



Prognostic significance of the pattern of pathological N1 lymph node metastases for non-small cell lung cancer

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Background: In patients with non-small cell lung cancer (NSCLC) the pathologic lymph node status N1 is a heterogeneous entity, and different forms of lymph node involvement may represent different prognoses. For methodological reasons, the 8th edition of the TNM staging system for NSCLC makes no official changes to the N descriptor. However, there is evidence that different subforms of N1 disease are associated with different prognoses, and it is now recommended that clinicians record the number of affected lymph nodes and nodal stations for further analyses. In this investigation we sought to determine whether patients with different levels and types of N1 lymph node involvement had significantly different 5-year survival rates.

Methods: We retrospectively identified 90 patients with NSCLC (61 men, 29 women), who were treated between 2008 and 2012 and found to have pathologic N1 lymph node involvement and tumor sizes corresponding to T1 or T2. All patients were treated in curative intent with surgical lung resection and systematic mediastinal and hilar lymph node dissection.

Results: The overall 5-year survival rate was 56.3%. In the univariate analysis, lower tumor stage and tumor histology other than large-cell carcinoma were significantly associated with better long-term survival. Patients with solitary lymph node metastases also had longer disease-free survival than those with multiple nodal metastases. In the multivariate analysis, large-cell carcinoma and Union for International Cancer Control (UICC) stage IIB were independently associated with worse survival, while pneumonectomy, compared to lobar or sublobar resection, was independently associated with better survival.

Conclusions: Although we did not observe significant prognostic differences between N1 subcategories within our patient population, other analyses may yield different results. Therefore, these data highlight the need for large, well-designed multicenter studies to confirm the clinical significance of N1 subcategories.

Keywords: Non-small cell lung cancer (NSCLC); staging; N-descriptor; prognosis

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Introduction

In contrast to the TNM classification schemes for many other types of cancer, the classification of lymph node metastases in non-small cell lung cancer (NSCLC) relies

on anatomical location alone. Some investigations have suggested that the total number of affected lymph nodes or lymph nodes stations may more accurately reflect prognosis (1,2). Initial analyses performed by the International Association for the Study of Lung Cancer (IASLC) for its

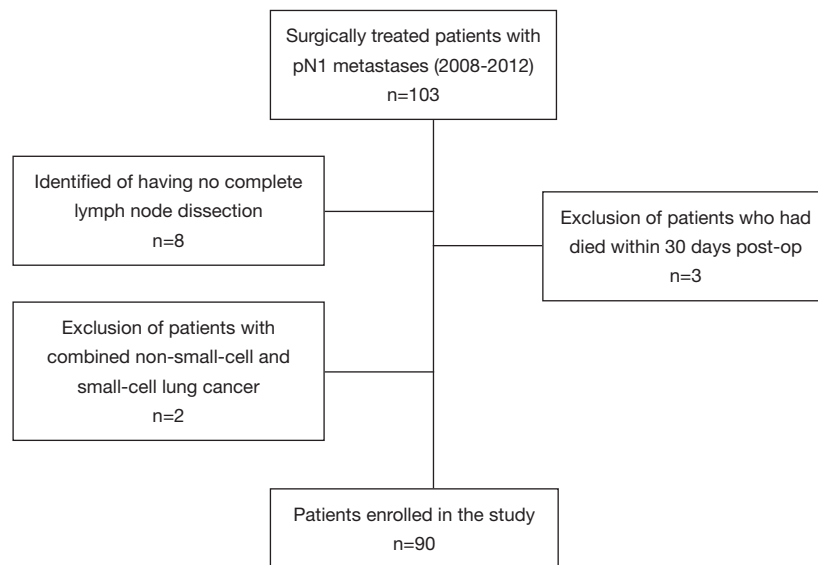


Figure 1 Flow-chart: patient selection.

updated 8th edition of the TNM classification system also suggested that a more differentiated classification of nodal metastases is needed (3).

Although the IASLC analyses were based on an enormous volume of data, in many cases the data on number and location of affected lymph nodes was either missing or complete. Additionally, Japan—which provided nearly 60% of the data—uses a different lymph node map than much of the non-Asian world. In the Asian (Naruke map) classification for example lymph nodes along the inferior border of the main stem bronchus are classified as N1, while in Europe and North America they are classified as N2. For these reasons the IASLC ultimately decided against making any definitive changes to the N descriptor in its 8th edition update. Clinicians, however, are still urged to document the number of affected N1 and N2 lymph nodes and lymph node stations to provide data for future analyses (4).

Despite advances in positron emission tomography-computed tomography (PET-CT), ultrasound-guided endobronchial biopsy, and video assisted biopsy, the clinical and pathological N statuses frequently disagree. It thus seems reasonable for any investigation of nodal disease to consider the cN and pN statuses separately. In this retrospective study of surgically treated NSCLC patients we restricted our analysis to patients with pathologically confirmed N1 disease and sought to determine whether those with multiple N1 metastases had worse outcomes than those with single N1 metastases.

Methods

We retrospectively scanned the database of patients who had undergone surgical resection for NSCLC between 2008 and 2012 at the Heckeshorn Lung Clinic. For the sake of simplicity, we only considered patients with small tumors (pT1 or pT2 based on the 7th edition of TNM classification) and pathologically confirmed N1 status. We excluded patients where complete tumor resection had not been possible (not R0) and also patients where the lymph node data was not complete. Additionally, we excluded patients who had died within 30 days of surgical resection, in order to eliminate the potentially confounding factor of death due to immediate postoperative complications (*Figure 1*).

We identified 90 patients, who fit our criteria, and then extracted patient data on age, sex, tumor histology, infiltration of pulmonary and mediastinal lymph nodes, 5-year overall survival (OS), and 5-year disease-free survival (DFS).

The institutional review board waived the need for registration because all data had been gathered for internal quality control, and patients had already given their informed consent to have their data used for research purposes.

Patients were evaluated preoperatively by physical examination, bronchoscopy, chest radiograph, and FDG-PET/CT scans. Brain CT or magnetic resonance imaging (MRI) scans were only performed when clinical signs and symptoms suggestive of cerebral metastases were present.

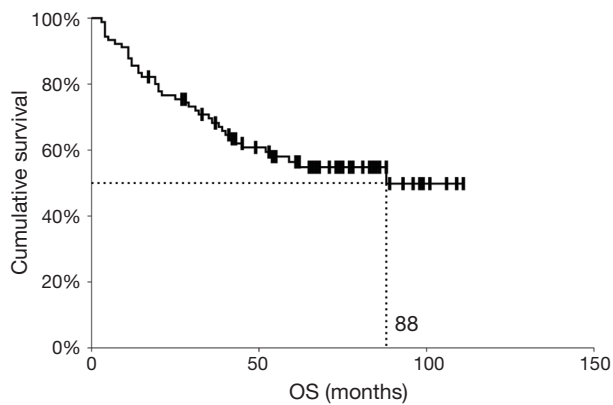


Figure 2 Overall survival of the entire cohort (n=90). Kaplan-Meier statistics. OS, overall survival.

All patients included in this study were treated in curative intent with lobectomy, pneumonectomy, or sublobar resection. In all cases systematic hilar and mediastinal lymph node dissection was performed according to standard practice (5). Thus, right-sided lung resections included dissection of the paratracheal, subcarinal, inferior mediastinal, interlobar, and hilar lymph nodes, and left-sided resections included dissection of aortic, infracarinal, inferior mediastinal, interlobar, and hilar lymph nodes. The pathologic specimens were assessed according to the IASLC map for patterns of tumor spread (6), and lobar (stations 12 and 13), hilar (station 10), and interlobar (station 11) lymph node metastases were classified as N1.

In most cases dissected lymph node stations were labeled by the surgeon, but the pathologist determined the lymph node status for the lobar stations (stations 12 and 13), as well as the total number of affected and non-affected N1 and N2 lymph nodes postoperatively.

For this investigation we retrospectively established a subcategory that differentiated between patients with multiple N1 metastases and those with a single N1 metastasis. We established a further subcategory that differentiated between cases in which hilar and lobar lymph node involvement was due to direct extension of the tumor and those in which the involvement was due to metastasis (with no direct connection to the primary tumor). In these cases, the distance between the nodal metastases and the primary tumor was coded in the preoperative CT scan. Cases with lymph node involvement due to both direct extension and metastasis were assigned the category of metastatic disease. Finally, we scanned pathology reports for patients with N1 nodal metastases that extended beyond the

lymph node capsule, and looked at whether they had worse prognoses than patients with N1 metastases that did not extend beyond the capsule.

Statistical analysis

All data were analyzed using NCSS 12 Statistical Software 2018, (NCSS LLC, Kaysville, Utah, USA, ncss.com/software/ncss). Categorical variables were analyzed using the χ^2 test and Fischer's exact tests. Continuous variables were analyzed using either the Student's *t*-test (normally distributed) or the Mann-Whitney test (not normally distributed). We used the Kaplan-Meier method to determine probability of survival (7), with the date of lung cancer surgery as the starting point and 5-year OS and DFS as end points. We used the log-rank test to analyze differences between subgroups, and we used Cox's proportional hazards model to evaluate incremental risk factors influencing survival (8). Variables with a significance level of $P < 0.2$ in the univariate survival analysis were included in the multivariate analysis. Probability values of less than 0.05 were considered statistically significant.

Results

The last follow-up date included in this analysis was October 1st, 2018, and the median follow-up period for surviving patients (censored patients) was 74 months (range, 3–111 months). Among 90 patients who had N1 disease, 39 patients died within the follow-up period and 22 patients were lost to follow-up with no up-to-date information available. The 5-year OS rate was 56.3%, and the median survival time was 88 months (*Figure 2*). Patient demographics are summarized in *Table 1*. A median of 10 N1 lymph nodes (range, 3–50) and a median of 13 N2 lymph nodes (range, 3–35) were resected per patient.

Results from the univariate analysis are presented in *Table 2*. Here, patients with large-cell carcinomas and higher UICC stage (IIB *vs.* IIA) had worse OS and DFS. Patients with multiple N1 metastases had worse DFS than patients with single N1 metastases, but for OS this relationship was not significant (*Figure 3*). We found no significant differences in either OS or DFS for the other variables investigated: age (≤ 65 *vs.* > 65 years), sex, tumor location (right *vs.* left or central *vs.* peripheral), compartment with lymph node metastases, metastatic spread beyond the lymph node capsule *vs.* no extra-nodal spread, N1 due to direct tumor spread *vs.* due to metastasis, higher T indicator

Table 1 Patient characteristics

Variables	Frequency (n=90)	Percentage (%)
Sex		
Male	61	67.8
Female	29	32.2
Histology		
Adenocarcinoma	37	41.1
Squamous-cell carcinoma	41	45.6
Large cell carcinoma	12	13.3
pT stage		
pT1	31	34.4
pT2	59	65.6
Stage UICC (7th edition)		
IIA	66	73.3
IIB	24	26.7
Surgery types		
Sublobar resection	8	8.9
Lobectomy	66	73.3
Pneumonectomy	16	17.8
Tumor size		
<2 cm	9	10.0
2 to <3 cm	19	21.1
>3 cm	62	68.9
Central/peripheral located primary tumor		
Yes	46	51.1
No	44	48.9
No. of lymph nodes		
1–10	5	5.6
10–20	26	28.9
20–30	27	30
>30	32	35.5
No. of lymph node metastases		
1	44	48.9
2–3	31	34.4
>3	15	16.7
Direct versus separate lymph node metastases		
Yes	49	54.4
No	41	45.6

Table 1 (continued)

Table 1 (continued)

Variables	Frequency (n=90)	Percentage (%)
No. of patients with lymph node compartments involved		
Hilar	40	44.4
Interlobar	19	21.1
Pulmonary	49	54.4
Two compartments	18	20.0
No. of patients with extranodal tumor extension	33	36.7
No. of patients with adjuvant chemotherapy	47	57.9

UICC, Union for International Cancer Control.

(pT1 *vs.* pT2), and adjuvant standard chemotherapy *vs.* no adjuvant chemotherapy (Table 2).

In the Cox multivariate analysis, we found that large-cell carcinoma, compared to other histological types ($P=0.0036$, hazard ratio: 4.323, 95% confidence interval: 1.611–11.598), and UICC stage IIB cancer ($P=0.0417$, hazard ratio: 2.197, 95% confidence interval: 1.030–4.686) was associated with a worse OS prognosis. Pneumonectomy, compared to more conservative resections, was associated with a better prognosis ($P=0.046$, hazard ratio: 0.252, 95% confidence interval: 0.065–0.976) (Table 3).

Discussion

The primary finding of this study, that single N1 lymph node metastases are not associated with a better OS than multiple N1 metastases, is somewhat surprising. In the univariate analysis patients with multiple N1 lymph nodes did in fact have a lower rate of 5-year DFS than those with a single N1 metastasis (42.3% *vs.* 62.9%), but in the multivariate analysis this association was not significant. This may suggest that we were simply underpowered and that this relationship was outweighed by the much stronger association between prognosis and histological type.

At the same time, although the existing literature suggests that greater overall burden of lymph node metastases is associated with a worse prognosis (1,2,9,10), the relationship is far from clear. The IASLC data used for the 8th edition demonstrated that patients with a single station of N1 metastases had better 5-year OS than those with multiple stations of N1 metastases, but this analysis was limited by missing data and variation in the lymph node maps used (4). While Wei *et al.* found an association

between greater number of metastatic lymph nodes and worse outcome, this effect was much stronger for N2 nodes than for N1 nodes (1). Lee *et al.* found that a greater number of nodal metastases was associated with worse outcome, but the study did not differentiate between N1 and N2 nodes (11). Kang *et al.*, in contrast, found that the number of metastatic nodes was not associated with a worse prognosis but that the number of affected nodal stations was (12). Interestingly, these studies all drew from largely Asian populations, treated in Asian hospitals. This is significant because of the differences in lymph node maps used in Asia and elsewhere. Additionally, certain cancer biological genetic differences, which needs further to be investigated, may exist as well.

Regarding the other N1 subcategories investigated, there is some evidence that N1 nodal disease from direct tumor extension has a better prognosis than N1 nodal disease from metastasis (13,14). In our analysis we only observed a non-significant trend in this direction, but here too we may simply have been underpowered. Our finding that extracapsular extension of lymph node metastases was not significantly associated with worse prognosis was only somewhat surprising. Although extracapsular extension seems to negatively influence outcome in breast cancer (15), malignant melanoma (16), and head and neck carcinoma (17) it currently has no place in the TNM classification for NSCLC. Moreover, although some studies suggest that it is associated with a worse prognosis in NSCLC (18), others—in concordance with our finding—report no association (19).

There is a high degree of variation in how resected lymph nodes are labeled and counted. This makes accurate lymph node analysis difficult and is an important limitation of both our study and others. Additionally, nodal classification

Table 2 Univariate analysis of clinical-pathologic potential prognostic factors

Patient characteristics	5-year overall survival		5-year disease-free survival	
	Rate (%)	P value	Rate (%)	P value
Sex		0.880		0.560
Male	59.7		58.1	
Female	53.4		46.1	
Tumor location		0.670		0.830
Right	52.8		55.6	
Left	59.6		48.3	
Histology		0.0015		0.0002
Squamous cell carcinoma	71.8		67.3	
Adenocarcinoma	49.9		47.2	
Large-cell carcinoma	25.0		16.7	
Type of resection		0.190		0.321
Sublobar resection	37.5		37.5	
Lobectomy	55.5		50.9	
Pneumonectomy	68.7		62.5	
Compartment of lymph node metastases				
Hilar, yes/no	55.2/58.9	0.709	53.8/47.7	0.417
Interlobar, yes/no	59.6/44.0	0.241	55.3/39.7	0.195
Pulmonary, yes/no	52.8/59.2	0.260	46.7/55.6	0.296
Extranodal lymph node involvement		0.570		0.399
Yes	59.3		56.8	
No	54.6		49.0	
Lymph node involvement due to		0.350		0.880
Direct tumor involvement	59.5		52.2	
Metastatic lymph node involvement	53.2		51.0	
Number of lymph node metastases		0.126		0.045
Single	64.5		62.9	
Multiple	49.3		42.3	
Central tumor location (<2 cm)		0.170		0.386
Yes	62.3		56.9	
No	50.3		47.1	
T descriptor		0.580		0.460
pT1	59.1		56.0	
pT2	55.5		50.1	
UICC stage		0.051		0.011
IIA	63.0		60.0	
IIB	38.9		31.1	
Adjuvant chemotherapy		0.560		0.639
Yes	57.9		53.9	
No	55.2		50.3	

UICC, Union for International Cancer Control.

is highly dependent on the information provided by the surgeon as well as on the dissection approach employed by the pathologist. International differences between lymph node maps have already been discussed, but as El-Sherief

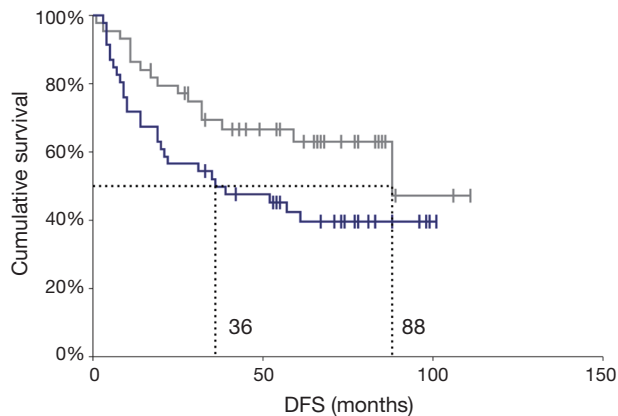


Figure 3 Disease-free survival of the cohort separated for single (grey line) versus multiple (blue line) N1 metastases. Log-rank analysis ($P_{u,v}=0.0045$). DFS, disease-free survival; u.v., univariate analysis.

et al. have demonstrated, even within the same geographical region the IASLC lymph node map is frequently used both inconsistently and inaccurately (20). The right-sided boarder between lymph node stations 4 and 10, for example, is particularly problematic. An affected lymph node labeled as station 4 leads to a diagnosis of N2, while a lymph node labeled as station 10 leads to a diagnosis of N1. If the azygos vein is not dissected, however, correct classification can be difficult.

Additionally, fragmentation of lymph nodes during dissection can lead to an erroneously high number of metastases. For technical reasons N1 lymph nodes—the focus of our study—may be particularly prone to fragmentation and incorrect quantification. While mediastinal nodes are generally removed in a packet with the surrounding fatty tissue, N1 lymph nodes must be dissected from the narrow space of the hilum and from within the lung tissue. This highlights the need for surgeons to make every effort to avoid fragmentation of harvested lymph nodes and to be especially vigilant in labeling correctly. Moreover, it highlights the need for pathologists

Table 3 Relationship of individual variables to death (Cox proportional hazards method)

Variable	P value	Hazard ratio (HR)	95% confidence limit
Histology			
Squamous cell carcinoma	–	Reference	Reference
Adenocarcinoma	0.264	1.608	0.698–3.703
Large cell carcinoma	0.0036	4.323	1.611–11.598
Lung resection			
Segment resection	–	Reference	Reference
Lobectomy	0.117	0.461	0.174–1.216
Pneumonectomy	0.046	0.252	0.065–0.976
Lymph node metastases			
Single	–	Reference	Reference
Multiple	0.2816	1.503	0.715–3.155
Tumor location			
Central tumor <2 cm	–	Reference	Reference
Peripheral tumor	0.360	1.416	0.672–2.981
UICC			
IIA	–	Reference	Reference
IIB	0.0417	2.197	1.030–4.686

UICC, Union for International Cancer Control.

to follow a standardized and consistent protocol for dissecting and quantifying affected lymph nodes. Finally, it is important to consider how many lymph nodes and lymph node compartments need to be dissected intraoperatively to permit accurate assessment of nodal status. The IASLC currently recommends intraoperative dissection of at least three N1 nodes and three N2 nodes, as well as postoperative dissection of pulmonary specimens to search for intralobar metastases (21). It is unclear, however, whether this is sufficient.

Our secondary finding, that patients with large cell carcinoma have a worse prognosis than patients with other NSCLC histologic types, is in concordance earlier findings (22,23). This is unsurprising, as large-cell carcinoma is characterized by poorer differentiation—neither truly squamous nor glandular—and in other types of cancer as well, poorer differentiation is associated with poorer prognosis.

Interestingly, the T descriptor (pT1 *vs.* pT2) was not significant in this study, but the UICC stage (IIA *vs.* IIB) was, both for OS and for DFS. Since all patients in this analysis had pN1 status, the critical difference seems to be in the T descriptors: pT2a (>3–5 cm) and pT2b (>5–7 cm) (based on the 7th edition). Although we did not recode the T descriptors to align with the 8th edition, in most cases this difference would have been reflected in the 8th edition as the difference between pT2 (>3–5 cm) and pT3 (>3–5 cm) status and thus the difference between stages IIB and IIIA.

Interestingly, patients treated with pneumonectomies had the best outcomes (OS and DFS), and patients treated with sublobar resections had the worst outcomes. This finding, however, must be viewed with caution. Luzzi *et al.* found that pneumonectomy offered better locoregional control in patients with pN1 disease (24), but other investigations found that patients with lobectomies had better outcomes (25,26). Moreover, it is important to consider possible biases in patient selection. Candidates for pneumonectomy require better overall fitness and lung function than candidates for lobectomy. Since lobectomy, when possible, is the standard practice in our clinic, patients undergoing mere sublobar resections are generally limited by serious comorbidities such as advanced pulmonary emphysema or heart disease. Although these comorbidities likely have an independent detrimental effect on long term survival, we did not control for them as this was not the primary focus of our investigation. Furthermore, the better outcome for patients with pneumonectomies may be related to the fact

that we excluded those who died within 30 days of surgery, which may have played more of a role in these patients than in lobectomy patients. Due to the enormous volume loss that pneumonectomy entails, a recommendation to perform this procedure for peripheral tumors cannot be recommended.

Our observations must be interpreted in the context of our study's potential limitations. Here it is important to consider the retrospective nature of the study, as well as the complexity of the classification proposal for N1 disease. Since the study period, practice patterns have changed, as the prevalence of minimally invasive surgical modalities for N1 metastatic disease has increased. Within the study period all surgical resections were performed with an open thoracotomy approach. Additionally, we acknowledge that given the small sample size, this study may be underpowered for detecting all potential prognosticators between nodal status and survival. Thus, our findings will require validation in larger cohorts. Furthermore, given that standard helical CT imaging was used for follow-up to evaluate the patterns of failure after surgery, it is not clear, how these results will apply to other imaging modalities such as FDG-PET/CT.

In summary it seems clear that future classification systems for NSCLC could be improved by a more specific N indicator. Although we did not observe significant prognostic differences for long-term survival between single and multiple metastases in N1 disease, other studies may report different findings. The need for a standardized map as well as standardized practices among surgeons and pathologists will continue to remain of critical importance. A careful assessment of mediastinal, hilar, and interlobar lymph node involvement is always warranted. Moreover, future updates of the TNM staging system should incorporate more quality criteria recommendations that are both logical and easy to use in clinical routine. Only then will it be possible to generate reliable data that can be compared and incorporated into larger multi-center clinical trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The institutional review board waived the need for registration because all data had been gathered for internal quality control, and patients had already given their informed consent to have their data used for research purposes.

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