Screening and Validation of a Novel T Stage-Lymph Node Ratio Classification for Colon Cancer

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Research Article

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Abstract

Purpose Lymph node ratio (LNR) has advantages in predicting prognosis over the American Joint Committee on Cancer (AJCC) N stage. However, the prognostic value of establishing a novel T stage-Lymph Node Ratio classification (TLNR) for colon cancer by combining LNR and T stage is currently unknown.

Methods We included 62,294 stage I-III colon cancer patients from the SEER data base as a training cohort. An external validation was performed in 3,327 additional patients. A novel LNR stage was established and included into a novel TLNR classification by combining with T stage. Patients with similar survivals were grouped according to T and LNR stages, with T1LNR1 as a reference.

Results We developed a novel TLNR classification: stages I (T1LNR1-2, T1LNR4), IIA (T1LNR3, T2LNR1-2, T3LNR1), IIB (T1LNR5, T2LNR3-4, T3LNR2, T4aLNR1), IIC (T2LNR5, T3LNR3-4, T4aLNR2, T4bLNR1), IIIA (T3LNR5, T4aLNR3-4, T4bLNR2), IIIB (T4aLNR5, T4bLNR3-4), and IIIC (T4bLNR5). In the training cohort, the TLNR had better prognostic discrimination [area under receiver operating characteristic curve (AUC), 0.621 vs. 0.608, $P < 0.001$], superior model-fitting ability in predicting overall survival [Akaike information criteria (AIC), 561,129 vs. 562,052], and better net benefits than the AJCC 8th tumor/node/metastasis (TNM) classification. Those results were successfully validated in predicting both overall and disease-free survivals in an independent validation set.

Conclusions The TLNR classification has better prognostic discrimination, model-fitting ability and net benefits than the AJCC 8th TNM classification for better stratifying operable colon cancer patients, especially in patients with less than 12 retrieved lymph nodes.

Background

Colon cancer is one of the most frequently diagnosed cancers and has become an health burden worldwide (Siegel et al. 2020). The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification of colon cancer has been the most import prognostic assessment tool for colon cancer (Amin MB 2017). However, the current AJCC 8th TNM classification of colon cancer has a limited ability to predict survivals, that is, stage III patients have better prognosis than stage II (Amin MB 2017; Chu et al. 2016; Kim et al. 2015). There are possible reasons for this paradox. It was suggested that in the TNM staging system, pT stage had a much lower weight compared with the pN stage (Li et al. 2014; Li et al. 2016). However, it was also revealed that the pT stage had comparable importance to pN stage, regarding that T4N0 colon cancer patients had significantly poorer survivals than T1-2N1-2a patients, regardless of the number of retrieved lymph nodes (Chan et al. 2019; Rottoli et al. 2012).

Patient survival is also affected by the total number of retrieved lymph nodes, possibly due to the therapeutic benefits from an optimal lymphadenectomy, or more accurate staging from more harvested lymph nodes, which remains controversial. To reduce staging migration, no less than 12 lymph nodes should be retrieved to ensure an optimal staging (Amin MB 2017). However, the average number of

retrieved lymph nodes is often less than 12 (Prandi et al. 2002; Wong et al. 2007), because that many factors might be associated with total number of retrieved lymph nodes, such as, surgical skills, surgical technique, the way the pathologist in collecting the lymph nodes, the actual number of regional lymph nodes surrounding tumors, and immune responses of patients (Simunovic and Baxter 2007). Lymph node ratios (LNR) had been proposed to reduce stage migration (Berger et al. 2005; Rosenberg et al. 2010; Rosenberg et al. 2008). LNR is defined as the ratio between number of metastatic lymph nodes and total number of retrieved lymph nodes. It takes into account both number of positive lymph nodes and total number of retrieved lymph nodes, and it has been reported with a higher predictive accuracy rate than the pN stage, especially when an insufficient number of lymph nodes was retrieved (Pei et al. 2019).

The prognostic advantages of LNR in colorectal cancer have been widely confirmed (Berger et al. 2005; Rosenberg et al. 2010; Rosenberg et al. 2008), especially for patients with inadequate number of retrieved lymph nodes (Chen et al. 2011). However, the prognostic value of establishing a novel T stage-Lymph Node Ratio (TLNR) classification for colon cancer by combining LNR and pT stage is currently unknown. We therefore aimed to establish a novel TLNR classification for optimal prognosis based on the updated 1973–2015 Surveillance, Epidemiology, and End Results Program (SEER) of colon cancer (Surveillance Epidemiology End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Custom Data (With Additional Treatment Fields). Nov 2017 Sub (1973–2015 varying) - Linked To County Attributes - Total U.S., 1969–2016 Counties. National Cancer Institute, DCCPS, Surveillance Research Program (2018)). We compared its discrimination performance, model-fitting ability, and net benefits with those of the AJCC 8th TNM classifications in the training cohort (SEER), and further validated the prognostic capacity of the novel TLNR classification in an independent validation cohort.

Patients And Methods

Patients and eligibility criteria

Operable stage I-III colon cancer patients were included from the SEER data base as a training cohort (Howlader et al. 2015), which was mainly applied to develop the novel LNR stage and TLNR classification. The eligibility criteria were: (1) primary and single colon cancer; (2) necessary information was available; (3) without distant metastasis (M0); (4) meet criteria for pathologic staging; (5) underwent surgical treatment; (6) follow-up at least five years or until death; (7) postoperative survival time more than 1 month; (9) aged at least 18 years (Supplementary Figure 1). The last date of follow-up for the SEER cohort was December 2015. The data-use agreement of the SEER 1973–2015 research data file was approved.

The external validation was conducted by the data base of China Medical University Cancer Hospital, which was applied to validate the predictive performance of the novel TLNR classification. The eligibility criteria for the external validation cohort was same as that for the training cohort. The last date of follow-up was January 2020. The ethical review was approved by the Institute Ethics Committees of China Medical University Cancer Hospital (20210206K), and written informed consents were obtained.

Colon cancer with distant metastasis (M1) has been widely considered as the most advanced stage with the poorest prognosis and is generally considered incurable. Therefore, we only included colon cancer patients who underwent curable surgical treatments in this study. In this study, T1-4b and N0-2b are applied to simply present pT1-4b and pN0-2b in both the TNM and novel TLNR classifications.

Statistical Analysis

Overall survival (OS) was calculated from surgery until death from any cause, and disease-free survival (DFS) was calculated from surgery to the identification of cancer recurrence and/or metastasis or until death (if no recurrence or metastasis occurs before death). Log-rank tests with Kaplan–Meier survival curves were conducted to analyze survival differences in overall and disease-free survival rates. Cox proportional hazards models were applied to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

Establishment of a novel LNR stage

In the training cohort, all patients were classified into 21 groups (LNR from 0 to 1) in units of 0.05. Cox proportional hazards model was performed to estimate HRs for all the 21 groups (LNR = 0 as a reference), and all the 21 groups were orderly sorted according to the HR values from the lowest (LNR = 0) to the highest (LNR > 0.95). Then, log-rank tests for overall survival were conducted between two sequential LNR stages and 21 c^2 values were generated. Four largest c^2 values were identified as the cutoff values. Finally, using these 4 c^2 cutoff values, we created five categories and developed the novel LNR stage that paralleled to the AJCC 8^{th} pN stage.

Establishment of a novel TLNR classification

In the training cohort, the novel LNR and pT stages were combined into 25 groups, and the HR value of T1LNR1 were selected as the reference. HR values of 25 T stage and LNR stage combinations were ordered from the lowest (T1LNR1) to the highest (T4bLNR5) (Table 1). Then, log-rank tests for overall survival were conducted between two sequential stages and 24 c^2 values were generated. Among the 24 c^2 values, six largest c^2 values were identified as cutoff values (Table 1). Finally, using these six c^2 values, we created seven categories of the novel TLNR classification that paralleled to the AJCC 8^{th} classification.

The model discrimination performance and model-fitting ability between the novel LNR and previous reported LNR stages, and the novel TLNR and the AJCC 8^{th} TNM classifications, were assessed by the area under the receiver operating characteristic (ROC) curve (AUC) and Akaike information criteria (AICs), respectively. A higher AUC value suggested better discrimination performance and a lower AIC value indicated superior model-fitting ability (Hanley and Mcneil 1982). Statistically significant differences in AUCs were confirmed using Hanley and McNeil tests (Hanley and Mcneil 1982). The clinical benefits were evaluated by decision curve analyses (Fitzgerald et al. 2015). Besides, the prognostic discrimination

performances of the novel LNR stage and novel TLNR classification based on 5-year OS and DFS rates, log-rank tests, and HRs of Cox proportional hazards models were further assessed.

The SEER database was extracted by the SEER*Stat version 8.3.5. Statistical analyses were conducted using SPSS version 22.0 and R version 3.5.3. Hanley and McNeil tests were conducted with MedCalc version 18.11.3. All tests were two-sided and a *P* value < 0.05 was defined as statistically significant.

Results

Patient characteristics

A total of 62,294 patients with operable stage I-III colon cancer were finally included from the SEER data base as a training cohort (Supplementary Figure 1). In addition, 3,327 patients with operable stage I-III colon cancer from China Medical University Cancer Hospital were included as an external validation cohort. The characteristics of the baseline of the training and validation cohorts were presented (Supplementary Table 1). The mean ages (± SD) were 68.1 (± 13.8) and 59.9 (± 11.6) years in the training and validation cohorts, respectively. The mean number (± SD) of retrieved lymph nodes was 17.2 (± 9.6) and 16.7 (±10.0) in the training and validation cohorts, respectively. A total of 26.8% patients in the training cohort and 31.6% patients in the validation cohort had less than 12 retrieved lymph nodes.

LNR stages

A novel LNR stage was established using four identified cutoff values (LNR, 0.05, 0.3, 0.5, and 0.7). Using these four cutoff values, we classified patients in the training cohort as follows: $0 \leq LNR1 \leq 0.05$, $0.05 < LNR2 \leq 0.3$, $0.3 < LNR3 \leq 0.5$, $0.5 < LNR4 \leq 0.7$, and $0.7 < LNR5 \leq 1$ (Supplementary Table 2). There were two previous LNR stages which we named as LNR-Berger (Berger et al. 2005) and LNR-Rosenberg (Rosenberg et al. 2010). The cutoff values of these two LNR stages were: LNR-Berger (LNR, 0.05, 0.19, and 0.39) and LNR-Rosenberg (LNR, 0, 0.17, 0.41, and 0.69). Kaplan-Meier curves were presented to estimate the survivals of the AJCC 8th pN stage and these three LNR stages (Supplementary Figure 2).

TLNR classification

A novel TLNR classification was generated by combining the novel LNR and pT stages into 25 groups. Using these six identified cutoff values, we clustered patients of the 25 groups into seven clusters as follows: stage I (T1LNR1-2, T1LNR4), stage IIA (T1LNR3, T2LNR1-2, T3LNR1), stage IIB (T1LNR5, T2LNR3-4, T3LNR2, T4aLNR1), stage IIC (T2LNR5, T3LNR3-4, T4aLNR2, T4bLNR1), stage IIIA (T3LNR5, T4aLNR3-4, T4bLNR2), stage IIIB (T4aLNR5, T4bLNR3-4) and stage IIIC (T4bLNR5) (Table 1, Figure 1).

LNR stages versus the AJCC 8th pN stage

We compared the model discrimination performance and model-fitting ability of different LNR stages with the AJCC 8th pN stage in the training cohort. Compared to the AJCC 8th pN stage, all these three LNR stages showed significantly better prognostic discrimination (Hanley and McNeil test, all *P* < 0.001) and

superior model-fitting ability (Supplementary Table 3). Similar findings were observed in patients with < 12 and ≥ 12 retrieved lymph nodes (Supplementary Table 3).

TLNR classification versus the AJCC 8th TNM classification

In the training cohort, model discrimination and model-fitting between the novel TLNR and the AJCC 8th TNM classifications were compared. Kaplan-Meier curves with log-rank tests confirmed that the novel TLNR classification showed superior model discrimination performance than the AJCC 8th TNM classification, that the 5-year overall survival rates of the TLNR classification steadily decreased as stage increased, and HRs increased as stage increased (HRs, TLNR stages I to IIIC, 1.00, 1.48, 2.13, 3.07, 4.87, 6.94, and 9.70) (Table 2, Figure 2A, 2B). The novel TLNR showed better prognostic discrimination (AUC, 0.621 vs. 0.608; Hanley and McNeil test, $P < 0.001$) and superior model-fitting ability (AIC, 561,129 vs. 562,052) than the AJCC 8th TNM classification for overall survival (Table 3). Similar findings were observed in patients with adequate (≥ 12) or inadequate (< 12) retrieved lymph nodes (Table 3). We further performed decision curve analyses to assess clinical utility, and the novel TLNR classification had superior net benefits over the AJCC 8th TNM classification between the threshold probabilities of 30–45% in the training cohort (Supplementary Figure 3A). The details of the novel TLNR and the AJCC 8th TMM classifications are presented (Figure 3).

External validation

In the external validation cohort, the TLNR still showed better model discrimination performance than the AJCC 8th TNM classification, that the 5-year overall survival rates of the TLNR classification steadily decreased as stage increased, and HRs increased as stage increased in both overall survival (HRs, TLNR stages I to IIIC, 1.00, 1.76, 2.54, 3.40, 6.35, 10.4, and 16.0) and disease-free survival (HRs, TLNR stages I to IIIC, 1.00, 2.46, 3.71, 4.94, 8.84, 13.8, and 18.1) (Table 2, Figure 2C, 2D, 2E, and 2F). The novel TLNR classification showed superior prognostic discrimination (AUC of overall survival, 0.646 vs. 0.604; AUC of disease-free survival 0.646 vs. 0.622, Hanley and McNeil test, all $P < 0.001$) than the AJCC 8th TNM classification (Table 3). Similar findings were observed in patients with inadequate lymph nodes retrieved (< 12) but not in patients with adequate lymph nodes retrieved (≥ 12), suggested the advantages of the novel TLNR classification, especially in patients with inadequate lymph nodes retrieved (Table 3). The decision curve analyses further revealed that the TLNR had superior net benefits over the AJCC 8th TNM classification between threshold probabilities of around 20–30% in overall survival and around 22–35% in disease-free survival (Supplementary Figure 3B, Supplementary Figure 3C).

A web tool was developed basing on the novel TLNR classification which could individually predict the overall survival (Figure 4, http://123.206.185.159:6070/).

Discussion

The AJCC TNM classification of colon cancer has long been considered with a limited ability to predict survivals that some stage III patients had better prognosis than some patients in stage II (Amin MB 2017; Chu et al. 2016; Kim et al. 2015). It was previously believed that stage migration from an inadequate number of retrieved lymph nodes might be one reason (Hari et al. 2013; O'Connell et al. 2004). Some experts thought that patient survival was affected by the total number of retrieved lymph nodes, and therapeutic benefits could be obtained from an optimal lymphadenectomy. Others believed that this survival benefits might only due to a more accurate staging of the tumors from a more harvested number of lymph nodes. However, for patients with adequate lymph nodes, many patients in stage III still have better survivals than patients in stage II, which could not explain this paradox.

However, even full efforts are made, the total number of retrieved lymph nodes is frequently inadequate that 26.8% patients in the training cohort and 31.6% in the validation cohort had inadequate number of retrieved lymph nodes, which is similar with previous reports (Prandi et al. 2002; Wong et al. 2007). This might be associated with multiple factors of surgical skills, surgical technique, the way the pathologist in collecting the lymph nodes, the actual number of regional lymph nodes surrounding tumors, and even immune responses of patients (Becerra et al. 2017; Jestin et al. 2005; Stocchi et al. 2011). Furthermore, some studies suggested that in the AJCC TNM classification, pT stage had a much lower weight than the pN stage (Li et al. 2014; Li et al. 2016; Zhang et al. 2020), however, the pT stage was proved to have comparable importance to the pN stage, regardless of the number of retrieved lymph nodes (Chan et al. 2019; Rottoli et al. 2012). Take all these above into considerations, the current AJCC TNM 8th TNM classification could not obtain a satisfied ability to predict survival, leading a call for a modification or revision of the current classification.

The LNR take into account both the influence of the number of positive lymph nodes and the number of examined lymph nodes on the stage, and it has been proved to have a higher predictive advantages in prognosis over the AJCC pN stage for colon cancer (Berger et al. 2005; Rosenberg et al. 2010; Rosenberg et al. 2008). However, the prognostic value of establishing a novel TLNR classification for colon cancer by combining LNR and pT stages is still unknown. We established a novel LNR stage, with better prognostic discrimination than the AJCC 8th pN stage, and our novel LNR stage showed comparable prognostic discrimination with previous studies (Berger et al. 2005; Rosenberg et al. 2010; Rosenberg et al. 2008). Since we confirmed that the LNR stage was better than the pN stage, we established a novel TNLR classification for colon cancer by combining LNR and pT stages, and it was confirmed that the novel TLNR classification showed superior prognostic discrimination, model-fitting ability and clinical usefulness than the AJCC 8th TNM classification, especially in patients with inadequate lymph nodes retrieved.

The performance of a classification can be evaluated by the homogeneity within the subgroups, the ability to distinguish between different groups, and the monotonicity of the gradient shown by the correlation between stages and survivals (Ueno et al. 2001). The novel TLNR classification has several advantages over the AJCC 8th TNM classification. First, HRs and 5-year overall survival rates differed statistically significantly between each pair of stages groups in the novel TLNR classification, suggesting

an enhanced stratification ability. Second, AUCs of the novel TLNR classification were significantly increased than the AJCC 8th TNM classification, indicating a better prognostic discrimination. Third, the TLNR classification showed superior net benefits than the AJCC 8th TNM classification by decision curve analysis. Stratified analyses further confirmed that the novel TLNR classification had good model applicability, especially in the patients with inadequate lymph node retrieved. We further validated those findings in disease-free survival and the novel TLNR classification still showed superior predictive performance than the AJCC 8th TNM classification. Therefore, the current findings of this study should be considered reliable; given that they were based on a large-sampled SEER training set and validated by an external validation set, suggesting the TLNR is a more reasonable classification than the AJCC 8th TNM classification. It should be considered as a better alternative to the AJCC 8th TNM classification for better stratifying, especially for patients with inadequate lymph nodes retrieved.

To the best of our knowledge, this study was the first to establish a TLNR classification by combining pT and LNR stages for colon cancer. Besides, this study was based on a training cohort with a large population and was successfully validated by an external validation cohort. The current novel TLNR classification was established by only LNR and pT stages; surgical strategies, adjuvant chemotherapy regimens (Lai et al. 2016; Sineshaw et al. 2018), and the molecular markers of microsatellite instability, KRAS, and BRAF can also affect prognosis; future studies are still required to validate the novel TLNR classification.

Conclusions

In conclusion, the novel TLNR classification provides a better prognostic performance for operable stage I–III colon cancer than the AJCC 8th TNM classification, especially for patients with inadequate lymph nodes retrieved. It is a prognosis-based classification for better stratifying and can be considered as a good alteration of the current AJCC 8th TNM classification for operable colon cancer patients.

Abbreviation

AIC, Akaike information criterion; AJCC, American Joint Committee on Cancer;

AUC, area under receiver operator characteristics curve; CI, confidence interval;

HR, hazard ratio; LNR, lymph node ratio; pT stage, pathological T stage;

pN stage, pathological N stage; ROC, receiver operating characteristic;

SEER, Surveillance, Epidemiology, and End Results; TNM, tumor/node/metastasis;

UICC, Union for International Cancer Control.

Declarations

Acknowledgments

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Ethics approval and consent to participate

The study was performed according to ethics approval and consent. The ethical review was approved by the Institute Ethics Committees of China Medical University Cancer Hospital (20210206K). SEER is a publicly available database with anonymized data, no ethical review was required.

Consent for publication

Written informed consents of all participants of China Medical University Cancer Hospital has been obtained.

Conflicts of interest

The authors declare no potential conflicts of interest.

Data availability statement

The data will be available from the corresponding author on reasonable request.

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Tables

Table 1 The proposed TLNR classification in the training cohort.

Stage	5-Y OS, % (95% CI)	HR (95% CI)†	Log-rank (Mantel-Cox)‡	
			c^2 value	*P* value
Stage I	83.1 (82.1-84.1)	–	–	–
T1LNR1 (n=5,260)	83.4 (82.4-84.4)	1.00 (reference)	–	–
T1LNR4 (n=23)	73.9 (50.9-87.3)	1.00 (0.45-2.24)	0	0.999
T1LNR2 (n=511)	80.7 (77.0-83.9)	1.06 (0.89-1.26)	0.024	0.877
Stage IIA	75.0 (74.5-75.4)	–	–	–
T2LNR1 (n=8,941)	78.8 (77.9-79.6)	1.31 (1.23-1.40)	5.79§	0.016
T2LNR2 (n=1,465)	76.8 (74.5-78.9)	1.37 (1.24-1.52)	0.925	0.336
T1LNR3 (n=65)	72.3 (59.7-81.6)	1.50 (1.00-2.24)	0.192	0.662
T3LNR1 (n=22,931)	73.3 (72.8-73.9)	1.57 (1.49-1.66)	0.067	0.796
Stage IIB	63.2 (62.3-64.0)	–	–	–
T2LNR3 (n=221)	68.6 (62.0-74.3)	1.75 (1.42-2.16)	1.08§	0.298
T2LNR4 (n=56)	69.4 (55.5-79.8)	1.83 (1.24-2.70)	0.048	0.826
T3LNR2 (n=10,504)	63.6 (62.7-64.5)	2.10 (1.98-2.23)	0.434	0.510
T1LNR5 (n=20)	63.5 (38.3-80.7)	2.35 (1.30-4.25)	0.131	0.717
T4aLNR1 (n=1,945)	60.1 (57.8-62.2)	2.40 (2.21-2.61)	0.003	0.959
Stage IIC	49.7 (48.5-50.9)	–	–	–
T4bLNR1 (n=1,499)	55.1 (52.5-57.6)	2.72 (2.49-2.96)	6.36§	0.012
T3LNR3 (n=2,845)	50.9 (49.0-52.7)	2.99 (2.79-3.21)	5.11	0.024
T4aLNR2 (n=1,422)	47.4 (44.7-49.9)	3.25 (2.98-3.53)	3.05	0.081
T2LNR5 (n=46)	43.5 (29.0-57.1)	3.49 (2.43-5.00)	0.168	0.682
T3LNR4 (n=1,082)	42.5 (39.6-45.5)	3.73 (3.40-4.08)	0.131	0.718
Stage IIIA	33.6 (31.7-35.4)	–	–	–
T4aLNR3 (n=490)	38.6 (34.2-42.9)	4.23 (3.76-4.76)	2.92§	0.088
T4bLNR2 (n=823)	35.3 (32.0-38.6)	4.68 (4.25-5.15)	1.85	0.174
T4aLNR4 (n=207)	31.8 (25.6-38.2)	4.99 (4.23-5.09)	0.808	0.369
T3LNR5 (n=997)	30.0 (27.2-32.9)	5.43 (4.97-5.93)	1.06	0.304

Stage IIIB	22.2 (19.3-25.3)	–	–	–
T4bLNR3 (n=318)	24.4 (19.8-29.3)	6.52 (5.71-7.44)	4.05§	0.044
T4bLNR4 (n=148)	22.3 (16.0-29.3)	6.76 (5.63-8.11)	0.098	0.754
T4aLNR5 (n=288)	19.8 (15.4-24.6)	7.70 (6.72-8.81)	1.59	0.207
Stage IIIC	13.4 (8.9-18.8)	–	–	–
T4bLNR5 (n=187)	13.4 (8.9-18.8)	9.76 (8.28-11.50)	4.45§	0.035

Abbreviations: 5-Y OS, 5-year overall survival; CI, confidence interval; HR, hazard ratio; LNR, lymph node ratio; No., number.

†Log-rank tests were conducted between two sequential stages and twenty-one c^2 values were generated. All stages were compared with T1LNR1 as reference by values of HRs of Cox proportional hazards.

‡Log-rank tests were conducted between two sequential stages.

§Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model, with T1LNR1 = 0 as the reference in the training cohort. Twenty-five HR values were ordered from the lowest (T1LNR1) to the highest (T4bLNR5). Then, log-rank tests for 5-year overall survival were conducted between two sequential stages and 24 c^2 values were generated. Among the 24 c^2 values, six largest c^2 values were identified as the optimal cutoff values (5.79, 1.08, 6.36, 2.92, 4.05, 4.45), and

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

Table 2 Survival comparisons of the AJCC 8th pN versus LNR stages and the AJCC 8th TNM versus TLNR classifications in the training and validation cohorts.

Outcomes	HR (95% CI)	5-Y OS or DFS, % (95% CI)	Outcomes	HR (95% CI)	5-Y OS or DFS, % (95% CI)
Training cohort (Overall survival) (N=62,294)					
AJCC 8th pN stage			LNR stage		
pN0 (n=37,998)	1.00 (reference)	74.6 (74.2-75.0)	LNR1 (n=40,576)	1.00 (reference)	74.5 (74.1-75.0)
pN1a (n=7,694)	1.27 (1.22-1.32)	66.8 (65.7-67.8)	LNR2 (n=14,725)	1.45 (1.40-1.49)	62.4 (61.6-63.1)
pN1b/1c (n=7,705)	1.48 (1.43-1.54)	61.0 (59.9-62.1)	LNR3 (n=3,939)	2.13 (2.04-2.22)	48.6 (47.0-50.1)
pN2a (n=4,988)	1.88 (1.81-1.96)	52.7 (51.3-54.1)	LNR4 (n=1,516)	2.61 (2.45-2.78)	40.6 (38.1-43.0)
pN2b (n=3,909)	2.72 (2.61-2.84)	39.8 (38.3-41.3)	LNR5 (n=1,538)	3.96 (3.74-4.20)	26.9 (24.7-29.2)
AJCC 8th TNM classification			TLNR classification		
I (n=13,828)	1.00 (reference)	80.5 (79.8-81.1)	I (n=5,794)	1.00 (reference)	83.1 (82.1-84.1)
IIA (n=21,102)	1.33 (1.28-1.38)	73.1 (72.5-73.7)	IIA (n=33,402)	1.48 (1.41-1.56)	75.0 (74.5-75.4)
IIB (n=1,708)	2.02 (1.88-2.17)	60.3 (57.9-62.5)	IIB (n=12,746)	2.13 (2.01-2.25)	63.2 (62.3-64.0)
IIC (n=1,360)	2.28 (2.11-2.46)	55.3 (52.6-57.9)	IIC (n=6,894)	3.07 (2.90-3.26)	49.7 (48.5-50.9)
IIIA (n=2,384)	1.04 (0.97-1.13)	78.0 (76.2-79.6)	IIIA (n=2,517)	4.87 (4.55-5.21)	33.6 (31.7-35.4)

IIIB (n=16,270)	1.86 (1.79-1.93)	61.5 (60.7-62.2)	IIIB (n=754)	6.96 (6.34-7.63)	22.2 (19.3-25.3)
IIIC (n=5,642)	3.56 (3.41-3.72)	38.3 (37.0-39.5)	IIIC (n=187)	9.70 (8.24-11.4)	13.4 (8.90-18.8)
Validation cohort (Overall survival) (N=3,327)					
AJCC 8th pN stage			LNR stage		
pN0 (n=1,298)	1.00 (reference)	81.0 (78.4-83.2)	LNR1 (n=1,513)	1.00 (reference)	80.9 (78.6-83.1)
pN1a (n=723)	1.38 (1.13-1.70)	79.6 (75.8-82.8)	LNR2 (n=1,308)	1.48 (1.26-1.74)	76.8 (73.8-79.5)
pN1b/1c (n=709)	1.78 (1.47-2.16)	73.6 (69.3-77.4)	LNR3 (n=285)	2.20 (1.74-2.80)	66.4 (58.8-72.9)
pN2a (n=345)	2.09 (1.65-2.65)	71.5 (65.1-77.0)	LNR4 (n=93)	3.21 (2.31-4.47)	54.9 (41.6-66.3)
pN2b (n=252)	3.76 (3.01-4.71)	52.1 (44.0-59.5)	LNR5 (n=128)	4.95 (3.84-6.38)	44.0 (34.2-53.4)
AJCC 8th TNM classification			TLNR classification		
I (n=26)	1.00 (reference)	90.9 (50.8-98.7)	I (n=21)	1.00 (reference)	90.0 (47.3-98.5)
IIA (n=520)	1.78 (0.25-12.8)	84.4 (80.3-87.8)	IIA (n=731)	1.76 (0.25-12.6)	84.8 (81.4-87.7)
IIB (n=520)	2.34 (0.33-16.8)	80.0 (76.0-83.5)	IIB (n=1,413)	2.54 (0.36-18.1)	79.8 (77.1-82.1)
IIC (n=232)	2.76 (0.38-19.9)	76.7 (70.5-81.7)	IIC (n=737)	3.40 (0.48-24.3)	73.2 (69.4-76.6)

IIIA (n=56)	0.24 (0.02-3.81)	97.7 (84.6-99.7)	IIIA (n=328)	6.35 (0.89-45.4)	58.2 (51.7-64.1)
IIIB (n=1,460)	3.29 (0.46-23.4)	78.0 (75.3-80.5)	IIIB (n=84)	10.4 (1.44-75.6)	47.0 (34.7-58.4)
IIIC (n=513)	7.36 (1.03-52.5)	56.3 (51.0-61.3)	IIIC (n=13)	16.0 (2.05-125)	36.9 (12.5-62.0)
Validation cohort (Disease-free survival) (N=3,327)					
AJCC 8th pN stage			LNR stage		
pN0 (n=1,298)	1.00 (reference)	77.9 (75.2-80.2)	LNR1 (n=1,513)	1.00 (reference)	77.7 (75.3-80.0)
pN1a (n=723)	1.47 (1.22-1.77)	73.8 (69.9-77.3)	LNR2 (n=1,308)	1.63 (1.40-1.89)	70.7 (67.7-73.4)
pN1b/1c (n=709)	1.91 (1.60-2.28)	66.9 (62.7-70.8)	LNR3 (n=285)	2.48 (2.00-3.07)	57.9 (50.7-64.5)
pN2a (n=345)	2.30 (1.86-2.85)	65.5 (59.3-70.9)	LNR4 (n=93)	3.29 (2.41-4.48)	48.3 (35.8-59.8)
pN2b (n=252)	3.83 (3.11-4.72)	45.9 (38.4-53.1)	LNR5 (n=128)	4.93 (3.87-6.28)	38.2 (29.0-47.4)
AJCC 8th TNM classification			TLNR classification		
I (n=26)	1.00 (reference)	90.9 (50.8-98.7)	I (n=21)	1.00 (reference)	90.0 (47.3-98.5)
IIA (n=520)	2.60 (0.36-18.7)	81.3 (77.0-84.8)	IIA (n=731)	2.46 (0.34-17.6)	81.5 (78.0-84.6)
IIB (n=520)	3.18 (0.45-22.8)	77.0 (72.8-80.6)	IIB (n=1,413)	3.71 (0.52-26.4)	74.6 (71.9-77.1)

IIC (n=232)	4.03 (0.56-29.1)	73.1 (66.8-78.5)	IIC (n=737)	4.94 (0.69-35.2)	67.6 (63.7-71.2)
IIIA (n=56)	1.14 (0.13-10.2)	90.1 (75.3-96.2)	IIIA (n=328)	8.84 (1.24-63.1)	51.3 (45.0-57.2)
IIIB (n=1,460)	5.08 (0.71-36.2)	71.9 (69.1-74.5)	IIIB (n=84)	13.8 (1.91-99.8)	39.8 (28.3-51.0)
IIIC (n=513)	10.5 (1.48-75.1)	49.7 (44.6-54.6)	IIIC (n=13)	18.1 (2.32-141)	36.9 (12.5-62.0)

Abbreviations: 5Y-OS, 5-year overall survival; DFS, disease-free survival; HR, hazard ratio; No., number; LNR, lymph node ratio.

Table 3 Comparisons of the TLNR and the AJCC 8th TNM classifications in the training and validation cohorts.

Comparisons	AIC†	AUC (95% CI)‡	*P* value*
Training cohort (Overall survival)			
Overall patients (N=62,294)			<0.001
AJCC 8th classification	562,052	0.608 (0.604-0.612)	
TLNR classification	561,129	0.621 (0.617-0.624)	
Patients with lymph nodes < 12 (n=16,674)			<0.001
AJCC 8th classification	132,571	0.605 (0.597-0.612)	
TLNR classification	132,337	0.617 (0.609-0.624)	
Patients with lymph nodes ≥ 12 (n=45,620)			<0.001
AJCC 8th classification	398,469	0.610 (0.605-0.614)	
TLNR classification	397,780	0.622 (0.618-0.627)	
Validation cohort (Overall survival)			
Overall patients (N=3,327)			<0.001
AJCC 8th classification	11,500	0.604 (0.587-0.620)	
TLNR classification	11,505	0.646 (0.629-0.662)	
Patients with lymph nodes < 12 (n=1,052)			<0.001
AJCC 8th classification	3,736	0.587 (0.556-0.617)	
TLNR classification	3,732	0.641 (0.611-0.670)	
Patients with lymph nodes ≥ 12 (n=2,275)			0.071
AJCC 8th classification	6,719	0.621 (0.601-0.641)	
TLNR classification	6,716	0.643 (0.623-0.663)	
Validation cohort (Disease-free survival)			
Overall patients (N=3,327)			0.008
AJCC 8th TNM classification	13,954	0.622 (0.606-0.639)	
TLNR classification	13,968	0.646 (0.629-0.662)	
Patients with lymph nodes < 12 (n=1,052)			<0.001
AJCC 8th classification	4,313	0.598 (0.568-0.628)	

TLNR classification	4,305	0.640 (0.611-0.670)	
Patients with lymph nodes ≥ 12 (n=2,275)			0.774
AJCC 8th classification	8,418	0.641 (0.621-0.661)	
TLNR classification	8,433	0.645 (0.625-0.664)	

Abbreviations: AIC, Akaike's information criterion; AUC, Areas under the receiver-operating characteristic curve;

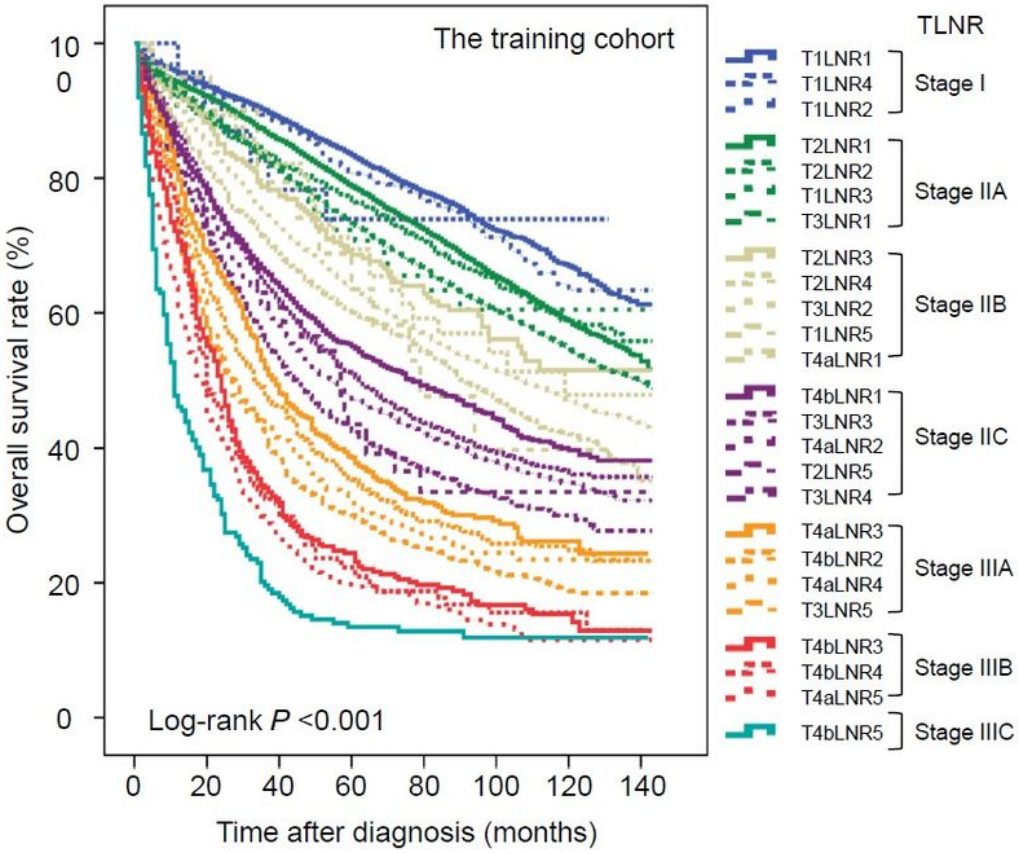
CI, confidence interval.

[†]A lower AIC indicates superior model-fitting.

[‡]A higher AUC indicates better discrimination.

[*]*P* value of Hanley & McNeil test of AUCs.

Figures



Number at risk

5794	5425	5124	4718	3111	1769	823	107	Stage I
33402	30126	27292	24383	16296	9461	4365	639	Stage IIA
12746	10807	9171	7841	5132	2918	1390	197	Stage IIB
6894	5294	4131	3341	2173	1284	628	86	Stage IIC
2517	1580	1076	822	526	322	168	21	Stage IIIA
754	395	226	162	105	61	32	5	Stage IIIB
187	71	33	25	17	13	7	2	Stage IIIC

Figure 1

Kaplan–Meier estimates of the proposal novel T stage-Lymph Node Ratio classification (TLNR) in the training cohort.

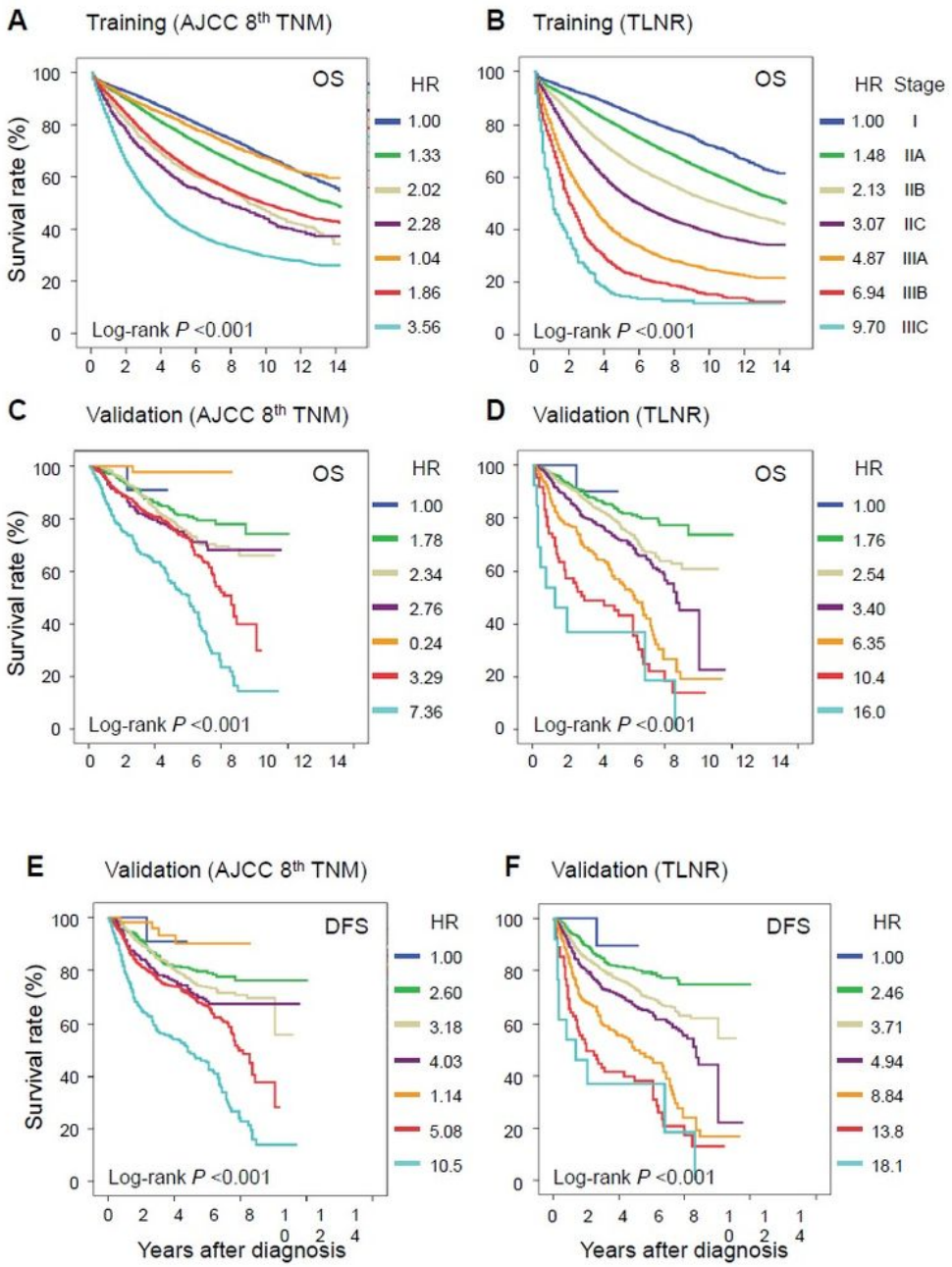


Figure 2

Kaplan–Meier estimates of the AJCC 8th TNM classification and TLNR classification in the training and validation cohorts. (A) AJCC 8th TNM classification in the training cohort predicting overall survival (OS); (B) TLNR classification in the training cohort predicting overall survival; (C) AJCC 8th TNM classification in the validation cohort predicting overall survival; (D) TLNR classification in the validation cohort

predicting overall survival; (E) AJCC 8th TNM classification in the validation cohort predicting disease-free survival (DFS); (F) TLNR classification in the validation cohort predicting disease-free survival.

A AJCC 8th TNM (8th TNM) classification

8th TNM	N0	N1a	N1b/1c	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 TLNR classification

TLNR	LNR1	LNR2	LNR3	LNR4	LNR5
T1	I	I	IIA	I	IIB
T2	IIA	IIA	IIB	IIB	IIC
T3	IIA	IIB	IIC	IIC	IIIA
T4a	IIB	IIC	IIIA	IIIA	IIIB
T4b	IIC	IIIA	IIIB	IIIB	IIIC

Figure 3

Details of two classifications. (A) The AJCC 8th TNM classification; (B) The TLNR classification.

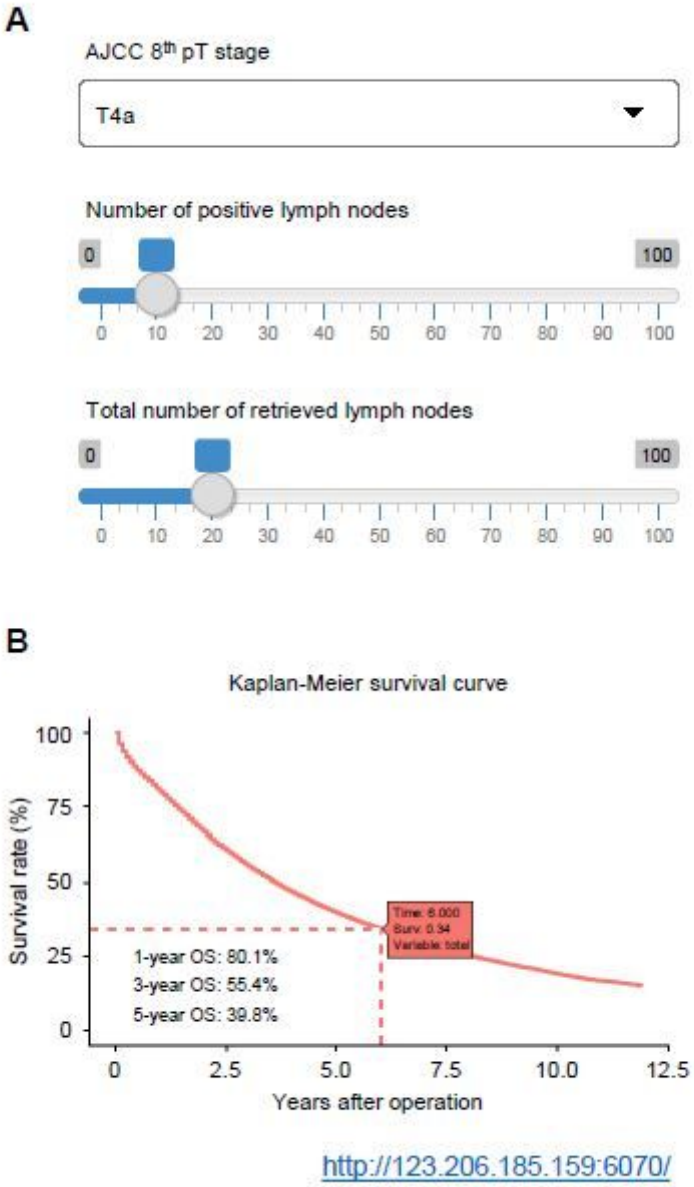


Figure 4

A web tool based on the novel TLNR classification individually predicting overall survival (http://123.206.185.159:6070/). (A) Valuables include AJCC 8th pT stage, number of positive lymph nodes, and total number of retrieved lymph nodes. (B) Kaplan–Meier estimates of individual survival curves based on a web tool. LNR = number of positive lymph nodes / total number of retrieved lymph nodes. Number of positive lymph nodes should be no more than the total number of retrieved lymph nodes.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- s1.jpg
- s2.jpg
- s3.jpg
- supptables.docx