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Number of involved nodal stations: a better lymph node classification for clinical stage IA lung adenocarcinoma

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ABSTRACT

Background: With the popularization of lung cancer screening, more early-stage lung cancers are being detected. This study aims to compare three types of N classifications, including location-based N classification (pathologic nodal classification [pN]), the number of lymph node stations (nS)-based N classification (nS classification), and the combined approach proposed by the International Association for the Study of Lung Cancer (IASLC) which incorporates both pN and nS classification to determine if the nS classification is more appropriate for early-stage lung cancer.

Methods: We retrospectively reviewed the clinical data of lung cancer patients treated at the Cancer Hospital, Chinese Academy of Medical Sciences between 2005 and 2018. Inclusion criteria was clinical stage IA lung adenocarcinoma patients who underwent resection during this period. Sub-analyses were performed for the three types of N classifications. The optimal cutoff values for nS classification were determined with X-tile software. Kaplan–Meier and multivariate Cox analyses were performed to assess the prognostic significance of the different N classifications. The prediction performance among the three types of N classifications was compared using the concordance index (C-index) and decision curve analysis (DCA).

Results: Of the 669 patients evaluated, 534 had pathological stage N0 disease (79.8%), 82 had N1 disease (12.3%) and 53 had N2 disease (7.9%). Multivariate Cox analysis indicated that all three types of N classifications were independent prognostic factors for prognosis (all $P < 0.001$). However, the prognosis overlaps between pN (N1 and N2, $P = 0.052$) and IASLC-proposed N classification (N1b and N2a1 [$P = 0.407$], N2a1 and N2a2 [$P = 0.364$], and N2a2 and N2b [$P = 0.779$]), except for nS classification subgroups (nS0 and nS1 [$P < 0.001$] and nS1 and nS >1 [$P = 0.006$]). There was no significant difference in the C-index values between the three N classifications ($P = 0.370$). The DCA results demonstrated that the nS classification provided greater clinical utility.

Conclusion: The nS classification might be a better choice for nodal classification in clinical stage IA lung adenocarcinoma.

1. Introduction

Since the 1990s, the overall cancer mortality rate has declined, partly due to the decrease in lung cancer mortality rates.[1] The reasons for the better prognosis of lung cancer are largely due to the reduction in smoking, early detection, effective treatment modalities, and improved staging systems. The most commonly used lung cancer staging system is the TNM staging system. In the eighth edition of the TNM staging of lung cancer, the pathologic nodal classification (pN) is still based on the location of metastatic lymph nodes.

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Nodal involvement affects patient prognosis and the formulation of postoperative treatment plans. The 5-year survival rates for patients with lung cancer are 75%, 49%, 36%, and 20% for N0, N1, N2, and N3 patients, respectively.[2] However, with the widespread application of this N-staging system in clinical practice, deficiencies of this system have become increasingly apparent, such as failure to reflect the heterogeneity of lymph node involvement within the same N category, including factors such as the number and location of involved nodes.[3] Studies have found that even with the same N stage, the prognosis of patients is inconsistent; in particular, the prognosis of skip N2 metastasis is better than that of nonskip N2 metastasis.[4-6] Researchers have proposed other N classifications, such as the number of metastatic lymph nodes, the ratio of metastatic lymph nodes to the total number of resected lymph nodes, or the log odds,[7-9] but these methods have not been validated in large populations. The International Association for the Study of Lung Cancer (IASLC) proposed a new N classification based on the location of metastatic lymph nodes and the number of involved stations (nS) .[2] Although there was no significant difference in survival between pN1b and pN2a1 or between pN1b and pN2a2 patients, the combined location and nS based N classification revealed potential benefits in predicting prognosis.[10,11] Additionally, *Xu et al*[12] found that nS classification tends to have greater predictive capability than location-based N classification.

With the popularization of lung cancer screening and the impact of the new coronavirus epidemic, an increasing number of early-stage lung cancers have been detected.[13,14] Therefore, it is necessary to verify whether the nS classification is more suitable for early-stage lung cancer. In this study, we aimed to assess the discriminatory ability and prognostic performance of three N classifications: the location-based N classification (pN classification), the nS classification, and the IASLC-proposed N classification that combines location and nS in clinical stage IA lung adenocarcinoma.

2. Materials and methods

2.1. Study participants

We retrospectively reviewed the clinical data of lung cancer patients treated at the Cancer Hospital, Chinese Academy of Medical Sciences between 2005 and 2018. Inclusion criteria was clinical stage IA lung adenocarcinoma patients who underwent resection during this period. Exclusion criteria were as follows: no enhanced high-resolution computed tomography (HRCT) image or positron emission tomography (PET)-CT within two weeks before surgical resection, clinical stage more advanced than IA, unavailable clinicopathologic data, preoperative therapy (e.g., radiotherapy, chemotherapy, target therapy), previous malignancy with evidence of disease within 5 years, fewer than six resected lymph nodes, and a follow-up of less than 6 months without metastasis or death. In total, 669 cases were included in the analysis.

2.2. N classification

Nodal classification was described by the following three methods: (1) pN (N0, N1, N2); (2) IASLC-proposed N (N0, N1a, N1b, N2a1, N2a2, N2b); and (3) nS (nS0, nS1, nS2, nS3, nS4, nS5, nS6, nS7, nS8).

2.3. Clinicopathological characteristics

For our analysis, clinical characteristics including age, sex, and surgical procedure (sublobar resection and lobectomy), CT features including nodule consistency, boundaries, sharpness, deep lobulation and necrosis, and treatment (surgery alone, or adjuvant chemoradiotherapy plus surgery) were evaluated. Tumors were classified in accordance with the 2011 IASLC/American Thoracic Society/European Respiratory Society classification and the 2021 WHO classification.[15,16] We defined adenocarcinoma with a size of 1 cm or less in diameter as small adenocarcinoma.[17] Tumors were divided into two groups according to histological subtype: lepidic adenocarcinoma (including precursor glandular lesions, minimally invasive adenocarcinoma, lepidic predominant invasive adenocarcinoma [IAC]) and nonlepidic adenocarcinoma (including acinar predominant IAC, papillary predominant IAC, micropapillary predominant IAC, solid predominant with mucin production IAC, variants of predominant IAC and invasive mucinous adenocarcinoma).[18]

2.4. Follow-up strategy

All patients who underwent sublobar resection or lobectomy were followed-up from the day after surgery. Postoperative follow-up procedures consisted of physical examination, chest radiography every 3 months, and chest CT scans every 6 months for the first 2 years after surgery. Thereafter, chest radiography was performed every 6 months, and chest CT examination was performed annually. The median follow-up period was 62 months. Survival outcomes and disease progression were obtained by reviewing the medical records and through telephone interviews by trained staff members. If a patient or family member could not be reached on the follow-up date, the date and survival information were excluded on the date of the last follow-up. Disease-free survival (DFS) was selected as the endpoint. DFS was defined as the time from surgery to the date of metastasis or recurrence.

2.5. Statistical analyses

The frequency distribution and descriptive statistics were determined for all variables. Data were expressed as the mean ± standard deviation when normally distributed or as the median (interquartile range, IQR) when the normality assumptions were not met. Optimal cutoff values for nS classification were determined using X-tile software (version 3.6.1; Rimm Lab, New Haven, CT).[19] The Kaplan–Meier method and log-rank test were used to compare prognostic differences among subgroups, and multivariate Cox regression was used to evaluate the association between each classification and survival outcomes with an adjustment for potential prognostic factors. The concordance index (C-index) was used to determine the clinical practical value of the prediction models by quantifying the three types of N classifications. The Kruskal-Wallis test was used to compare the C-index values among the three N classifications, and the Dunn-Holm–Sidak test was used for pairwise comparisons. Decision curve analysis (DCA) was performed to evaluate the clinical utility of the three N classifications by calculating net benefits at different threshold probabilities. Statistical analyses were performed by SPSS software (version 25; IBM, Armonk, NY) and R software (version 4.1.1; The R Foundation for Statistical Computing, Vienna, Austria), and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinicopathological characteristics

Of 2,077 patients identified with clinical stage IA lung adenocarcinoma, 669 met the inclusion criteria (1,048 were excluded) (Fig. 1). The median age was 58 years (IQR: 50–64), 412 patients (61.6%) were female, and 257 (38.4%) were male. The median follow-up period was 62 months (IQR: 55–72). The primary tumor was mainly located in the right upper lobe (n = 235, 35.1%), followed by the left upper lobe (n = 175, 26.2%), right lower lobe (n = 115, 17.2), left lower lobe (n = 89, 13.3%), and right middle lobe (n = 55, 8.2%). The pathological subtype of lung adenocarcinoma was precursor glandular lesions in 64 (9.6%) patients and IAC in 605 (90.4%) patients. The median tumor size was 1.5 cm (IQR: 1.0–2.0). Lobectomy was performed in 575 (85.9%) patients, and sublobar resection was performed in 94 (14.1%) patients. After surgery, 124 (18.5%) patients received adjuvant therapy. Most patients had pathological stage N0 disease (n = 534, 79.8%), followed by N1 (n = 82, 12.3%) and N2 (n = 53, 7.9%) diseases. The median number of resected lymph nodes was 14 (IQR: 10–20) (Table 1).

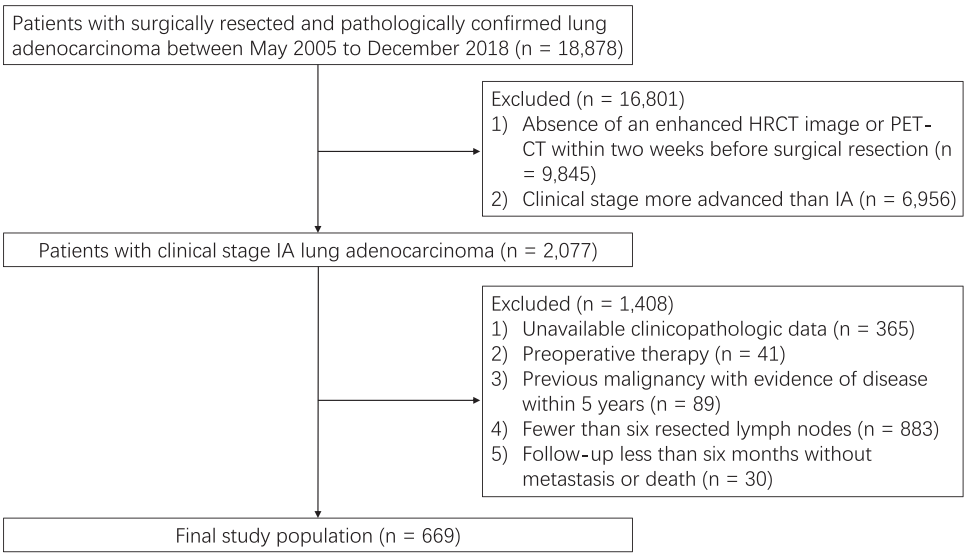

Fig. 1. Flowchart of the patient selection process in the study. HRCT, high-resolution computed tomography; PET-CT, positron emission tomography-computed tomography.

According to the IASLC-proposed N classification, 534 (79.8%) patients were classified as having N0 disease, 61 (9.1%) patients as N1a, 21 (3.1%) patients as N1b, 15 (2.2%) patients as N2a1, 23 (3.4%) patients as N2a2, and 15 (2.2%) patients as N2b.

The nS ranged from 0 to 8. The optimal cutoff value of the nS classification system for survival was 1 based on patients with lymph node metastasis, which was calculated by X-tile software (Supplementary Fig. 1). Patients were classified into three categories: (1) nS0 (n = 534 [79.8%]), no metastasis; (2) nS1 (n = 73 [10.9%]), metastasis in one nodal station; and (3) nS > 1 (n = 62 [9.3%]), metastasis in two or more nodal stations.

3.2. Survival analysis based on different N classifications

In the multivariate analyses, pN, IASLC-proposed N, and nS classifications were independent risk factors for DFS (Supplementary Tables 1–3). The five-year DFS rates were 98.0%, 51.0%, and 47.0% for N0, N1 and N2 patients, respectively (Table 2). After adjustment for potential prognostic factors, the result showed that the DFS between patients with N0 and N1 disease was significantly different (P < 0.001). However, the DFS for patients with N2 disease was not statistically distinguishable from that of patients with N1 disease (P = 0.052) (Table 3, Fig. 2).

The five-year DFS rates were 98.0%, 55.0%, 40.0%, 58.0%, 44.0% and 40.0% for N0, N1a, N1b, N2a1, N2a2, and N2b patients, respectively (Table 2). The adjusted multivariate analysis comparing the two adjacent stages of the IASLC-proposed N classification showed that the prognosis after surgery differed between patients with N0 disease and those with N1a disease (P = 0.001), as well as between patients with N1a and N1b disease (P = 0.042). There was no statistically significant difference in DFS between N1b and N2a1 (P = 0.407), N2a1 and N2a2 (P = 0.364), and N2a2 and N2b (P = 0.779) (Table 3, Fig. 3).

When categorized based on nS, the 5-year DFS rates were 98.0%, 56.0%, and 43.0% for the nS0, nS1, and nS > 1 categories, respectively (Table 2). After adjusted for sex, adjuvant therapy, size and pathological subtype, multivariate analysis showed that the DFS between patients with nS0 and nS1 disease (P < 0.001), as well as between patients with nS1 and nS > 1 disease (P = 0.006), was significantly different (Table 3, Fig. 4).

3.3. Comparison of predictive capability between pN, IASLC-proposed N, and nS classifications

The C-index was 0.926 (95% confidence interval [CI], 0.929–0.941) for the pN classification, 0.929 (95% CI, 0.907–0.944) for the IASLC-

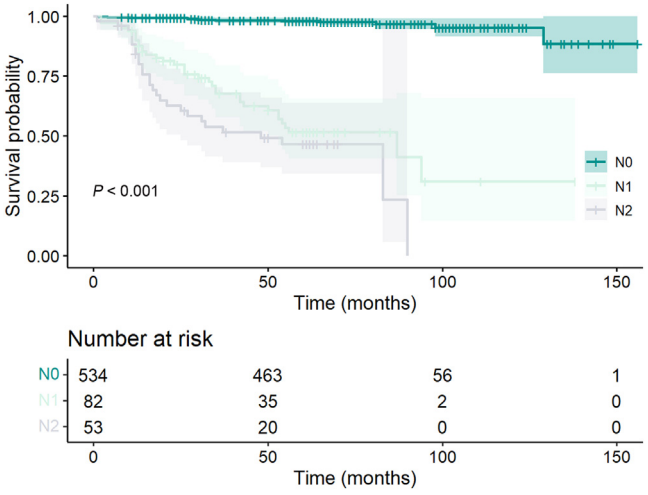

Fig. 2. Disease free survival of patients with N0, N1, and N2 disease according to pathologic nodal classification.

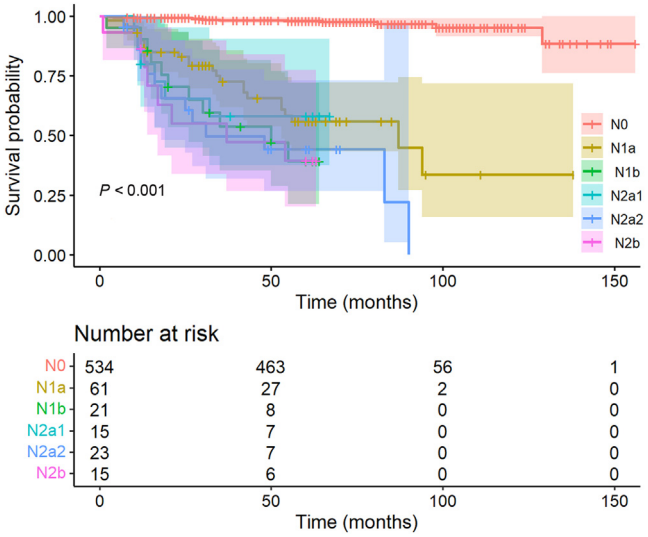

Fig. 3. Disease free survival of patients with N0, N1a, N1b, N2a1, N2a2, and N2b disease according to IASLC-proposed N classification.

Table 1
Clinical and pathological characteristics of patients (n = 669).

Characteristics	No. of patients (%)[a]
Sex	
Male	257 (38.4)
Female	412 (61.6)
Age (IQR), years	58 (50–64)
Nodule consistency	
pGGN	121 (18.1)
PSN	380 (56.8)
SN	168 (25.1)
Boundary of tumor	
Clear	623 (93.1)
Fuzzy	46 (6.9)
Deep lobulation	
Absent	597 (89.2)
Present	72 (10.8)
Necrosis	
Absent	595 (88.9)
Present	74 (11.1)
Sharpness	
Absent	459 (68.6)
Present	210 (31.4)
Location of tumor	
Right upper lobe	235 (35.1)
Right middle lobe	55 (8.2)
Right lower lobe	115 (17.2)
Left upper lobe	175 (26.2)
Left lower lobe	89 (13.3)
Surgical procedure	
Sublobectomy	94 (14.1)
Lobectomy	575 (85.9)
Treatment	
Surgery alone	545 (81.5)
Surgery plus adjuvant therapy	124 (18.5)
Diameter of tumor (IQR), cm	1.5 (1.0–2.0)
Tumor stage[b]	
T1	65 (9.7)
T1a	182 (27.2)
T1b	198 (29.6)
T1c	93 (13.9)
T2a	131 (19.6)
Nodal stage[b]	
N0	534 (79.8)
N1	82 (12.3)
N2	53 (7.9)
Pathological stage[b]	
0 or Tis	65 (9.7)
IA1	180 (26.9)
IA2	155 (23.2)
IA3	49 (7.3)
IB	85 (12.7)
IIB	82 (12.3)
IIIA	53 (7.9)
Pathological subtype	
Procursor glandular lesions	64 (9.6)
Invasive adenocarcima	605 (90.4)
No. of resected lymph nodes (IQR)	14 (10–20)
IASLC-proposed N classifications	
0	534 (79.8)
N1a	61 (9.1)
N1b	21 (3.1)
N2a1	15 (2.2)
N2a2	23 (3.4)
N2b	15 (2.2)
nS classification	
nS0	534 (79.8)
nS1	73 (10.9)
nS > 1	62 (9.3)

[a] Unless otherwise indicated, data in parenthess are percentages.
[b] 8th staging classification of International Association for the Study of Lung Cancer.
Abbreviations: IASLC, the International Association for the Study of Lung Cancer; IQR, interquartile range; nS, the number of lymph node stations; pGGN, pure ground glass nodule; PSN, part solid nodule; SN, solid nodule.

Table 2
Prognosis of all lung cancer patients by stage under pN, IASLC-proposed N, and nS classifications in this study (n = 669).

Stage	Event rate (n/N)[a]	MST, month	5-year DFS, %
pN classification			
N0	13/534	150	98
N1	35/82	81	51
N2	27/53	47	47
IASLC-proposed N classification			
N0	13/534	150	98
N1a	24/61	86	55
N1b	11/21	52	40
N2a1	6/15	60	58
N2a2	13/23	39	44
N2b	8/15	38	40
nS classification			
nS0	13/534	150	98
nS1	29/73	86	56
nS > 1	33/62	49	43

[a] Event rate (n/N) is the proportion of patients who experienced recurrence or metastasis, where n is the number of events and N is the total number of patients.
Abbreviations: No., number; MST, median survival time; DFS, disease free survival; IASLC, the International Association for the Study of Lung Cancer; nS, number of lymph node stations; pN, pathologic nodal classification.

Table 3
Cox analyses of disease-free survival for all patients under pN, IASLC-proposed N, and nS classifications (n = 669).

Comparasion	HR	P values[a]
pN classification		
N0 vs N1	0.125	< 0.001
N1 vs N2	0.604	0.052
IASLC-proposed N classification		
N0 vs N1a	0.250	0.001
N1a vs N1b	0.470	0.042
N1b vs N2a1	1.525	0.407
N2a1 vs N2a2	0.637	0.364
N2a2 vs N2b	0.881	0.779
nS classification		
nS1 vs nS0	0.116	< 0.001
nS1 vs nS > 1	0.489	0.006

[a] Ajusted P value of < 0.025 was considered statistically significant based on Bonferroni correction.
Abbreviations: pN, pathologic nodal classification; IASLC, the International Association for the Study of Lung Cancer; nS, the number of lymph node stations; HR, hazard ratio; P, probability.

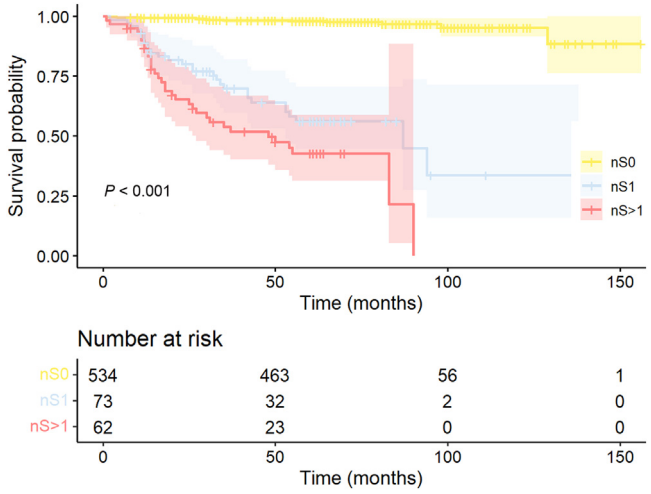

Fig. 4. Disease free survival of patients with nS0, nS1, and nS > 1 disease according to the nS classification. nS, the number of lymph node stations.

Table 4
Comparison of N classifications using C-index and confidence intervals ($n = 669$).

	C-index (95% CI)	*P* value[a]	*P'* value[b]
pN vs IASL-proposed N classification	0.926 (0.905–0.941)	0.370	0.218
IASLC-proposed N classification vs nS	0.929 (0.907–0.944)		0.422
nS vs pN	0.928 (0.906–0.942)		0.240

[a] *P* value among three groups by Kruskal–Wallis test.
[b] *P'* values by Dunn Holm–Sidak test between.
Abbreviations: CI, confidence interval; IASLC, the International Association for the Study of Lung Cancer; nS, the number of lymph node stations; pN, pathologic nodal classification.

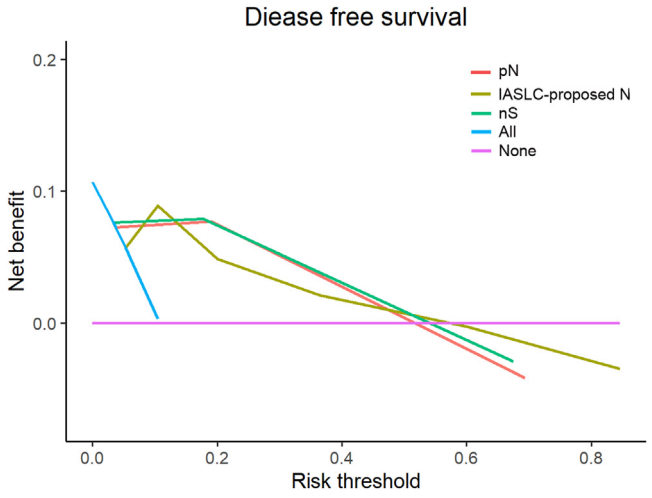

Fig. 5. Decision curve analysis for pN, IASLC-proposed N, and nS classification. IASLC, the International Association for the Study of Lung Cancer; nS, the number of lymph node stations; pN, pathologic nodal classification.

proposed N classification, and 0.928 (95% CI, 0.906–0.942) for the nS classification. The C-index among the three N classifications showed no statistically significant difference ($P = 0.370$), and there was also no statistically significant difference found in pairwise comparisons between the models (all $P > 0.005$) (Table 4). The DCA demonstrated that the nS classification provided a larger standardized net benefit for survival prediction compared with the IASLC-proposed N classification for DFS (Fig. 5).

Since only one patient had metastasis in the small adenocarcinoma group, we validated the survival impact of various N classifications in the non-small adenocarcinoma group ($n = 445$, Supplementary Table 4). The prognostic differences were statistically significant for DFS between N0 and N1 disease ($P < 0.001$), N0 and N1a disease ($P < 0.001$), nS0 and nS1 disease ($P < 0.001$), and nS1 and nS > 1 disease ($P = 0.024$). In contrast, no significant differences in DFS were observed between patients with N1 and N2 disease ($P = 0.183$), N1a and N1b disease ($P = 0.058$), N1b and N2a1 disease ($P = 0.380$), N2a1 and N2a2 disease ($P = 0.537$), and N2a2 and N2b disease ($P = 0.846$) in the non-small adenocarcinoma group (Supplementary Figs. 2–4).

4. Discussion

Our study compared the prognostic significance of pN, IASLC-proposed N, and nS classifications and found that they were all independent prognostic factors for patients with clinical stage IA adenocarcinoma. As the adjacent subcategories of the pN and IASLC-proposed N classifications overlap, they were unsatisfactory for distinguishing the prognosis of different groups, while nS can significantly distinguish different groups in terms of prognosis. Although there was no significant difference in their predictive accuracy as measured by the C-index and confidence intervals, DCA suggested that nS classification had better clinical benefit. Therefore, nS classification might be a better choice for nodal classification in clinical stage IA lung adenocarcinoma.

pN is very convenient to use in clinical practice. However, this staging evaluates lymph nodes simply by the location of lymph node metastasis and cannot explain the inconsistent prognosis of different patients under the same N staging. In our results, there was no difference in the 5-year DFS between patients with N1 or N2 disease (51.0% and 47.0%, respectively, $P = 0.052$). Studies have found that the number of involved lymph nodes, which represents tumor burden, has more important impact on prognosis than location.[20-22] However, this classification has a huge flaw. How many lymph nodes should be resected during complete lymph node dissection is not standardized. It has been proposed by the Council of the European Society of Thoracic Surgery that at least 6 lymph nodes should be removed,[23] whereas other studies recommend that at least 10 lymph nodes should be resected.[24,25] The number of lymph nodes removed varies widely among lung cancer patients,[26] which means that the number of metastatic lymph nodes dissected may also vary widely.

The overlapping prognosis of patients with different IASLC-proposed N stages have been extensively studied.[2,10,12,27] We also found a similar problem for clinical stage IA lung adenocarcinoma. *Xu et al*[12] suggested that one possible reason for this discrepancy could be attributed to variations in the lymph node map used for lung cancer staging among different countries or institutions. In addition, this classification is cumbersome and may not be suitable for extensive clinical work.

Studies have found that nS staging displays good performance in accurate prognostic stratification,[12,28-30] which is consistent with our results. These studies involved patients with non-small cell lung cancer of all stages, and our study specifically focused on patients diagnosed with clinical stage IA lung adenocarcinoma. This difference in patient selection is an essential distinction that significantly influenced the results of our study. Our study narrowed the focus to provide a more comprehensive and detailed understanding of the disease at this crucial stage of its progression.

In our study, we found that the nS classification outperformed the pN and IASLC-proposed N classifications in distinguishing adjacent categories and providing more favorable clinical benefits. Although the C-index values of the nS and IASLC-proposed N classifications were not significantly different ($P = 0.422$), it should be noted that the IASLC-proposed N classification had the highest C-index among the three classifications. Thus, it may still be a useful tool for clinical purposes, but it is less effective for clinical stage IA adenocarcinoma due to the relatively low lymph node metastasis rate. Moreover, the location of lymph node stations is a crucial factor in determining the extent of lymph node dissection. Further research is necessary to explore how to effectively incorporate the location of lymph node stations into the nS-based N classification.

There are several limitations in our study. First, this is a single-center retrospective study, and many patients were excluded due to the absence of CT and/or PET-CT images before surgery. Multicenter prospective studies are needed to validate the results. Second, this study concentrated on early-stage lung adenocarcinoma due to the increasing detection of lung adenocarcinoma, and other histological subtypes of non-small cell lung cancer need to be further studied.

5. Conclusions

In summary, our results indicate that the nS classification might be more suitable for nodal classification in clinical stage IA lung adenocarcinoma. However, further research is needed to determine how to effectively incorporate the location of lymph node stations into the nS classification.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Ethics statement

This retrospective study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board Committee of Cancer Hospital Chinese Academy of Medical Sciences (approval number: NCC2022C-693), and the requirement for informed consent was waived given its retrospective nature.

Acknowledgments

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Author contribution

M.L. and L.Z. conceived the presented idea and designed the work. L.M., R.Z., L.Z., S.Y., J.L. and C.L. conducted the data collection. M.L. and X.L. performed the data analysis and interpretation. M.L. drafted the article. M.L. and L.Z. jointly supervised the study. All authors discussed the results and contributed to the final manuscript.

Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.07.001.

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