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ORIGINAL ARTICLE

Including positive lymph node count in the AJCC N staging may be a better predictor of the prognosis of NSCLC patients, especially stage III patients: a large population-based study

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Abstract

Background The study was designed to explore the value of including positive lymph node count in the TNM staging system of non-small cell lung cancer.

Patients and methods The X-tile model was applied to determine the cutoff values of positive lymph node count. Survival curves were generated using the Kaplan–Meier method and differences in survival among subgroups were examined using the log-rank test. The influence of different variables on overall survival and lung cancer-specific survival was further evaluated using univariate and multivariate Cox proportional hazard models. All statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). All p values were 2-sided and $p < 0.05$ was considered statistically significant.

Results The overall survival and lung cancer-specific survival between stage IIIA and IIIB classified by the sixth edition TNM staging system show no statistically significant difference ($p = 0.479$ for overall survival; $p = 0.081$ for lung cancer specific survival). The X-tile model was used to screen three different cutoff values including nN = 0, nN1–3 and nN4-. The nN value is a significant independent prognostic factor that affects overall survival and lung cancer-specific survival of non-small cell lung cancer patients (all, $p < 0.001$). We obtained the hypothesized TNM sub-stages based on location and the number of PLN. There were significant differences between the hypothesized stage IIIA and IIIB regarding overall survival and lung cancer-specific survival (all, $p < 0.001$).

Conclusions It needs to be considered that N stage in combination with positive lymph node count may be used to predict the prognosis of non-small cell lung cancer for stage III cases with increased accuracy than category location-based stage.

Keywords Non-small cell lung cancer · Tumor-node-metastasis · Lymph node · Stage · Prognosis

Abbreviations

NSCLC	Non-small cell lung cancer
TNM	Tumor-node-metastasis
PLN	Positive lymph nodes
nN	Number of positive lymph nodes
LNs	Lymph nodes
SEER	Surveillance Epidemiology and End Results
AJCC	American Joint Committee on Cancer
OS	Overall survival
LCSS	Lung cancer-specific survival
HR	Hazard ratio
CI	Confidence interval
pN	Pathological lymph nodes
pT	Pathological tumor

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with approximately 85% of lung cancer patients having non-small cell lung cancer (NSCLC) [1]. The tumor node metastasis (TNM) staging system is crucial for both prognosis and treatment strategy selection for patients with

resectionable NSCLC. Patients with positive lymph node (LN) metastasis have a high risk of disease recurrence and a poor prognosis; thus, LN status is one of the most important determinants.

The eighth edition of the TNM classification of NSCLC has been updated [2], with some modifications of the previous edition [3]. However, the LN stages are the same as those in the previous edition and is based solely on the anatomical location of LN involvement. A study from the Tokyo National Cancer Center Hospital proposed that nN category is a better prognostic determinant than the location-based pN stage classification [4]. In recent years, few studies have focused on this issue, while their results are generally inconsistent and inconclusive. As we all know, for certain other solid tumors, such as breast, gastric, and colorectal tumors, the number of metastatic lymph nodes has been included in the TNM staging system. Hence, we need to consider whether the current N staging has limitations.

In this study, we retrospectively evaluated the association between the number of PLN and the prognosis of patients with resected stage IA–IIIB NSCLC and compared the hypothesized TNM staging system with the current TNM stage classification.

Methods

Patient selection

The Surveillance Epidemiology and End Results database (SEER) was used to screen out appropriate patients with stage IA–IIIB NSCLC, according to the sixth edition of TNM staging system. SEER is supported by the Surveillance Research Program, which provides national leadership in the science of cancer surveillance as well as analytical tools and methodological expertise in collecting, analyzing, interpreting, and disseminating reliable population-based statistics [5]. SEER*Stat 8.3.5 software was used to screen stage IA-IIIB NSCLC patients diagnosed between 2004 and 2010. Patients included also met the following criteria: diagnosed as IA–IIIB NSCLC with surgical resection that was microscopically confirmed; at least 10 LNs removed; only one primary tumor; and without distant metastasis. Variables including age, race, sex, N stage should be clearly available. In addition, patients diagnosed prior to 2004 were excluded due to undetailed staging.

Statistical analysis

The baseline characteristics of the patients were compared using a Chi-square test. We choose overall survival (OS) and lung cancer-specific survival (LCSS) as the main end points. Survival curves were generated using the Kaplan–Meier method, and differences on survival among subgroups were examined using the log-rank test. The X-tile model was applied to determine the cutoff values for the number of PLN. The influence of different variables on OS and LCSS was further evaluated using univariate and multivariate Cox proportional hazard models. All statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). All p values were 2-sided and $p < 0.05$ was considered statistically significant.

Ethics statement

Personal identification information is not included in the SEER database, so informed consent was not required. This study was approved by the ethics committee of the Shandong Cancer Hospital affiliated to Shandong University.

Results

Patient demographics

According to the study exclusion and inclusion criteria, data from a total of 7,568 stage IA–IIIB NSCLC patients were included in the study. The 7,568 patients consisted of 4,034 men and 3,534 women and were divided into two groups at 65 years old (< 65: 40.7%, $n = 1{,}434$; ≥ 65: 50.7%, $n = 4{,}490$). Most patients were of a white racial background (85.8%, $n = 6{,}490$). Adenocarcinoma was found in 58.1% ($n = 4{,}399$) of the patients, while the other patients had a histological type of squamous cell carcinoma (41.9%, $n = 3{,}169$). A large portion of the patients were at an early T stage. According to sixth TNM staging system, the proportion of patients at T1, T2, T3 and T4 stages was 33.7% ($n = 2{,}548$), 50.9% ($n = 3{,}855$), 6.9% ($n = 522$) and 8.5% ($n = 643$), respectively. In addition, the proportion of patients at pN0, pN1, pN2 and pN3 stages was 61.4% ($n = 4{,}645$), 21.9% ($n = 1{,}658$), 16.3% ($n = 1{,}237$), and 0.9% ($n = 28$), respectively. Overall, 61.4% of patients had no positive LNs and 38.6% of patients had more than one positive LN. Detailed patient data are presented in Table 1.

Current issues of TNM staging system

The TNM stages of the patients included were classified according to the sixth edition TNM staging system based on surgical pathology. The Kaplan–Meier survival curve analysis showed that the OS survival curve of stage IIIA was close to that of stage IIIB. There was no statistically significant difference between the two groups ($p = 0.479$) (Fig. 1a). We found similar results for LCSS. As Fig. 1b shows, patients

Table 1 Characteristics of NSCLC with AJCC stage IA–IIIB extracted from SEER database

Variables	Numbers	(%)
Age		
< 65	3078	40.7
≥ 65	4490	59.3
Race		
White	6490	85.8
Black	585	7.7
Others	493	6.5
Sex		
Female	3534	46.7
Male	4034	53.3
Histology		
Adenocarcinoma	4399	58.1
Squamous	3169	41.9
T stage		
T1	2548	33.7
T2	3855	50.9
T3	522	6.9
T4	643	8.5
pN stage		
pN0	4645	61.4
pN1	1658	21.9
pN2	1237	16.3
pN3	28	0.4

NSCLC non-small cell lung cancer, *AJCC* American Joint Committee on Cancer, *SEER* Surveillance, Epidemiology and End Results

with stage IIIB had a better prognosis than patients with stage IIIA, although no statistical significance was observed ($p = 0.081$). Evidently from a survival prognosis perspective, the TNM staging system is unreasonable and has limitations concerning the prognosis of NSCLC.

Cutoff values for PLN count based on survival

Next, we assumed that combining the TNM staging system with PLN count may have a powerful discriminative ability in discerning the prognosis of NSCLC. Then, the X-tile model was used to determine the cutoff values of nN. Based on the cutoff values of nN for OS, patients were classified into three nN categories: nN0, no LN metastasis; nN1–3, metastasis in one to three nodes; and nN4-, metastasis in four or more LNs (Fig. 2a). The cutoff values for LCSS were the same (Fig. 2b). 4,645 patients (61.38%) were categorized as stage nN0, 1,897 patients (25.07%) were categorized as stage nN1–3 and 1,026 patients (13.56%) were categorized as stage nN4-.

PLN count and survival

The OS survival curves of each nN category are well distributed and proportional, and a clear tendency towards the deterioration of OS from nN0 to nN4- was observed. Moreover, there was a significant difference between nN categories (all, $p < 0.001$) (Fig. 3a). The LCSS survival curves showed similar results. Patients of stage nN0 had a better prognosis than patients of stage nN1–3 and stage nN4- (all, $p < 0.001$) (Fig. 3b).

To explore the prognostic value of nN on OS and LCSS based on the cutoff values of nN, we conducted a multivariable Cox regression analysis. The present study revealed that nN stage is an independent and significant prognostic factor of OS and LCSS for patients (for OS, nN1–3 vs. nN0, hazard ratio [HR] 1.639; 95% CI 1.529–1.756; nN4- vs. nN0, HR 2.283; 95% CI 2.102–2.479; all, $p < 0.001$; for LCSS, nN1–3 vs. nN0, HR 1.968; 95% CI 1.812–2.136; nN4- vs. nN0, HR 2.952; 95% CI 2.692–3.238; all, $p < 0.001$) (Table 2).

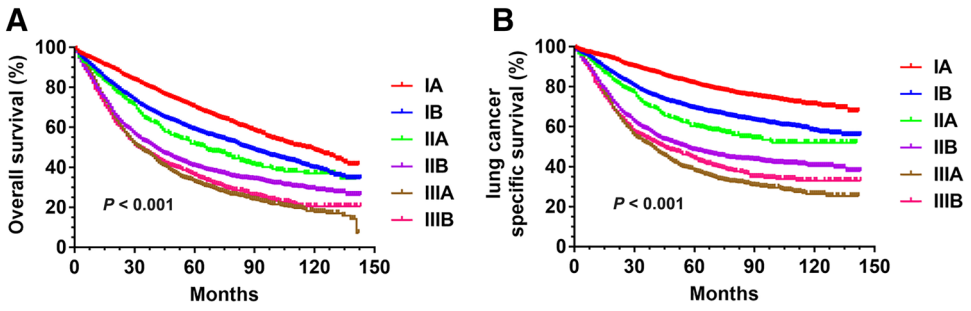

Fig. 1 The survival difference among different groups of the sixth TNM staging system. **a** OS differences between patients at stage IA–IIIB of the sixth TNM staging system. **b** LCSS differences between patients at stage IA–IIIB of the sixth TNM staging system. *TNM* tumor node metastasis, *OS* over survival, *LCSS* lung cancer-specific survival

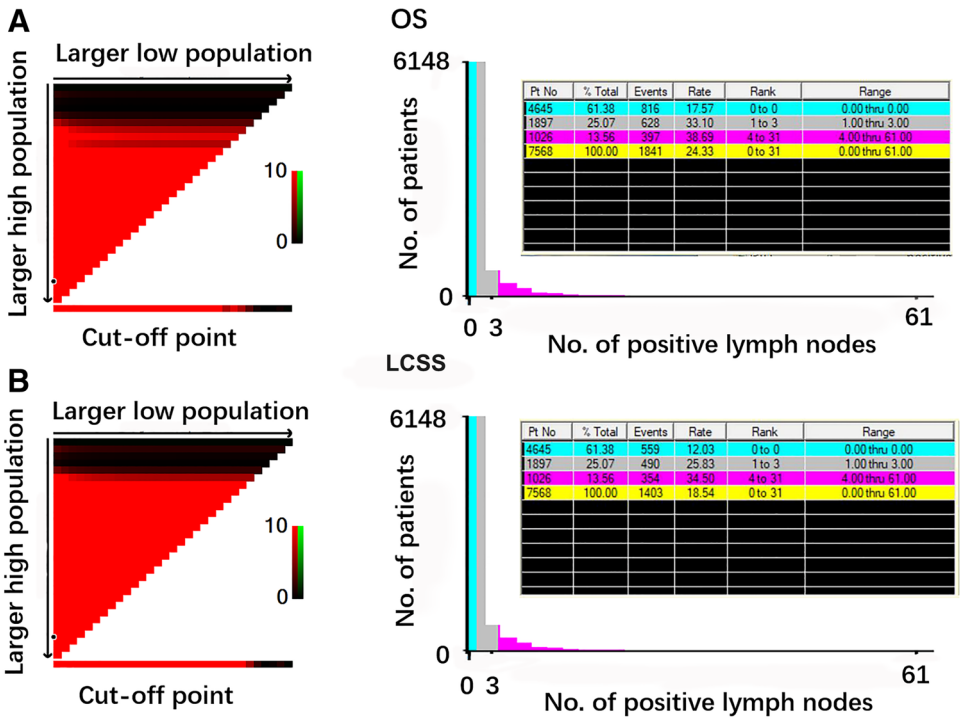

Fig. 2 The optimal threshold of PLN count for OS and LCSS as determined by the X-tile model. **a** (left) X-tile plots based on PLN count for OS. **a** (right): The optimal cut-off point is shown in blue (no. of PLN = 0), gray (no. of PLN 1 ≤ and ≤ 3) and violet (no. of PLN ≥ 4) panels. Information on patients with specific nN stages, blue panel: 4645 patients (61.38%) with nN0; gray panel: 1897 patients (25.07%) with nN1–3; violet panel: 1026 patients (13.56%) with nN4–61; yellow panel: a total of 7568 patients. **b** (left): X-tile plots based on PLN count for LCSS. **b** (right): The optimal cut-off point is shown by the blue (no. of PLN = 0), gray (no. of PLN 1 ≤ and ≤ 3) and violet (no. of PLN ≥ 4) panels. Information on patients with specific nN stages, blue panel: 4645 patients (61.38%) with nN0; gray panel: 1897 patients (25.07%) with nN1–3; violet panel: 1,026 patients (13.56%) with nN4–61; yellow panel: a total of 7568 patients. *PLN* positive lymph nodes, *OS* over survival, *LCSS* lung cancer-specific survival

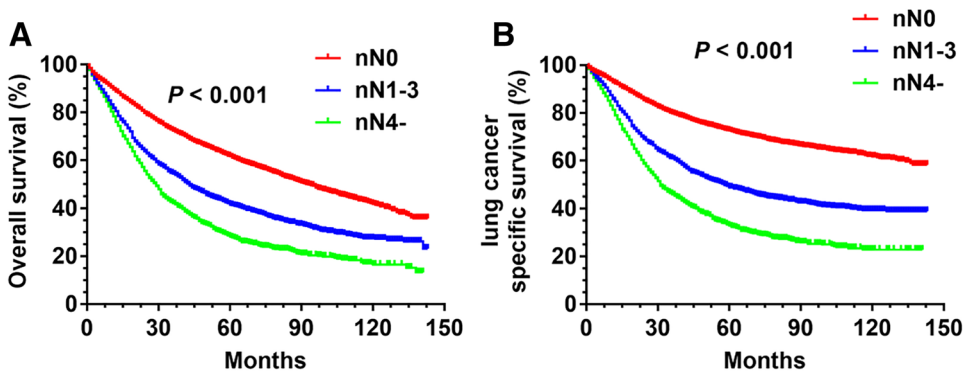

Fig. 3 Survival differences among different groups based on nN status. **a** OS differences among the patients of nN0 to nN4- (all, $p < 0.001$). **b** LCSS differences among patients of nN0 to nN4- (all, $p < 0.001$). *OS* overall survival, *LCSS* lung cancer-specific survival

Prediction of OS and LCSS of hypothesized stage IIIA and IIIB

Combining pN stage with nN stage, we classified the patients into the following categories, according to sixth TNM staging system: pT3N1 (1–3), pT3N1 (4-), pT1N2 (1–3), pT1N2 (4-), pT2N2 (1–3), pT2N2 (4-), pT3N2 (1–3), pT3N2 (4-), pT4N0 (0), pT4N1 (1–3), pT4N1 (4-), pT4N2 (1–3) and pT4N2 (4-) (4A-4B). The study showed that the 5-year OS of stage IIIB categories, such as pT4N0M0 and pT4N2 (1–3) M0, was better than that of most stage IIIA categories (Fig. 4a). The 5-year LCSS of stage IIIB categories, such as pT4N0M0 and pT4N2 (1–3) M0, were also better than that of most categories of stage IIIA (Fig. 4b). The Kaplan–Meier survival curve analysis showed that the partial OS survival curve of stage IIIB patients was better than that of patients of stage IIIA.

Table 2 The effect of different subgroup variables on OS and LCSS for NSCLC with AJCC stage IA–IIIB analyzed using a Cox proportional hazard model

Variables	Multivariate analysis (OS)		Multivariate analysis (LCSS)	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age		< 0.001		< 0.001
< 65	Reference		Reference	
≥ 65	1.593 (1.496–1.696)	< 0.001	1.372 (1.276–1.476)	< 0.001
Race		0.002		
White	Reference		Not included	
Black	1.051 (0.937–1.178)	0.394		
Others	0.806 (0.710–0.915)	0.001		
Sex		< 0.001		< 0.001
Female	Reference		Reference	
Male	1.307 (1.229–1.390)	< 0.001	1.232 (1.148–1.323)	< 0.001
Histology		< 0.001		
Squamous	Reference		Not included	
Adenocarcinoma	0.867 (0.815–0.922)	< 0.001		
pT stage		< 0.001		< 0.001
pT1	Reference		Reference	
pT2	1.297 (1.208–1.392)	< 0.001	1.525 (1.397–1.664)	< 0.001
pT3	1.861 (1.654–2.094)	< 0.001	2.453 (2.144–2.807)	< 0.001
pT4	1.830 (1.642–2.039)	< 0.001	2.153 (1.895–2.446)	< 0.001
nN stage		< 0.001		< 0.001
pN0	Reference		Reference	
pN1–3	1.639 (1.529–1.756)	< 0.001	1.968 (1.812–2.136)	< 0.001
pN4-	2.283 (2.102–2.479)	< 0.001	2.952 (2.692–3.238)	< 0.001

OS overall survival, *LCSS* lung cancer-specific survival, *NSCLC* non-small cell lung cancer, *AJCC* American Joint Committee on Cancer

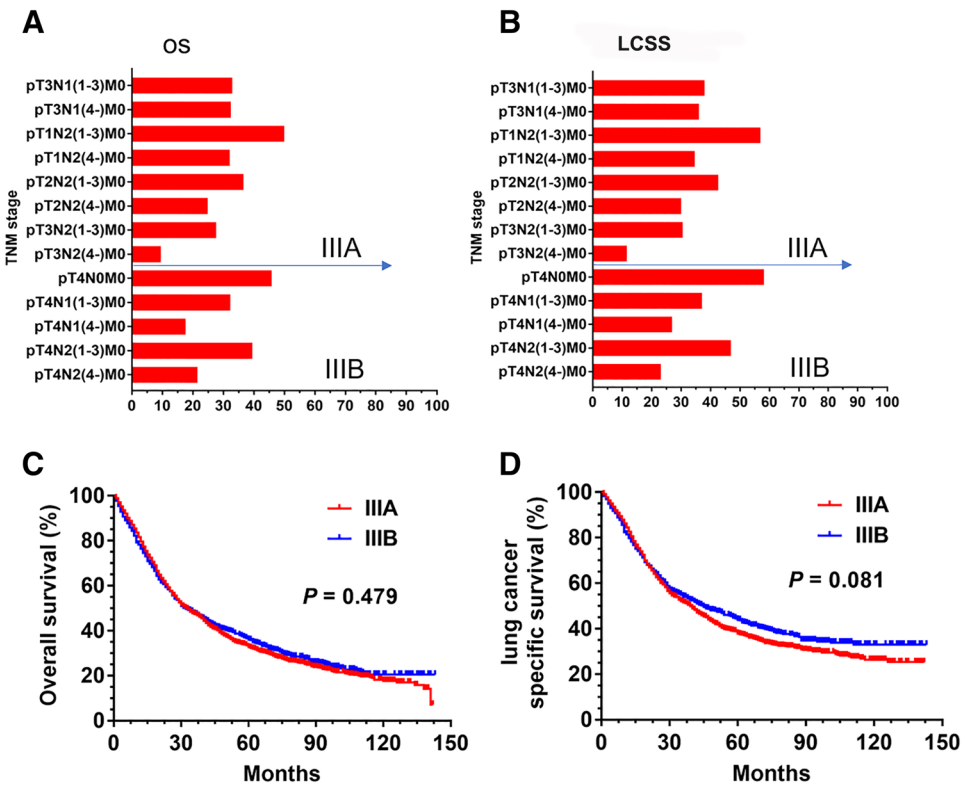

Fig. 4 Survival difference between IIIA and IIIB according to sixth TNM staging system. **a** The OS of IIIA-IIIB in the sixth TNM staging system combined with nN; **b** the LCSS of IIIA–IIIB in the sixth TNM staging system combined with nN. **c** The OS survival curves of stage IIIA–IIIB in the sixth TNM staging system ($p = 0.479$). **d** The LCSS survival curves of stage IIIA–IIIB in the sixth TNM staging system ($p = 0.081$). *TNM* tumor-node-metastasis, *OS* over survival, *LCSS* lung cancer-specific survival

There was no statistically significant difference between the two groups ($p = 0.479$) (Fig. 4c). For 5-year LCSS, patients of stage IIIB had a better prognosis than patients of stage IIIA. However, no statistical significance was observed ($p = 0.081$) (Fig. 4d).

According to the length of OS for the different patient stages, we adjusted the sixth TNM stages and obtained a hypothesized stage III. Based on the number of lymph nodes, we categorized groups pT4N0 (0), pT4N1 (1–3) and pT4N2 (1–3), with good prognosis, into a hypothesized stage IIIA, while groups pT2N2 (4-), pT3N2 (1–3) and pT3N2 (4-), with poor prognosis, were categorized into a hypothesized stage IIIB (Fig. 5a, b). The survival difference between hypothesized stage IIIA and IIIB was examined using the log-rank test. Specifically, Kaplan–Meier curve analysis showed that patients with hypothesized stage IIIA had comparatively better OS ($p < 0.001$) (Fig. 5c) and better LCSS ($p < 0.001$) (Fig. 5d).

Discussion

Precise staging is the key for effective therapeutic scheduling and predicting prognosis of patients with NSCLC who show signs of LN metastasis. This study mainly discussed the limitations of the current TNM staging system based on anatomical location of lymph node in providing details on staging and prognosis of NSCLC and the rationality of combining it with LN count.

As is well known, LN status plays an important role in the precision of staging. The nodal status of the current TNM staging assesses tumor burden in the regional hilar and mediastinal nodes [6] and is defined as N0 (no nodal involvement), N1 (peribronchial, interlobar, hilar node involvement), N2 (ipsilateral mediastinal nodal involvement) and N3 (contralateral mediastinal, contralateral hilar or supraclavicular nodal involvement), depending on the location of the metastatic lymph nodes.

The number of resected LNs has been shown to be a prognostic factor for resected NSCLC [4, 7–9]. Ludwig and his associates recommend that an evaluation of nodal status should include anywhere between 11 and 16 LNs [10]. Saji showed that patients with > 14 nodes assessed demonstrate better survival prediction in both the upstaged and non-upstaged cohorts, compared with patients with fewer than 14 nodes, based on data from the national cancer database [11]. The Staging Manual of Thoracic Oncology of the International Association for the Study of Lung Cancer (IASLC) recommends that patients defined as pN0 need at least six LN stations to be removed or sampled and histologically confirmed to be free of disease [12]. Sajj et al. demonstrated that resection of 10 or more LNs influences survival and maintains the quality of surgery [7]. Therefore, for the present analysis, we excluded patients who had fewer than 10

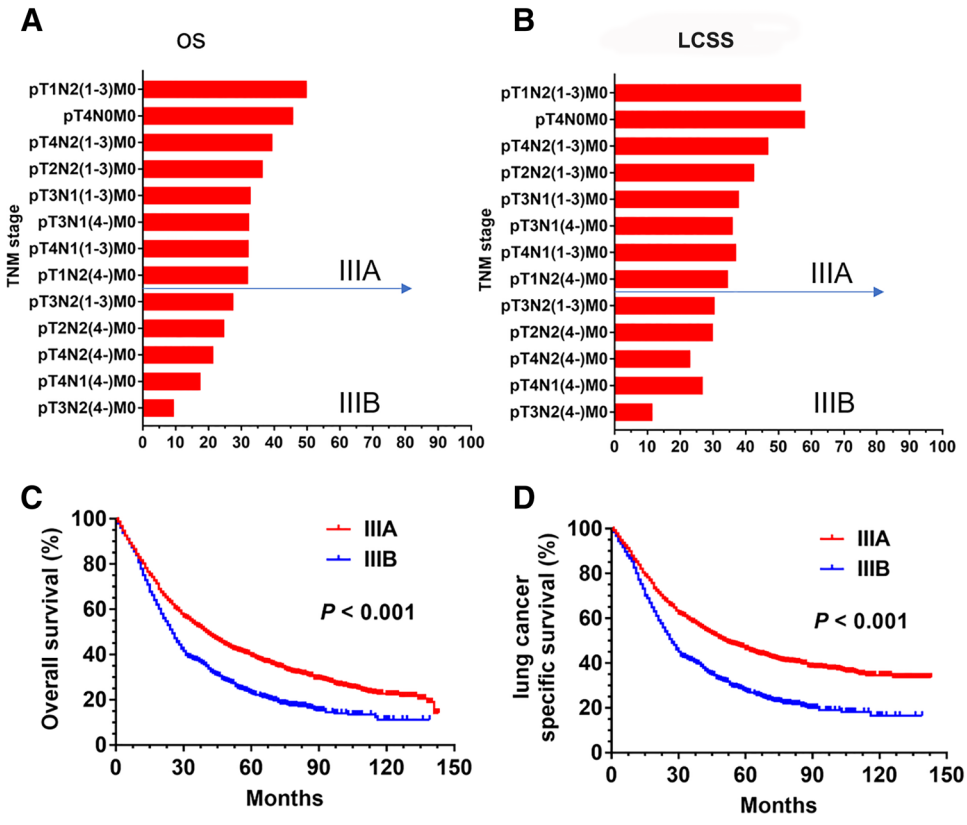

Fig. 5 Survival differences between hypothesized stage IIIA and IIIB. **a** OS of hypothesized stage IIIA–IIIB combined with nN; **b** LCSS of hypothesized stage IIIA–IIIB combined with nN. **c** OS difference between hypothesized stage IIIA and IIIB ($p < 0.001$). **d** LCSS difference between hypothesized stage IIIA and IIIB ($p < 0.001$). *OS* over survival, *LCSS* lung cancer-specific survival

lymph nodes examined. It is well known that T4 includes pleural or pericardial nodules or malignant pleural or pericardial effusion and belongs to M1a in the eighth edition of TNM staging. In this study, patients included in the study were diagnosed between 2004 and 2010. In January 2017, the eighth edition of the staging system was formally promulgated and implemented. Therefore, the patient staging in this study was based on the sixth edition of TNM staging. In addition, we are using SEER*Stat 8.3.5 software to screen suitable patients. Due to the limitations of the software, we are unable to obtain sufficient information to determine which part of T4 patients suffer from pleural or pericardial nodules or malignant pleura or pericardial effusion. Therefore, as long as more than 10 lymph nodes are removed, all T4 is included.

Many studies have indicated that anatomically based pN classification has some unsatisfactory aspects. Of these, the heterogeneity of pN1 and pN2 regarding prognosis is the most notable [8, 13–18]. Consistent with these results, our study has also shown that the 5-year OS and LCSS of stage IIIB categories, such as pT4N0M0 and pT4N2 (1–3) M0, are better than that of most categories of stage IIIA, with no statistical differences observed between the results for stage IIIA and IIIB. This is perhaps due to differences in T stage, combined with cardiovascular, cerebrovascular diseases or other serious diseases. These results reveal the irrationality of the sixth TNM staging system in predicting prognosis.

The number of positive LNs in early NSCLC has been proven to be a prognostic factor that influences survival, similar to that of colorectal, breast, and bladder cancer [19–24]. In solid tumors, such as that of breast, gastric, and colorectal tumors, the number of metastatic lymph nodes has been included in the TNM staging system. We wondered if improper LN staging had led to this unreasonable prognosis. Some oncologists have focused on this key clinical issue, but the issue remains controversial. A study from Tokyo National Cancer Center Hospital showed that the nN category is a better prognostic determinant than location-based pN stage classification [4]. Another single-center study performed in Tokyo has demonstrated that a combined anatomically based pN stage classification and numerically based nN stage classification are more of an accurate prognostic predictor for patients with NSCLC, especially for the prognostically heterogeneous pN1 and pN2 category cases [25]. Liang et al. showed that a greater number of ELNs are associated with more accurate node staging and better long-term survival of resected NSCLC patients [26]. However, there are no large sample studies that have been done to explore whether the nN category or the pN stage classification is a better prognostic prediction factor for lung cancer.

Fukui et al. showed that positive lymph node count is a strong independent prognostic factor for non-small cell lung cancer, when patients were divided into four groups based on their positive LN number (N0, N1–3, N4–6, N7-) [8]. In the present study, according to the cutoff values of nN calculated using the X-tile model, we divided patients into three groups (N0, N1–3 and N4-). Our study revealed that nN stage is an independent prognostic factor that affects patient OS and LCSS. These results imply that the current pN classification that is based only on the anatomical position of lymph nodes has poor discriminative ability with regard to the prognosis of patients with lymph node metastasis.

We categorized the groups pT4N0 (0), pT4N1 (1–3) and pT4N2 (1–3), with good prognosis, into the hypothesized stage IIIA, according to the number of lymph nodes, while groups pT2N2 (4-), pT3N2 (1–3) and pT3N2 (4-), with poor prognosis, were categorized into hypothesized stage IIIB. The patients with pT3N1 (4-) and pT1N2 (4-) were re-classified to stage IIIA. The Kaplan–Meier curve analysis showed that patients with hypothesized stage IIIA had better OS and LCSS than patients of hypothesized stage IIIB. This is reasonable. Our study shows that for stage III non-small cell lung, N staging combined with the number and anatomic location of positive lymph nodes may be more accurate than the staging based on localization alone. The prognosis of stage III non-small cell lung cancer was closely related to lymph node metastasis. The number of positive lymph nodes is not the only index to judge the prognosis of lung cancer. The anatomic location of positive lymph nodes and tumor size also have an impact on the prognosis. Based on the above factors, patients with pT3N1 (4-) and pT1N2 (4-) were not divided into IIIB stage but IIIA stage. Based on the finding in this study, pT4N0 (0), pT4N1 (1–3), and pT4N2 (1–3) with good prognosis in stage IIIB according to the sixth TNM staging system were attributed to the lower number of metastatic lymph nodes.

This study has several limitations that should be noted. First, we cannot avoid the impact of selection bias on some baseline variables of this retrospective study, despite the relatively rather large sample size. Second, the scope of this study involves only cases that received surgical treatment, because there is no effective examination to accurately assess the number of lymph nodes in patients who are not resected. Moreover, at least 10 LNs had to be removed for patient data to be included in the study. The hypothesized stages combined with PLN count may have limitations when being applied to patients with less than 10 LNs to be removed. Finally, the study explores the value of the number of positive lymph nodes in predicting prognosis of stage III NSCLC patients. Larger samples and further multiple institutional studies using identical protocols are needed to explore whether this method is suitable for other stages.

Conclusion

The current results demonstrate a new nodal classification system combining the pN (anatomical location) and nN (positive number) status of LN involvement for predicting the prognosis of stage III NSCLC patients, with increased accuracy than the categorization of stages based on location alone.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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