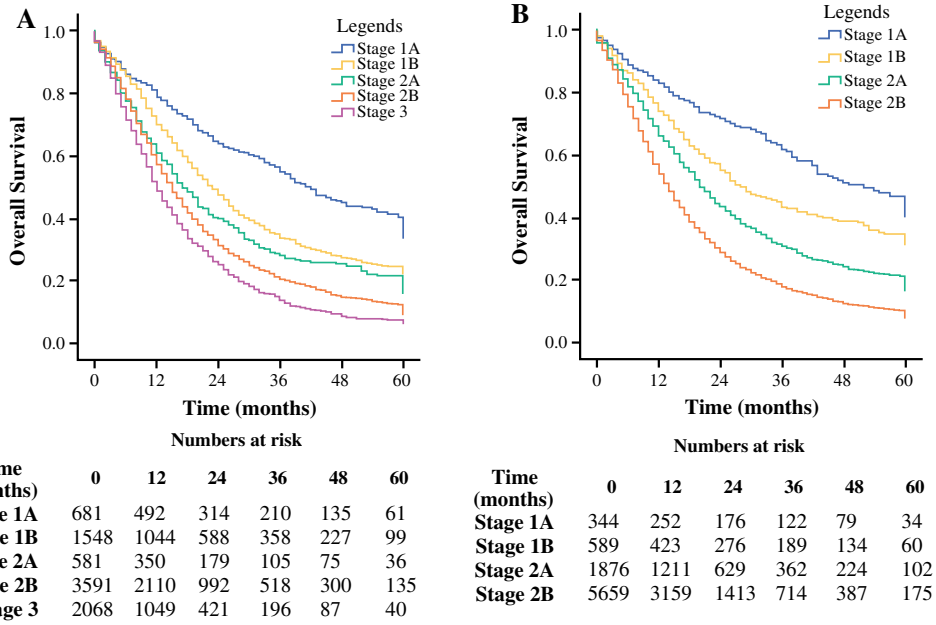
Further analyses were performed to determine the prognostic impact of the AJCC 8th edition *N* classification system by *T* classification (*T*1 vs. *T*2 vs. *T*3) (Table 6). The risk of death was significantly higher for the patients with *T*1 tumors who had *N*1 (HR, 1.69; 95% CI, 1.47–1.95; $p < 0.0001$) or *N*2 (HR, 1.92; 95% CI, 1.57–2.34; $p < 0.0001$) disease than for those who had node-negative disease. However, increasing the *T* classification reduced the impact of *N* classification on death. For instance, the c-index for *N* classification of the patients with *T*1 disease was 0.60 (95% CI, 0.57–0.63; $p < 0.0001$) compared with 0.57 (95% CI, 0.55–0.69; $p < 0.001$) for *T*2 tumors and 0.54 (95% CI, 0.51–0.57; $p = 0.003$) for *T*3 tumors.

Accuracy of the Staging System for Patients Receiving Neoadjuvant Radiotherapy

Additional analyses were performed to assess the staging system's discrimination for the patients receiving neoadjuvant radiotherapy due to the potential impact of this preoperative intervention on nodal disease identified at the time of surgery. Only 229 patients (4%) received neoadjuvant radiotherapy before surgical resection, and the two periods did not differ significantly ($p = 0.3$). The patients receiving neoadjuvant radiotherapy were more likely to be younger, but no difference in sex or grade of tumor was observed. In the neoadjuvant group, 142 (62%) of the patients had *N*0 disease, significantly more than in the surgery-only group ($n = 1954/5692$, 34 %). A significantly

TABLE 4 Distribution of the AJCC 7th and 8th edition staging system

7th Edition	8th Edition					
	1A	1B	2A	2B	3	Total n (%)
1A	369	0	0	0	0	369 (4)
1B	0	458	160	0	0	618 (7)
2A	364	1206	450	0	0	1983 (22)
2B	0	0	0	3793	2197	5990 (67)
Total	723 (8 %)	1647 (18 %)	606 (7 %)	3793 (42 %)	2197 (25 %)	8960



Numbers at risk

Time (months)	0	12	24	36	48	60
Stage 1A	681	492	314	210	135	61
Stage 1B	1548	1044	588	358	227	99
Stage 2A	581	350	179	105	75	36
Stage 2B	3591	2110	992	518	300	135
Stage 3	2068	1049	421	196	87	40

Numbers at risk

Time (months)	0	12	24	36	48	60
Stage 1A	344	252	176	122	79	34
Stage 1B	589	423	276	189	134	60
Stage 2A	1876	1211	629	362	224	102
Stage 2B	5659	3159	1413	714	387	175

FIG. 1 American Joint Committee on Cancer (AJCC) Staging Systems predict overall survival for patients with resected pancreas cancer and indicate the corresponding number of patients at risk. **a** AJCC 8th edition. **b** AJCC 7th edition

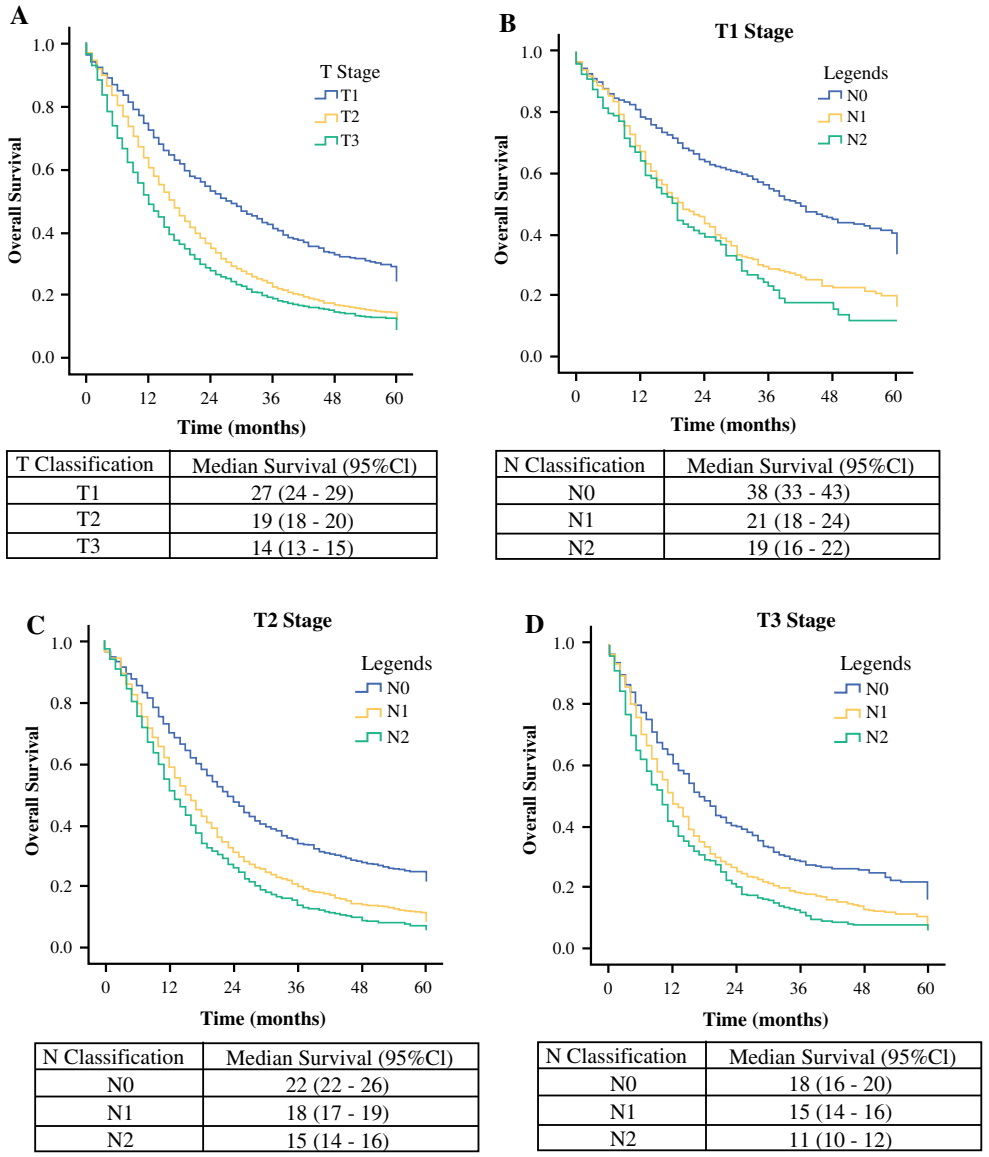
lower number of LNs were examined in the neoadjuvant group than in the surgery-only group (median, 12 vs. 14; $p = 0.001$). For the patients undergoing neoadjuvant radiotherapy, the corresponding c-index for the AJCC 8th edition staging system was 0.61 (95% CI, 0.53–0.68), marginally better than for the AJCC 7th edition staging system (0.60; 95% CI, 0.53–0.68).

DISCUSSION

Using a nationally representative data set, this study demonstrated that the AJCC 8th edition staging system is valid for stratifying patients with resected pancreatic adenocarcinoma in a nationally representative cohort. Furthermore, this new staging system allows for finer stratification of prognosis, primarily due to nodal status. The new system also may improve reproducibility of staging by eliminating extrapancreatic invasion as a staging criterion. However, overall discrimination was similar to that of the staging system in the previous edition.

The revised *T* classification incorporates tumor size, replacing "extension beyond the pancreas" for *T*3 tumors. Several studies have demonstrated that tumor size is a significant prognostic factor for patients undergoing surgical resection for pancreatic adenocarcinoma.[8,11,12] A study by Sohn et al.[11] consisting of 616 patients undergoing surgical resection for pancreatic adenocarcinoma demonstrated that tumor size smaller than 3 cm had the strongest impact on overall survival. In addition, resection of tumors smaller than 3 cm was more likely to achieve an R0 resection margin, which further influenced overall survival. Furthermore, emphasis on tumor size in the *T* classification system allows for reproducibility among radiologists and pathologists to allow respectively for accurate clinical and pathologic staging of the tumor. For instance, Morganti et al.[13] demonstrated that assessment of tumor size for prognostication had better reproducibility for both clinical and pathologic staging. Assessment of extrapancreatic extension using imaging can be difficult due to the desmoplastic reaction to the tumor between the pancreas and the extrapancreatic tissue.[14,15] Similarly, assessment of extrapancreatic invasion on surgical pathology can be dependent on sectioning of the specimen.

Lymph node status also is a recognized prognostic factor of both disease-free and overall survival. Stratification of LN status into *N*1 (1–3 positive LNs) and *N*2 (≥4 positive LNs) classification helps in guiding the prognosis of patients based on the extent of disease spread. Such *N* classification systems are being used for colorectal and breast cancers. Although different cutoffs have been used in different studies,[16,17] the cutoffs for *N*0 versus *N*1 versus *N*2 nodal classification have been adopted into the staging system based on available data.[8,18–20] Strobel et al.[18] demonstrated that stratification by more than one *N* classification helped to improve prognostic accuracy in LN-positive resectable pancreatic adenocarcinoma. Median survival in their study was reduced significantly with increasing positive LNs (PLN) (2–3 PLN: 26.1 months; 4–7 PLN: 21.9 months; ≥8 PLN: 18.3 months; $p < 0.0001$). However, survival did not differ significantly between *N*0 and *N*1 patients. Furthermore, the impact of *T* classification diminished with increasing *N* classification. This finding is consistent with the notion that primary tumor size should lose prognostic relevance as the risk of



T Classification	Median Survival (95%Cl)
T1	27 (24 - 29)
T2	19 (18 - 20)
T3	14 (13 - 15)

N Classification	Median Survival (95%Cl)
N0	38 (33 - 43)
N1	21 (18 - 24)
N2	19 (16 - 22)

N Classification	Median Survival (95%Cl)
N0	22 (22 - 26)
N1	18 (17 - 19)
N2	15 (14 - 16)

N Classification	Median Survival (95%Cl)
N0	18 (16 - 20)
N1	15 (14 - 16)
N2	11 (10 - 12)

FIG. 2 Overall survival of 8960 patients who underwent resection for pancreatic adenocarcinoma. **a** Overall survival by T classification according to the American Joint Committee on Cancer (AJCC) 8th edition for all N classification. **b** Overall survival of T1 patients (AJCC 8th edition) stratified by nodal classification. **c** Overall survival of T2 patients (AJCC 8th edition) stratified by nodal classification. **d** Overall survival of T3 patients (AJCC 8th edition) stratified by nodal classification

TABLE 5 Impact of *T* and *N* classification on survival in the American Joint Committee on Cancer (AJCC) 8th-edition staging system, stratified by *N* classification

	*N*0		*N*1		*N*2	
	HR (95 % CI)	*p* Value	HR (95 % CI)	*p* Value	HR (95 % CI)	*p* Value
*T*1	REF		REF		REF	
*T*2	1.43 (1.26–1.61)	<0.0001	1.26 (1.13–1.40)	<0.0001	1.34 (1.12–1.60)	<0.0001
*T*3	1.84 (1.60–2.12)	<0.0001	1.48 (1.31–1.67)	<0.0001	1.71 (1.42–2.07)	<0.0001

TABLE 6 Impact of *T* and *N* classification on survival in AJCC 8th edition staging system, stratified by *T* classification

	*T*1		*T*2		*T*3	
	HR (95 % CI)	*p* Value	HR (95 % CI)	*p* Value	HR (95 % $CI_)$	*p* Value
*N*0	REF		REF		REF	
*N*1	1.69 (1.47–1.95)	<0.0001	1.49 (1.37–1.61)	<0.0001	1.31 (1.16–1.48)	<0.0001
*N*2	1.92 (1.57–2.34)	<0.0001	1.80 (1.64–1.96)	<0.0001	1.68 (1.47–1.91)	<0.0001

HR hazard ratio, *CI* confidence interval

systemic recurrence (as indicated by the extent of nodal disease) rises.

The overall discrimination of the AJCC 8th edition staging system was comparable with that of the AJCC 7th edition staging system. The c-index of 0.60 indicates moderate discrimination and is comparable with c-indices of other AJCC staging systems.[8,21–27] Staging systems often maintain a degree of simplicity for use in clinical practice, at the cost of discriminatory power. Revisions to the staging system may not necessarily be expected to increase the c-index. Historically, the AJCC staging system for pancreatic cancer has had values ranging between 0.57 and 0.60.[8,26] Importantly, however, this new system allows for finer stratification of resectable tumors. For example, the survival rates for patients with stage 2A and 2B tumors are similar until 20 months. At that point, the curves diverge, indicating a potential delayed impact of nodal disease on survival. As novel neoadjuvant and adjuvant approaches are evaluated, the ability to stratify patients with resectable tumor more finely may prove increasingly useful.

The limitations of our study included the lack of information on the resection margin status of these tumors. Because these data are not included in the AJCC staging system, they are not routinely collected. However, our study demonstrated results similar to those reported by Allen et al.[8] using a R0 cohort, suggesting that survival discrimination of the new staging system may be independent of resection margin status.

Another limitation of the SEER dataset is a lack of centralized pathologic review of all specimens. This highlights the advantage of using tumor size, a measurement likely to be more reproducible between pathologists than assessment of extrapancreatic invasion. A notable strength of our study was its robust long-term follow-up assessment of survival provided by SEER.

CONCLUSION

In summary, the new AJCC 8th edition staging system allows for finer stratification of patients according to the *T* and *N* classifications after resection for pancreatic adenocarcinoma without loss of discriminatory performance. Further studies incorporating other prognostic markers, such as CA 19-9 tumor marker levels, circulating tumor cells, cell-free DNA, and integrated pathway subtypes (squamous vs pancreatic progenitor vs. immunogenic) into the staging system may help refine the existing staging system to guide management of patients with adjuvant treatment. Development of a more robust prognostic model for predicting prognosis after surgical resection may help in guiding postoperative management of patients and allow more accurate stratification for clinical trials.

CONFLICT OF INTEREST There are no conflicts of interest.

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