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Proposal of a new nodal classification for operable non-small cell lung cancer based on the number of negative lymph nodes and the anatomical location of metastatic lymph nodes

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Abstract

Lymph node metastasis is one of the most important prognostic indicators in patients with radically resected non-small cell lung cancer (NSCLC). This retrospective study aimed to compare the predictive value of metastatic lymph nodes (MNs), lymph node ratio (LNR), resected lymph nodes (RNs), and negative lymph nodes (NNs) with the currently used pathologic nodal (pN) staging category.

We conducted a retrospective analysis of 1019 consecutive NSCLC patients treated with complete resection in a single institution. Prognostic values of various lymph node factors were evaluated by analysis of univariate and multivariate Cox proportional hazards model, and the results were compared with those using the location-based pN stage classification.

The median follow-up duration was 47 months. During this period, 353 cases of cancer recurrence and 337 deaths were reported. Multivariate cox analysis indicated that both pN and NN categories were independent predictors of patient survival. The patients were divided into six groups on the basis of pN and NN categories. The survival rates of the groups were as follows: pN0, NN≥8, 81.4%; pN0, NN<8, 73.8%; pN1, NN≥8, 61.4%; pN1, NN<8, 54.2%; pN2, NN≥8, 48.4%; and pN2>1, NN<8, 35.0%. Comparison of the predictive values of the lymph node factors showed that the new N category was a more valuable prognostic factor in operable NSCLC.

The combination of anatomically based pN stage classification and the number of MNs is an accurate prognostic determinant in patients with operable NSCLC which can be equal to 8th N category.

Abbreviations: ADCs = adenocarcinomas, AIC = akaike information criterion, AUC = area under the curve, BIC = Bayesian information criterion, CT = computed tomography, LNR = lymph node ratio, MNs = metastatic lymph nodes, MRP = Martingale residual plots, NNs = negative lymph nodes, NSCLC = non-small cell lung cancer, pN = pathologic nodal, RNs = resected lymph nodes, SCCs = squamous cell carcinomas, TNM = tumor node metastasis.

Keywords: lymph node metastasis, non-small cell lung cancer, prognosis

1. Introduction

Lymph node metastasis is one of the most important prognostic indicators in non-small cell lung cancer (NSCLC) patients who underwent surgery treatment.[1–3] The eighth edition of the TNM classification for Lung Cancer has been introduced. The T, M, and N factors, as well as TNM staging have been considerably improved relative to those found in the 7th edition of TNM classification.[4] Studies indicate that NSCLC patients with N1 and N2 nodal involvement consist of subgroups exhibiting heterogeneity with respect to prognosis.[5,6] In the recent edition, the N factor has added the concept of skip metastasis to mediastinal lymph node in order to subdivide N1 and N2, whereas in the 7th edition, the definition of "mediastinal lymph node" was limited to the anatomic location of metastatic lymph nodes (MNs). Some lymph nodes factors which are useful in the assessment of patient prognosis merit attention. The number of MNs has been demonstrated to be a more powerful prognostic indicator than their location (pN), and is included in the nodal classification in the TNM classification system for perihilar cholangiocarcinoma, breast cancer, gastric cancer, and colorectal cancer.[7,8] Various reports indicated that the number of MNs was an independent prognostic factor in operable lung cancer.[9–12] In addition to the number of lymph node metastasis,

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the number of resected lymph nodes (RNs) is an important predictor of overall survival (OS) after curative resection.[11,13,14] A recent study suggested that the ratio between MNs and total number of lymph nodes (lymph node ratio, LNR), which reflects the degree of lymph node metastasis was a better predictor than MN and pN.[15] Owing to variations in patient population and focus of interest, RN, LNR, MN, and pN factors exhibited different predictive efficiencies in operable NSCLC in various reports.

The involvement of the lymph node factors such as LNR, MN, and RN in current lymph node staging could help clinicians with high-accuracy lymph node staging and precise discrimination of the heterogeneous subgroups of pN1 and pN2. The present study aimed to explore whether the lymph node factors were associated with the prognosis of NSCLC patients who underwent radical resected operation and the degree of correlation of these factors with patient survival. The predictive value of pN as a prognostic factor was also compared with those of RN, MN, and LNR categories.

2. Patients and methods

2.1. Patients

The study was approved by the Research Ethics Committee of Provincial Hospital Affiliated to Shandong University, Shandong University, China. Informed written consent for the use of their clinical data was obtained from the patients at the time of surgery.

We retrospectively reviewed our clinical cancer biobank database (Department of Thoracic Surgery of Provincial Hospital Affiliated to Shandong University, Jinan, China). The intrusion criteria are as follows:

(1) The diagnosis time ranging from January 2009 to December 2015.
(2) NSCLC patients.
(3) operable cases with lobectomy.

The exclusion criteria included:

(1) patients refuse operation or subsequent treatment.
(2) cases "lost to follow-up".
(3) patients who refused to cooperate.

We finally identified 1019 patients with NSCLC who had undergone same pulmonary resection (lobectomy). All patients had undergone routine preoperative evaluations to exclude contraindications, including computed tomography (CT) scan of the thorax, abdomen ultrasonography, brain CT, or magnetic resonance imaging and whole-body bone scintigraphy.

2.2. Data acquisition

We investigated the clinical profiles of the patients, including their medical records, laboratory results, and pathology reports. Demographics and hematologic counts were measured before the surgery. Histopathological findings were classified in accordance with the World Health Organization, and pathological stages of the disease were described in accordance with the Union for International Cancer Control eighth TNM staging system for NSCLC.

2.3. Follow-up strategy and statistical analysis

Patients were evaluated every 3 months by CT scan of the thorax and abdomen ultrasonography for the first 2 years after surgery and annually thereafter. Survival time was calculated from the day of surgery to the last checkup or death by any cause. Nominal data were analyzed using Crosstabs and the Fisher exact test. Martingale residual plots (MRP) analysis of the Cox model was conducted to check the functional form of investigational variables. Cut-offs allowed transforming continuous variables into categorical variables. We evaluated the predictive capacity of the categories by considering measures of discrimination. Discrimination refers to the ability to distinguish between different risk groups of patients. In this study, discrimination was quantified using the Akaike information criterion (AIC), Bayesian information criterion (BIC), Harrell C index, and the area under the curve (AUC). The Cox proportional hazards model was used to identify relevant variables affecting survival. Median values are shown with a 95% confidence interval. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed with SPSS 24.0 (SPSS Inc, Chicago, IL). Significance was set at $P < .05$.

3. Results

3.1. Patient characteristics

Patient characteristics are listed in Table 1.

Approximately 70.0% of the patients were male (713 of 1019 individuals). The mean age was 59.07 ± 9.76 years (range: 21–84 years). Lobectomy was performed in all patients. In the recruited cases, 331 were identified as squamous cell carcinomas (SCCs), 529 as adenocarcinomas (ADCs), and 159 as other types of lung cancer, including large cell carcinoma, adenosquamous cell carcinoma, and carcinoid. Exactly 712 patients received 2 to 6 cycles of postoperative adjuvant platinum-based chemotherapy. The median follow-up duration was 47 months (range: 3–96 months). During this period, cancer recurrence in 353 patients was reported, and the recurrence sites were mostly locoregional

Table 1

Clinical characteristics of all 1019 NSCLC patients.

Characteristic	Data
No. of patients	1019
Age (years) Mean ± SD (range;median)	59.07 ± 9.76 (21–84;60.0)
Gender	
Male/Female	713 (70.0%)/306 (30.0%)
Smoke status	
Never smoker/Smoker	388 (38.1%)/631 (61.9%)
Histology	
SCC/ADC/Others	331 (32.5%)/529 (51.9%)/159 (15.6%)
Tumor size	
T1/T2/T3/T4	346 (34.0%)/556 (54.6%)/82 (8.0%)/35 (3.4%)
TNM stage	
I/II/III	458 (44.9%)/358 (35.1%)/203 (19.9%)
Chemotherapy	
No/Yes	712 (69.9%)/307 (30.1%)
pN stage	
pN0/pN1/pN2	569 (55.8%)/217 (21.3%)/233 (22.9%)
tRN Mean ± SD (range;median)	15.60 ± 8.80 (0–61;14.0)
tMN Mean ± SD (range;median)	2.20 ± 4.36 (0–51;0.0)
tNN Mean ± SD (range;median)	13.40 ± 8.25 (0–61;12.0)
tLNR Mean ± SD (range;median)	0.132 ± 0.213 (0.000–1.000;0.000)
DFS (months)Median/Mean ± SD	35.0/34.9 ± 21.5
OS (months)Median/Mean ± SD	47.0/45.93 ± 23.0

DFS = disease-free survival, NSCLC = non-small cell lung cancer, OS = overall survival.

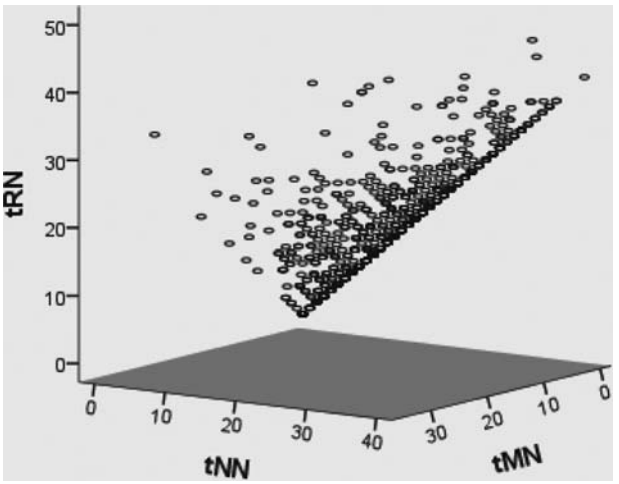

Figure 1. 3D-scattered plot of correlation between number of resected lymph nodes (RNs), number of metastatic nodes (MNs), and number of negative lymph nodes (NNs).

sites, brain, adrenal gland, and liver, among others. A total of 337 patients died from cancer or intercurrent diseases.

All patients underwent mediastinal lymph node dissection. A total of 15,897 resected nodes (RNs) were removed at an average of 15.60 ± 8.80 nodes per patient. Total metastatic nodes (MNs) were 2245 and at an average of 2.20 ± 4.36 nodes per patient. The mean total negative nodes (NNs) were 13.40 ± 8.25, and the mean lymph nodes ratio (LNR) was 0.132 ± 0.213. The distribution and relationships among the MNs, NNs, and RNs are presented in Figure 1.

In accordance with the Martingale residuals of the Cox model, the cut-off values of RN and NN were determined as 9 and 8, respectively. The best cut-off values discriminated MN as 0, 1, and ≥2. The optimal cut-off values of LNR were also determined as 0 and 0.07.

3.2. Univariate and multivariate analyses

The risk factors for disease-free survival (DFS) or overall survival (OS) were analyzed using the univariate Cox regression hazard model (Table 2). As categorical variables, age, gender, smoking status, postoperative chemotherapy, pT stage, pN stage as well as NN, MN, and LNR were correlated with patient DFS ($P = .000$,

Table 2

Univariate proportional hazards (Cox) regression analyses according to DFS and OS.

	DFS		OS	
Variables in the equation	***P***	**Hazard ratio (95%CI)**	***P***	**Hazard ratio (95.0% CI)**
Age (<65 vs ≥65)	.000	1.492 (1.206–1.846)	.000	1.599 (1.288–1.986)
Gender (Male vs Female)	.024	0.759 (0.597–0.964)	.001	1.475 (1.171–1.857)
Smoke status (Never vs Smoker)	.000	1.499 (1.196–1.879)	.018	1.331 (1.050–1.688)
Chemotherapy (No vs Yes)	.000	1.655 (1.338–2.046)	.000	1.654 (1.332–2.055)
Histology				
SCC	.349	NA	.499	NA
ADC	.148	0.844 (0.671–1.062)	.240	0.868 (0.686–1.099)
Others	.497	0.896 (0.651–1.231)	.561	0.908 (0.655–1.258)
Tumor size				
T1	.000	NA	.000	NA
T2	.000	1.559 (1.215–2.000)	.000	1.574 (1.221–2.209)
T3	.000	2.799 (1.955–4.007)	.000	2.828 (1.960–4.080)
T4	.024	1.878 (1.086–3.246)	.024	1.921 (1.091–3.380)
Node stage				
N0	.000	NA	.000	NA
N1	.000	2.355 (1.801–3.080)	.000	2.301 (1.745–3.033)
N2	.000	3.526 (2.922–4.815)	.000	3.751 (2.922–4.815)
tRN (<9 vs ≥9)	.319	1.141 (0.880–1.478)	.238	1.174 (0.900–1.532)
tNN (<8 vs ≥8)	.000	0.650 (0.521–0.811)	.000	0.663 (0.529–0.832)
tMN				
tMN =0	.000	NA	.000	NA
tMN=1	.000	2.089 (1.559–2.799)	.000	2.039 (1.505–2.761)
tMN≥2	.000	3.753 (2.495–4.007)	.000	3.924 (3.079–4.999)
tLNR				
tLNR=0	.000	NA	.000	NA
0<tLNR<0.07	.009	1.815 (1.162–2.836)	.043	1.634 (1.016–2.628)
tLNR≥0.07	.000	3.243 (2.589–4.061)	.000	3.371 (2.677–4.243)
New N category				
pN0, NN≥8	.000		.000	
pN0, NN<8	.068	1.436 (0.974–2.116)	.109	1.385 (0.930–2.064)
pN1, NN≥8	.000	2.408 (1.745–3.324)	.000	2.380 (1.711–3.311)
pN1, NN<8	.000	3.058 (2.020–4.629)	.000	2.830 (1.834–4.367)
pN2, NN≥8	.000	3.414 (2.526–4.615)	.000	3.564 (2.620–4.849)
pN2, NN<8	.000	4.867 (3.458–6.850)	.000	5.235 (3.699–7.408)

DFS = disease-free survival, OS = overall survival.

Table 3

Multivariate proportional hazards (Cox) regression analyses according to DFS and OS.

	DFS		OS	
Variables in the equation	***P***	**Hazard ratio (95%CI)**	***P***	**Hazard ratio (95.0% CI)**
Age (<65 vs ≥65)	.000	1.903 (1.524–2.376)	.000	1.862 (1.492–2.325)
Smoke status (Never vs Smoker)	.052	1.364 (0.998–1.865)	.080	1.333 (0.966–1.840)
Tumor size				
T1	.000	NA	.001	NA
T2	.041	1.299 (1.010–1.671)	.032	1.323 (1.024–1.709)
T3	.000	2.200 (1.526–3.171)	.000	2.209 (1.521–3.208)
T4	.435	1.247 (0.716–2.172)	.438	1.254 (0.708–2.221)
Node stage				
N0	.000	NA	.000	NA
N1	.000	2.214 (1.678–2.922)	.000	2.191 (1.649–2.911)
N2	.000	3.446 (2.667–4.453)	.000	3.786 (2.916–4.916)
tNN (<8 vs ≥8)	.001	0.685 (0.548–0.857)	.002	0.702 (0.558–0.883)
tMN				
tMN = 0	.120	–	.000	NA
tMN = 1	.049	–	.026	3.141 (1.148–8.593)
tMN ≥ 2	.075	–	.001	5.613 (2.022–15.586)
Chemotherapy (No vs Yes)	.018	1.309 (1.048–1.634)	.051	–
Gender (Male vs Female)	.943	1.028 (0.729–1.449)	.944	–
tLNR				
tLNR = 0	.397	–	.191	–
tLNR < 0.07	.397	–	.191	–
tLNR≥0.07	.397	–	.191	–

DFS = disease-free survival, OS = overall survival.

.024, .000, .000, .000, .000, and .000, .000, and .000, respectively). Age, female gender, smoking status, postoperative chemotherapy, low pT stage, low pN stage, as well as low NN, MN, and LNR (*P* = .000, .001, .018, .000, .000, .000, and .000, .000, .000, respectively) were favorable predictors for OS. However, RN exhibited no correlation with either patient DFS or OS.

All factors which were statistically significant evaluated in the univariate analyses were included in multivariate analyses (Table 3). Multivariate Cox regression analysis according to DFS revealed that age, smoke status, chemotherapy, pT stage, NN, and pN category were significant independent prognostic factors. Age, smoke status, tMN, pT stage, NN, and pN category were determined as the independent predictive factors for OS.

3.3. Proposal of a new N category in lymph node staging of lung cancer

Considering the powerful and independent predictive abilities of both pN and NN categories in multivariate analysis, we divided the patients into 6 new groups: pN0, NN≥8 (n = 439), pN0, NN<8 (n = 130), pN1, NN≥8 (n = 158), pN1, NN<8 (n = 59), pN2, NN≥8 (n = 153), and pN2, NN<8 (n = 80). The survival curves of the 6 new N categories in accordance with DFS and OS (*P* = .000 and .000, respectively) are shown in Figure 2. The new N category exhibited the strong ability to separate OS and DFS in operable lung cancer.

The pN category and the new N category were linearly related; thus, we entered the new N categories into multivariate analysis individually without the pN category (Table 4). We then compared the hazard ratios of the pN category and the new N category in accordance with the patient OS. The hazard ratios were 2.301 for pN1, 3.751 for pN2 compared to the pN0 subset, and 1.385, 2.380, 2.830, 3.564, 5.235 for the elevated new N category relative to the new N category group 1 (pN0, NN≥8). These findings suggest that the new N category could more efficiently distinguish the different prognostic groups.

3.4. Comparison of predictive values among various lymph node factors

We determined the AIC, BIC, and AUC of each lymph node factor, which could evaluate the predictive capacity of the categories. The AIC and BIC were calculated by logistic regression according to the survival status of patients after the follow-up. The Harell C index and AUC values were calculated using the Cox model and receiver operating characteristic curves. All values are listed in Table 5. The new N category had the smallest AIC (107.206), and also held the largest Harell C index and AUC (0.673 and 0.687, respectively) compared with those of the other lymph node factors and pN category in the eighth edition. The new N category had a BIC value only larger than the eighth pN category. AIC is the prior index to evaluate the goodness of fit of the model, considering the large number of samples. In addition, the pN, MN, and LNR categories had similar values for the aforementioned factors, indicating that MN and LNR had equal predictive values, which were not superior to those of the pN category. The receiver operating characteristic curves of the lymph node factors are presented in Figure 3. On the basis of the aforementioned results, the new N category exhibited the strongest predictive ability, compared with the other lymph node factors.

4. Comment

Precise tumor staging plays a crucial role in the management of NSCLC patients, including the selection of patients for adjuvant therapy and predicting patient prognosis. The TNM staging system was widely adopted to provide high specificity for

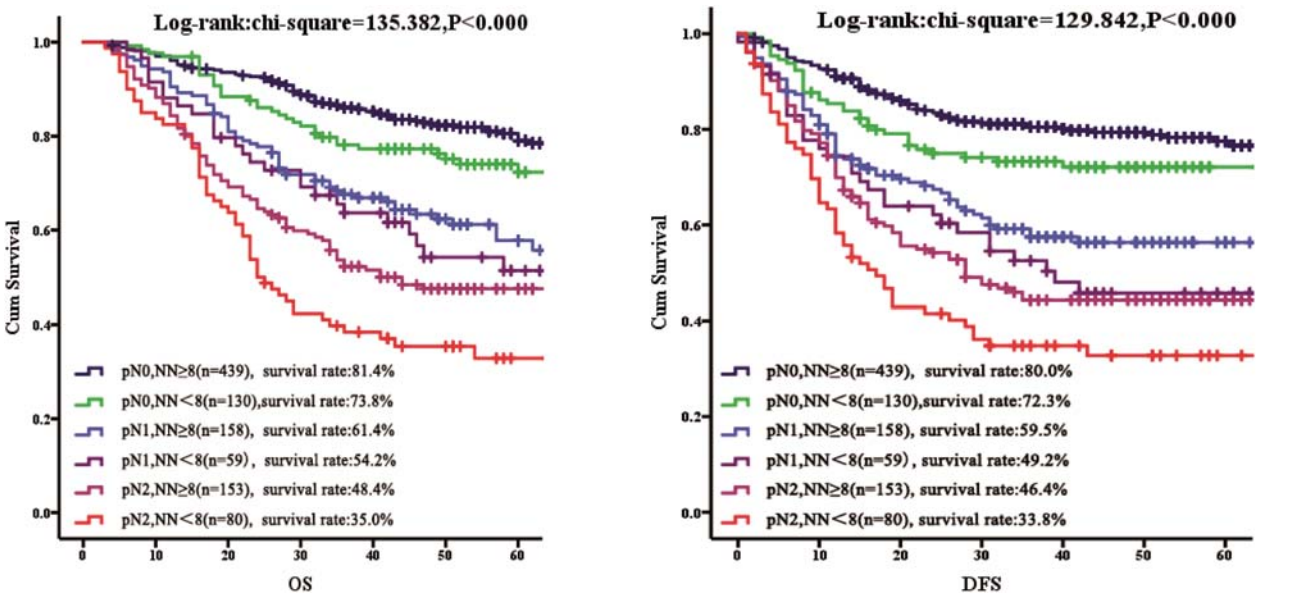

Figure 2. Comparison of Kaplan–Meier curves for different new N category groups for disease-free survival (a) and overall survival (b) of the subgroup with radically resected non-small cell lung cancer (NSCLC).

discriminating different groups of patient prognosis. Lymph node metastasis was considered one of the most important predictors for survival. Significant changes in the T, N, and M descriptors were introduced in the eighth edition of the TNM staging system for NSCLC.[4] However, some lymph node factors, such as MNs or RNs, were ignored.

Various reports have recently shown that the number of MN classified into several categories was significantly associated with the OS and DFS of the patient, as well as the anatomical location-based pN category for operable NSCLC.[9–12] Hisashi Saji et al[12] determined the number of MNs in resected NSCLC and observed a clear tendency toward the deterioration of OS from nN0 to nN4- in the same pT category. Multivariate analysis indicated that not only the pN status but the nN status as well was a major independent prognostic factor for both OS and DFS. These results showed that both pN and nN categories exhibited powerful discriminative abilities with respect to the prognosis of NSCLC. Another study demonstrated that the nN category was a better prognostic determinant than the location-based pN stage classification.[9] Our results indicated that the MN category classified into 0, 1, and >1 groups had equal rather than superior values to that of the pN category.

Subsequently, we demonstrated that LNR was positively associated with the OS and DFS of patients with NSCLC. LNR could provide statistical results with increased precision by providing comprehensive information on nodal metastasis and

Table 4

Multivariate proportional hazards (Cox) regression analyses according to DFS and OS.

	DFS		OS	
Variables in the equation	***P***	**Hazard ratio (95%CI)**	***P***	**Hazard ratio (95.0% CI)**
Age (<65 vs ≥65)	.000	1.732 (1.392–2.155)	.000	1.861 (1.490–2.323)
Gender (Male vs Female)	.742	1.058 (0.757–1.480)	.823	1.040 (0.736–1.471)
Smoke status (Never vs Smoker)	.051	1.368 (0.999–1.873)	.072	1.346 (0.973–1.862)
Chemotherapy (No vs Yes)	.028	1.279 (1.027 -1.592)	.035	1.272 (1.018–1.589)
Tumor size				
T1	.000	NA	.001	NA
T2	.040	1.301 (1.012–1.674)	.032	1.324 (1.025–1.711)
T3	.000	2.205 (1.527–3.184)	.000	2.199 (1.512–3.198)
T4	.426	1.253 (0.719–2.183)	.428	1.260 (0.711–2.234)
New N category				
pN0, NN≥8	.000	NA	.000	NA
pN0, NN<8	.026	1.560 (1.055–2.307)	.053	1.485 (0.995–2.219)
pN1, NN≥8	.000	2.324 (1.675–3.224)	.000	2.328 (1.665–3.253)
pN1, NN<8	.000	3.093 (2.027–4.719)	.000	2.847 (1.833–4.442)
pN2, NN≥8	.000	3.498 (2.565–4.771)	.000	3.738 (2.724–5.131)
pN2, NN<8	.000	5.143 (3.633–7.281)	.000	5.662 (3.974–8.065)

DFS = disease-free survival, OS = overall survival.

Table 5

Compare AIC, BIC, Harrell's C index, and ROC among different lymph node categories.

Category	AIC	BIC	Harrell C	ROC	
				AUC	*P*
tRN category	109.943	169.061	0.515	0.513	.507
tNN category	110.547	174.593	0.546	0.447	.006
tMN category	111.906	171.025	0.659	0.677	.000
tLNR category	109.848	168.967	0.655	0.673	.000
pNcategory	110.547	174.593	0.661	0.673	.000
8th N category	109.997	159.263	0.666	0.679	.000
New N category	107.206	161.398	0.673	0.687	.000

AIC = Akaike information criterion, AUC = area under the curve, BIC = Bayesian information, ROC = receiver operating characteristic curve.

immune conditions against the malignant disease.[15] Several studies showed that LNR was an independent predictor of survival in patients with operable NSCLC, particularly in patients with pathologic N1 NSCLC.[16] Meanwhile, a high LNR is associated with poor survival in patients with resected, node-positive NSCLC.[17] Similar to the MN category, LNR also exhibited an equal rather than superior efficiency in discriminating different prognostic groups of NSCLC patients. In multivariate analysis, only the pN category was the independent prognostic factor for OS and DFS; neither the MN category nor the LNR category was regarded as an independent prognostic factor, indicating that they were linearly correlated with the pN category and were eliminated during Cox regression because of their linear correlations. In multivariate Cox analysis which adopted " forward: LR", some factors will be excluded because of the liner correction with others.

Further, we demonstrated that the number of NNs was significantly correlated with the OS and DFS of the patients. In multivariate analysis, the NN category, together with the pN category, was a significant independent predictor for patient survival. The immune condition against the malignant disease and micro-metastasis from the primary tumor could be responsible for the ability of NN to affect survival. A new lymph node staging classification system was then generated in accordance with the pN and NN categories. We classified the patients into 6 categories combining the pN and NN statuses, as follows: pN0-NN≥8, pN0-NN<8, pN1-NN≥8, pN1-NN<8, pN2-NN≥8, and pN2-NN<8. The OS and DFS survival curves of each new N category were well distributed and proportional. For each pT category, a clear tendency toward the deterioration of OS from the 6 new N categories was observed (data not shown). Multivariate Cox regression analysis indicated that the hazard ratios of the new N categories were more representative of the patient prognosis than that of the pN categories. The AIC was the smallest, whereas Harell C was the largest for the new N category. Comparison of ROCs among these lymph node factors

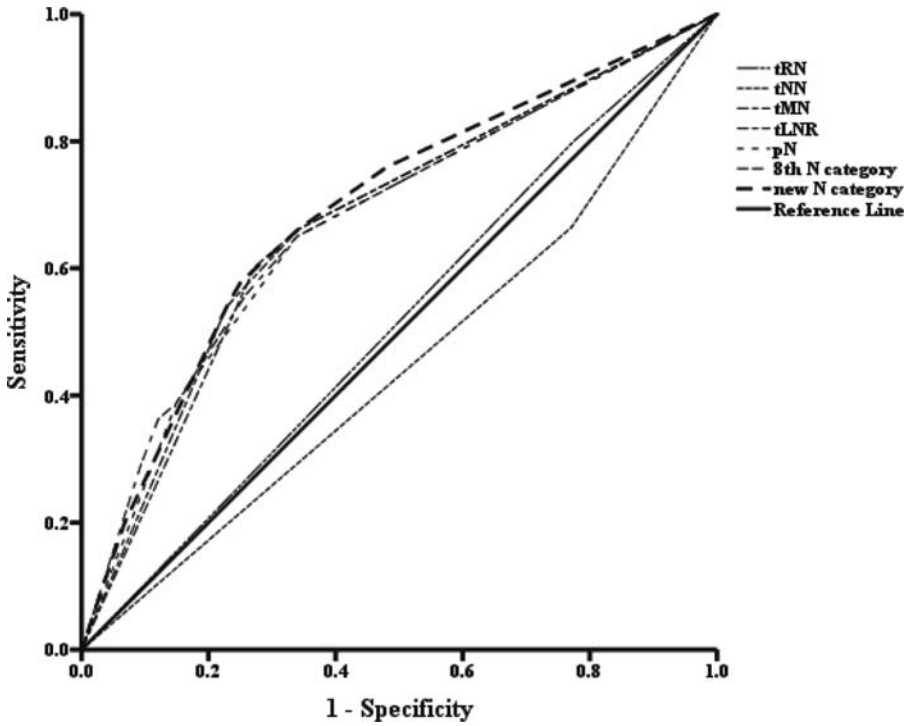

Figure 3. Receiver operating characteristics curve of the eighth N category, pN, MN, LNR, NN, and new N category for predicting survival of non-small cell lung cancer (NSCLC) patients with radical resection.

also showed that the new N category was a more valuable prognostic factor than relatively prognostic factors in operable NSCLC. Furthermore, the comparison between the ROC curves of the new N category and pN category in the eighth edition showed that both of them had equal ability for evaluating NSCLC patients' prognosis ($P = .2278$, data from MedCalc).

The anatomically based pN category showed several unsatisfactory facets. Heterogeneities existed in each pN0, pN1 and pN2 subgroup with regard to patient prognosis. Thus, various reclassification methods were proposed. The number of RN was involved in dividing patients with pN0 NSCLC into different prognostic subgroups.[18–20] In patients with pN1 disease, the LNR category was recommended for further classification.[16,21] With regard to pN2 disease, a broad spectrum of prognosis could be observed. Lymph node stations, zones, and chains, as well as MN and LNR, were indicated in further grouping.[22,23] In general, Hisashi Saji et al[12] proposed the combination of the total number and anatomical location of involved lymph nodes for nodal classification in NSCLC and ultimately classified the patients into 4 categories: pN0-nN0, pN1-nN1-3, pN1-nN4-plus pN2-nN1-3, and pN2-nN4-. There were significant tendencies to vary between the new N1 and new N2a as well as between the new N2a and new N2b categories in accordance with the OS survival curves of the new classification. Our results identified 6 groups of patients with different prognoses, indicating that our classification method could provide more information than that provided by Hisashi Saji et al.

However, the current study includes certain limitations, one of which is that the analysis was a retrospective single-center study. In addition, this study included both traditional open surgery and video-assisted thoracoscopic surgery, which may vary in lymph node dissection. Finally, our prognostic model requires further validation.

Author contributions

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