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Original Article

Prognostic factors and classification of pathological single and multiple N1 in non-small cell lung cancer patients

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Abstract

Aim: We compared outcomes between "single pathologic N1" (pN1a) and "multiple pathologic N1" (pN1b) patients and investigated whether all pN1b patient subgroups had the same outcomes in non-small cell lung cancer (NSCLC).

Materials and Methods: We retrospectively analyzed 487 pN1 patients with NSCLC between 2010 and 2016. There were 284 single N1 (pN1a Group) and 203 multiple N1 (pN1b Group) patients. pN1b Group was divided into two subgroups; invasion of intraparenchymal lymph nodes (pN1b-without hilar group, n=48) and pN1b provided that one of the metastatic lymph nodes LN(s) has to be 10 and/or 11 (pN1b with hilar group, n=155). Overall survival (OS) and disease-free survival (DFS) rates were compared between subgroups of N1 patients.

Results: The mean age was 59.3 ± 8.3. The majority of the patients were male (n=462, 94.9%). The OS rate of pN1 patients was 53.2%, while the DFS rate was 48.8%. Multivariate analysis showed that adenocarcinoma histology (p=0.030), presence of pleural invasion (p=0.001) and perineural invasion (p=0.034) had worse effect on overall survival in pN1 patients. Both OS and DFS rates were statistically better in the pN1a Group than the pN1b Group (OS; 56.2% vs 48.3% p=0.03; DFS; 51.9% vs 44.4%, p=0.03). Although both OS and DFS rates were better in the pN1b-without hilar group patients than in pN1b-with hilar group, it was not significant (OS; 56.0% versus 44.5% p=0.187; DFS; 53.9% vs 40.6%, p=0.115).

Conclusion: The pN1a Group had significantly better survival than the pN1b Group. However, the patients in the latter group without hilar LN(s) invasion exhibited better survival rates than those with hilar LN(s) involvement, although this was not significant. We think that the survival advantage in multiple N1 without hilar lymph node involvement should be evaluated with a larger patient series.

Keywords: Lung cancer; multiple N1; single N1; TNM staging

INTRODUCTION

Nodal (N) status is one of the most important prognostic factors in non-small cell lung cancer (NSCLC) patients without distant metastasis (1). Classification of lymph nodes (LN) based on localization has been defined since the first edition of the Tumor-Node-Metastasis (TNM) staging system and has been used both in clinical (c) and pathological (p) staging and has not been changed at all. According to this classification system, the absence of lymphatic invasion is referred to as N0 disease, while metastasis to hilar and/or intraparenchymal LN(s) is N1 disease, and metastasis to ipsilateral mediastinal LN(s) is N2 disease (2). Single-zone (intraparenchymal or hilar LNs) versus multi-zone (intraparenchymal and hilar LNs), single pN1 (pN1a) versus multiple pN1 (pN1b) or classification based on the number of metastatic LNs have been discussed for TNM staging. However differences in survival have not been demonstrated sufficiently to justify changing the current classification system (3-4). The 2015 meeting of the International Association for the Study of Lung Cancer (IASLC) recommended that physicians record the number of metastatic LNs and for further testing, classify the N category using new descriptors; such as single-zone N1 (N1a), multi-zone N1 (N1b), single-zone N2 (N2a), and multi-zone N2 (N2b), and N3 (5).

In this study, we focused solely on pN1 disease and compared the survival rates and prognoses between pN1a and pN1b patients. We also aimed to investigate whether all pN1b subgroup patients have the same poor prognosis in NSCLC.

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MATERIALS and METHODS

This study was performed with a retrospective study design. Approval for the study was obtained from the institutional review board at Istanbul Training and Research Hospital clinical research Ethics Committee (2270/08.05.2020).

We reviewed the hospital charts of 549 N1 disease patients with NSCLC, who underwent anatomic resection at the department of the thoracic surgery's clinic during the period from 2010 to 2016. Histologic types other than squamous cell, adenocarcinoma, large cell, and adenosquamous cell carcinoma were excluded from the study (n=24). The general approach to lymph node dissection in our hospital is; regardless of tumour size and location, patients undergo a systematic mediastinal nodal dissection. All mediastinal LN stations from 5 to 9 on the left side and 2 to 9 on the right side and hilar LNs (stations 10 and 11) were dissected en bloc, not sampled. Resected materials and LNs were assessed histopathologically by the same pathologist team. It is recommended, at least six LNs are removed; three from N1 and three from N2 stations at the drainage path of the lobe. This was described as the minimum requirement for a diagnosis of N0 (6). Even though a diagnosis of pN1 was made in the postoperative pathological evaluation, 18 patients were excluded from the study due to insufficient LN dissection (<3 N1, <3 N2 LN station dissection in the drainage path of the lobe). Twenty cases who received neoadjuvant chemotherapy (CT) and/or radiotherapy (RT) were excluded. A total of 84 cases were excluded from the study. 487 pN1 cases who underwent complete resection with systematic LN dissection were included in the study. There were 284 patients with pN1a (pN1a Group) and 203 patients with pN1b (pN1b Group).

PET-CT and fiberoptic bronchoscopy was routinely performed for clinical staging. Staging mediastinoscopy was routinely performed except for patients with negative positron emission tomography (PET-CT) findings, those with a mediastinal LN of less than 1 cm on thoracic computerized tomography (CT), and cT1N0M0 patients diagnosed with squamous cell carcinoma. Operable patients, who were diagnosed with cN0 or cN1, underwent surgery directly as long as their general status was fit for thoracic surgery according to their respiratory and cardiac values.

The need for adjuvant therapy was evaluated by a multidisciplinary council. Clinical follow-ups of the patients were performed once every 3 months for the first 2 years, once every 6 months for 2-5 years, and once a year after the 5th year. Non–contrast chest CT was performed every 6 months. PET–CT was requested for patients with suspected recurrences or metastases, and cranial magnetic resonance imaging was performed when deemed necessary.

In the present study, the lymph node map defined by IASCL in 2009 was used (7). Single N1 LN invasion was defined as pN1a Group. More than one N1 LN station's invasion regardless of localization was defined as, pN1b Group. Station 12 and 13 LNs were defined as peripheral or intraparenchymal LNs, station 10 and 11 LNs were defined as extralobar or hilar LNs. The invasion of both station 12 and 13 LNs together were defined as; pN1b-without hilar group and multiple N1 provided that one of the metastatic LNs is 10 and/or 11 LN(s) was defined as; pN1b-with hilar group. At least one LN from parenchymal and at least one LN from hilar LN involvement were defined as pN1b-multi-zone.

Statistical Analysis

The data were entered into the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, United States). The influences of the following factors on survival were analyzed: age; sex; histologic type; type of resection; TNM staging; pT status; pN status: and pN categories. Overall survival was the time between surgery and death from any cause. Disease-free survival (DFS) was accepted as the time between surgery and finding a recurrence somewhere. Survival was estimated by the Kaplan–Meier method, and survival comparison between the groups was performed by using the log-rank analysis. Multivariate survival analysis was performed using the Cox proportional hazards model to examine the association between survival and potential prognostic factors. Variables that were found to affect survival in univariate analysis were included in the multivariate analysis. The chi-square test was used to determine whether the proportions of independent groups were statistically significantly different. A p value < 0.05 was considered statistically significant.

RESULTS

The mean age was 59.3 ± 8.3 (range 35-84 years). The majority of the patients were male (n=462, 94.9%). Most common histologic type was squamous cell carcinoma (n=358, 73.5%) and the mean tumor size was 5.22±2.33 (range 1-17 cm). Demographic and pathological features of the patients are presented in Table 1. While 284 (58.3%) of the patients constituted pN1a, 203 (41.7%) were pN1b. There was no difference between the N1 subgroups in terms of age (p=0.975), gender (p=0.861), histologic type (p=0.461), side (p=0.765), pleural invasion (PL) status (p=0.376), pathological vascular and lymphatic invasion status (p=0.784, p=0.101). Patients in the pN1b group appeared to have more perineural invasion (p=0.002), larger tumor diameter (p=0.006), and a higher T stage (p=0.001), while patients in the pN1a group were shown to undergo more lobectomies (p<0.001). Among pN1a patients, LN metastasis was most frequently found in station 12 (n=109, 38.3%), whereas among pN1b patients, multi-zone LN metastasis was found most frequently (n=144, 70.9%). While 160 of the patients in the pN1b Group had two different N1 LN station metastases, 43 of them had three or four different LN station metastases (Table 2).

Table 1. Demographic and pathological features of the patients. Comparison of pN1a and pN1b

Features of the patients	Total (n=487)	pN1a Group (n=284)	pN1b Group (n=203)	p value
Age, mean±SD	59.3±8.3	59.1±8.2	59.1±8.4	0.975
Gender, n (%)				0.861
Female	25 (5.1%)	15 (5.3%)	10 (4.9%)	
Male	462 (94.9%)	269 (94.7%)	193 (95.1%)	
Histologic type				0.461
Sqcc	358 (73.5%)	203 (71.5%)	155 (76.4%)	
Adeno	114 (23.4%)	71 (25.0%)	43 (21.2%)	
*Others	15 (3.1%)	10 (3.5%)	5 (2.5%)	
Tumor size, cm±SD	5.22±2.33	5.01±2.35	5.53±2.28	**0.006**
Tumor lateralization n(%)				0.765
Left	248 (50.9%)	143 (50.4%)	105 (51.7%)	
Right	239 (49.1%)	141 (49.6%)	98 (48.3%)	
Resection type				**<0.001**
Lbc	250 (51.3%)	177 (62.3%)	73 (36.0%)	
Pnmc	237 (48.7%)	107 (37.7%)	130 (64.0%)	
Pleural status, n (%)				0.376
PL0	358 (73.5%)	217 (76.4%)	141 (69.5%)	
PL1	52 (10.7%)	26 (9.2%)	26 (12.8%)	
PL2	35 (7.2%)	19 (6.7%)	16 (7.9%)	
PL3	42 (8.6%)	22 (7.7%)	20 (9.9%)	
Invasion rate, %				
Vascular	198 (40.7%)	114 (40.1%)	84 (41.4%)	0.784
Lymphatic	308 (63.2%)	171 (60.2%)	137 (67.5%)	0.101
Perineural	159 (32.6%)	77 (27.1%)	82 (40.4%)	**0.002**
pT status, n (%)				**0.001**
T1	80 (16.4%)	58 (20.4%)	22 (10.8%)	
T2	163 (33.5%)	105 (37.0%)	58 (28.6%)	
T3	111 (22.8%)	58 (20.4%)	53 (26.1%)	
T4	133 (27.3%)	63 (22.2%)	70 (34.5%)	
TNM status, n (%)				**<0.001**
IIB	243 (49.9%)	163 (57.4%)	80 (39.4%)	
IIIA	244 (50.1%)	121 (42.6%)	123 (60.6%)	

Adeno: Adenocarcinoma, Lbc: Lobectomy, N: Node, n: Number, Pnmc: Pneumonectomy, pN1a:Single N1, pN1b: Multiple N1, PL0: Tumor does not invade past the elastic layer, PL1: Penetration beyond the elastic layer of visceral pleura, PL2: Invasion of visceral pleura, PL3: Parietal pleura invasion, SD: Standard deviation, Sqcc: Squamous cell carcinoma, T:Tumor, TNM: Tumor-node-metastasis
*Large cell or adenosquamous cell carcinoma

Table 2. Number of pN1 node levels and locations

Station	One level involved (pN1a)	pN1b (with 2 levels)	pN1b (>2 levels)	p value
10	10 (3.5%)	32 (10.0%)	27 (20.4%)	69 (9.3%)
11	86 (30.2%)	91 (28.4%)	40 (30.3%)	217 (29.4%)
12	109 (38.3%)	122 (38.1%)	40 (30.3%)	271 (36.8%)
13	79 (27.8%)	75 (23.4%)	25 (18.9%)	179 (24.3%)
Total n (%)	284 (58.3%)	320*	132*	736
Number of patients	284	160	43	484

	Number of patients in pN1b	
	203	
pN1b single-hilar zone (10 + 11 LN)	11 (5.4%)	**pN1b-with hilar group**
pN1b-multi-zone (12 ± 13 and 11 ± 10 LN)	144 (70.9%)	
pN1b-without hilar group (12 + 13 LN)	48 (23.6%)	**pN1b-without hilar group**

*Total number of involved node levels is 452
n: Number, LN: Lymph node, pN1a: pathological single N1, pN1b: pathological multiple N1

Univariate and multivariate analysis for survival

The mean follow-up time was 58.2 months. On follow-up, 267 patients (53.3%) died and 82 patients (16.8%) had recurrence. While distant metastasis was observed in 46 patients, local recurrence was observed in 36 patients. While the 5-survival rate was 53.2% (median 73.2 months) in the N1 population, DFS was 48.8% (median 57.4 months). The overall 5-year survival rate for pN1a Group was 56.2% (median 92.8 months), and DFS rate was 51.9%, while for pN1b Group, it was 48.3% for 5-year survival (median 53.3 months) and 44.4% for DFS (Figure 1a, 1b). There was a significant difference between groups in terms of 5-year survival and DFS (p=0.03, p=0.03 respectively).

According to univariate analysis; age (p=0.117), gender (p=0.404), resection type (p=0.163), tumor side (p=0.678), vascular and lymphatic invasion (p=0.102, p=0.681 respectively) and TNM stage (p=0.154) did not affect

overall survival. However, tumor type adenocarcinoma (p=0.035), tumor size (p=0.024), absence of pleural invasion (p<0.001), presence of perineural invasion (p=0.030) and multiple N1 LN involvement (p=0.030) had a significant negative effect on overall survival. Multivariate analysis showed that adenocarcinoma (p=0.030), presence of pleural invasion (p=0.001) and perineural invasion (p=0.034) negatively affected overall survival (Table 3).

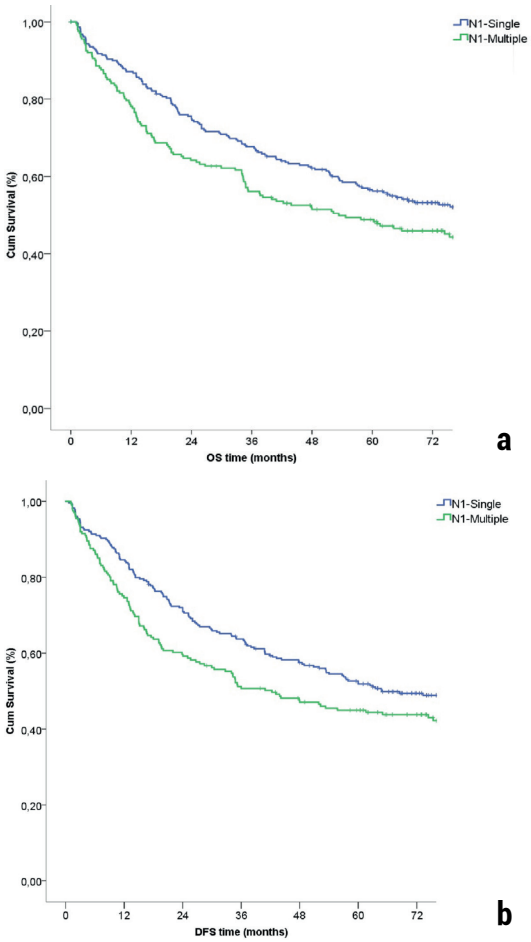

Figure 1. a) 5-year survival rates of pN1a group vs pN1b group; b) 5-year Disease-Free Survival rates of pN1a group vs pN1b group

Survival comparison for Multiple N1 subgroups

It was found that survival deteriorated as the number of metastatic LN stations increased. The 5-year survival was 49.1% (median 57.7 months) for two positive N1 stations (n=160) and 42.5% (median 35.2 months) for three or four positive N1 stations. However, the difference was not significant (p=0.599). Patients in the pN1b Group were divided into two subgroups to investigate whether the involvement of hilar LN(s) affected survival in the pN1b Group. pN1b-without hilar group (n=48), and pN1b with hilar group (n=155). OS and DFS rates of the pN1b-without hilar group were better than the pN1b-with hilar group. However, the difference in terms of OS and DFS was not statistically significant (OS: 56.0% versus 44.5%, median 85.9 months versus 42.3 months; p=0.187, Figure 2a; DFS: 53.9% versus 40.6%, p=0.115, Figure 2b).

In order to investigate which hilar LN is responsible for negative affect on OS and DFS, patients in the pN1b-with hilar group (n=155) were further grouped as: pN1b-with only 10 (n=24), pN1b-with only 11 (n=96) and pN1b-with both 10+11 (n=35).

Table 3. Univariate and multivariate analyses for the survival of all pN1 patients

	Univariate	Multivariate		
Variables	**P value**	**HR**	**95% CI**	**p value**
Age	0.177			
Gender (Male vs Female)	0.404			
Histologic type (Non-adenocarcinoma vs Adenocarcinoma)	**0.035**	0.731	0.551-0.969	0.030
Tumor size	**0.024**	1.020	0.967-1.075	0.458
Tumor lateralization (Left vs Right)	0.678			
Resection type (Lbc vs Pnmc)	0.163			
Pleural status, (PL0 vs PL1,2,3)	**<0.001**	1.561	1.186-2.054	**0.001**
Vascular invasion (Yes vs No)	0.102			
Lymphatic invasion (Yes vs No)	0.681			
Perineural invasion (Yes vs No)	**0.030**	1.325	1.022-1.719	**0.034**
pT status (T1/2 vs T3/4)	0.154			
pN1 subcategories (pN1a vs pN1b)	**0.030**	1.207	0.945-1.541	0.132

Adeno: Adenocarcinoma, CI: Confidence interval, cm: Centimeter, HR: Hazard Ratio, Lbc: Lobectomy n: Number, Pnmc: Pneumonectomy, pN:pathologic Node, pN1a: Single N1, pN1b: Multiple N1, PL0: No Visceral Pleural inv. PL1: Penetration beyond the elastic layer of visceral pleura, PL2: Invasion of visceral pleura, PL3: Parietal pleura invasion, T: Tumor, TNM: Tumor-node-metastasis

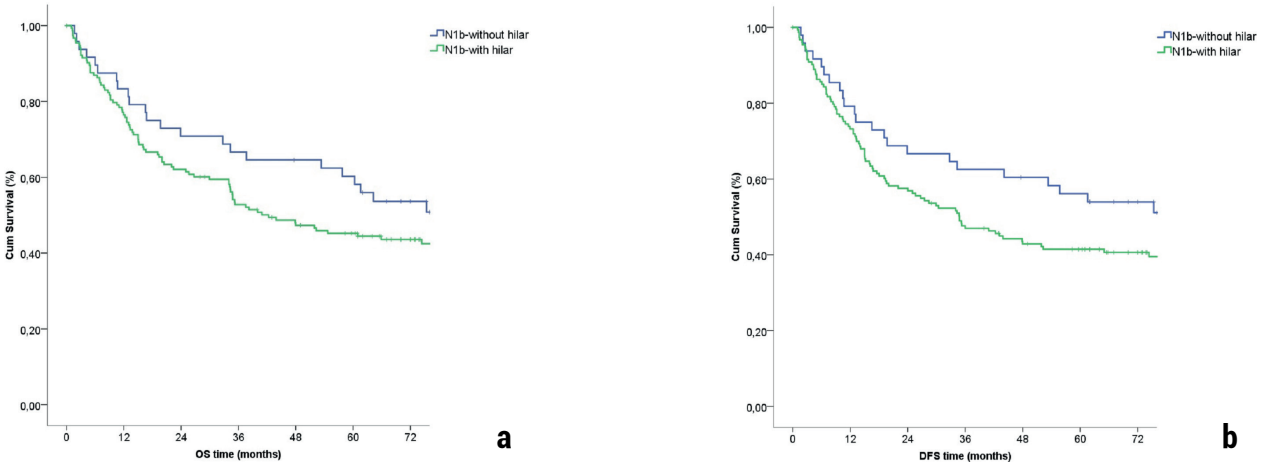

Figure 2. a) 5-year survival rates of pN1b-without hilar group versus pN1b-with hilar group; b) 5-year Disease-free survival rates of pN1b-without hilar group versus pN1b-with hilar group

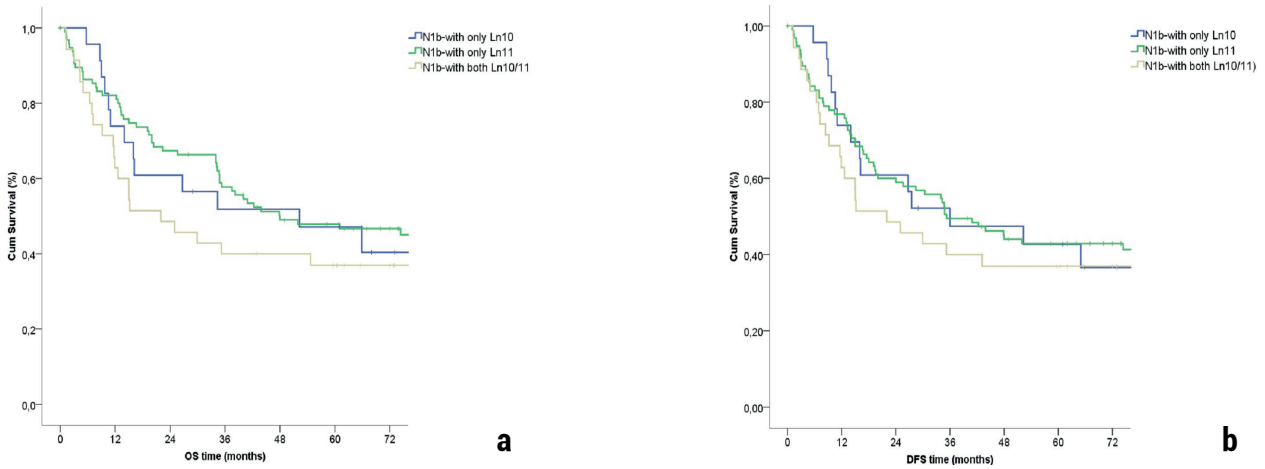

Figure 3. a) 5-year survival rate of pN1b with only 10 - pN1b with only 11 - pN1b-with both 10 and 11; b) 5-year DFS survival rates of pN1b with only 10 - pN1b with only 11 - pN1b-with both 10 and 11

Table 4. 5-year survival rates and DFS survival rates of N1 subgroups

	Overall survival			DFS		
N1 subgroups (n = 487)	**5-y survival**	**MST**	**p value**	**5-y survival**	**MST**	**p value**
pN1a (n = 284)	56.2%	92.8	**0.03**	51.9%	64.7	**0.03**
pN1b (n = 203)	48.3%	53.3		44.4%	42.3	
pN1b subgroups (n = 203)	**5-y survival**	**MST**	**p value**	**5-y survival**	**MST**	**p value**
Two N1 LNs metastases (n = 160)	49.1%	57.7	0.599	44.9%	44.1	0.859
Three or four N1 LNs metastases (n = 43)	42.5%	35.2		35.6%	25.0	
pN1b-without hilar group (n = 48)	56.0%	85.9	0.187	53.9%	74.7	0.115
pN1b-with hilar group (n =155)	44.5%	42.3		40.6%	34.8	
pN1b-with hilar group (n = 155)	**5-y survival**	**MST**	**p value**	**5-y survival**	**MST**	**p value**
pN1b-with only 10 (n = 24) (12 ± 13 + 10)	47.1%	52.2	0.410	42.7%	36.0	0.725
pN1b-with only 11 (n = 96) (12 ± 13 + 11)	46.7%	49.9		41.3%	35.2	
pN1b-with both 10+11 (n = 35) (12 ± 13 + 10 + 11)	36.9%	22.0		36.9%	22.0	

MST; median survival time (months), DFS: Disease-free survival, y: Year, pN1a: Single N1, pN1b: Multiple N1, n: Number

Among these groups, patients with the worst overall survival were pN1b-with both 10+11 (5-year overall survival 36.9%, median 22 months). The overall 5-year survival was almost similar between group pN1b-with only 10 and pN1b-with only 11 (47.1% and 46.7%, median 52.2 and 49.9 months respectively) (Figure 3a). There was no significant difference between the groups in terms of DFS (p=0.410). There was als no significant difference between the groups in terms of DFS (median 36 months for pN1b-with only 10, median 35.2 months for pN1b-with only 11, median 22 months for pN1b-with both 10+11, p=0.725) (Figure 3b). Overall survival and DFS of all patients are summarized in Table 4.

DISCUSSION

Accurately determining the pathological N status during lung cancer staging is important for determining the most appropriate treatment and predicting life expectancy. Although the T and M parameters of the TNM staging system have been revised in recent years, N status has remained unchanged. Studies of N1 patients before 2007 were discussed at the "Proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer" meeting. As a result of this meeting, multiple N1 groups of patients, metastasis to peripheral LNs, together with only 11 LN or only 10 LN, or those with 11 and 10 LNs suffer gradually worsening survival (median survival; 48, 36 and 28 months respectively) (8). However, the survival difference between the groups was not significant, probably because a large number of N1 patients did not undergo a prognostic evaluation (n=521). Only the single and multiple N1 patients differed significantly in terms of survival.

Akiko et al. (9) reported a significant difference in survival rates between N1 patient subgroups when they formed similar subclassifications. They suggested that N1 patients can be classified according to the highest level of N1 lymph node involvement. We noted a remarkable difference in survival between our "pN1b-with both 10+11 LN" group (22 months) and the "pN1b with only 10" (52.2 months) and "pN1b with only 11" (49.9 months) groups.

At the 2015 "Proposals for the revision of the N descriptors in the forthcoming eighth edition of the TNM classification for lung cancer" meeting, distinguishing single and multiple N1 groups for the purpose of survival analysis was discussed, and the survival rate was better for pN1a than pN1b patients. However, it was pointed out that more prospective studies are needed to change the current staging system (10). In the current study, the 5-year survival rates of the N1 patient groups were very similar to those reported at the latest IASLC meeting (IASLC vs present study; pN1, 53.2% vs. 49%; pN1a, 56.2% vs. 58%; and pN1b, 48.3% vs. 50%, respectively).

We found that the difference in survival rates between the pN1a and pN1b groups was significant in univariate analysis; however, it lost its significance in the multivariate analysis. Grif et al. (11) reported similar results; the survival difference between pN1a and pN1b groups seen in a univariate analysis disappeared in a multivariate analysis and, as in our study, tumor histology played a dominant role in determining the prognosis according to the multivariate analysis.

Differences in prognostic values between multiple N1 patients have been demonstrated apart from single N1 versus multiple N1; subgroups of multiple N1 include two stations-multiple N1, more than two stations-multiple N1, pN1b-with hilar LNs, pN1b-without hilar LNs, single-zone multiple N1 and multi-zone multiple N1 (12-14). Whether the prognosis differs among these subgroups remains unclear. We suggest that the difference between the results of the univariate and multivariate analyses may be due to differences in prognosis among the pN1b subgroups. There was a large difference in overall survival between the pN1b-without hilar group and pN1b-with hilar groups (85.9 vs. 42.3 months). However, the difference was not significant, probably because of the small number of patients. It was noteworthy that the pN1b-without hilar group showed similar 5-year survival rates with the pN1a Group (56% vs. 56.2%), which led us to question whether the pN1b-without hilar LNs patients should be really considered as multiple N1. A large series demonstrated better survival in a pN1b group with "peripheral spread" of LNs (15-16). Riquet et al. (17) reported similar results in a group of 256 N1 patients. They observed similar survival between patients with peripheral N1 involvement and N0 group; extralobar involvement and early stage N2 disease groups also had similar survival rates. As shown by many studies, the reason for the difference in survival between peripheral N1 cases and other subgroups may be attributed to direct extension of the tumor rather than metastasis to the LN. Van Velzen et al. (18) investigated this in their study and suggested that peripheral LN involvement should not be considered as a form of metastasis, but rather as indicative of direct extension and/or involvement of the tumor. They discussed the significant survival difference between "peripheral multiple N1" patients and "multi-zone N1" patients in their series. Direct extension of the tumor into adjacent LNs was defined as regional rather than metastatic disease, thus corresponding to an earlier disease stage. In many studies in the literature and in this study, hilar LN involvement appears to be a worse prognostic factor than peripheral LN involvement. We think that the poor prognostic factor of hilar LN involvement in N1 disease should be investigated with larger patient series.

Our study had some limitations, including its retrospective nature and the complexity of the proposed N1 disease classification system. Also, the clinical stages of the patients were unknown. Due to the small number of patients (n=11) in the single-hilar zone pN1b (isolated invasion of both station 10 and 11 LNs together) patient group, we could not analyze this group in terms of survival. The major strength of our study was that with a large patient series we only focused solely on N1 disease and multiple N1 subgroups, to shed more light on the impact of multiple N1 LNs invasion on the survival of

N1 patients. As we are a high-volume hospital that has been performing lung cancer surgeries for many years, we believe that our patients were staged appropriately given the experience of the thoracic surgeons in LN dissection, and the experience of our pathology team.

CONCLUSION

Although the nodal classification for NSCLC remains unchanged, a significant survival difference between pN1a and pN1b patients has been demonstrated by many studies. Further refinements of the classification system for N1 patients with NSCLC could be made. We also found a significant survival difference between the pN1a and pN1b patients in univariate analysis. However, this difference disappeared in the multivariate analysis. The pN1b patients without hilar metastasis tended to have better survival than the pN1b patients with hilar metastasis; the survival rate of the pN1b patients without hilar metastasis was similar to that of the single N1 patients. We think that this should be considered for the definition of multiple N1 in future staging systems with the support of prospective studies with large patient series.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Approval for the study was obtained from the institutional review board at Istanbul Training and Research Hospital clinical research Ethics Committee (2270/08.05.2020).

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