Clinicopathological outcome and prognostication in pancreatic surgery

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Publication date
2020
Document Version
Other version
License
Other

10

CHAPTER 10

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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JAMA Surgery 2018

ABSTRACT

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.

INTRODUCTION

Over the past decades, the American Joint Committee on Cancer (AJCC) has established a well-defined system for cancer staging, based on three key components: local tumor extent (T stage), dissemination to the regional lymph nodes (N stage), and metastatic spread to distant sites (M stage).[1] The AJCC TNM staging classification 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 effects, and is informative to patients themselves.[5,6]

Since only a minority of patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) is amenable to surgical resection, a single TNM classification must apply to both clinical and pathologic staging.[3] The 7th edition was criticized for its poorly applicable and non-specific T stage, where the vast majority of PDACs are classified as extrapancreatic.[7] The preponderance of T3 tumors, due to the absence of a true capsule around the pancreas, reduced distribution in T stage and subsequently the discriminative ability of the 7th edition.[7] The N stage of the 7th edition was found to be outdated due to its dichotomous nature, as numerous studies now support the prognostic value of both the number of positive lymph nodes, as well as the lymph node ratio (number of positive lymph nodes divided by total number of lymph nodes) in pancreatic cancer.[8-11] Previously mentioned disadvantages limited the clinical applicability and utility in daily practice of the TNM 7th edition.

As of January 2018, the 8th edition of the AJCC cancer staging manual, including the TNM classification for tumors arising from the exocrine pancreas, is being used.[2] In the 8th edition, extend beyond the pancreas was no longer considered as stage T3, since T staging was replaced by a size-based system (except for pT4 tumors), as shown in Table 1. Furthermore, the 8th edition subdivided the N1 stage from the 7th edition into N1 and N2 according to the number of positive regional lymph nodes (Table 1).[2] The new AJCC staging system is largely based on single-institution series in high-volume academic centers in a homogeneous patient population,[7,12,13] which questions the generalizability in other settings.[14]

Our objective was to compare the 7th and 8th edition of the TNM classification systems for pancreatic cancer in distribution and overall prognostic accuracy in an international cohort who underwent pancreatoduodenectomy (PD) for PDAC. Additionally, recently proposed modifications to the TNM 8th edition[15,16] were also evaluated, as these new modifications have not been externally validated yet and concordance analyses might reveal the incremental value of these proposed changes.

TABLE 1. Definition of the AJCC staging according to the 7th and 8th edition[1,2].

	T and N stage according to the 7th edition			T and N stage according to the 8th edition		
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension			Maximum tumor diameter ≤2 cm		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension			Maximum tumor diameter >2 and ≤4 cm		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery			Maximum tumor diameter >4 cm		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)			Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
N0	No regional lymph node metastasis			No regional lymph node metastasis		
N1	Regional lymph node metastasis			Metastasis in 1 - 3 regional lymph nodes		
N2	Non-existent			Metastasis in ≥4 regional lymph nodes		
	Staging grouping according to the 7th edition			**Stage grouping according to the 8th edition**		
Stage IA	T1	N0	M0	T1	N0	M0
Stage IB	T2	N0	M0	T2	N0	M0
Stage IIA	T3	N0	M0	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0	T1, T2, T3 T4	N2 Any N	M0 M0
Stage IV	Any T	Any N	M1	Any T	Any N	M1

METHODS

Data collection

Patients who underwent pancreatoduodenectomy for non-metastatic PDAC were retrospectively identified from institutional databases at four referral centers from across Europe and one in the United States. Participating centers included Amsterdam UMC (AMC), Amsterdam, the Netherlands; Beth Israel Deaconess Medical Center (BIDMC), Boston, MA, US; Erasmus MC (EMC), Rotterdam, the Netherlands; University Hospital Southampton NHS Foundation Trust (UHS), Southampton, United Kingdom; and Verona University Hospital (VUH), Verona, Italy.This study was approved by the local Institutional Review Board of each participating center. The inclusion period slightly differed between institutions, depending on the database of each institution (AMC, 2000-2014; BIDMC 2000-2014; EMC 2000-2015; UHS 2007-2014; VUH 2000-2014). 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, since consensus is lacking on how to measure tumor size after treatment regression.[17] Also, patients with grossly positive resection margins (R2) were excluded, as macroscopically residual disease prevents knowledge of the true tumor size and therefore hinders accurate staging. Apart from some differences in inclusion period, all participating centers used the

same inclusion and exclusion criteria. Clinical and pathologic characteristics were provided by each participating center, as well as the corresponding survival data. Resections were considered margin-negative when no tumor cells were found within 1mm of each microscopically assessed margin according to the definition of the Royal College of Pathologists.[18] Venous resection (i.e. superior mesenteric or portal vein resection), but not arterial resections (i.e. superior mesenteric artery or hepatic artery), were performed as necessary.

TNM classification

Pathologic T and N stage was originally recorded according to the AJCC TNM 5th edition during the years 2000-2002, 6th edition 2003-2009, and 7th edition 2010-2015.[1,3,4] Although several editions were originally used, no significant changes were made in the TNM classification for pancreatic cancer until the 8th edition.[2] Patients were retrospectively staged according to the AJCC TNM 8th edition, based on pathologic tumor size as shown in Table 1 (T1: ≤2cm maximal diameter, T2: >2 and ≤4cm maximal diameter, T3: >4cm maximal diameter, T4: involves celiac axis or superior mesenteric artery), and the number of positive lymph nodes during pathologic examination (N0: no positive lymph nodes, N1: 1-3 positive lymph nodes, 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 7th and 8th editions of the TNM staging system (Table 1).[1,2] All patients with undefined TNM 8 stage, due to missing values for tumor size or positive lymph nodes, or missing follow-up data were excluded from analysis (n=10). Patients were also grouped according to two recently proposed modifications to the 8th edition by Jiang et al. and Shi et al., based on a different grouping scheme, to assess prognostic accuracy.[15,16] Jiang et al. used recursive partitioning analysis (RPA) on the Surveillance, Epidemiology, and End Results (SEER) database to reclassify subjects based on a combination of parameters from the TNM 7th and 8th edition, while Shi et al. maintained the T, N, and M definitions of the 8th edition but regrouped the substages according to prognostic performance on the SEER database (supplementary Figures S1 and S2).[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% confidence intervals (CI), or 5-year survival rate derived from the Kaplan-Meier estimates. Overall survival was calculated as the time in months between the date of surgery and the date of death, or censored at the date of 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 related to prognosis. Prognostic accuracy on overall survival of the 7th and 8th edition of the TNM staging system was assessed using concordance statistics (Uno's 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] Uno's C-statistic is comparable to a routinely used C-statistic, but accounts for a covariate-dependent censoring distribution, and 95% CI's 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 subjects.[21] The ROC curve and NRI calculate the ability to predict survival for a fixed moment in time, for which we chose 3 and 5 years after surgery (i.e. 3- and 5-year survival). Patients without sufficient follow-up time (i.e. 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, Cary, NC). Study data were collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tools hosted at BIDMC.[22]

RESULTS

Patient and tumor characteristics

In total, 1525 consecutive patients were included for analysis, of whom 252 underwent surgery at AMC, Amsterdam; 275 at BIDMC, Boston; 180 at Erasmus MC, Rotterdam; 171 at UHS, Southampton; and 647 at VUH, Verona. Baseline and tumor characteristics are presented in Table 2. The median age was 66 years (IQR 58-72) and 52.6% of the patients were male. Vascular resection performed in 232 patients (15.2%). The median tumor size was 27 millimeters (IQR 20-35). The median lymph node retrieval of the entire cohort was 18 (IQR 11-28), which differed considerably between centers (10 at AMC and EMC, 13 at BIDMC, 16 at UHS, 29 at VUH). 853 patients (55.9%) had microscopically negative resection margins (definition ≥1mm). As shown in Table 3, stage IA, IB, IIA, IIB and III were 2.7%, 2.8%, 13.1%, 80.6%, 0.8% in the 7th edition and 7.7%, 9.4%, 1.4%, 42.2%, 39.2% in the 8th edition, respectively. Using the 8th edition classifications, 774 (50.8%) patients migrated to a different stage, of whom 183 (12.0%) patients were assigned to a lower stage and 591 (38.8%) patients were assigned to a higher stage.

TABLE 2. Baseline characteristics of the entire cohort.

	AMC, Amsterdam n= 252	BIDMC, Boston n = 275	Erasmus MC, Rotterdam n = 180	UHS, Southampton n = 171	VUH, Verona n = 647	Total cohort n = 1525
Age, median (IQR)	66 (59-72)	66 (59-74)	68 (59-73)	67 (59-72)	65 (57-71)	66 (58-72)
Male, n (%)	133 (52.8%)	140 (50.9%)	105 (58.3%)	84 (49.1%)	340 (52.6%)	802 (52.6%)
Vascular resection, n (%)	53 (21.0%)	24 (8.7%)	26 (14.4%)	57 (33.3%)	72 (11.1%)	232 (15.2%)
Margin status, n (%)						
R0	114 (45.2%)	157 (57.1%)	112 (62.2%)	64 (37.4%)	406 (62.8%)	853 (55.9%)
R1	138 (54.8%)	118 (42.9%)	68 (37.8%)	106 (62.0%)	241 (37.3%)	671 (44.0%)
Unknown	0	0	0	1 (0.6%)	0	1 (0.1%)
Harvested lymph nodes, median (IQR)	10 (7-15)	13 (9-18)	10 (6-15)	16 (13-21)	29 (21-39)	18 (11-28)[a]
Positive lymph nodes, median (IQR)	2 (1-4)	2 (0-4)	1 (0-3)	2 (1-5)	4 (2-7)	2 (1-5)
Tumor size in millimeter, median (IQR)	28 (22-35)	26 (20-35)	28 (20-35)	30 (24-35)	25 (20-31)	27 (20-35)[b]
Tumor differentiation, n (%)						
Well	16 (6.4%)	58 (21.1%)	11 (6.1%)	23 (13.5%)	34 (5.3%)	142 (9.3%)
Moderately	159 (63.1%)	159 (57.8%)	110 (61.1%)	101 (59.1%)	416 (64.3%)	945 (62.0%)
Poorly/undifferentiated	71 (28.2%)	56 (20.4%)	54 (30.0%)	47 (27.5%)	197 (30.5%)	425 (27.9%)
Unknown	6 (2.4%)	2 (0.7%)	5 (2.8%)	0	0	13 (0.9%)
AJCC T stage 7th ed., n (%)						
T1	17 (6.8%)	22 (8.0%)	16 (8.9%)	7 (4.1%)	27 (4.2%)	89 (5.8%)
T2	52 (20.6%)	34 (12.4%)	25 (13.9%)	8 (4.7%)	48 (7.4%)	167 (11.0%)
T3 / T4	183 (72.6%)	219 (79.7%)	139 (77.2%)	156 (91.3%)	572 (88.4%)	1269 (83.2%)
AJCC N stage 7th ed., n (%)						
N0	52 (20.6%)	76 (27.6%)	56 (31.1%)	29 (17.0%)	72 (11.1%)	285 (18.7%)
N1	200 (79.4%)	199 (72.4%)	124 (68.9%)	142 (83.0%)	575 (88.9%)	1240 (81.3%)
Adjuvant therapy, n (%)						
Chemotherapy alone	127 (50.4%)	52 (18.9%)	51 (28.3%)	155 (90.6%)[c]	342 (52.9%)	727 (47.7%)
Radiotherapy alone	0	6 (2.2%)	0	0	3 (0.5%)	9 (0.6%)
Chemoradiation	11 (4.4%)	137 (49.8%)	26 (14.4%)	0	174 (26.9%)	348 (22.8%)
None	111 (44.1%)	80 (29.1%)	103 (57.2%)	9 (5.3%)	108 (16.7%)	411 (27.0%)
Unknown	3 (1.2%)	0	0	7 (4.1%)	20 (3.1%)	30 (2.0%)

[a] There were 3 (0.2%) patients with unknown number of harvested lymph nodes. [b] There were 17 (1.1%) patients with missing values for tumor size. [c] Adjuvant therapy advised at postoperative multidisciplinary meeting, not clear whether all these patients actually received adjuvant chemotherapy.

TABLE 3. Cross-tabulation of the 7th and 8th Edition of the TNM staging system.

			TNM Stage 8			
TNM Stage 7	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage III	Total
Stage IA	41 2.7%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	41 2.7%
Stage IB	0 0.0%	38 2.5%	5 0.3%	0 0.0%	0 0.0%	43 2.8%
Stage IIA	77 5.1%	106 7.0%	17 1.1%	0 0.0%	0 0.0%	200 13.1%
Stage IIB	0 0.0%	0 0.0%	0 0.0%	643 42.2%	586 38.4%	1229 80.6%
Stage III	0 0.0%	0 0.0%	0 0.0%	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%

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 months (IQR 20.8 – 63.6). The median overall survival for the entire cohort was 24.4 months (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 7th edition and the 8th edition are presented in Figure 1A and 1B, respectively. Five-year survival rates changed from 38.2%, 34.7%, 35.3%, 16.5%, 0% (log-rank p<0.0001) in the 7th edition, to 39.2%, 33.9%, 27.6%, 21.0% and 10.8% (log-rank p<0.0001) in the 8th edition for stage IA, IB, IIA, IIB and III, respectively. In the subgroup of node-negative patients (n=284, 18.6%), neither T stage according to the 7th edition (supplementary Figure S1), nor according to the 8th edition (Figure 1C), was discriminative for survival (log-rank p=0.99 and p=0.24, respectively). The new classification of the N stage in the 8th edition was highly discriminative as shown in Figure 1D, with 5-year survival rates of 35.6%, 20.8% and 10.9% for N0, N1 and N2 patients, respectively (log-rank p<0.0001). Adjusted for other pathological variables, multivariate analysis of the 8th edition demonstrated that pathological T1 tumors were associated with a significantly decreased hazard ratio (HR) versus 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 to T3 tumors (p=0.18 and p=0.40, respectively). With N0 patients as a reference group, a significantly increased hazard ratio was found for N1 patients (HR 1.40, 95% CI 1.18-1.67) and for N2 patients (HR 1.83, 95% CI 1.53-2.19) in the 8th edition. All hazard ratios are shown in supplementary Figure S2.

FIGURE 1A. Overall survival by TNM Stage according to the 7th Edition.

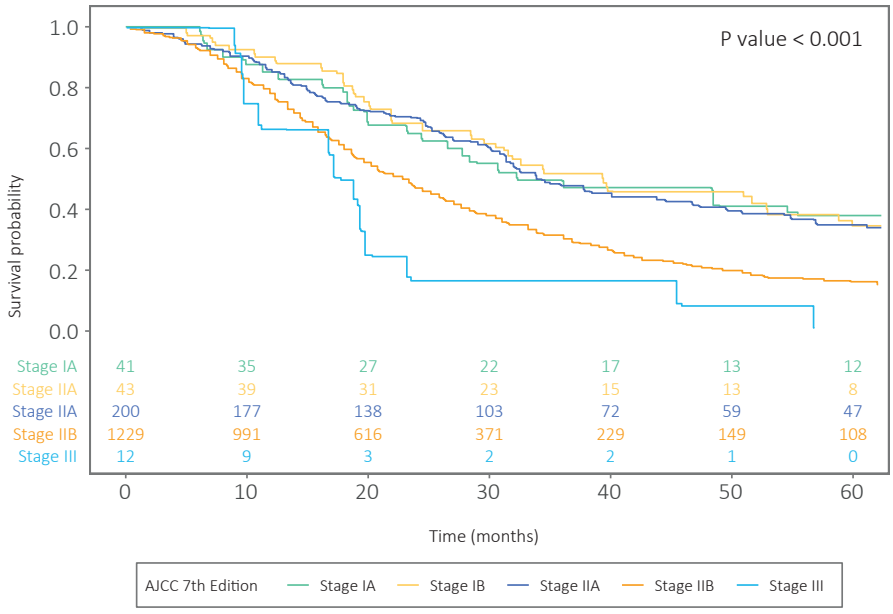


FIGURE 1B. Overall survival by TNM Stage according to the 8th Edition.

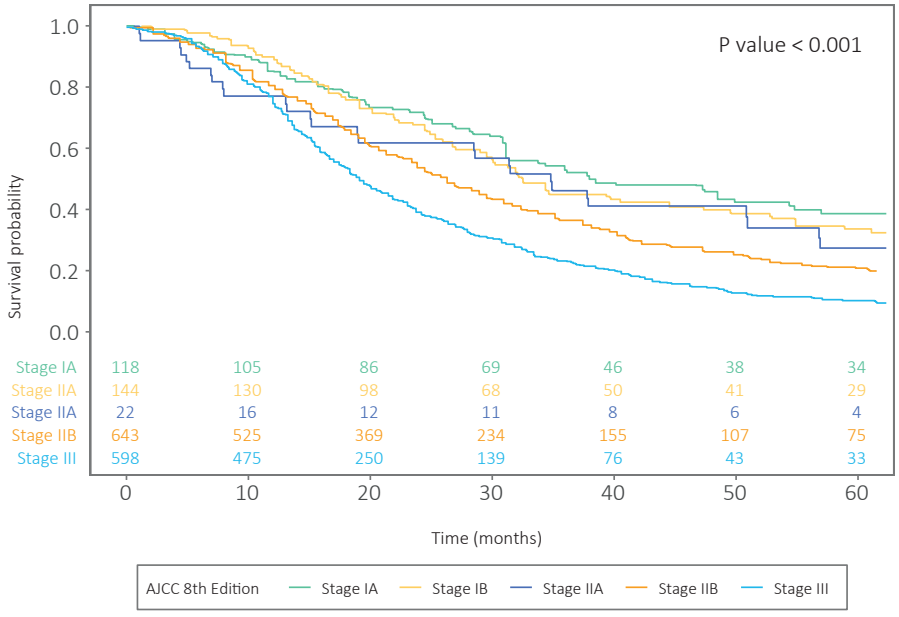


FIGURE 1C. Overall survival by T Stage 8th Edition – only node negative patients.

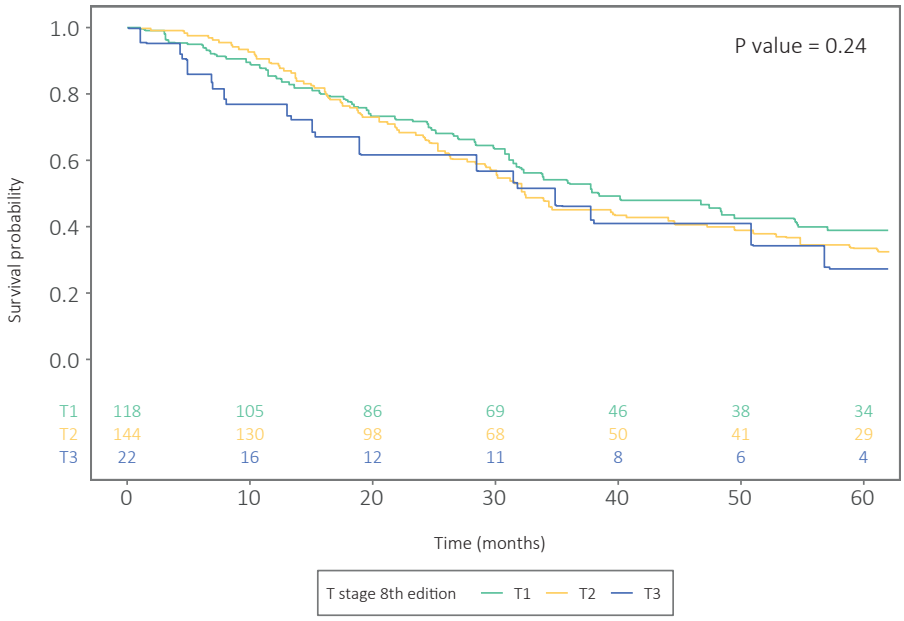
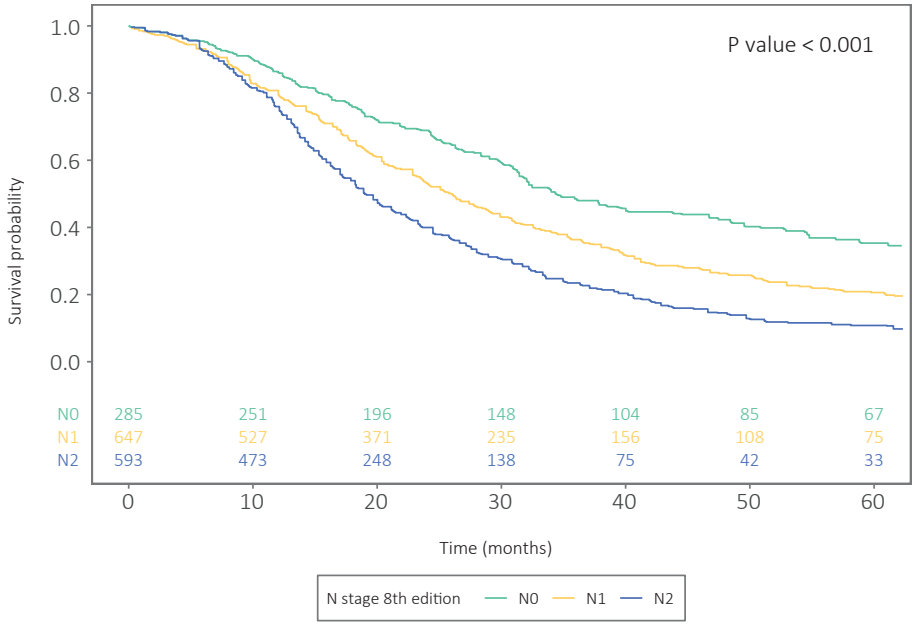


FIGURE 1D. Overall survival by N Stage 8th Edition.



Prognostic accuracy

When assessing prognostic accuracy on overall survival, Uno's C-statistic was 0.55 (95% CI 0.53-0.57) for the 7th edition and 0.57 (95% CI 0.55-0.60) for the 8th edition of the TNM staging system. The ROC curve at 3 years after surgery demonstrated an AUC of 0.56 for the 7th and 0.61 for the 8th edition for the prediction of survival, and prediction of 5-year survival demonstrated an AUC of 0.59 for the 7th and 0.65 for the 8th edition, as depicted in Figure 2A and 2B. The time-dependent AUCs demonstrates a superior AUC for the 8th edition compared to the 7th edition for prediction of survival beyond 6 months following surgery (supplementary Figure S3). Of the total cohort, 1247 (81.8%) patients had a known vital status at 5 years after surgery and were used for the calculation of reclassification outcomes. Overall, 347 of the 1072 patients with an event (32.4%) were correctly upstaged and 10 of the 175 patients without an event (5.7%) were correctly downstaged with the 8th edition. These findings result in an additive net reclassification index (NRI) of +0.38 and an absolute NRI of 28.6%.

FIGURE 2A. ROC curve at 3 years.

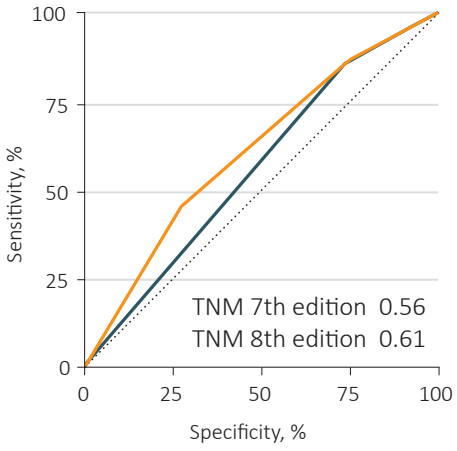
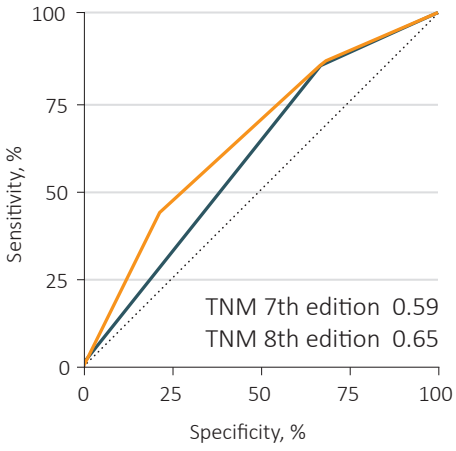


FIGURE 2B. ROC curve at 5 years.



Proposed modifications to the 8th edition

Patients were also re-staged using two newly proposed modifications to the 8th edition staging criterion, as defined by Jiang et al. and Shi et al (supplementary Figures S1 and S2).[15,16] Using the RPA modified classification of Jiang et al., the distribution of patients was as follows: stage IA, IB, IIA, IIB, III were 2.7%, 7.9%, 27.3%, 30.4%, 29.9%, respectively, with 1.9% of the patients unable to stage due to missing tumor size or T4 tumors. Regrouping the TNM 8 stages according to Shi et al., stage IA, IB, IIA, IIB, IIIA, IIIB were 7.7%, 21.5%, 35.2%, 28.4%, 5.3% and 0.8%, respectively. Similarly, 1.1% of the patients were left

unstaged due to missing tumor size. Kaplan-Meier estimates are presented in the supplementary material (Figure S4 and S5). Uno's 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. and Shi et al., respectively.[15,16]

DISCUSSION

The 8th edition of the TNM staging system demonstrated a more equal distribution among stages and increased prognostic accuracy compared to the AJCC 7th edition, in addition to positive reclassification outcomes. The new T stage did not demonstrate significant correlation with survival on univariate nor on 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 8th edition of the TNM classification 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 7th and 8th edition TNM parameters demonstrated negligible improvement in prognostic accuracy, while a modified regrouping scheme of unchanged 8th edition TNM parameters offered slightly improved prognostication relative to the original TNM 8th edition.[15,16]

Several studies have previously validated the 8th edition AJCC staging system,[12,14,23] including two proposed modifications for the next edition of the TNM staging system;[15,16] however, only limited concordance statistics were assessed and the cohorts were relatively homogeneous. 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. A strength of the present study is the generalizability with five centers from Europe and US, and a longer follow-up time.

A recent study from the US, including 2318 patients, found a barely negligible increase in predictive ability with a C-statistic of 0.57 and 0.58 for the 7th and 8th edition, respectively.[12] Besides, it should be noted that the study excluded patients who underwent a microscopically margin-positive resection (R1), representing a serious limitation of this study since TNM staging is also applied to patients who underwent a R1 resection. A recent dual-center study from Germany in a cohort of 523 PDAC patients, found that the new pT but not pN stage improved the prognostication of the 8th edition.[23] Notably, the median tumor size of this German cohort was considerably higher (35 millimeters) than in any of the participating centers in the present study, which might reflect different measurements or tumors and

may have led to this conclusion. It remains unclear whether the lack of correlation between tumor size and survival in node-negative patients in the present study is due to 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 node-negative patients,[23] the previously mentioned validation study from the US showed significant discrimination of T stage for node-negative patients.[12] Patients with node-negative disease remain the most challenging in prognostic stratification (i.e. discriminating stage IA, IB and IIA), and the contradicting results in the literature warrant further research on the correlation between tumor size and survival, especially in node-negative patients.

One of the limitations 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 (ISGPS).

This study represents the first international validation of the AJCC TNM 8th edition in a cohort from four different countries across Europe and the US. 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 AJCC TNM 8th edition compared to the 7th edition. The new size-based T stage alone showed to be a poor predictor of survival, which resulted in poor discrimination of survival among node-negative patients (i.e. stage IA, IB and IIA). The new N stage is a strong predictor of survival and adds significantly to the predictive ability of the TNM 8th edition.

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 impact of neoadjuvant therapy on tumor size measurements during pathological examination and subsequently T staging, 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 is a useful predictor in early-stage pancreatic cancer. While each subsequent AJCC staging edition continues to incrementally improve upon prognostication in pancreatic cancer, larger strides may require the incorporation of novel biomarkers, information on tumor microenvironment and/or the immune system.

ACKNOWLEDGMENTS

Research reported in this publication was supported by the NIDDK of the NIH under Award Number T32DK007754. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry.

S.R. and M.G.B. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank Sing Chau Ng, MS, biostatistician at Boston Medical Center, Boston, MA for providing statistical guidance throughout the analyses and helping with the interpretation of the results. The present study was not supported by any funding.

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