Review Article

Alternative methods of lymph node staging in lung cancer: a narrative review

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Abstract: The nodal status indicator in non-small cell lung cancer is one of the most crucial prognostic factors available. However, there are still many arguments among scientists regarding whether the currently used nodal status descriptor should be changed in the forthcoming editions of the Tumor Node Metastasis classification or whether it is precise enough and should be maintained as is. We reviewed studies concerning nodal factor classifications to evaluate their accuracy in non-small cell lung cancer patients and to address the previously mentioned challenge. We reviewed the PubMed database regarding the following classifications: ongoing 8th edition of the Tumor Node Metastasis classification, number of positive lymph nodes, number of negative lymph nodes, number of dissected lymph nodes, lymph node ratio, nodal chains, log odds of positive lymph nodes, zone-based classification and one that is based on the number of lymph node stations involved. Moreover, we analysed data regarding various combinations of these classifications. Our analysis showed that the present nodal staging may not accurately categorize every lung cancer patient. The number of positive lymph nodes and lymph node ratio or the log odds of positive lymph nodes (as the mathematical modification of lymph node ratio) are more legitimate, as they possess very robust data and should be considered initially as additional factors that can be incorporated in ongoing nodal staging systems. Forthcoming non-small cell lung cancer staging systems could benefit from the addition of quantitative-based parameters. Additionally, the minimal extent of lymphadenectomy should be established as staging benefits from it. International, prospective validation studies need to be performed to optimize the cut-off values and prognostic groups and to confirm the superiority of the newly suggested descriptors in non-small cell lung cancer nodal staging.

Keywords: Lung cancer; nodal staging; lymphadenectomy; review

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Introduction

Lung cancer is one of the most common cancers in the world. According to statistics, in the United States, nearly 1.8 million people are diagnosed with lung cancer each year only, and more than 600,000 people died because of this malignancy in 2019 (1). According to the literature, the 5-year overall survival (OS) rate of patients with non-small cell lung cancer (NSCLC), accounting for approximately 80% of all cases of lung cancer, is 18% (2). The current clinical nodal (cN) and pathological nodal (pN) NSCLC classifications are based only on the anatomical location of nodal metastases. The nodal stages are used to predict the 5-year OS rates both in clinical staging (60%, 37%, 23%, and 9% for cN0-3, respectively) and in pathological staging (75%, 49%, 36%, and 20% for pN0-3, respectively) (3). The International Association for the Study of Lung Cancer (IASLC) did not introduce any changes in nodal categorization since the 6th edition (4). Nonetheless, the current classification has some limitations. Ongoing N descriptors of the 8th Tumor Node Metastasis classification (TNM) create heterogeneous divisions of NSCLC patients due to situations such as skip N2 metastases, microscopic nodal metastases, and clinically occult pN2 disease (3,5,6). However, clinically, such anatomical staging is a valuable and easy system for making treatment decisions and is relatively visible and distinguishable in preoperative imaging and invasive nodal staging. Many alternative classifications have been suggested. In propositions for both the 7th and 8th editions of the NSCLC staging system, the IASLC suggested quantitative factors that were not ultimately adopted (3,4). In this study, we present a review of various suggested factors analysed as potential additions or successors to the current nodal staging of NSCLC. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1997).

Material and methods

We searched the PubMed database regarding ongoing and newly suggested lymph node descriptors in lung cancer. We used the following search terms and their combinations: “lung cancer”, “NSCLC”, “lymph node staging”, “number of positive lymph nodes”, “number of negative lymph nodes”, “number of dissected lymph nodes”, “lymph node ratio”, “log odds of positive lymph nodes”, “lymph node stations”, “skip N2 metastasis”, “lymph node zones”, and “nodal chains”. After the first search, we included additional articles retrieved from a manual search of cited references and articles that cited articles about particular classifications via a PubMed search. The inclusion criteria were as follows: original articles and articles published from 1990 to present. The exclusion criteria were as follows: no full text available and abstract/full text not in English.

Number of lymph nodes

Number of positive lymph nodes

The quantity of metastatic lymph nodes is a meaningful prognostic factor. Unlike lung cancer, the number of positive lymph nodes (NPLN) has already demonstrated a crucial role in the clinical and/or pathological TNM staging of various malignancies (e.g., breast cancer). Notably, esophageal cancer staging is also based on the NPLN despite the anatomical surroundings and lymph node drainage being comparable to those of lung cancer (7). There are many studies regarding the importance and usefulness of the NPLN in NSCLC. As shown in *Table 1*, we summarized the impact of the NPLN on OS. Various approaches were made towards use of the NPLN in staging. Some researchers used the number of metastatic lymph nodes as an addition to ongoing pN descriptors to subdivide patients (8-12,15). Promising results were achieved. pN2 patients with a few positive lymph nodes (PLN) (range from 1 to 3) had a better survival rate than pN2 patients with more PLN (range from 4 to 6). The subdivision of pN1 patients was not significant; however, the pN2 subgroup with 1–3 PLN had a similar OS rate as the pN1 subgroup. Skip N2 metastases and single-station disease were associated with fewer PLN, indicating the complex relationship of various factors for the revision of N staging (8). The significance of pN2 subdivision and the insignificance of pN1 subdivision were similarly observed in another study (NPLN groups: 1–3, 4–14, and ≥15) (9). However, in another study, pN1 subdivision was significant. Differences between pN2 with 1–3 PLN were not significantly different from pN1 with more PLN (range from 4 to 6). The authors suggested merging these two subgroups into a single prognostic group. However, no significance between the two subgroups could be a result of the small population included in these two subdivisions (10). This combined group was also used in another study (11). Rearrangement of the IIIA and IIIB stages of NSCLC based on the NPLN, values was suggested (15). Patients with less than 3 PLN had relatively

Table 1 Impact of NPLN on 5-year OS

Author	N	pN stage	NPLN	5-year OS
Fukui *et al.* (8)	289	pN0	0	77.0%
		pN1	1–3	57.0% (NS)
			4–6	57.0% (NS)
		pN2	1–3	59.0%
			4–6	40.0%
			≥7	6.0%
Lee *et al.* (9)	1,081	pN1, pN2	0	69.0%
			1–3	42.9%
			4–14	30.0%
			≥15	11.5%
Saji *et al.* (10)	689	pN0	0	79.2%
		pN1	1–3	69.2%
			≥4	48.6%†
		pN2	1–3	48.6%†
			≥4	30.8%
Lee *et al.* (11)	1,487	pN0	0	76.0%
		pN1	1–3	62.0%
			≥4	45.2%†
		pN2	1–3	45.2%†
			≥4	39.4%
Hanagiri *et al.* (12)	121	pN2	1	51.0%
			2	58.9%
			3	34.2%
			4	30.0%
			>5	20.4%
Wei *et al.* (13)	1,659	pN0	0	89.2%
		pN1, pN2	1–2	65.1%
			3–6	42.1%
			≥7	22.4%
Matsuguma *et al.* (14)	749	pN1, pN2	0	76.0%
			1–2	54.3%
			≥3	39.8%
			3–5	45.6%
			>5	31.7%

†, those high NPLN pN1 and low NPLN pN2 subgroups were merged as single prognostic groups. N, number of patients; NPLN, number of positive lymph nodes; NS, not significant; OS, overall survival.

Table 2 Suggested values of minimal NDLN as proper lymphadenectomy

Author	N	Minimal NDLN
Doddoli *et al.* (20)	465	10
Ludwig *et al.* (21)	16,800	11–16
Saji *et al.* (16)	928	10
Yang *et al.* (22)	428	7
Osarogiagbon *et al.* (23)	24,650	18–21
Becker *et al.* (24)	33,463	16
Bria *et al.* (25)	415	10
Dai *et al.* (26)	121	10
Liang *et al.* (27)	44,511	16
Ou *et al.* (28)	2,545	11–15
Samayoa *et al.* (29)	98,970	10
Shapiro *et al.* (30)	4,975	10
Wen *et al.* (31)	549	12

N, number of patients; NDLN, number of dissected lymph nodes.

better survival than those with more than 2 PLN (12).

Other researchers suggested changing N staging completely and using the NPLN alone (13). The number of metastatic lymph nodes (groups: 0; 1–2; 3–6; and ≥7) was a better prognostic factor than the pN1 and pN2 stages, which, in this study, were statistically insignificant and worse than the NPLN in the multivariate analysis. Subdivision of the pN1 and pN2 subgroups based on the NPLN was significant; nonetheless, subdivision of the NPLN categories into pN1 and pN2 was not. This result might imply that the NPLN creates more homogeneous subgroups and that the location of metastatic lymph nodes may not be related to survival (13). Nonetheless, the higher the pN status is, the larger the NPLN, which indicates the relationship of the anatomical extent of the N stage and the NPLN (9,13).

According to the literature, the NPLN cut-off values vary between studies. Additionally, as it highly depends on proper lymphadenectomy, the minimal number of dissected lymph nodes (NDLN) must be addressed to stage patients properly. One study, for example, suggested an NPLN cut-off value of 4 and proper lymphadenectomy for a minimum of 10 dissected nodes (16).

Number of negative lymph nodes

The number of negative lymph nodes (NNLN), as the antithesis of the NPLN, may also be used to predict patient survival. The NNLN has been studied in various cancers (e.g., esophageal cancer), but only a few analyses have been performed in terms of NSCLC (17). The most recent work (n=1,019) revealed that the new classification, based on current pN categories combined with the NNLN (cut-off equal to 8), has the strongest predictive value [compared to pN alone, NPLN and even lymph node ratio (LNR)] (18). The NPLN and LNR were excluded in the multivariate analysis, unlike pN-NNLN (18). Nonetheless, in another study from 2017 (n=482), the NNLN (cut-offs equal to 10 and 30) failed to be an independent prognostic factor in the multivariate analysis, unlike the LNR (cut-offs =20% and 55%). However, researchers suggested combining the classification based on the NNLN groups with the LNR subgroups (the classification based on the opposite LNR groups with NNLN subgroups was not significant), which stratified patients better than pN (19). The NNLN alone has an impact on survival. In one analysis, OS in patients with fewer NNLN (≤15) was better than that in patients with more NNLN (>15) (P=0.002). The survival curves were similar to those generated with pN0; however, differences were observed in the pN1 and pN2 subgroups (14).

Number of dissected lymph nodes

The NDLN is essentially the sum of the two parameters mentioned above (NDLN = NPLN + NNLN). Thus, the NDLN might also be used to predict patient survival. In the TNM classifications of many cancers, the minimum number of removed lymph nodes is determined (e.g., breast 6, colon 12, and stomach 16) (7). Many studies on the minimal NDLN in NSCLC have been performed. As shown in *Table 2*, we summarized the suggested minimal NDLN that were prognostically significant. It is possible that the number of lymph nodes is an individual characteristic of the patient and distributed as a Gaussian curve in the population. Thus, in this study, the NDLN had no impact on OS, unlike the extent of nodal metastasis (single-station *vs.* multi-station) (32).

Lymph node ratio

The LNR is defined as the ratio of the NPLN to the total

Table 3 Impact of LNR on 5-year OS and mean survival

Author	N	pN stage	LNR	5-year OS	Mean survival (months)
Taylor *et al.* (35)	302	pN1, pN2	<0.34	51.0%	–
			>0.34	18.0%	–
Wang *et al.* (36)	301	pN1, pN2	≤0.18	40.3%	38.0
			>0.18	10.5%	16.0
Matsuguma *et al.* (14)	651	rNO†	0.00	76.0%	–
		rN1†	<0.12	58.8%	–
		rN2†	>0.12	35.0%	–
		rN2a†	0.12–0.26	40.0%	–
		rN2b†	>0.26	27.5%	–
Hsieh *et al.* (37)	108	pN2	<0.4	–	62.0
			>0.4	–	24.0
Urban *et al.* (38)	11,324	pN1	<0.125	–	43.0
			0.125–0.249	–	40.0
			0.25–0.499	–	30.0
			>0.5	–	23.0
		pN2	<0.125	–	40.0
			0.125–0.249	–	32.0
			0.250–0.499	–	27.0
			>0.5	–	22.0
Renaud *et al.* (39)	152	pN2	<0.33	–	30.0
			≥0.33	–	16.0

†, suggested rN staging based solely on LNR value. LNR, lymph node ratio; N, number of patients; OS, overall survival.

number of all resected nodes $\left(LNR = \frac{NPLN}{NPLN + NNLN}\right)$. The role of the LNR has been well proven in many malignancies (e.g., esophageal malignancies) (33). Additionally, many scientific works have proven its role in lung cancer. One of the largest and most important studies regarding the role of the LNR in NSCLC was a recent meta-analysis of 20 high-quality retrospective studies (total n=76,929). Generally, the lower the LNR is, the better OS (hazard ratio 1.954, 95% CI: 1.746–2.169, P<0.001). Similar results were observed in terms of disease-free survival and cancer-specific survival (fewer studies were included, however, due to a lack of data). Although the group may have been heterogeneous, the subgroup analysis (pN1 and pN2 or type of lymph node dissection) remarkably diminished heterogeneity (34). As shown in *Table 3*, we summarized the results of various studies on the LNR to depict diverse suggested cut-off values and their impact on OS. When compared to other classifications, the LNR (followed by the NPLN) was far superior to pN (14). Additionally, the combination of pN and the LNR demonstrated superiority in comparison to pN, the LNR, the NPLN, and pN-NPLN (40). In one study, the LNR (cut-off 0.35) and its impact on survival were significant in the pN1 subgroup but not in the pN2 subgroup (41), but in many other studies, the LNR had a significant impact on survival in the case of pN2 (35-37). pN1 patients with a high LNR could create a single prognostic group with pN2 patients with a low LNR (35,36).

Many studies have aimed to determine optimal LNR values for the selection of patients who could benefit from adjuvant therapy. For example, among the pN2 groups, patients with an LNR higher than 0.50 should

undergo postoperative therapy (38). Interestingly, the survival outcomes of patients with an LNR less than 0.18 were not different regardless of whether they underwent chemotherapy (36). The usefulness of the LNR was also confirmed when predicting the survival of patients who underwent neoadjuvant therapy (39) and in predicting brain metastases of NSCLC (42). The LNR could be an alternative to positron emission tomography scans according to one study. In terms of the prediction of recurrence, an LNR >0.12 was the second-best predictor after the maximum standardized uptake value (>6.5). Thus, the LNR could be a great compromise for countries where these scans are not accessible due to various reasons (43).

Despite having robust usefulness and being generally better than the NPLN, the LNR also has some limitations. Heterogeneity in this system is also possible. For instance, when 0 of 2 resected lymph nodes is positive and 0 of 17 resected lymph nodes is positive (both 0), the ratio is equal to 0. Mathematically, more situations such as these are possible (e.g., 2/2 and 14/14 are both equal to 1). The log odds of positive lymph nodes (LODDS) would discriminate such situations, as its formula would yield different results. This was proven in the work by Deng *et al.*, where the LODDS was particularly better than the LNR in the case of an LNR equal to 0 and 1 (44). When the minimal NDLN is agreed on, situations such as those observed with the LNR could be avoided, at least partially. This was also proven in that study. The LODDS was superior to the LNR only when the NDLN was less than 10. In the case of proper lymphadenectomy, the LODDS was surpassed (44).

Log odds of positive lymph nodes

The LODDS is defined as the logarithm of the ratio of the NPLN to the NNLN. $LODDS = \log \frac{NPLN + 0.5}{NNLN + 0.5}$. The aim of adding 0.5 to both the numerator and the denominator is to avoid an infinite value. The importance of the LODDS has already been well established in various cancers (e.g., esophageal cancer) (45). There is also increasing interest in making use of this indicator in the staging of lung cancer. Nonetheless, only a few studies regarding its role in NSCLC have been conducted.

In various studies, the LODDS was found to be a better descriptor than the LNR and current pN staging (44,46-48). Lv *et al.* even suggested the so-called TLM (Tumor, LODDS, Metastases) staging, which was identified as an independent risk factor, unlike the current TNM staging. This descriptor was good at diminishing heterogeneity in pN and in cases of an LNR less than 0.036 (46). The LODDS was especially better in higher-stage patients. In the case of lower stage survival, the curves for pN, the LNR and the LODDS were similar. Only the LODDS was identified as an independent risk factor in the multivariable analysis. However, in that study, only the adenocarcinoma group was included (47). Introducing the LODDS into the staging system would allow us to classify some pN1 patients into the pN2 group and pN2 patients into the pN1 group based on survival (48). As already mentioned in other classifications, the LODDS is becoming increasingly important, especially in the case of 0 PLN and an LNR equal to 1 (44). Zero PLN (thus pN0) seems to be particularly interesting because some programmes treat selected pN0 patients postoperatively because of their poor prognosis. Additionally, in the case of the LODDS, cut-off values vary between studies. In two studies, there was a single cut-off value: –1.142 (46) and 0.26 (44). In one study, there were 4 different groups based on values ranging from –2.10 to 1.74 (47). Even more groups (seven) existed in the most recent work, where values ranged from –6 to 2 (48).

In comparison to the NPLN or LNR, the LODDS seem to be the least faulty system (especially when there is no consensus on the minimal NDLN). Its usefulness is narrow due to limited data; nonetheless, as the mathematical modification of the ratio, it may be very robust. Previous descriptors are usually reported in pathological results or can be easily calculated.

Single or multiple station involvement

In 2015, the IASLC suggested a new subclassification of N staging in lung cancer for the 8th edition of the TNM staging system based on single/multiple station disease and skip metastases (3). Although it was not accepted, as data were not sufficient, in the future, such a system might be adapted into everyday practice. The subclassification of N descriptors is as follows: pN1 is subdivided into single (pN1a) and multiple (pN1b) stations, and pN2 is also subdivided into single (pN2a) and multiple (pN2b) stations. Further, pN2a is again subdivided into a lack of N1 involvement (pN2a1, so-called skip-N2) and with N1 involvement (pN2a2). pN3 remains intact. All of these subdivisions yielded significantly distinct groups (3). Since then, many studies have been performed to validate this classification (*Table 4*). Additional N2b subdivision into N2b1 and N2b2 based on skip N2 metastases might be

Table 4 Impact of single/multiple-station status and skip metastases presence on 5-year OS

Author	N	5-years overall survival (%)										
		pN0	pN1	pN1a	pN1b	pN2	pN2a	pN2a1	pN2a2	pN2b	pN2b1	pN2b2
Asamura *et al.* (3)	26,236	75.0	49.0	58.0	50.0*	36.0	47.0	52.0*	41.0	36.0	–	–
Chen *et al.* (49)	570	76.1	53.4	60.0	39.3*	26.3	40.3*	NS	NS	15.3	33.3*	11.4
Yun *et al.* (50)	3,971	82.8	62.6	64.6	51.7	45.3	–	61.8	47.9	34.6	–	–
Park *et al.* (51)†	1,228	–	–	62.6*	57.0*	–	–	64.7*	48.4	42.8	–	–
Park *et al.* (51)†	1,228	–	–	62.6	57.0*	–	–	64.7*	48.4*	42.8	–	–
Bertoglio *et al.* (52)	93	–	–	–	–	33.0	–	45.5	31.5*	23.5*	–	–
Sayar *et al.* (53)	181	75.0	45.0	45.0	32.0*	31.0	31.0*	–	–	0.0	–	–
Keller *et al.* (54)	488	–	52.0	–	–	32.0	NS	–	–	NS	–	–
Sezen *et al.* (55)	119	–	–	–	–	29.3	38.6	–	–	11.0	–	–
Ichinose *et al.* (56)	402	–	–	–	–	31.0	43.0	–	–	17.0	–	–
Nakagiri *et al.* (57)	121	–	–	–	–	42.0	45.5	–	–	38.5	–	–
Martini *et al.* (58)	214	–	39.0	45.0	31.0	–	–	–	–	–	–	–

†, Park *et al.* suggested two potential combined prognostic groups: pN1a + pN1b + pN2a1 or pN1b + pN2a1 + pN2a2; *, represent potential merged prognostic groups. NS, not significant; N, number of patients; pN1a, single-station pN1; pN1b, multiple-station pN1; pN2a, single-station pN2; pN2a1, pN2a with skip metastasis; pN2a2, pN2a without skip metastasis; pN2b, multiple-station pN2b; pN2b1, pN2b with skip metastasis; pN2b2, pN2b without skip metastasis.

used. N2b1 and N2b2 are significantly distinct groups. Unlike other works, the N2a1 and N2a2 subgroups showed no significant difference (49). Potential combined prognostic groups seem to vary, and based on statistical significance, researchers have suggested many possibilities (*Table 4*) Nonetheless, some of combinations may be the result of small samples in subgroups (50,51). Compared with other propositions, this system is worse than the LNR and NPLN (52).

Years before Asamura's idea, many studies were made on the role of multiple and single station disease in the prognosis of NSCLC patients were performed. In some studies, the difference between pN1 subgroups was not significant, as was sometimes the case for pN2 subgroups (54). In other works, the distinction between multiple stations and a single station was significant in both N1 (53,58) and N2 (55-57) patients. Interestingly, tumor location might have an impact on single and multiple station statuses (56,59). Skip N2 metastases, as a distinct prognostic group, were also either significant or insignificant in various analyses (55,57).

Even the authors of the largest IASLC study noted limitations because most of the records were based on the Japanese population and nodal staging was based on the Naruke-Japanese nodal map (3). Currently, only the Mountain-Dresler modification of the American Thoracic Society is recommended. The recognition of each nodal station might be challenging, and errors are possible. Some stations could be indistinguishable because of their adjacency (e.g., to the paratracheal), and this could lead to an incorrect diagnosis. That is why some researchers suggested grouping nodal stations into zones (levels).

Other classifications

During propositions for the 7th edition of the TNM staging system in 2007, the IASLC suggested a system for grouping lymph node stations into zones (levels) that was not implemented and eventually discarded (4). Compared to the LNR and NPLN, zone-based staging is inferior and not as prognostic (60). Propositions for the 7th and 8th editions of the TNM staging system were combined into a single staging system by Yun *et al.* (based on single/multiple zones and skip metastasis). In comparison to the station-based system, the zone-based system is as equal, and some patients (7.1%) are downstaged (50).

All suggestions disregarded extranodal metastases, which are important according to the nodal chains (NC) system.

Each NC consists of at least one lymph node vessel and various lymph nodes at different stations. This staging classification was studied as the ratio between positive and resected NC (61). Excluding extranodal metastases, NC are an intermediate system between zones and stations and could have a single status or multiple statuses (62).

Interestingly, when multiple-station cases are limited to a single-zone or single-chain, survival is as good as single-station cases (50,62). Unfortunately, these and other systems (e.g., systems based on a relationship between tumor location and station/zone of the involved lymph node) extend beyond the framework of our article (63).

Discussion

The minimal number of resected lymph nodes in NSCLC has not been established, and according to various studies and our opinion, it has to change. In the 8th edition of the TNM staging system, it is suggested that at least 6 lymph nodes should be resected for adequate staging; however, it is not enforced as mandatory, and it is not an appropriate number according to various studies (7). Among these studies, 10 was the most frequent minimal value of harvested lymph nodes that was prognostically significant (*Table 2*). More extensive lymph node resection might be even more beneficial; for instance, an NDLN equal to 16 was the best value in regard to OS, and the other best value ranged from 18 to 21, which demonstrated the best benefit for patients (21,23). Nonetheless, such numbers might not be achieved in some cases because of anatomical interindividual differences (32). Regardless, we should aim to achieve such values and, if not possible, approach such patients individually (e.g., by the LODDS) or classify and treat such patients at least as pNx. In practice, there are many possibilities for proper nodal dissection. Lymphadenectomy provides good staging, and sampling decreases the surgery time and complication rate (20,64). The lobe-specific method allows the dissection of lymph nodes according to lymphatic drainage and anatomy (65). Targeted sampling decreases the rate of the dissection of dangerous lymph nodes (e.g., station 7 and postoperative ischaemic bronchitis) (66).

The main limitation of the studies included in our review is their retrospective nature. Selection bias could be possible. Additionally, most of the studies used different inclusion or exclusion criteria (e.g., minimal NDLN).

In this review, we summarized the most important and prominent suggestions to consider as potential pN descriptors in NSCLC. The vastness of newly suggested NSCLC classifications and IASLC suggestions indicate the need for upcoming changes. As we already mentioned in our criticism of the ongoing 8th edition of the TNM staging system, heterogeneity in N descriptors is the main reason behind the need for such changes. It is necessary to determine the optimal pN classification to refer eligible patients for adequate adjuvant therapies. When considering other organs, multiple classifications are applied. The staging of esophageal cancer, an anatomically related malignancy to NSCLC, is based on the NPLN (7). Therefore, based on the reviewed papers, a quantity-based pN descriptor should be introduced. All of the suggested methods have their pros and cons. Each of the proposed classifications tends to eliminate NSCLC subgroup heterogeneity while potentially being able to create new prognostic groups. Interestingly, only the LODDS is superior in terms of pN0 heterogeneity elimination (44). Cut-off values and potential prognostic groups vary from study to study, and they must be validated and determined in prospective international studies (e.g., IASLC Lung Cancer Staging Project). Additionally, in such a study, we could determine which of the descriptors is superior and should be introduced. Data regarding the NPLN and LNR are more robust (albeit retrospective) than other suggested N classifications, which need additional analyses. Hence, in our opinion, these 2 parameters or the LODDS (as the mathematical modification of the LNR) are more legitimate and should be considered first. Many more studies, especially regarding other classifications, need to be performed in the future. The minimal NDLN, in addition to being a good assessment of lymphadenectomy, is a factor that can be used to increase the objectivity of various proposed staging methods. The LODDS is potentially superior when minimal lymphadenectomy is not established. The NPLN is highly dependent on having a proper minimal NDLN. The LNR also benefits from more dissected lymph nodes, which was proven by Deng *et al.* (44).

It seems necessary that pN and cN descriptors should be divided (as in breast cancer), as quantity parameters of lymph nodes are not easily accessible in preoperative imaging and staging (7). For cN, ongoing TNM staging seems to be a good compromise for making treatment decisions. Additionally, as most of the data reviewed here are based on a population of resectable NSCLC patients (thus mostly pN), any changes regarding cN would not be appropriate. Even if a new nodal classification is introduced to the pathological staging of lung cancer, the nodal clinical

staging would probably remain unchanged.

To summarize our review:

(I) Minimal lymphadenectomy in NSCLC should be settled;

(II) A quantity-based descriptor of lymph node metastases should be considered as an addition in the next TNM staging system;

(III) Prospective international validation study or studies need to be performed to validate optimal cut-off values and prognostic groups and to determine which newly suggested descriptor is superior.

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Footnote

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