Research Article

Prognostic spotlight on N1 disease in NSCLC patients and its relation with tumor characteristics

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Abstract
Lung cancer is still one of the most common and potentially lethal cancers. N1 is considering a bad prognostic factor. We aimed to re-identify its prognostic aspects and its relation with the T descriptor. We have operated on 865 patients who were operated on for non-small cell lung cancer (NSCLC) between 2005-2019. Patients with any mediastinal lymph node and distal metastasis were excluded. A total of 667 T1-4N0-1M0 patients were investigated. Survival analysis was made via Cox regression. Five-year survival rate was 72% months in N1 patients. We have shown that increased tumor size and T score were related to higher incidence of N1 positivity T1 has the lowest rate while T3 and T4 have the highest (p<0.001). Lymphovascular invasion decreases overall survival (OR:0.540, p=0.008). The number of parenchymal and hilar lymph nodes was associated with survival regardless of the lymph node positivity (p=0.017). The mean survival of solitary hilar lymph node metastasis 129 months (95% Confidence Interval: 114-143 months) like N0 patients who had overall survival of 133 months (95% Confidence Interval: 125-142 months). Higher T stage is related with higher chance of N1 disease. Surgical and pathological LND from N1 stations are more important in these cases. N1 diseases with STAS and LVI positivity should be assessed with care, and one shall beware with potentially lower survival. Solitary hilar lymph node metastasis with no parenchymal lymph node metastasis had similar survival outcome to N0 patients which may indicate a need for reevaluation in staging.

Keywords: NSCLC, survival, lymph node dissection, parenchymal lymph nodes, N1 disease

1. Introduction

According to the estimations of the American Cancer Society, lung and bronchial cancers are defined as the second most common cancer type in both genders and the cancer type that causes the most deaths (1). Non-small cell lung cancers account for 80% of all lung cancers (2).

Historically, the TNM staging system was first developed by Denoix in 1952 and CF Mountain adapted this classification for lung cancer staging in 1974 and 1997(3-5). The 7th staging system for lung cancer, which was proposed for the first time on an international patient database, was published by the International Association for Lung Cancer Research (IASLC) in 2010 (6). Subsequently, the 8th staging system, based on an expanded dataset of 94,708 cases from 19 countries and 46 centers, was unveiled by the IASLC in 2017 (7).

According to the results of the studies, no change was proposed to T descriptive factors from the previous edition. Sub-classifications of N2 diseases (mediastinal lymph node metastasis) will be proposed including N2a as single mediastinal lymph node metastasis and N2b as multiple N2 disease. No change was offered in terms of N1 (hilar and parenchymal lymph node) metastases (8).

Our study aimed to aimed to analyze the prognostic value of N1 disease, the prevalence and its relation with tumor characteristics.

2. Material and Methods

Non-small cell lung cancer patients who were operated on between January 2005 and December 2019 were evaluated.

2.1. Data Collection

Demographic details, lung cancer types, resection methods, surgical approaches, additional pathological findings such as tumor size, metastatic lymph node stations, presence of lymphovascular invasion (LVI), perineural invasion (PNI), visceral pleural invasion (VPI), spread through air spaces (STAS) etc, TNM stages according to the latest 8th edition, smoking history, follow-up information were recorded. No additional tests or intervention was performed to the patients.

2.2. Patient Population

Patients with small cell components, with insufficient follow-up data and cases who were considered inoperable for either oncological or medical reasons were excluded from the study. There were 804 patients remaining. In addition, patients who received neoadjuvant therapy and patients with any N2 and M1 disease were excluded (Fig. 1). A total of 667 patients (546 males and 121 females) with T1-4N0-1M0 were considered eligible for our study.

The majority of our patients (n=558; 83.7%) underwent

lobectomy. The most common histopathological subtype was adenocarcinoma with 287 patients and squamous cell carcinoma with 257 patients (43% and 38.5% respectively) (Table 1).

Even though minimally invasive approaches are more common nowadays, since the study includes a wide range of years, open thoracotomy was the leading surgical approach with 471 patients while VATS was performed on 196 patients (70.6% and 29.4% respectively) (Table 1).

Our patient population was mostly in the early stages. Among them 307 patients were stage 1 and 243 patients were stage 2 (45.9% and 36.6% respectively). The percentage of stage 3 patients was 17.5% (n=117) (Table 1).
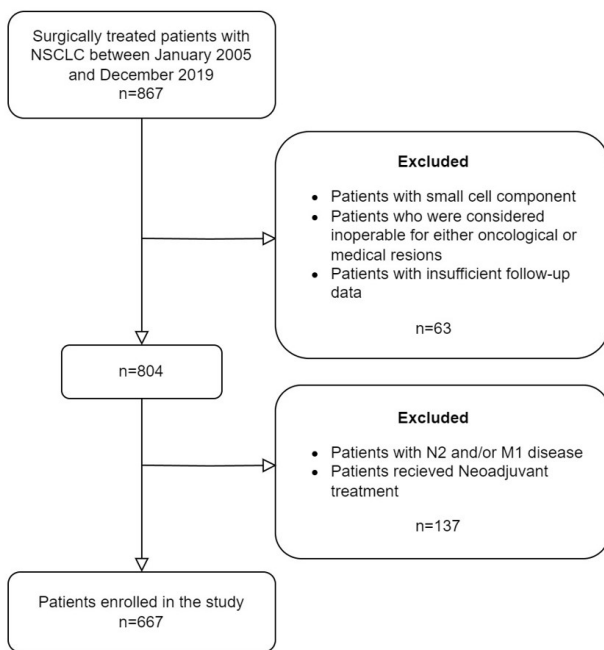

Fig. 1. Flow-chart of patient selection

2.1. Statistical Anaylsis

The Kaplan-Meier method was used for survival analysis. Univariate (log-rank) and multivariate analysis (Cox) were done for the disclosure of prognostic factors. Independent t test or Mann-Whitney U test was performed where appropriate. The relationship between categorical variables was evaluated with the chi-square test. Pearson correlation test was used to analyze the relationship of independent variables.

Continuous variables were shown as mean ±standard deviation and interquartile range. Categorical variables were shown as numbers and percentages. Odds ratios are presented with 95% confidence intervals. SPSS® for Windows version 25.0 (IBM, Chicago, IL, United States) proram was used for statistical analysis. Statistical significance level was accepted as p<0.05.

Table 1. Includes patient demographic data. number, mean and Percentage values are given

Patient Characteristics	n (%)
Age	
≤ 65 years	402 (60.3%)
> 65 years	265 (39.7%)
Gender	
Male	546 (81.9%)
Female	121 (18.1%)
Histopathology	
Adenocarcinoma	287 (43%)
Squamous Cell Carcinoma	257 (38.5%)
Carcinoid Tumor	25 (3.7%)
Adenosquamous	22 (3.3%)
Pleomorphic	19 (2.9%)
Large Cell	18 (2.7%)
Mucoepidermoid	10 (1.5%)
Other NSCLC	29 (4.4%)
Resection Type	
Sublobar	12 (1.8%)
Lobectomy	558 (83.7%)
Pneumonectomy	97 (14.5%)
Surgical Method	
Video-Assisted Thoracic Surgery	196 (29.4%)
Thoracotomy	471 (70.6%)
Pleural Invasion	
0	328 (49.2%)
1	187 (28%)
2	75 (11.3%)
3	77 (11.5%)
STAS	
Negative	555 (83.2%)
Positive	112 (16.8%)
Lymphovascular Invasion	
Negative	159 (22.3%)
Positive	518 (77.7%)
Perineural Invasion	
Negative	423 (63.4%)
Positive	244 (36.6%)
T status	
1a	40 (6%)
1b	101 (15.1%)
1c	98 (14.7%)
2a	148 (22.2%)
2b	68 (10.2%)
3	136 (20.4%)
4	76 (11.4%)
N status	
0	496 (74.4%)
1	171 (25.6%)
Stage	
1A1	36 (5.4%)
1A2	93 (13.9%)
1A3	81 (12.1%)
1B	97 (14.5%)
2A	48 (7.3%)
2B	195 (29.3%)
3A	117 (17.5%)

3. Results

The mean overall survival time in all patients was 136 (95% CI: 129-143 months). Five and 10-year survival rates were 72% and 57.3% respectively.

Overall survival was found to be shorter in males (mean 132 months; 95% CI: 124-140 months) than females (mean

146 months; 95% CI: 131-162 months) in all cases (p=0.032).

Patients older than 65 years old (n=246) had a significantly lower survival rate with a mean OS 115 months (95% CI: 103-127 months) compared to that of younger patients (n=375) with a mean OS of 149 months (95% CI: 140-159 months) (p<0.001).

In all patients N1 positivity had lower survival although not statistically significant (OS=110 months, 95% CI: 98-121 months) compared to that of N0 patients (OS=138 months, 95% CI: 129-147 months) (p=0.17). The survival of stage 2 patients (IIA and IIB) was statistically significantly lower overall survival (129 [95% 119-139 months] versus 145 months [95% CI: 134-157 months] (p=0.024)) compared to patients with stage 1 NSCLC.

STAS positivity was found to be a statistically significant prognostic factor (110 ±10 vs 136 10 months; OR: 0.673; 95% CI:0.474 - 0.955) (p=0.025). Similarly, lymphovascular invasion indicated worse survival (128 ±4 vs 138 ± 15 months [RR:2.11 95%CI: 1.42 - 3.20] (p<0.001). Perineural invasion was also found to be a prognosticator cases (n=244, 36.6%) related to lower survival with (121 ±7 vs 140 ±10 months; RR; 0.611; 95% CI: 0.464 - 0.806) (p<0.001).

Pleural invasion is also found to be associated with poor prognosis with significantly lower OS of 117 ±5 months (p<0.001) (Table 2).

Multivariate analysis showed that, older age, male gender, LVI and pleural invasion were independently associated with lower survival (Table 2).

Table 2. Cox regression analysis for overall survival among groups by age, sex, STAS, LVI, perineural invasion and pleural invasion status

	Univariate Analysis			Multivariate Analysis		
	Risk Ratio	95% CI	p Value	Risk Ratio	95% CI	p Value
Age (years)						
≤ 65 / > 65	0.555	0.422 - 0.729	<0.001*	0.548	0.411 - 0.731	<0.001*
Gender						
Female/Male	0.646	0.431 - 0.968	0.032*	0.596	0.382 - 0.932	0.023*
STAS						
Negative/Positive	0.673	0.474 - 0.955	0.025*	0.736	0.505 - 1.071	0.109
LVI						
Negative/Positive	0.473	0.317 - 0.705	<0.001*	0.540	0.342 - 0.853	0.008*
Perineural Invasion						
Negative/Positive	0.611	0.464 - 0.806	<0.001*	0.843	0.623 - 1.141	0.268
Pleural Invasion						
NegativE/Positive	0.572	0.423 - 0.774	<0.001*	0.664	0.486 - 0.908	<0.001*

STAS: Spread Through Air Spaces , LVI: Lymphovascular Invasion , CI: Confidence Interval
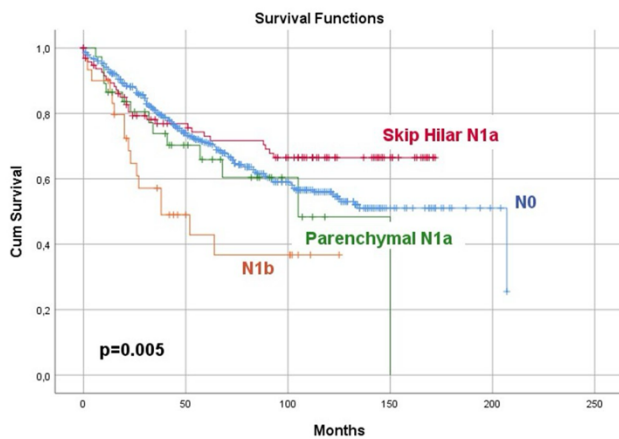*: p values smaller than 0.05 were considered as statistically significant.

Fig. 2. Survival of NSCLC patients with N0 and skip hilar and other N1 metastasis

Higher T factor was found to be associated with N1 lymph node positivity(p<0.001).

Of patients with N1 disease, 79 patients (46.2%) had solitary hilar lymph node (station #10) metastases, 50(29.2%) and 42 patients had solitary pulmonary lymph node (station 11 to 14) metastases and 42 patients (24.6%) had single(N1a) and multiple N1(N1b) involvement respectively. Overall survival of the patients with single and skip hilar lymph node metastasis

was 129 months (95% Confidence Interval: 114-143 months) which is similar to that of N0 patients (overall survival of 133 months [95% Confidence Interval: 125-142 months]) (Fig. 2). Those survivals were statistically significantly better than the overall survival of patients with N1a and N1b disease (p=0.017) (Fig. 2).

4. Discussion

In our study, we investigated the prognostic importance of N1 involvement and histopathological factors in patients who underwent resectional surgery for non-small cell lung cancer. In our study, a strong correlation was detected between the increase in T stage and the presence of N1. There was a higher rate of N1 presence in patients at T3 and T4 stages. Considering this data, it is plausible to perform systematic lymph node dissection with hilar and interlobar lymph node dissection in addition to mediastinal lymph node dissection to avoid undermine the N1 involvement in patients with T3 and T4 tumors. It would improve the accuracy of N staging.

Pleural invasion was one of the negative prognosticators (9,10). It was first included in the T descriptive factors in the 7th staging system (11). Pleural invasion can be designated as PL1, PL2, and PL3 according to the degree of invasion of the primary tumor to the pleural surface (12). A tumor with

invasion at the PL1-2 level is considered an upstage for a tumor of 3 cm or less in diameter from T1 to T2 (12). Invasion at the PL3 level is defined as T3 even for a tumor with 5 cm diameter or smaller (12). In our study, the presence of pleural invasion has been identified as a poor prognostic factor for survival in both univariate and multivariate analyses, independent of T and N stages. Although pleural invasion appears to be associated solely with the T stage, its impact on poor prognosis should not be overlooked.

Lymphovascular invasion and perineural invasion have been included in the pathological evaluation and it provides information about the invasive nature of the tumor (13). In a systematic review and meta-analysis published in 2014, Mollberg et al showed that LVI can be deemed as a prognostic marker in patients with Stage I non-small cell lung cancer (14). Wang et al. recommend that Stage IA NSCLC tumors with LVI should be upgraded to Stage IB (15). In our study, the identification of lymphovascular invasion as a poor prognostic factor in multivariate analyses underscores the importance of tumor characteristics. In addition, prognostic factors such as lymphovascular invasion can play a role in patient follow-up.

Intra-alveolar tumor dissemination, or STAS, was introduced in the WHO classification in 2015 and began to take place in pathological evaluations (16). This new histopathological finding, which has caused controversy since that year, was presented by two large independent cohort studies (17). In these studies, STAS was found to be a poor prognostic element. However, it also was stated that STAS is an artifact that can be encountered during sectioning (18). Blaauwgeers et al. designed a prospective study and argued that mechanical artifacts may arise while obtaining tissue material and observations of tumor cells in the airways should not be considered as an invasion criterion (18). The prevalence of STAS positivity in lung cancer reported differently in various studies ranging between 14.8% and up to 46.3% (19). The low percentage (16.8%) of STAS positivity in our patient group may be due to technical factors or population-based disparity. We confirmed in our case series that positivity for STAS was a poor prognostic finding in the survival analysis. However, in the multivariate analysis STAS presented only a borderline significance.

In addition to the currently accepted modalities in the surgical treatment of Lung Cancer, lobectomy, and systemic lymph node dissection (LND), there is an increasing interest in sublobar resections (20). Segmentectomy is considered a viable option in cases with low respiratory function, without preoperative histopathological diagnosis, as well as in patients with smaller tumors (<2 cm in diameter) and patients with small subsolid lesions (21).

Lymph node staging is considered as a very important prognostic factor in NSCLC cases, and the role of lymph node sampling or dissection for a correct staging has been well defined (22). Some studies suggest examining intersegmental lymph nodes with frozen sections during the operation and proceeding to lobectomy in cases with N1 lymph node positivity (23). If LND is neglected it may lead to under-detection of possible N1 disease and it may lead to failure to apply the correct treatment modality (24). We also have found that patients with T3 or T4 tumors had a higher chance of having N1 disease. Our findings suggest that surgical and pathological lymph node dissection is even more important in these patients since the rate of N1 involvement is higher.

The lung patients with NSCLC with skip hilar lymph node metastasis had a similar survival to those of N0 disease and this survival was significantly better than those with non-skip N1 disease. The mechanism behind this prognostic advantage and verification of our findings needs further studies with larger patient series. There are limitations in our study. It was single-centered trial of surgical NSCLC patients. We also were not able to analyze recurrence-free survival of the patients.

N1 involvement patterns and histopathological factors can be accounted for new (9th) staging system for lung cancer. The first recommendation articles for this new staging system were published in early 2024 and this staging is scheduled to take effect by the year 2025 (8,25).

The results of our study were obtained from a single center, and more accurate results can be revealed with IASLC lung cancer staging project study. Their validity and efficacy can be confirmed by adapting them to larger datasets across the globe. We hope that the results we obtained may be guiding in future staging efforts and other prognosis studies.

Authors' contributions
Concept: İ.S., A.T., Design: İ.S., A.T., Data Collection or Processing: İ.S., Ş.B., B.K., V.K., E.E., Analysis or Interpretation: İ.S., G.Ö.I., A.T., Literature Search: K.K., A.T., Writing: İ.S., K.K., A.T.

Ethical Statement
This retrospective cohort study was approved by the Medical Research Ethics Committee of Istanbul University-Cerrahpaşa, approval number: 17109671-600-85480) and patients' personal

data were processed in accordance with confidentiality principles according to the Declaration of Helsinki and Patient Rights Regulation.

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