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Article

A Modified Tumor-Node-Metastasis Classification for Primary Operable Colorectal Cancer

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Abstract

Background: The American Joint Committee on Cancer (AJCC) 8th tumor-node-metastasis (TNM) classification for colorectal cancer (CRC) has limited ability to predict prognosis. **Methods:** We included 45 379 eligible stage I-III CRC patients from the Surveillance, Epidemiology, and End Results Program. Patients were randomly assigned individually to a training (n = 31 772) or an internal validation cohort (n = 13 607). External validation was performed in 10 902 additional patients. Patients were divided according to T and N stage permutations. Survival analyses were conducted by a Cox proportional hazard model and Kaplan-Meier analysis, with T1N0 as the reference. Area under receiver operating characteristic curve and Akaike information criteria were applied for prognostic discrimination and model fitting, respectively. Clinical benefits were further assessed by decision curve analyses. **Results:** We created a modified TNM (mTNM) classification: stages I (T1-2N0-1a); IIA (T1N1b, T2N1b, T3N0); IIB (T1-2N2a-2b, T3N1a-1b, T4aN0); IIC (T3N2a, T4aN1a-2a, T4bN0); IIIA (T3N2b, T4bN1a); IIIB (T4aN2b, T4bN1b); and IIIC (T4bN2a-2b). In the internal validation cohort, compared with the AJCC 8th TNM classification, the mTNM classification showed superior prognostic discrimination (area under receiver operating characteristic curve = 0.675 vs 0.667, respectively; 2-sided $P < .001$) and better model fitting (Akaike information criteria = 70 937 vs 71 238, respectively). Similar findings were obtained in the external validation cohort. Decision curve analyses revealed that the mTNM had superior net benefits over the AJCC 8th TNM classification in the internal and external validation cohorts. **Conclusions:** The mTNM classification provides better prognostic discrimination than AJCC 8th TNM classification, with good applicability in various populations and settings, to help better stratify stage I-III CRC patients into prognostic groups.

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Colorectal cancer (CRC) is a public health concern worldwide (1-3). Although its incidence and mortality rates have been declining in recent decades, CRC remains the fourth most frequently diagnosed cancer and second-leading cause of cancer-related death in the United States (2,3).

The American Joint Committee on Cancer (AJCC)–Union for International Cancer Control tumor-node-metastasis (TNM) classification has been the main prognostic assessment tool for cancer for several decades. The AJCC TNM classification of CRC has been revised several times to improve its prognostic ability, and the latest 8th edition was released in 2016 (4). In both the AJCC 7th and 8th TNM classifications, the N component (regional lymph node involvement) is considered to be a more important prognostic factor than the T component (depth of tumor invasion into the colorectal wall), considering that T1N1a is staged as IIIA, whereas T4bN0 is staged as IIC (4,5). However, multiple studies have indicated that the T and N components have comparable importance, given that T4N0 tumors had statistically significantly poorer outcomes than T1-2N1-2a tumors, regardless of the number of lymph nodes examined (6-11). This suggests that the discrimination and accuracy of prognostic assessments using the AJCC TNM classification remain controversial, especially for stage II and III CRC, leading to calls for a modified TNM (mTNM) classification.

We therefore aimed to establish a mTNM classification for CRC based on the updated 1973-2015 Surveillance, Epidemiology, and End Results (SEER) program (12). We created the mTNM classification for optimal prognostic classification and compared the discrimination, model-fitting performance, and net benefits of the mTNM with those of the AJCC 8th TNM classifications in a training cohort drawn from the SEER database. We validated the prognostic capacity of mTNM classification in both the internal and external validation cohorts.

Methods

Data Source and Eligibility Criteria

We included eligible primary operable stage I-III CRC patients from the SEER database (https://seer.cancer.gov/) (12). The eligibility criteria for SEER cohort were as follows: 1) primarily single tumor in colon or rectum; 2) availability of necessary information for analyses, (ie, sex, age, race, location, tumor size, histological grade, pathological T (pT) stage, pathological N (pN) stage, and number of retrieved lymph nodes); 3) no distant metastasis (M0) at the time of surgery; 4) criteria met for pathologic staging; 5) no preoperative treatments (chemotherapy and/or radiotherapy); 6) underwent surgical treatment for tumor; 7) follow-up of at least 5 years or until death; 8) postoperative survival of at least 1 month; 9) age 18-72 years at diagnosis (Supplementary Figure 1, available online). The last date of follow-up for the SEER cohort was December 2015. Patients diagnosed after 2010 were excluded to ensure adequate follow-up data (≥60 months) for analyses of 5-year overall survival rates. A data-use agreement for the SEER 1973-2015 research data file was approved. Patients were randomly assigned individually to the training or internal validation cohorts using R software, at a randomization ratio of 7:3. The training cohort was mainly used to develop the mTNM classification, whereas the internal and external validation cohorts were specifically used to validate prognostic prediction capacity of the mTNM classification.

External validation was performed using the database of Cancer Hospital of China Medical University and Fudan University Shanghai Cancer Center. The eligibility criteria for the external validation cohort were as follows: the necessary information was available for analyses (ie, sex, age, race, location, tumor size, histological grade, pT stage, pN stage, and number of retrieved lymph nodes; no distant metastasis (M0) at the time of surgery; and postoperative survival of at least 1 month. Ethical reviews were approved by the Ethics Committees of the Cancer Hospital of China Medical University and Fudan University Shanghai Cancer Center, and written informed consents were obtained from all patients in the external validation cohort.

Regarding the cutoff age of the CRC patients, the average life expectancy at birth in the United States was 78.8 years in 2015 (13), and patients younger than 72 years in the SEER were included in the training and internal validation cohorts to allow the long-term effect (eg, 5-year overall survival rates) to be assessed. Because rectal and colon cancers usually have similar survival outcomes (2,3,14) and share the same classification system (4,5), both were included in the current study. The presence of tumor deposits was a statistically significant negative prognostic factor in CRC and was included in the AJCC 7th TNM classification as N1c stage (15). In the current study, 198 N1c patients (0.4%) were classified into stage N1b because of the small sample size and the similarity of their prognosis with that of N1b patients. Furthermore, distant metastatic disease (M1) has long been regarded as the most advanced stage with the poorest prognosis, irrespective of T and N category, and is generally considered incurable. Only curable patients who underwent surgical treatment were included in the current study. The study was reported according to the STROBE checklist for cohort studies (16,17)

The AJCC TNM Classification

The AJCC 7th TNM classification was released in 2010, and the AJCC 8th TNM classification was released in 2016 (4,5). Importantly, there was no substantial alteration between the 7th and 8th classifications (4,5) except in relation to stage IV CRC (Supplementary Table 1, available online). Because the AJCC 8th TNM classification was released in 2016, we retrospectively reclassified patients according to the AJCC 8th TNM classification based on pT and pN stage. In this study, we dealt with only pathological stages, and the terms of T1-4b and N0-2b are used to simplify descriptions of pT1-4b and pN0-2b in TNM and mTNM stages.

Statistical Analysis

Overall survival (OS) was calculated from the date of diagnosis until death from any cause. Differences in overall survival rates were analyzed by log-rank tests with Kaplan-Meier (K-M) survival curves. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model (18), with stage T1N0 as the reference in the training cohort. Hazard ratio values of 25 T and N stage combinations were ordered from the lowest (T1N0) to the highest (T4bN2b) (Figure 1 and Table 1). Then, log-rank tests for 5-year overall survival were conducted between 2 sequential stages, and 24 χ^2 values were generated. Among 24 χ^2 values, 6 largest χ^2 values were identified except as a χ^2 value between T4bN2a and T4bN2b because these stages are nearest sequences (Supplementary Figure 2, available online). Finally, using these 6 χ^2 values, we

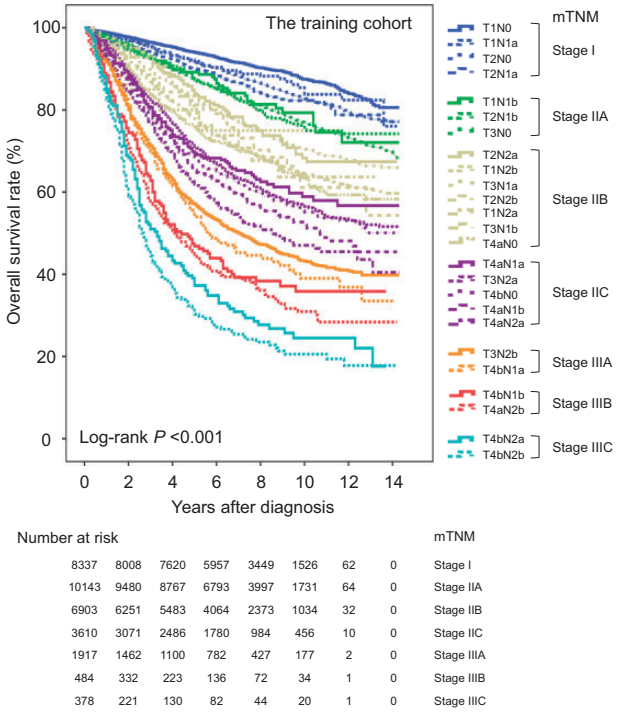

Figure 1. Kaplan-Meier estimates of the proposal modified tumor-node-metastasis (mTNM) classification in the training cohort.

created 7 categories of the modified TNM classification that paralleled to those of the AJCC 7th and 8th classifications.

The model discrimination and model-fitting performance of the 2 TNM classifications were evaluated by analyzing the area under the receiver operating characteristic curve and Akaike information criteria (AICs), respectively (19,20). A higher area under the curve (AUC) indicated better discrimination, and a lower AIC indicated superior model fitting. A statistically significant difference in AUCs between the 2 classifications was confirmed by applying Hanley and McNeil tests to the training cohort and the internal and external validation cohorts (19). The clinical benefits were further measured by decision curve analyses (DCAs) (21-23). DCAs were used to compare clinical benefits between the modified TNM and AJCC 8th TNM classifications in 5-year OS. Moreover, the prognostic discrimination of the mTNM classification based on 5-year OS rates, log-rank tests of pairwise comparisons, and hazard ratios in the training cohort was further tested in the internal and external validation cohorts.

Data were extracted with SEER*Stat version 8.3.5 from the SEER. Statistical analyses and graphs were conducted with SPSS version 22.0 and R version 3.5.3. Hanley and McNeil tests with AUC values were conducted using MedCalc version 18.11.3. We used stringent α level of .005 to improve the reproducibility of our results (24).

Results

Patient Characteristics

After excluding ineligible patients in the SEER, a total of 45 379 stage I to III CRC patients were finally included (Supplementary Figure 1, available online). Among them, 31 772 patients were assigned to the training cohort, and 13 607 patients were assigned to the internal validation cohort. Additional 10 902 stage I to III CRC patients in the database of Cancer Hospital of China Medical University and Fudan University Shanghai Cancer Hospital were used as the external validation cohort. The baseline characteristics of the training, internal, and external cohorts are shown in Supplementary Table 2 (available online).

In the training cohort, patients were staged according to the AJCC 8th classification as follows: stage I (n = 7428, 23.4%); IIA (n = 9422, 29.7%); IIB (n = 709, 2.2%); IIC (n = 606, 1.9%); IIIA (n = 1673, 5.3%); IIIB (n = 8838, 27.8%); and IIIC (n = 3096, 9.7%).

The AJCC 8th TNM Classification

Stage distributions and the 5-year overall survival rates based on the AJCC 8th TNM classification in the training cohort are shown in Supplementary Table 3 (available online; log-rank test, pairwise comparisons, IIB vs IIC: $P = .002$, others $P < .001$). These results indicated that the AJCC 8th classification did not show optimal prognostic discrimination, given that stage IIIA was associated with a statistically significantly better 5-year overall survival rate than stages IIB and IIC, and patients with stage IIIB had a statistically significantly better 5-year overall survival rate than those with stage IIC.

We further assessed the prognostic discrimination performance of the AJCC 8th TNM classification by presenting 5-year overall survival rates, log-rank tests, and hazard ratios for different population sets of the training cohort (Supplementary Table 3, available online). The AJCC 8th TNM classification showed poor prognostic discrimination in analyses stratified by sex, age (younger than 60 years, 60 years or older), race, location (colon, rectum), tumor size (<4 cm, ≥4 cm) (25), and number of retrieved lymph nodes (<12, ≥12, ≥20, ≥30) (4,5) (Supplementary Figure 3 and Supplementary Table 3, available online).

The mTNM Classification

The mTNM classification was generated using 6 identified χ^2 values. Using these values, we classified patients as follows: stages I (T1N0, T1N1a, T2N0, T2N1a); IIA (T1N1b, T2N1b, T3N0); IIB (T1N2a, T1N2b, T2N2a, T2N2b, T3N1a, T3N1b, T4aN0); IIC (T3N2a, T4aN1a, T4aN1b, T4aN2a, T4bN0); IIIA (T3N2b, T4bN1a); IIIB (T4aN2b, T4bN1b); and IIIC (T4bN2a, T4bN2b) (Figure 1 and Table 1). The details of the mTNM and AJCC 8th TNM classifications are shown in Figure 2.

The 5-year overall survival rates of the mTNM classification in the training cohort steadily decreased as stage number increased, and hazard ratios increased as stage number increased (Supplementary Table 4, available online).

The mTNM vs the AJCC 8th TNM Classification

Stage distributions based on the mTNM classification in the internal validation cohort are shown in Figure 3 and Table 2.

In the training cohort, we compared the model discrimination and model-fitting performance of the mTNM and AJCC 8th TNM classifications. Compared with the AJCC 8th TNM classification, the mTNM showed superior prognostic discrimination (AUC, 0.670 vs 0.658; Hanley and McNeil test, $P < .001$) and better model fitting (AIC, 175 506 vs 176 436). Similar findings were observed in additional stratified analyses (Supplementary Table 5, available online).

Table 1. The proposed modified TNM classification in the training cohort

Stage[a]	No.	3-year OS, % (95% CI)	5-year OS, % (95% CI)	HR (95% CI)[b]	Log-rank (Mantel-Cox)[c]	
					χ^2	*P*
Stage I	8337	94.6 (94.1 to 95.1)	91.0 (90.4 to 91.6)			
T1N0	3034	95.7 (94.9 to 96.3)	92.8 (91.8 to 93.6)	1 (Referent)	—	—
T1N1a	283	94.0 (90.5 to 96.2)	90.4 (86.3 to 93.3)	1.19 (0.86 to 1.65)	1.08	.30
T2N0	4394	94.2 (93.5 to 94.9)	90.2 (89.3 to 91.0)	1.37 (1.21 to 1.56)	0.74	.39
T2N1a	626	93.0 (90.6 to 94.7)	88.9 (86.1 to 91.1)	1.48 (1.20 to 1.84)	0.57	.45
Stage IIA	10 143	91.0 (90.4 to 91.5)	85.1 (84.4 to 85.8)			
T1N1b	187	91.9 (87.0 to 95.1)	86.4 (80.6 to 90.6)	1.85 (1.33 to 2.57)	1.40[d]	.24
T2N1b	534	91.5 (88.8 to 93.6)	85.2 (81.9 to 88.0)	1.91 (1.56 to 2.36)	0.049	.83
T3N0	9422	90.9 (90.3 to 91.5)	85.1 (84.3 to 85.8)	1.94 (1.70 to 2.17)	0.008	.93
Stage IIB	6903	85.1 (84.2 to 85.9)	76.3 (75.2 to 77.3)			
T2N2a	219	89.0 (84.1 to 92.5)	81.2 (75.3 to 85.8)	2.53 (1.94 to 3.31)	4.49[d]	.03
T1N2b	20	80.0 (55.1 to 92.0)	75.0 (50.0 to 88.7)	2.53 (1.05 to 6.12)	<0.001	.99
T3N1a	2724	87.4 (86.1 to 88.6)	79.8 (78.2 to 81.2)	2.54 (2.24 to 2.88)	<0.001	.99
T1N2a	43	90.5 (76.6 to 96.3)	73.8 (86.3 to 93.3)	3.15 (1.85 to 5.37)	0.62	.43
T2N2b	96	84.4 (75.4 to 90.3)	79.1 (69.5 to 86.0)	3.17 (2.21 to 4.55)	<0.001	.99
T3N1b	3092	83.8 (82.5 to 85.1)	73.8 (72.2 to 75.3)	3.22 (2.86 to 3.63)	0.015	.90
T4aN0	709	80.9 (77.8 to 83.7)	72.4 (68.9 to 75.5)	3.45 (2.93 to 4.05)	0.91	.34
Stage IIC	3610	77.0 (75.6 to 78.3)	65.4 (63.8 to 66.9)			
T4aN1a	254	77.1 (71.4 to 81.8)	68.3 (62.2 to 73.6)	3.94 (3.15 to 4.92)	1.32[d]	.25
T3N2a	2081	79.0 (77.2 to 80.7)	66.9 (64.8 to 68.9)	4.24 (3.75 to 4.79)	0.43	.51
T4bN0	606	74.2 (70.5 to 77.5)	65.2 (61.2 to 68.8)	4.52 (3.85 to 5.30)	0.77	.38
T4aN1b	352	74.7 (69.8 to 79.0)	62.7 (57.4 to 67.6)	4.98 (4.14 to 6.00)	0.86	.35
T4aN2a	317	72.1 (66.8 to 76.7)	57.4 (51.7 to 62.6)	5.70 (4.74 to 6.86)	1.53	.22
Stage IIIA	1917	65.3 (63.2 to 67.4)	52.7 (50.5 to 55.0)			
T3N2b	1726	65.5 (63.2 to 67.7)	53.2 (50.8 to 55.6)	6.48 (5.75 to 7.32)	2.24[d]	.13
T4bN1a	191	64.1 (56.8 to 70.5)	48.2 (40.9 to 55.1)	7.16 (5.79 to 8.85)	0.83	.36
Stage IIIB	484	53.5 (48.9 to 57.9)	41.9 (37.4 to 46.3)			
T4bN1b	181	55.0 (47.4 to 61.9)	43.9 (36.5 to 51.1)	8.51 (6.87 to 10.5)	1.25[d]	.26
T4aN2b	303	52.6 (46.8 to 58.1)	40.8 (35.2 to 46.3)	9.45 (7.95 to 11.2)	0.93	.33
Stage IIIC	378	42.3 (37.3 to 47.3)	30.7 (26.1 to 35.5)			
T4bN2a	175	46.3 (38.7 to 53.5)	34.9 (27.8 to 42.0)	11.5 (9.43 to 14.1)	2.45[d]	.12
T4bN2b	203	38.9 (32.1 to 45.6)	27.2 (21.2 to 33.5)	13.7 (11.4 to 16.5)	2.02	.16

[a]Log-rank tests were conducted between 2 sequential stages, and 24 χ^2 values were generated. CI = confidence interval; HR = hazard ratio; OS = overall survival; TNM = tumor-node-metastasis; — = not estimated.

[b]All stages were compared with T1N0 as reference by values of hazard ratios of Cox proportional hazards.

[c]Log-rank tests were conducted between 2 sequential stages.

[d]Hazard ratios with 95% confidence intervals were estimated using a Cox proportional hazards model, with stage T1N0 as the reference in the training cohort. Hazard ratios values of 25 T and N stage combinations were ordered from the lowest (T1N0) to the highest (T4bN2b). Then, log-rank tests for 5-year overall survival were conducted between 2 sequential stages, and 24 χ^2 values were generated. Among 24 χ^2 values, 6 largest χ^2 values were identified except as a χ^2 value between T4bN2a and T4bN2b because these stages are nearest sequences. Finally, using these 6 χ^2 cutoff values (1.40, 4.49, 1.32, 2.24, 1.25, 2.45), we created 7 categories of the modified TNM classification that paralleled to those of the AJCC 7th and 8th classifications.

In the internal validation cohort, the 5-year overall survival rates of the mTNM classifications also steadily decreased as stage number increased according to the mTNM classification, and hazard ratios increased as stage number increased (Table 2). Compared with the AJCC 8th TNM classification, the mTNM showed superior prognostic discrimination (AUC, 0.675 vs 0.667; Hanley and McNeil test, $P < .001$) and better model fitting (AIC, 70 937 vs 71 238) (Supplementary Figure 4, A, available online; Table 3). Stratified analyses suggested that the mTNM had better prognostic discrimination and superior model-fitting performances compared with the AJCC 8th TNM classification in various populations in the internal validation cohort (Supplementary Figure 4, C and E, available online; Table 3).

We further performed DCA to assess the clinical utility of the modified TNM and AJCC 8th TNM classification in the internal validation cohort. The DCA revealed that the mTNM had superior net benefits over the AJCC 8th TNM classification between threshold probabilities of 18%-32% in CRC patients of the internal validation cohort. Similar results were found both in colon cancer and rectal cancer (Supplementary Figure 5, A, C, and E, available online).

We conducted additional analyses by adding a total of 10 152 CRC patients who were older than 72 years or received preoperative treatment into the internal validation cohort (total n = 23 759). The results showed that the mTNM classification showed better prognostic discrimination and net benefits (eg, K-M curves, receiver operating characteristic curves, and DCA curves) than the AJCC 8th TNM classification in CRC, colon cancer, and rectal cancer (Figure 3, B, D, and E; Supplementary Figures 4, B and D, and 5, B, D, and E, available online).

External Validation

In the external validation cohort, we observed similar findings regarding the 5-year overall survival rates and hazard ratios

A The AJCC 8th TNM (8th TNM) classification

8^{th}TNM	N0	N1a	N1b	N2a	N2b
T1	I	IIIA	IIIA	IIIA	IIIB
T2	I	IIIA	IIIA	IIIB	IIIB
T3	IIA	IIIB	IIIB	IIIB	IIIC
T4a	IIB	IIIB	IIIB	IIIC	IIIC
T4b	IIC	IIIC	IIIC	IIIC	IIIC

B The modified TNM (mTNM) classification

mTNM	N0	N1a	N1b	N2a	N2b
T1	I	I	IIA	IIB	IIB
T2	I	I	IIA	IIB	IIB
T3	IIA	IIB	IIB	IIC	IIIA
T4a	IIB	IIC	IIC	IIC	IIIB
T4b	IIC	IIIA	IIIB	IIIC	IIIC

Figure 2. Details of 2 tumor-node-metastasis (TNM) classifications. (A) AJCC 8th TNM classification; B) mTNM classification.

based on the mTNM classifications (Supplementary Figure 6 and Supplementary Table 6, available online). The mTNM classifications also showed better prognostic discrimination (AUC, 0.659 vs 0.636; Hanley and McNeil test, $P = .02$) and net benefits compared with the AJCC 8th TNM classification in the external validation cohort (Supplementary Figures 7 and 8 and Supplementary Table 7, available online).

Discussion

In the current study, we established a modified and reasonable TNM classification and validated it in both the internal and external validation cohorts. This mTNM classification showed superior prognostic discrimination and model-fitting performances and applicability in various populations and settings compared with the AJCC 8th TNM classification.

The AJCC TNM classification of CRC, which has been revised several times to improve its prognostic ability and accuracy, has been considered the most important prognostic tool in this field. However, it has demonstrated inadequate prognostic discriminatory performance, especially for stage II and III CRC, and its prognostic accuracy therefore remains controversial. Rottoli et al. showed that stage IIC (T4N0) cancers had poorer outcomes than IIIA (T1-2N1) cancers and were comparable to IIIB (T3N1) cancers, regardless of the number of retrieved lymph nodes (6). In addition, Kim et al. reported that stage IIC (T4N0) colon cancers had poorer oncologic outcomes than IIIA and B (T1-2N1) cancers (8), and Chan et al. demonstrated that stage IIC (T4N0) and IIIB (T3N1) colon cancer had similar outcomes (11). Similar results were obtained in our study. Patients with T4bN0 CRC (74% of 3-year OS rate, 65% of 5-year OS rate) showed statistically significantly poorer survival than patients with T1N1a CRC (3-year OS rate: 94%; 5-year OS rate: 90%). This result suggests that the prognostic weight of the T component should be increased in further AJCC TNM classifications.

We further assessed the prognostic discriminatory ability of the AJCC 8th TNM classification in populations stratified by sex, age, race, location, tumor size, and the number of retrieved lymph nodes. The AJCC 8th TNM classification showed poor prognostic discrimination in all of these populations, although the reasons for this poor performance are unclear (26). Some experts believe that an inadequate number of retrieved lymph nodes would cause stage migration, associated with poor survival rates in patients with CRC (27-29). Chen et al. also showed that more extensive lymph node retrieval improved survival outcomes in patients with stages I-III colon cancer (30). We therefore hypothesized that an inadequate number of retrieved lymph nodes could explain the inferior prognostic discrimination performance and accuracy of the current AJCC 8th TNM classification. However, this classification also demonstrated poor prognostic discrimination even in patients with adequate retrieved lymph nodes ($\geq$12, $\geq$20, $\geq$30), suggesting that too few retrieved lymph nodes was not the main reason for its poor performance, consistent with several previous studies (31-33). Further investigations are therefore needed to explain its poor performance in other datasets with more detailed clinical information.

The mTNM classification has several advantages over the AJCC 8th TNM classification. First, hazard ratios, 5-year OS rates, and log-rank tests differed statistically significantly between each pair of stage groups using the mTNM, suggesting enhanced stratification. Second, AUCs were statistically significantly increased in the mTNM classification, indicating better prognostic discrimination. Third, the mTNM classification showed better model fitting, indicated by a smaller AIC value. Fourth, the mTNM classification was shown to have superior net benefits by DCA. Furthermore, stratified analyses confirmed that the mTNM classification had good model applicability in various populations and settings. The results of the current study should be considered reliable, given that they were based on the large-sample SEER database with internal and external validations. The current evidence thus suggests that the mTNM is a more reasonable classification than the AJCC 8th TNM classification.

Colon and rectal cancers were included in the current study based on the colorectal continuum model (34,35). However, there is a possibility that the mTNM classification is devoid of patients with advanced rectal cancer because we excluded patients receiving preoperative therapy in the training cohort. Therefore, we validated the mTNM classification in the internal and external validation cohorts including patients receiving preoperative therapy. Furthermore, we also validated the mTNM classification in both colon and rectal cancer. These results suggest that the mTNM classification can be useful for both colon cancer and rectal cancer, including locally advanced rectal cancer.

The AUCs (model discrimination) and AICs (model fitting) between the mTNM and AJCC 8th TNM classifications showed a statistically significant difference in the training cohort, whereas it appeared a statistically significant but relatively small difference in the internal validation cohort. Therefore, we further performed DCAs in the internal validation cohort to assess the clinical utility of the modified TNM classification. In the internal validation cohort, mTNM had superior net benefits over the AJCC 8th TNM classification between threshold probabilities for additional treatment of 18%-32%, but both depicted little difference across other ranges of threshold probabilities. Similar findings were observed in the external validation cohort. Further prospective studies with more detailed clinical information (especially on treatment) are needed to clarify the clinical utility of the modified TNM classification.

We acknowledge some limitations of our study. First, the current mTNM classification was established based on survival outcomes; thus, those unavailable factors, including surgical

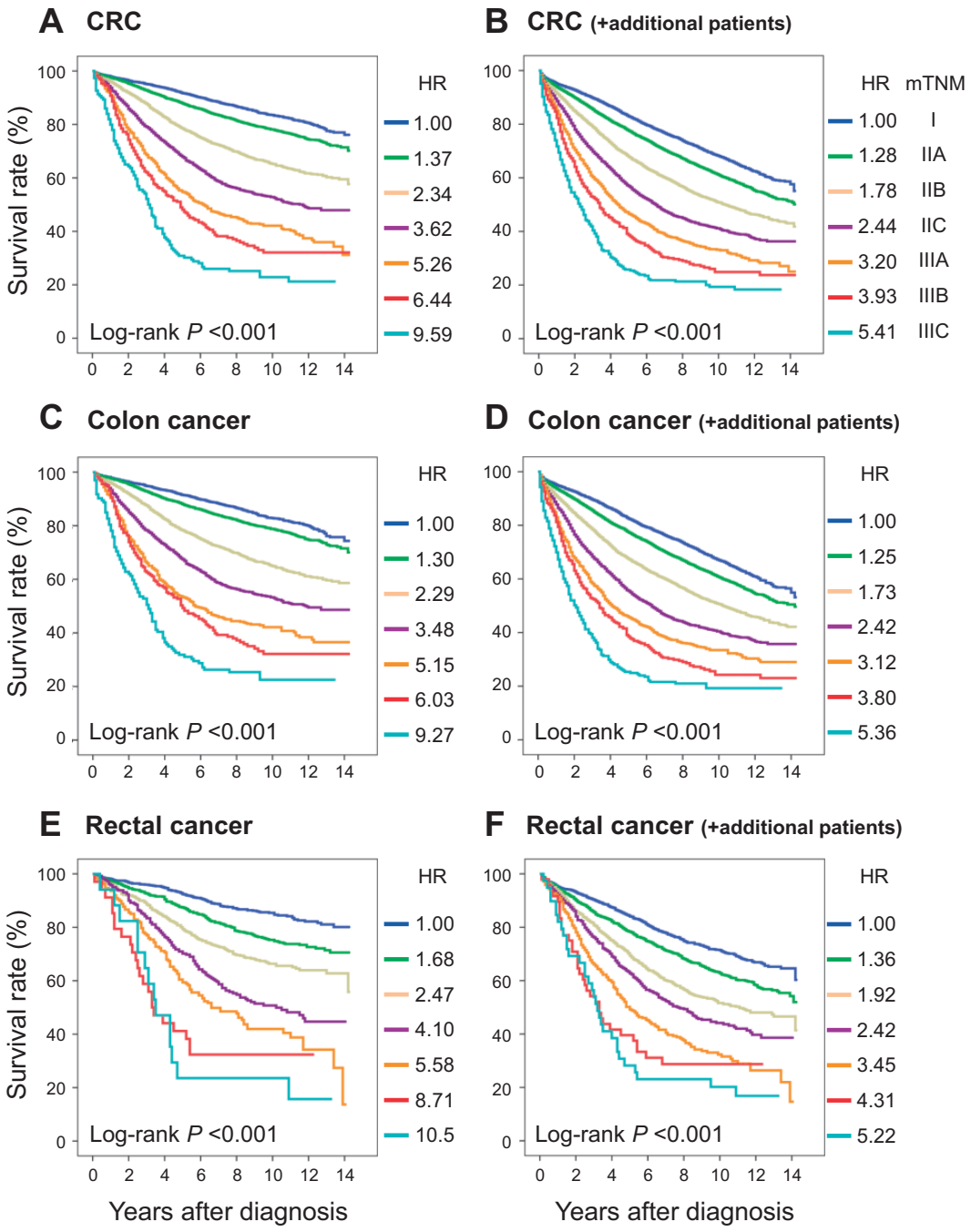

Figure 3. Kaplan-Meier estimates of the modified tumor-node-metastasis (mTNM) classification in the internal validation cohort. (A) Colorectal cancer (CRC); B) CRC (+10 152 additional patients); C) Colon cancer; D) Colon cancer (+7956 additional patients); E) Rectal cancer; F) Rectal cancer (+2156 additional patients). Additional patients were those who were older than 72 years or received preoperative treatments. All statistical tests were 2-sided. HR = hazard ratio.

strategy and use of postoperative adjuvant chemotherapy regimen, could also affect the prognosis (36,37). Second, although the SEER used in the current study is well-established data in the United States, it has inherent limitations in terms of underrepresentation of young patients. The incidence of colorectal cancer in the young population group (ie, younger than 50 years) is increasing in the United States (38). Also, younger CRC patients may have different prognosis than older CRC patients included in SEER data. Similarly, those patients older than 72 years of age who were excluded in the training cohort and internal validation cohort may also have different prognosis. Using the external validation cohort including both the younger and the older patients, we confirmed that compared with AJCC 8th TNM classification, the mTNM classification shows better prognostic discrimination and net benefits. Third, we were not able to include important molecular markers, including microsatellite instability, *KRAS*, or *BRAF*, in the mTNM classification. Integrating these factors could further improve classification. Lastly, approximatively 26% of patients in the training cohort had less than 12 retrieved lymph nodes, which could also affect the accuracy of the mTNM classification. However, it remains controversial how many retrieved lymph nodes are optimal for

Table 2. Validation of the modified TNM classification in the internal validation cohort

Characteristics	I	IIA	IIB	IIC	IIIA	IIIB	IIIC	Overall
Overall (n = 13 607)								
5-y OS, % (95% CI)	90.0 (89.0 to 91.0)	85.8 (84.7 to 86.8)	75.0 (73.4 to 76.6)	63.1 (60.7 to 65.5)	50.5 (47.0 to 54.0)	43.4 (37.0 to 49.6)	28.1 (21.1 to 35.5)	78.5 (77.8 to 79.2)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.37 (1.24 to 1.53)	2.34 (2.11 to 2.60)	3.62 (3.24 to 4.05)	5.26 (4.65 to 5.95)	6.44 (5.39 to 7.70)	9.59 (7.83 to 11.74)	—
Sex								
Female (n = 6278)								
5-y OS, %	91.3 (89.8 to 92.6)	87.2 (85.6 to 88.5)	76.6 (74.3 to 78.8)	62.8 (59.2 to 66.3)	53.7 (48.4 to 58.7)	48.2 (38.8 to 57.0)	23.5 (14.3 to 34.1)	79.8 (78.7 to 80.7)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.41 (1.19 to 1.66)	2.45 (2.07 to 2.89)	4.24 (3.57 to 5.04)	5.51 (4.54 to 6.70)	7.01 (5.35 to 9.18)	12.31 (9.14 to 16.57)	—
Male (n = 7329)								
5-y OS, %	89.0 (87.5 to 90.3)	84.6 (83.1 to 86.0)	73.6 (71.3 to 75.8)	63.4 (60.0 to 66.6)	48.0 (43.2 to 52.6)	39.0 (30.4 to 47.5)	32.1 (22.2 to 42.5)	77.4 (76.5 to 78.4)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.36 (1.19 to 1.56)	2.30 (2.01 to 2.63)	3.23 (2.80 to 3.74)	5.14 (4.38 to 6.03)	6.16 (4.85 to 7.83)	7.84 (5.93 to 10.36)	—
Age								
<60 y (n = 6690)								
5-y OS, %	93.9 (92.6 to 95.0)	89.5 (88.1 to 90.8)	79.1 (76.9 to 81.0)	68.0 (64.6 to 71.1)	56.5 (51.8 to 61.0)	45.5 (36.6 to 53.9)	28.2 (19.1 to 37.9)	81.7 (80.8 to 82.7)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.52 (1.26 to 1.84)	3.11 (2.59 to 3.73)	4.90 (4.05 to 5.91)	7.06 (5.77 to 8.64)	10.3 (7.89 to 13.44)	15.31 (11.45 to 20.47)	—
≥60 y (n = 6917)								
5-y OS, %	86.8 (85.2 to 88.2)	82.4 (80.8 to 83.9)	70.8 (68.4 to 73.1)	57.9 (54.3 to 61.4)	43.0 (37.8 to 48.1)	41.0 (31.9 to 50.0)	27.9 (17.3 to 39.4)	75.4 (74.4 to 76.4)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.34 (1.18 to 1.52)	2.11 (1.86 to 2.41)	3.25 (2.83 to 3.74)	4.95 (4.21 to 5.82)	4.97 (3.86 to 6.39)	7.44 (5.53 to 10.02)	—
Race								
White (n = 10 419)								
5-y OS, %	90.3 (89.1 to 91.3)	86.5 (85.3 to 87.6)	76.2 (74.3 to 77.9)	65.1 (62.3 to 67.7)	52.7 (48.6 to 56.6)	43.5 (36.3 to 50.5)	30.9 (22.6 to 39.6)	79.5 (78.7 to 80.3)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.34 (1.19 to 1.51)	2.28 (2.02 to 2.57)	3.46 (3.04 to 3.92)	4.99 (4.33 to 5.76)	6.52 (5.33 to 7.96)	9.24 (7.29 to 11.72)	—
Black (n = 1906)								
5-y OS, %	85.4 (81.7 to 88.4)	79.9 (76.6 to 82.9)	65.3 (60.7 to 69.5)	49.8 (43.0 to 56.1)	38.1 (29.3 to 46.9)	37.9 (20.9 to 54.9)	23.1 (9.4 to 40.3)	70.1 (68.0 to 72.1)
P[a]	—	<.001	<.001	.002	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.35 (1.05 to 1.74)	2.40 (1.88 to 3.08)	3.66 (2.80 to 4.80)	5.37 (3.98 to 7.25)	4.99 (3.04 to 8.19)	7.83 (4.95 to 12.39)	—
Other (n = 12 82)								
5-y OS, %	94.3 (91.0 to 96.3)	88.4 (84.9 to 91.1)	81.7 (76.6 to 85.8)	67.9 (59.5 to 75.0)	52.0 (40.2 to 62.6)	50.0 (27.1 to 69.2)	10.0 (0.6 to 35.8)	82.7 (80.4 to 84.6)
P[a]	—	.007	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.78 (1.17 to 2.69)	2.69 (1.77 to 4.09)	5.55 (3.63 to 8.50)	8.25 (5.22 to 13.05)	9.60 (4.94 to 18.65)	19.24 (9.13 to 40.55)	—
Location								
Colon (n = 10 768)								
5-y OS, %	89.8 (88.5 to 90.9)	86.0 (84.8 to 87.1)	75.0 (73.2 to 76.7)	62.9 (60.2 to 65.5)	49.3 (45.3 to 53.2)	45.2 (38.3 to 51.9)	28.7 (21.2 to 36.6)	78.1 (77.3 to 78.9)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.30 (1.15 to 1.46)	2.29 (2.03 to 2.58)	3.48 (3.07 to 3.95)	5.15 (4.47 to 5.93)	6.03 (4.96 to 7.34)	9.27 (7.44 to 11.54)	—
Rectum (n = 2839)								
5-y OS	90.8 (88.7 to 92.5)	84.8 (82.2 to 87.1)	75.3 (71.5 to 78.7)	64.2 (58.0 to 69.8)	54.5 (47.1 to 61.3)	32.4 (17.6 to 48.0)	23.5 (7.3 to 44.9)	80.0 (78.5 to 81.4)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.68 (1.35 to 2.08)	2.47 (1.98 to 3.08)	4.10 (3.22 to 5.22)	5.58 (4.34 to 7.17)	8.71 (5.59 to 13.55)	10.47 (6.04 to 18.17)	—

(continued)

Table 2. (continued)

Characteristics	I	IIA	IIB	IIC	IIIA	IIIB	IIIC	Overall
Tumor size								
<4 cm (n = 5840)								
5-y OS, %	90.0 (88.8 to 91.1)	85.9 (84.0 to 87.6)	74.2 (71.5 to 76.8)	65.1 (60.4 to 69.4)	55.3 (48.4 to 61.6)	43.6 (29.3 to 56.9)	29.2 (13.0 to 47.6)	82.4 (81.4 to 83.3)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.47 (1.28 to 1.70)	2.53 (2.20 to 2.91)	3.58 (3.02 to 4.24)	4.78 (3.89 to 5.88)	6.59 (4.55 to 9.55)	8.54 (5.33 to 13.70)	—
≥4 cm (n = 7767)								
5-y OS, %	90.0 (87.8 to 91.8)	85.7 (84.4 to 86.9)	75.5 (73.5 to 77.4)	62.4 (59.5 to 65.1)	48.8 (44.7 to 52.8)	43.3 (36.2 to 50.3)	27.9 (20.3 to 36.0)	75.6 (74.6 to 76.5)
P[a]	—	.001	.009	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.27 (1.06 to 1.52)	2.15 (1.79 to 2.57)	3.46 (2.89 to 4.15)	5.17 (4.27 to 6.26)	6.05 (4.77 to 7.68)	9.20 (7.11 to 11.91)	—
Retrieved lymph notes								
<12 (n = 3509)								
5-y OS, %	87.6 (85.7 to 89.4)	79.6 (77.0 to 81.9)	66.3 (62.7 to 69.6)	51.3 (45.8 to 56.6)	37.6 (27.0 to 48.2)	42.9 (26.4 to 58.3)	25.9 (11.5 to 43.1)	75.2 (73.7 to 76.6)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.61 (1.36 to 1.89)	2.63 (2.24 to 3.10)	4.15 (3.44 to 4.99)	5.57 (4.16 to 7.46)	5.59 (3.67 to 8.49)	7.91 (5.06 to 12.35)	—
≥12 (n = 10 098)								
5-y OS, %	91.3 (90.1 to 92.4)	87.7 (86.6 to 88.8)	78.0 (76.2 to 79.7)	66.3 (63.6 to 68.9)	51.9 (48.2 to 55.5)	43.5 (36.6 to 50.2)	28.6 (20.8 to 36.8)	79.6 (78.8 to 80.4)
P[a]	—	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.37 (1.19 to 1.57)	2.36 (2.06 to 2.71)	3.77 (3.28 to 4.35)	5.91 (5.09 to 6.86)	7.39 (6.01 to 9.07)	11.09 (8.78 to 14.00)	—
≥20 (n = 4758)								
5-y OS, %	92.8 (90.9 to 94.4)	89.8 (88.3 to 91.2)	80.4 (77.8 to 82.7)	69.3 (65.5 to 72.8)	54.2 (49.3 to 58.8)	45.2 (35.6 to 54.4)	23.2 (13.2 to 34.8)	80.6 (79.4 to 81.7)
P[a]	—	<.001	.008	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.37 (1.09 to 1.72)	2.55 (2.03 to 3.20)	4.21 (3.34 to 5.32)	6.63 (5.24 to 8.39)	8.52 (6.23 to 11.65)	14.45 (10.15 to 20.56)	—
≥30 (n = 1562)								
5-y OS, %	94.3 (90.8 to 96.4)	91.4 (88.7 to 93.5)	78.5 (73.7 to 82.5)	68.9 (61.6 to 75.1)	56.6 (48.2 to 64.2)	46.4 (31.1 to 60.4)	22.3 (7.1 to 42.8)	81.1 (79.0 to 83.0)
P[a]	—	<.001	.24	<.001	<.001	<.001	<.001	<.001
HR (95% CI)	1 (Referent)	1.31 (0.84 to 2.04)	3.34 (2.18 to 5.11)	4.85 (3.11 to 7.56)	7.13 (4.59 to 11.09)	9.71 (5.63 to 16.74)	18.53 (9.83 to 34.92)	—

[a]P value was obtained by a log-rank test to compare overall survivals for sequential stages. 5-y OS = 5-year overall survival; CI = confidence interval; HR = hazard ratio; mTNM = modified tumor-node-metastasis.

Table 3. Comparison of the modified TNM and AJCC 8th TNM classifications in the internal validation cohort

Characteristics	AJCC 8th TNM classification		mTNM classification		P[a]
	AIC	AUC (95% CI)	AIC	AUC (95% CI)	
Overall (n = 13 607)	71 238	0.667 (0.659 to 0.675)	70 937	0.675 (0.667 to 0.683)	<.001
Sex					
Female (n = 6278)	27 357	0.676 (0.665 to 0.688)	27 199	0.687 (0.675 to 0.698)	.002
Male (n = 7329)	38 504	0.662 (0.651 to 0.672)	38 361	0.668 (0.657 to 0.678)	.045
Age					
<60 y (n = 6690)	26 668	0.705 (0.694 to 0.716)	26 514	0.712 (0.701 to 0.723)	.06
≥60 y (n = 6917)	39 009	0.650 (0.638 to 0.661)	38 870	0.657 (0.646 to 0.668)	.007
Race					
White (n = 10 419)	51 266	0.662 (0.653 to 0.671)	51 030	0.671 (0.662 to 0.680)	<.001
Black (n = 1906)	10 103	0.680 (0.658 to 0.701)	10 083	0.680 (0.658 to 0.701)	.97
Other (n = 1282)	4057	0.691 (0.665 to 0.716)	4011	0.705 (0.680 to 0.730)	.06
Location					
Colon (n = 10 768)	55 393	0.666 (0.657 to 0.675)	55 175	0.673 (0.664 to 0.682)	.004
Rectum (n = 2839)	11 902	0.672 (0.655 to 0.689)	11 819	0.682 (0.665 to 0.700)	.04
Tumor size					
<4 cm (n = 5840)	24 185	0.651 (0.639 to 0.664)	24 090	0.658 (0.645 to 0.670)	.08
≥4 cm (n = 7767)	41 860	0.669 (0.659 to 0.680)	41 672	0.678 (0.668 to 0.688)	.002
Retrieved lymph nodes					
<12 (n = 3509)	18 839	0.662 (0.646 to 0.677)	18 757	0.671 (0.655 to 0.686)	.04
≥12 (n = 10 098)	47 445	0.681 (0.672 to 0.690)	47 191	0.690 (0.680 to 0.699)	<.001
≥20 (n = 4758)	19 380	0.695 (0.682 to 0.708)	19 240	0.706 (0.693 to 0.719)	.003
≥30 (n = 1562)	5177	0.720 (0.697 to 0.742)	5158	0.724 (0.701 to 0.746)	.55

[a]The Hanley and McNeil tests were applied to analyze whether statistically significant difference exist in AUCs between 2 TNM classifications in external validation cohort. AIC = Akaike information criterion; AJCC = American Joint Committee on Cancer; AUC = area under the curve; CI = confidence interval; mTNM = modified tumor-node-metastasis.

adequate staging. Several factors may be associated with the number of retrieved lymph nodes, such as surgical skills, actual numbers of lymph nodes surrounding tumors, and immune responses. In the current study, to avoid the selection bias, we did not exclude patients with an inadequate number of retrieved lymph nodes in the training cohort. Overall, to successfully apply the mTNM classification to clinical practice, future studies are needed to validate the mTNM classification in other validation cohorts that is inclusive of younger and older patients, locally advanced rectal cancer patients, and patients with adequate retrieved lymph nodes.

In conclusion, the mTNM provides better prognostic discrimination for stage I-III CRC than the AJCC 8th TNM and can help better stratify primary operable CRC patients into prognostic stages. It is a prognosis-based classification, with good applicability in various populations and settings to help better stratify primary operable CRC patients into prognostic groups. Moreover, evidence indicates that the current AJCC 8th TNM classification for CRC can be improved by further modification.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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