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International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM Staging System in Patients With Resected Pancreatic Cancer

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IMPORTANCE The recently released eighth edition of the American Joint Committee on Cancer TNM staging system for pancreatic cancer seeks to improve prognostic accuracy but lacks international validation.

OBJECTIVE To validate the eighth edition of the American Joint Committee on Cancer TNM staging system in an international cohort of patients with resected pancreatic ductal adenocarcinoma.

DESIGN, SETTING, AND PARTICIPANTS This international multicenter cohort study took place in 5 tertiary centers in Europe and the United States from 2000 to 2015. Patients who underwent pancreatoduodenectomy for nonmetastatic pancreatic ductal adenocarcinoma were eligible. Data analysis took place from December 2017 to April 2018.

EXPOSURES Patients were retrospectively staged according to the seventh and eighth editions of the TNM staging system.

MAIN OUTCOMES AND MEASURES Prognostic accuracy on survival rates, assessed by Kaplan-Meier and multivariate Cox proportional hazards analyses and concordance statistics.

RESULTS A total of 1525 consecutive patients were included (median [IQR] age, 66 (58-72) years; 802 (52.6%) male). Distribution among stages via the seventh edition was stage IA in 41 patients (2.7%), stage IB in 42 (2.8%), stage IIA in 200 (13.1%), stage IIB in 1229 (80.6%), and stage III in 12 (0.8%); this changed with use of the eighth edition to stage IA in 118 patients (7.7%), stage IB in 144 (9.4%), stage IIA in 22 (1.4%), stage IIB in 643 (42.2%), and stage III in 598 (39.2%). With the eighth edition, 774 patients (50.8%) migrated to a different stage; 183 (12.0%) were reclassified to a lower stage and 591 (38.8%) to a higher stage. Median overall survival for the entire cohort was 24.4 months (95% CI, 23.4-26.2 months). On Kaplan-Meier analysis, 5-year survival rates changed from 38.2% for patients in stage IA, 34.7% in IB, 35.3% in IIA, 16.5% in IIB, and 0% in stage III (log-rank $P < .001$) via classification with the seventh edition to 39.2% for patients in stage IA, 33.9% in IB, 27.6% in IIA, 21.0% in IIB, and 10.8% in stage III (log-rank $P < .001$) with the eighth edition. For patients who were node negative, the T stage was not associated with prognostication of survival in either edition. In the eighth edition, the N stage was associated with 5-year survival rates of 35.6% in N0, 20.8% in N1, and 10.9% in N2 (log-rank $P < .001$). The C statistic improved from 0.55 (95% CI, 0.53-0.57) for the seventh edition to 0.57 (95% CI, 0.55-0.60) for the eighth edition.

CONCLUSIONS AND RELEVANCE The eighth edition of the TNM staging system demonstrated a more equal distribution among stages and a modestly increased prognostic accuracy in patients with resected pancreatic ductal adenocarcinoma compared with the seventh edition. The revised T stage remains poorly associated with survival, whereas the revised N stage is highly prognostic.

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Invited Commentary
Supplemental content

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Over the past decades, the American Joint Committee on Cancer (AJCC) has established a well-defined system for cancer staging based on 3 key components: local tumor extent (T stage), dissemination to the regional lymph nodes (N stage), and metastatic spread to distant sites (M stage) (TNM staging).[1] The AJCC TNM staging system attempts to use anatomical and reproducible parameters to discriminate groups with different survival outcomes.[1-4] Reliable prediction of survival estimates is of paramount importance in cancer care. Accurate prognostication helps clinicians in guiding treatment decisions, provides researchers with a tool to adjust for cancer stage in evaluating treatment outcomes, and is informative to patients themselves.[5,6]

Since only a minority of patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) find that their case is considered resectable, a single TNM system must apply to both clinical and pathologic staging.[3] The seventh edition of the AJCC TNM staging system (2009) has been criticized for its poorly applicable and nonspecific T stages, in which nearly all cases of PDAC are classified as extrapancreatic.[7] The preponderance of T3 tumors, because of the absence of a true capsule around the pancreas, reduced distribution in the T stage and subsequently the discriminative ability of the seventh edition.[7] The N stage of the seventh edition was found to be outdated because of its dichotomous nature, since numerous studies now support the prognostic value of both the number of positive lymph nodes and the lymph node ratio (the number of disease-positive lymph nodes divided by the total number of lymph nodes) in patients with pancreatic cancer.[8-11] These previously mentioned disadvantages limited the clinical applicability and usefulness in the daily practice of the seventh edition of the TNM staging system.

As of January 2018, the eighth edition of *The AJCC Cancer Staging Manual*, including the TNM staging system for tumors arising from the exocrine pancreas, is in use.[2] In the eighth edition, extension beyond the pancreas is no longer considered stage T3, because staging in the T stage has been replaced by a size-based system (except for pT4 tumors), as shown in **Table 1**. Furthermore, the eighth edition subdivided the N1 stage from the seventh edition into N1 and N2 according to the number of positive regional lymph nodes (Table 1).[2] The new AJCC TNM staging system is largely based on single-institution studies in high-volume academic centers in a homogeneous patient population,[7,12,13] which questions the generalizability to other settings.[14]

Our objective was to compare the seventh and eighth edition of the TNM staging systems for pancreatic cancer in distribution and overall prognostic accuracy in an international cohort of patients who underwent pancreatoduodenectomy for PDAC. Additionally, recently proposed modifications to the eighth edition of the TNM staging system[15,16] were also evaluated, because these new modifications have not been externally validated yet and concordance analyses might reveal the incremental value of these proposed changes.

Key Points

Question What is the incremental value in prognostic accuracy of the American Joint Committee on Cancer eighth edition of the TNM staging system in resected pancreatic cancer, compared with the seventh edition?

Findings In this cohort study of 1525 patients with resected pancreatic cancer from Europe and the United States, the eighth edition of the TNM staging system demonstrated a concordance statistic of 0.57, compared with 0.55 via the seventh edition. The revised T stage alone does not add to the discriminatory power, whereas the revised N stage is highly prognostic.

Meaning The eighth edition of the TNM staging system provides additional prognostic accuracy in patients with resected pancreatic cancer compared with the seventh edition.

Methods

Data Collection

Patients who underwent pancreatoduodenectomy for nonmetastatic PDAC were retrospectively identified from institutional databases at 4 referral centers across Europe and 1 in the United States. Participating centers included Amsterdam UMC, AMC, Amsterdam, the Netherlands; Beth Israel Deaconess Medical Center, Boston, Massachusetts; Erasmus Medical Center (MC), Rotterdam, the Netherlands; University Hospital Southampton National Health Service Foundation Trust, Southampton, United Kingdom; and Verona University Hospital, Verona, Italy.

This study was approved by the local institutional review board of each participating center. Informed consent was waived because of the retrospective nature of this study.

The inclusion period slightly differed between institutions, depending on the database of each institution (Amsterdam UMC, 2000-2014; Beth Israel Deaconess Medical Center, 2000-2014; Erasmus MC, 2000-2015; University Hospital Southampton, 2007-2014; Verona University Hospital, 2000-2014). Apart from differences in the inclusion periods, all participating centers used the same inclusion and exclusion criteria. Clinical and pathologic characteristics, as well as the corresponding survival data, were provided by each participating center.

Patients who received preoperative treatment (chemotherapy and/or radiotherapy) or had metastatic disease at the time of surgery were excluded. Patients treated with neoadjuvant therapy were excluded, because consensus is lacking on how to measure tumor size after treatment regression.[17] Also, patients with grossly positive resection margins were excluded, because macroscopically residual disease prevents knowledge of the true tumor size and therefore hinders accurate staging. Resections were considered margin negative when no tumor cells were found within 1 mm of each microscopically assessed margin, according to the definition of the Royal College of Pathologists.[18] Venous resection (ie, superior mesenteric or portal vein resection), but not arterial resections (ie, of the superior mesenteric artery or the hepatic artery), were performed as necessary.

Table 1. Definition of Pancreatic Cancer in the Seventh and Eighth Editions of the American Joint Committee on Cancer TNM Staging System

Stage	Description
Seventh edition, stages in the T and N stages	
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension
T2	Tumor limited to the pancreas, >2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N2	Nonexistent
Eighth edition, stages in the T and N stages	
T1	Maximum tumor diameter ≤2 cm
T2	Maximum tumor diameter >2 and ≤4 cm
T3	Maximum tumor diameter >4 cm
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in ≥4 regional lymph nodes
Seventh edition staging groups	
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T3 N0 M0
IIB	T1, T2, T3 N1 M0
III	T4 any N M0
IV	Any T Any N M1
Eighth edition staging groups	
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T3 N0 M0
IIB	T1, T2, T3 N1 M0
III	T1, T2, T3 N2 M0
	T4 any N M0
IV	Any T any N M1

TNM Classification

The pathologic T stage and N stage of each patient were originally recorded according to the AJCC TNM staging system, fifth edition, from 2000 through 2002; the sixth edition, from 2003 through 2009; and the seventh edition, from 2010 through 2015.[1,3,4] Although several editions were originally used, no significant changes were made in the TNM staging system for pancreatic cancer until the eighth edition.[2] Patients were retrospectively staged according to the eighth edition of the TNM staging system based on pathologic tumor size (T1: ≤2 cm maximal diameter, T2: >2 to 4 cm maximal diameter, T3: >4 cm maximal diameter, and T4: a tumor involving the celiac axis or superior mesenteric artery), and the number of positive lymph nodes during pathologic examination (N0: no positive lymph nodes, N1: 1 to 3 positive lymph nodes, and N2: ≥4 positive lymph nodes). Tumor size was pathologically assessed in each center by measuring the maximal tumor diameter in millimeters on macroscopic inspection and was confirmed on microscopic examination. Subsequently, stage grouping was performed according to the prescribed classification of both the seventh and eighth editions of the TNM staging system (Table 1).[1,2] All patients with undefined TNM stage per the eighth edition (because of missing values with respect to tumor size, number of positive lymph nodes, or follow-up data) were excluded from analysis (n = 10).

Patients were also regrouped according to 2 recently proposed modifications (based on a different grouping scheme) to the eighth edition of the TNM staging system by Jiang et al[15] and Shi et al[16] to assess prognostic accuracy. Jiang et al[15] used recursive partitioning analysis on the Surveillance, Epidemiology, and End Results database to reclassify participants based on a combination of parameters from the seventh and eighth editions of the TNM staging systems, while Shi et al[16] maintained the T, N, and M definitions of the eighth edition but regrouped the substages according to prognostic performance on the Surveillance, Epidemiology, and End Results database.[15,16]

Statistical Analysis

Categorical baseline characteristics were displayed as frequencies and percentages. Numeric data were presented as medians and interquartile ranges (IQR). The primary outcome was overall survival, presented as median overall survival with 95% CIs or 5-year survival rate derived from the Kaplan-Meier estimates. Overall survival was either calculated as the time in months between the date of surgery and the date of death or last follow-up. Unadjusted overall survival was compared using the Kaplan-Meier method and log-rank tests. Multivariate analysis was performed using a Cox proportional hazards model to adjust for pathological variables, which are known to be associated with prognosis.

Prognostic accuracy on overall survival of the seventh and eighth edition of the TNM staging system was assessed using concordance statistics (Uno C statistic), the traditional receiver operating characteristic (ROC) curve, the time-dependent area under the curve (AUC), and the net reclassification index (NRI).[19-21] 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.[19] The time-dependent AUC can be appreciated as the predictive accuracy over time, as derived from each ROC curve.[20] The NRI is a measure that shows how well a new model reclassifies participants.[21] The ROC curve and NRI calculate the ability of a model to quantify prospective survival for a fixed moment in time, for which we chose 3 and 5 years after surgery (ie, 3-year and 5-year survival). Patients without sufficient follow-up time (ie, with unknown vital status at 5 years after surgery) were omitted from the NRI calculations.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute). Study data were collected and managed using the Research Electronic Data Capture electronic data capture tools hosted at Beth Israel Deaconess Medical Center.[22]

Table 2. Baseline Characteristics of the Cohort by Center

Characteristic	No. (%)					
	Total Cohort (N = 1525)	Amsterdam UMC (n = 252)	BIDMC (n = 275)	Erasmus MC (n = 180)	University Hospital Southampton (n = 171)	Verona University Hospital (n = 647)
Age, median (IQR), y	66 (58-72)	66 (59-72)	66 (59-74)	68 (59-73)	67 (59-72)	65 (57-71)
Male	802 (52.6)	133 (52.8)	140 (50.9)	105 (58.3)	84 (49.1)	340 (52.6)
Vascular resection	232 (15.2)	53 (21.0)	24 (8.7)	26 (14.4)	57 (33.3)	72 (11.1)
Margin status						
Margin negative[a]	853 (55.9)	114 (45.2)	157 (57.1)	112 (62.2)	64 (37.4)	406 (62.8)
Margin positive[b]	671 (44.0)	138 (54.8)	118 (42.9)	68 (37.8)	106 (62.0)	241 (37.3)
Unknown	1 (0.1)	0	0	0	1 (0.6)	0
Harvested lymph nodes, median (IQR)[c]	18 (11-28)[c]	10 (7-15)	13 (9-18)	10 (6-15)	16 (13-21)	29 (21-39)
Positive lymph nodes, median (IQR)	2 (1-5)	2 (1-4)	2 (0-4)	1 (0-3)	2 (1-5)	4 (2-7)
Tumor size, median (IQR), mm[d]	27 (20-35)[d]	28 (22-35)	26 (20-35)	28 (20-35)	30 (24-35)	25 (20-31)
Tumor differentiation						
Well	142 (9.3)	16 (6.4)	58 (21.1)	11 (6.1)	23 (13.5)	34 (5.3)
Moderately	945 (62.0)	159 (63.1)	159 (57.8)	110 (61.1)	101 (59.1)	416 (64.3)
Poorly or undifferentiated	425 (27.9)	71 (28.2)	56 (20.4)	54 (30.0)	47 (27.5)	197 (30.5)
Unknown	13 (0.9)	6 (2.4)	2 (0.7)	5 (2.8)	0	0
T stage per seventh edition						
T1	89 (5.8)	17 (6.8)	22 (8.0)	16 (8.9)	7 (4.1)	27 (4.2)
T2	167 (11.0)	52 (20.6)	34 (12.4)	25 (13.9)	8 (4.7)	48 (7.4)
T3 or T4	1269 (83.2)	183 (72.6)	219 (79.7)	139 (77.2)	156 (91.3)	572 (88.4)
N stage per seventh edition						
N0	285 (18.7)	52 (20.6)	76 (27.6)	56 (31.1)	29 (17.0)	72 (11.1)
N1	1240 (81.3)	200 (79.4)	199 (72.4)	124 (68.9)	142 (83.0)	575 (88.9)
Adjuvant therapy[e]						
Chemotherapy alone	727 (47.7)	127 (50.4)	52 (18.9)	51 (28.3)	155 (90.6)[c]	342 (52.9)
Radiotherapy alone	9 (0.6)	0	6 (2.2)	0	0	3 (0.5)
Chemoradiation and other	348 (22.8)	11 (4.4)	137 (49.8)	26 (14.4)	0	174 (26.9)
None	411 (27.0)	111 (44.1)	80 (29.1)	103 (57.2)	9 (5.3)	108 (16.7)
Unknown	30 (2.0)	3 (1.2)	0	0	7 (4.1)	20 (3.1)

Abbreviations: BIDMC, Beth Israel Deaconess Medical Center; IQR, interquartile range; MC, medical center; UMC, university medical center.

[a] R0.

[b] R1.

[c] There were 3 patients (0.2%) with unknown number of harvested lymph nodes.

[d] There were 17 patients (1.1%) with missing values for tumor size.

[e] Adjuvant therapy was advised at a postoperative multidisciplinary meeting, but it was unclear if all these patients actually received adjuvant chemotherapy.

Results

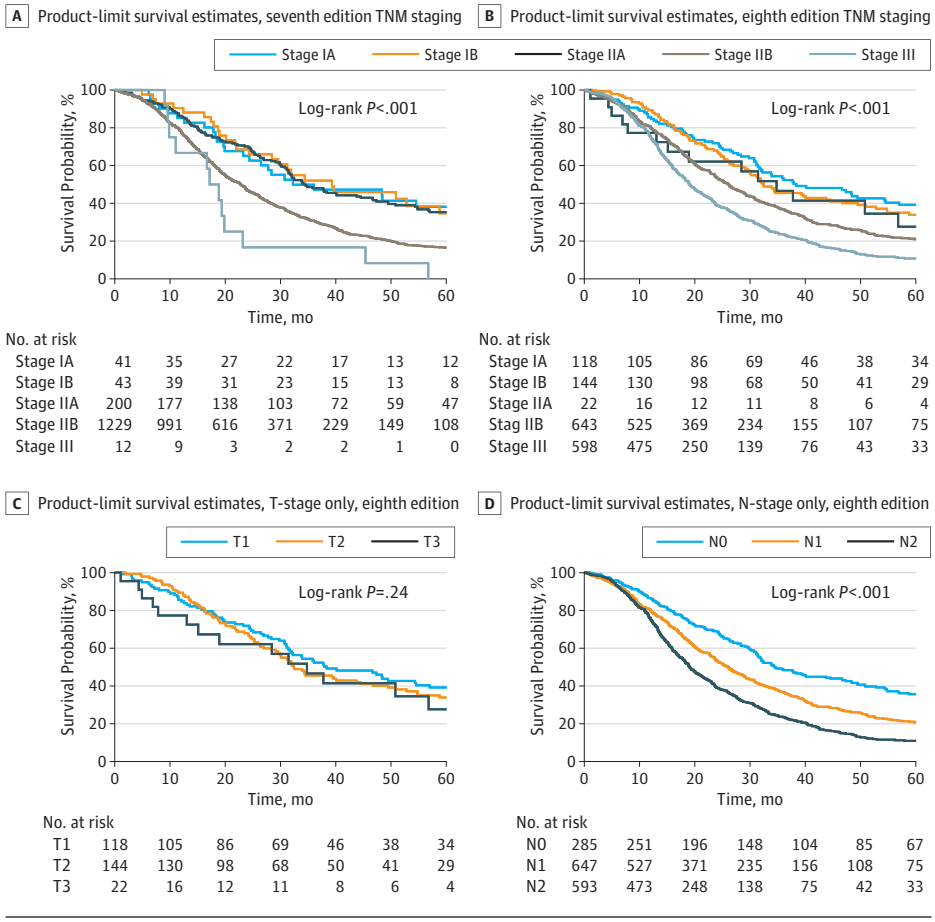
Patient and Tumor Characteristics

In total, 1525 consecutive patients were included for analysis, of whom 252 underwent surgery at Amsterdam UMC, AMC; 275 at Beth Israel Deaconess Medical Center; 180 at Erasmus MC; 171 at University Hospital Southampton; and 647 at Verona University Hospital. Baseline and tumor characteristics are presented in **Table 2**. The median age was 66 (IQR, 58-72) years, and 802 patients (52.6%) were male. Vascular resection was performed in 232 patients (15.2%). The median tumor size was 27 (IQR, 20-35) mm. The median lymph node retrieval of the entire cohort was 18 (IQR, 11-28) nodes, which differed considerably between centers (with median lymph node retrieval of 10 nodes at Amsterdam UMC and Erasmus MC, 13 at Beth Israel Deaconess Medical Center, 16 at University Hospital Southampton, and 29 at Verona University Hospital). A total of 853 patients (55.9%) had microscopically negative resection margins (defined as ≥1 mm). As shown in **Table 3**, via the seventh edition TNM staging system, stage IA was found in 41 patients (2.7%), stage IB in 43 patients (2.8%), stage IIA in 200 patients (13.1%), stage IIB in 1229 patients (80.6%), and stage III in 12 patients (0.8%), and via the eighth edition, stage IA was found in 118 patients (7.7%), stage IB in 144 patients (9.4%), stage IIA in 22 patients (1.4%), stage IIB in 643 patients (42.2%), and stage III in 598 patients (39.2%). Using the eighth-edition classifications, 774 patients (50.8%) migrated to a different stage, of whom 183 (12.0%) were assigned to a lower stage and 591 (38.8%) to a higher stage.

Table 3. Cross-Tabulation of the Seventh and Eighth Edition of the TNM Staging System

TNM Stage, Seventh Edition	TNM Stage, Eighth Edition, No. (%)					
	IA	IB	IIA	IIB	III	Total
IA	41 (2.7)	0	0	0	0	41 (2.7)
IB	0	38 (2.5)	5 (0.3)	0	0	43 (2.8)
IIA	77 (5.1)	106 (7.0)	17 (1.1)	0	0	200 (13.1)
IIB	0	0	0	643 (42.2)	586 (38.4)	1229 (80.6)
III	0	0	0	0	12 (0.8)	12 (0.8)
Total	118 (7.7)	144 (9.4)	22 (1.4)	643 (42.2)	598 (39.2)	1525 (100.0)

Figure 1. Overall Survival by TNM Stage



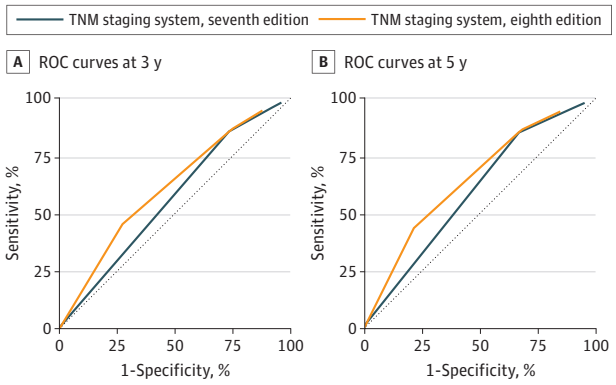
Overall survival by TNM stage according to the seventh edition (A), the eighth edition (B), the stage of the T stage of the eighth edition for patients who were node negative only (C), and the stage of the N stage of the eighth edition (D).

Clinical Outcomes by TNM Stage

At the time of last follow-up, 389 patients (25.5%) were alive, and the median follow-up time for this group was 33.4 (IQR, 20.8-63.6) months. The median overall survival for the entire cohort was 24.4 (95% CI, 23.4-26.2) months, and the 5-year survival rate was 20.2%. Kaplan-Meier curves for overall survival by TNM stage according to the seventh edition and the eighth edition are presented in **Figure 1**A and B, respectively. On Kaplan-Meier survival analysis, 5-year survival rates changed from 38.2% for patients in stage IA, 34.7% for those in stage IB, 35.3% for those in IIA, 16.5% for those in IIB, and 0% for those in stage III (log-rank $P < .001$) under seventh-edition classifications to 39.2% for patients in stage IA, 33.9% for those in stage IB, 27.6% for those in stage IIA, 21.0% for those in stage IIB, and 10.8% in stage III (log-rank $P < .001$) under eighth-edition classifications.

In the subgroup of patients who were node negative (n = 284 [18.6%]), neither T stage according to the seventh edition (eFigure 1 in the Supplement) nor T stage according to the eighth edition (Figure 1C) was discriminative for survival. The new classification of the N stage in the eighth edition was highly discriminative, as shown in Figure 1D, with 5-year survival rates by Kaplan-Meier analysis of 35.6% for patients in N0, 20.8% for patients in N1, and 10.9% for patients in N2 (log-rank $P < .001$). Adjusted for other pathological variables, multivariate analysis of the eighth edition demonstrated that pathological T1 tumors were associated with a significantly decreased hazard ratio (HR) com-

Figure 2. Receiver Operating Characteristic Curve at Selected Times After Surgery



A, Area under curve for the seventh edition: 0.5632; area under curve for eighth edition, 0.6120. B, Area under curve for the seventh edition: 0.5948; area under curve for eighth edition, 0.6481.

pared with T3 tumors (HR, 0.77 [95% CI, 0.62-0.95]), whereas pathological T2 and T4 tumors did not demonstrate a statistically significant survival difference compared with T3 tumors. With patients in N0 used as a reference group, a significantly increased HR was found for patients in N1 (HR, 1.40 [95% CI, 1.18-1.67]) and for patients in N2 (HR, 1.83 [95% CI, 1.53-2.19]) in the eighth edition. All HRs are shown in eFigure 2 in the Supplement.

Prognostic Accuracy

When assessing prognostic accuracy on overall survival, the Uno C statistic was 0.55 (95% CI, 0.53-0.57) for the seventh edition and 0.57 (95% CI, 0.55-0.60) for the eighth edition of the TNM staging system. The ROC curve at 3 years after surgery demonstrated an AUC of 0.56 for the seventh edition and 0.61 for the eighth edition for survival; 5-year survival demonstrated an AUC of 0.59 with the seventh edition and 0.65 with the eighth edition, as depicted in **Figure 2**A and B. The time-dependent AUCs demonstrated a superior AUC for the eighth edition compared with the seventh edition for survival beyond 6 months after surgery (eFigure 3 in the Supplement).

Of the total cohort, 1247 patients (81.8%) had a known vital status at 5 years after surgery and were included in a calculation of reclassification outcomes. Overall, 347 of 1072 patients with an event (32.4%) were correctly reclassified to a higher stage, and 10 of 175 patients without an event (5.7%) were correctly reclassified to a lower stage when criteria from the eighth edition were applied. These findings result in an additive NRI of 0.38 and an absolute NRI of 28.6%.

Proposed Modifications to the Eighth Edition

Patients were also restaged using 2 newly proposed modifications to the eighth edition staging criteria, as defined by Jiang et al[15] and Shi et al.[16] Using the recursive partitioning analysis–modified classification of Jiang et al,[15] the distribution of patients was 41 in stage IA (2.7%), 120 in stage IB (7.9%), 416 in stage IIA (27.3%), 463 in stage IIB (30.4%), and 456 in stage III (29.9%), with 29 patients (1.9%) unclassified because of missing tumor size or T4 tumors. Regrouping the TNM 8 stages according to Shi et al,[16] 117 patients were found in be in stage IA (7.7%), 328 in stage IB (21.5%), 537 in stage IIA (35.2%), 433 in stage IIB (28.4%), 81 in stage IIIA (5.3%), and 12 in stage IIIB (0.8%). Similarly, 17 patients (1.1%) were left unstaged because of missing tumor size. Kaplan-Meier estimates are presented in the supplementary material (eFigure 4 and 5 in the Supplement). The Uno C statistic demonstrated a prognostic accuracy of 0.57 (95% CI, 0.56-0.59) and 0.58 (95% CI, 0.57-0.60) for the proposed modification of Jiang et al[15] and Shi et al,[16] respectively.

Discussion

The eighth edition of the TNM staging system demonstrated a more equal distribution among stages and increased prognostic accuracy compared with the seventh edition of the AJCC TNM staging system, in addition to positive reclassification outcomes. The new T stage did not demonstrate significant correlation with survival on univariate or multivariate analysis, whereas the new N stage showed accurate discrimination of survival. Also, after adjusting for pathological variables such as margin status and tumor grade, our findings regarding the eighth edition of the TNM staging system remained unchanged. Moreover, the lack of correlation between the new T stage and survival in node-negative patients in this cohort was consistent among all institutions. The proposed modification using a combination of seventh and eighth edition TNM parameters demonstrated negligible improvement in prognostic accuracy, while a modified regrouping scheme of unchanged eighth edition TNM parameters offered slightly improved prognostication compared with the original TNM eighth edition.[15,16]

Several studies have previously validated the eighth edition AJCC TNM staging system,[12,14,23] including 2 proposed modifications for the next edition of the system[15,16]; however, only limited concordance statistics were assessed on relatively homogeneous cohorts. Furthermore, the validation results varied widely across studies and were at times conflicting. For instance, while some studies demonstrated the incremental prognostic value of the new size-based T stage,[7,23] it is remarkable that these findings were not supported in the present validation in an international cohort. Two strengths of the present study are the generalizability, with 5 centers from Europe and the United States, and the longer follow-up time.

A recent study from the United States that included 2318 patients found a barely negligible increase in predictive ability, with a C statistic of 0.57 and 0.58 for the seventh and eighth editions, respectively.[12] In addition, the study excluded patients who underwent a microscopically margin-positive resection, which represents a serious limitation, because TNM staging is also applied to patients who undergo margin-positive resections. A recent dual-center study from Germany in a cohort of 523 patients with PDAC found that the new pT stage, but not the pN stage, improved the prognostication of the eighth edition.[23] Notably, the median tumor size of this German cohort was considerably higher (35 mm) than that of the patient groups in any of the participating centers in the present study, which might reflect different measurements or tumors and might have led to this conclusion. It remains unclear whether the lack of correlation between tu-

mor size and survival in patients who were node negative in the present study is because of the variability in interpretation of pathologic parameters, the prognostic insignificance of the parameter itself, or both. Although the German study did not assess survival separately for the group of patients who were node negative,[23] the previously mentioned validation study from the United States showed significant discrimination of the T stage for patients who were node negative.[12] Patients with node-negative disease remain the most challenging in prognostic stratification (ie, in discriminating stage IA, IB, and IIA), and the contradicting results in the literature warrant further research on the association between tumor size and survival, especially in patients who are node negative.

Limitations

One of the limitations of this study is the lack of standardization in surgical procedure and pathological examination throughout all centers, resulting in considerable variability in lymph node yield, tumor size, and margin status.[24,25] These practice variations might blur the true correlation between pathological findings and clinical outcome after pancreatic cancer surgery and should be improved through standardization, potentially supported by an evidence-based statement of the International Study Group of Pancreatic Surgery.

Conclusions

This study represents the first international validation of the eighth edition of the AJCC TNM staging system in a cohort from 4 different countries across Europe as well as the United States. The results of this study are generalizable and clinically applicable, with an international cohort representing heterogeneity mainly in patients but also in pathological procedures, including different slicing techniques.[26,27] Overall, increased prognostic accuracy was found for the eighth edition of the AJCC TNM staging system compared with the seventh edition. The revised size-based T stage alone was shown to be poorly associated with survival, which resulted in poor discrimination of survival among patients who were node negative (ie, those with disease in stages IA, IB, and IIA). The revised N stage is strongly associated with survival and adds significantly to the prognosticative ability of the eighth edition of the TNM staging system.

The differences in pathological findings among institutions emphasize that standardization of surgical and pathological procedures remains a crucial topic for international studies and comparisons. Future studies will also need to assess the association of neoadjuvant therapy with tumor size measurements during pathological examination and subsequent staging in the T stage, since international consensus is still lacking on this topic among pathologists.[17] At the same time, it is still unclear whether local tumor extent alone has a useful association with outcomes of early-stage pancreatic cancer. While each subsequent AJCC staging edition continues to incrementally improve on prognostication in pancreatic cancer, larger strides may require the incorporation of novel biomarkers, information on tumor microenvironment, and/or the immune system.

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Correction: This article was corrected on February 20, 2019, to remove an errant "%" from the sentence "These findings result in an additive NRI of 0.38% and an absolute NRI of 28.6%." The sentence now reads "These findings result in an additive NRI of 0.38 and an absolute NRI of 28.6%." In addition, the label on the x-axis of both receiver operating characteristic curves in Figure 2 has been corrected to "1 – Specificity," instead of "Specificity."

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