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Original Article / *Özgün Makale*

The impacts of isolated N1 lymph nodes metastasis on prognosis in non-small cell lung cancer: A single-center experience

Küçük hücreli dışı akciğer kanserinde izole N1 lenf nodu metastazlarının prognoz üzerine etkileri: Tek merkez deneyimi

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ABSTRACT

Background: This study aims to investigate long-term results related to N1 group metastases with respect to anatomical localization and many external parameters and to examine the effect of these parameters on prognosis in patients with in non-small cell lung cancer.

Methods: Between January 2006 and May 2019, a total of 52 patients (44 males, 8 females; mean age: 59.9±9.5 years; range, 42 to 80 years) who underwent lobectomy due to primary lung malignancy were retrospectively analyzed. The N1 lymph nodes were divided into three anatomical groups as hilar, peribronchial, and intraparenchymal. Demographic features, tumor features, follow-up characteristics, and survival and disease-free survival parameters were analyzed for each group. The results were also examined in terms of number of metastasis, number of metastatic levels, rate of metastasis, and histopathological type.

Results: The five-year survival rate was 66.4% in the peribronchial group and 50% in the hilar group. The five-year disease-free survival rate was 45.7% in the peribronchial group and 37.5% in the hilar group. There was no statistically significant difference between the groups in terms of survival and disease-free survival for anatomical localization, number of metastasis, number of metastatic levels, rate of metastasis, and histopathological type (p>0.05 for all).

Conclusion: The structure that would be formed by examining N1 in terms of parameters such as subtitle levels, number of metastasis, number of metastatic stations, rate of metastasis or combinations of these would have a more impact on the decisions in the follow-up and treatment process in this patient population.

Keywords: Lung cancer, N1 lymph node, prognosis.

ÖZ

Amaç: Bu çalışmada küçük hücreli dışı akciğer kanseri hastalarında N1 grubu metastazlarının uzun dönem sonuçları anatomik lokalizasyon ve birçok farklı parametre açısından incelendi ve bu parametrelerin prognoz üzerine etkisi araştırıldı.

Çalışma planı: Ocak 2006-Mayıs 2019 tarihleri arasında primer akciğer kanseri nedeni ile lobektomi yapılan toplam 52 hasta (44 erkek, 8 kadın; ort. yaş: 59.9±9.5 yıl; dağılım, 42-80 yıl) retrospektif olarak incelendi. N1 lenf nodları hiler, peribronşiyal ve intraparankimal olmak üzere üç anatomik gruba ayrıldı. Her grup demografik özellikler, tümör özellikleri, takip özellikleri ve sağkalım ve hastalıksız sağkalım parametrelerine göre analiz edildi. Sonuçlar ayrıca metastaz sayısı, metastatik düzey sayısı, metastaz oranı ve histopatolojik tip açısından da incelendi.

Bulgular: Beş yıllık sağkalım oranı peribronşiyal grupta %66.4 ve hiler grupta %50 idi. Peribronşiyal grupta beş yıllık hastalıksız sağkalım oranı %45.7 ve hiler grupta %37.5 idi. Anatomik lokalizasyon, metastaz sayısı, metastatik düzey sayısı, metastaz oranı ve histopatolojik tip grupları arasında sağkalım ve hastalıksız sağkalım süresi açısından istatistiksel olarak anlamlı bir fark yoktu (hepsi için p>0.05).

Sonuç: Alt düzey, metastaz sayısı, metastatik istasyon sayısı, metastaz oranı veya bunların kombinasyonları gibi parametreler kullanılarak N1 incelenmesi ile oluşturulacak bir yapı bu hasta popülasyonunda takip ve tedavi kararlarında daha fazla etkiye sahip olacaktır.

Anahtar sözcükler: Akciğer kanseri, N1 lenf nodu, prognoz.

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Lymph node metastasis is one of the most important prognostic factors in non-small cell lung cancer (NSCLC).[1-6] The N part of the Tumor, Node, Metastasis (TNM) system used in lung cancer staging refers to the lymph node status. The N1 lymph node metastasis indicates a prognostically heterogeneous group.[1,4,7-10] In current staging, N1 identifies lymph node stations in many anatomical localizations, independent of number.[11] Therefore, N1 group definition in the staging is not completely sufficient.[12] Therefore, prognosis may vary among the patients who are in the same stage.[12,13]

Previous studies regarding the N1 group have mostly addressed survival based on anatomical localization of the tumor and, in some studies, some combinations have been examined, independent of only anatomical localization.[10,14] Evaluation of surgical and oncological results using a high number of parameters would provide more accurate results. Obtaining specific results for subgroups of N1 group would contribute to more precise information about this heterogeneous group. This may be effective in tailoring postoperative management decisions.[15]

In the present study, we aimed to investigate long-term results related to N1 group metastases with respect to anatomical localization and many external parameters such as anatomical localization, number of metastasis (nN), number of metastatic stations (sN), rate of metastasis (lymph node ratio [LNR]), and histopathological type and to examine the effect of these parameters on prognosis.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Kocaeli University, Faculty of Medicine, Department of Thoracic Surgery between January 2006 and May 2019. A total of 364 patients who underwent lobectomy due to primary lung malignancy were retrospectively reviewed. Data were obtained from patient records, pathology reports, radiological imaging records and phone calls. Patients with isolated N1 lymph node metastasis apart from the main tumor, who underwent R0 surgery, and who did not undergo preoperative chemoradiotherapy were examined. Patients other than Stage 2b were excluded. Finally, a total of 52 patients (44 males, 8 females; mean age: 59.9±9.5 years; range, 42 to 80 years) were included.

Initially, N1 lymph nodes were divided into three anatomical groups: hilar, peribronchial, and intraparenchymal. Age, sex, smoking status, disease history, respiratory parameters, size, localization and stage of the tumor, histopathological types, recurrence and metastases, death, chemoradiotherapy status, surgical margin, visceral-vascular invasion, overall survival (OS), and disease-free survival (DFS) data were analyzed for each group. The results were also examined in terms of number of metastasis (nN1a-b) (a:single - b:multiple), number of metastatic levels (sN1a-b) (a:single - b:multiple), rate of metastasis (metastatic lymph node number/total LNR), and histopathological subtype. As the number of intraparenchymal lymph node group was low, the survival and DFS calculations were not calculated, as it could have caused misinterpretation of the statistical results. Due to the low number of recurrence and metastasis, all newly developing lesions secondary to the tumor were used and classified together in the DFS calculation. The classification of the World Health Organization (WHO) was used in histopathological typing and the 8th International Association for the Study of Lung Cancer (IASLC) classification was used in N definitions.

Surgical features

Before surgery, tumors of all patients were diagnosed by transthoracic biopsy or bronchoscopy. Positron emission tomography (PET)-computed tomography (CT), pulmonary function tests (PFTs), echocardiography, and blood tests were performed.

All operations were performed by a posterolateral thoracotomy with mediastinal lymph node dissection. To achieve standardization, only patients who underwent lobectomy were included in the study. A stapler was used while cutting and combining parenchymal adhesions and bronchus. The vessels were tied with silk thread and cut. Tissue adhesives were not used. Lymph nodes were removed by the surgeon during the operation or examined by the pathologist from the specimen in the postoperative period. Postoperatively, the patients were followed by chest radiography and tube thoracostomy. Tube thoracostomies that had no air leakage for more than 24 h and whose daily drainages were less than 100 mL were terminated. In general, if there was no additional condition, the patients were discharged approximately one day after the end of the tube thoracostomy. Survival times were calculated as of the operation day.

Follow-up

After resection, pathology reports were shared with the medical oncology and radiation oncology team and evaluated together. Routinely, a physical

examination and chest X-ray follow-up were done at one and three weeks after discharge. Thoracic CT follow-up was performed every three months in the first year, every six months in the second year, and annually thereafter. Abdominal ultrasound and abdominal CT examinations were performed. The PET-CT, magnetic resonance imaging (MRI), bone scintigraphy or biopsy methods were also used for the diagnosis of recurrence and metastasis. The patients who were properly followed by our clinic or whose data were complete and could be found regularly in the central recording system (e-Nabız) were included in the study.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the assumption of normality. Continuous variables were presented in mean ± standard deviation (SD) or median (25^{th}-75^{th} percentile). Categorical variables were presented in number and frequency. The relationships between categorical variables were evaluated using the chi-square analysis. Comparisons of continuous variables between the groups were carried out using independent samples t-test or Mann-Whitney U test, where applicable. The Kaplan-Meier method with log-rank test was used for survival analysis. A two-sided *p* value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 90.38% (n=47) of them were smokers. The mean forced expiratory volume in 1 sec (FEV1) was 2.40±0.61 L, and the median diffusion capacity for carbon monoxide (DLCO) was 77 (range, 42 to 127) mL/mmHg/min. There was no statistically significant difference among the groups in terms of age, sex, smoking rate, disease history, and respiratory parameters (Table 1).

Histopathological diagnosis of 26 (50%) patients were adenocarcinoma and 26 (50%) were squamous cell carcinoma (SCC). The mean tumor diameter was 2.51±0.98 cm. There was no statistically significant difference among the groups in terms of distribution of the main tumor localization, T stage, histopathological diagnosis, mean tumor diameter, surgical margin, visceral pleural invasion, and vascular invasion (Table 2).

Furthermore, recurrence-metastasis was observed in 18 (34.62%) patients during follow-up

Table 1. Demographic and clinical features of patients

	Total (n=52)				Hilar group (n=16)			Peribronchial group (n=32)			Intraparenchymal group (n=4)			
	n	%	Mean±SD	Median (Q1-Q3)	n	%	Mean±SD	Median (Q1-Q3)	n	%	Mean±SD	Median (Q1-Q3)	n	%	Mean±SD	Median (Q1-Q3)	*p*
Age (year)			59.9±9.5				60.5±6.7				59.3±10.8				62.5±10.3		0.688†
Sex																	0.786§
Male	44	86.62			12	75			28	87.5							
Female	8	15.58			4	25			4	12.5					4	100	
Smoking history	47	90.38			13	81.25			31	96.88					3	75	0.586§
Disease history																	0.684§
Absent	13	25			2	12.5			11	34.38			2	50			
Pulmonary	11	21.15			2	12.5			7	21.88			1	25			
Cardiovascular	20	38.46			8	50			10	31.25			1	25			
Other	10	18.23			2	12.5			8	25							
Respiratory function values																	
FEV1 (L)			2.4±0.6				2.2±0.7				2.5±0.6				2.3±0.5		0.456†
DLCO (mL/mmHg/min)				77				76				77				80	0.842‡

SD: Standard deviation; Q1-Q3: 25^{th}-75^{th} percentile; FEV1: Forced expiratory volume in 1 sec; DLCO: Diffusion capacity for carbon monoxide; † Independent samples t-test; ‡ Mann-Whitney U test; § Chi-square test.

Table 2. Main tumor features

	Total (n=52)			Hilar group (n=16)			Peribronchial group (n=32)			Intraparenchymal group (n=4)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Localization													0.798†
Right upper lobe	16	30.77		6	37.5		8	25		2	50		
Right middle lobe	3	5.77					3	9.38					
Right lower lobe	20	38.46		7	43.75		11	34.38		2	50		
Left upper lobe	5	9.62					5	15.63					
Left lower lobe	8	15.38		3	18.75		5	15.63					
Tumor diameter (cm)			2.5±1.0			2.4±0.8			2.7±1.2			1.6±0.1	0.515‡
T													0.063†
1a*	7	13.46		2	12.5		3	9.38		2	50		
1b	10	19.23		4	25		6	18.75					
1c	5	9.62		1	6.25		4	12.5					
2a	26	50		8	50		16	50		2	50		
2b	4	7.69		1	6.25		3	9.38					
Surgical margin													0.696†
<1 cm	11	21.15		4	25		7	21.88					
≤1 cm	41	78.85		12	75		25	78.13		4	100		
Visceral-vascular invasion													
Visceral invasion	13	25		4	25		9	28.13					1.00†
Vascular invasion	12	23.08		4	25		7	21.88		1	25		0.468†

SD: Standard deviation; * 1a1-2-3 viewed in 1a; n: number; † Chi-square test; ‡ Mann-Whitney U test.

(Table 3). There was no statistically significant difference among the groups in terms of recurrence or metastasis, chemotherapy, radiotherapy and mortality rate (Tables 3 and 4). There were 32 (61.54%) peribronchial, 16 (30.77%) hilar, and four (7.69%) intraparenchymal metastatic lymph nodes. The mean number of lymph nodes removed during surgery was 9.13±7.97. There was no statistically significant difference among the groups in terms of mean number of removed lymph node, LNR, nN1a-b, sN1a-b, number of histopathology groups, and recurrence-metastasis rate (Table 4).

While local recurrence was observed in 4 (7.69%) patients, systemic spread was observed in 18 (34.62%) patients. There was no statistically significant difference among the groups in terms of

Table 3. Features based on follow-up

	Total (n=52)			Hilar group (n=16)		Peribronchial group (n=32)		Intraparenchymal group (n=4)		
	n	%	Mean±SD	n	%	n	%	n	%	*p*
Follow up (month)			45.6±32.3							
Recurrence and/or metastasis	18	34.62		6	37.5	10	31.25	2	50	1.00†
Local recurrence	4	7.69		2	12.5	2	6.25			
Systemic spreading	18	34.62		6	37.5	10	31.25	2	50	
Lung metastasis	7	13.46		2	12.5	4	12.5	1	25	
Bone metastasis	7	13.46		3	18.75	3	9.38	1	25	
Liver metastasis	2	3.85		1	6.25	1	3.13			
Cranial metastasis	2	3.85		1	6.25	1	3.13			
Chemotherapy	18	34.62		6	37.5	10	31.25	2	50	0.618†
Radiotherapy	13	25		6	37.5	6	18.75	1	25	0.230†
Mortality	24	46.15		9	56.25	13	25	2	50	0.079†

SD: Standard deviation; † Chi-square test.

Table 4. Lymph node features

	Total (n=52)			Hilar group (n=16)			Peribronchial group (n=32)			Intraparenchymal group (n=4)		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	*p*
Number of lymph nodes*			9.13±7.97			11.8±9.27			7.8±7.32			0.522†
Lymph node number status												0.46‡
Single	23	44.23		9	56.25		12	37.5		2	50	
Multiple	29	55.77		7	43.75		20	62.5		2	50	
LNR		0.25			0.26			0.28				0.514‡
Number of lymph node stations												0.32‡
Single	43	82.69		11	68.75		28	87.5		4	100	
Multiple	9	17.31		5	31.25		4	12.5				
Histopathology												0.454‡
Adenocarcinoma	26	50		10	62.5		14	43.75		2	50	
Squamous cell carcinoma	26	50		6	37.5		18	56.25		2	50	
Recurrence-metastasis				Adenocarcinoma						Squamous cell carcinoma		
Single lymph node metastasis	8	44.44		4	50					4	50	
Multiple lymph node metastasis	10	55.56		5	50					5	50	

SD: Standard deviation; LNR: Lymph node ratio; * Removed in operation; † Mann-Whitney U test; ‡ Chi-square test;.

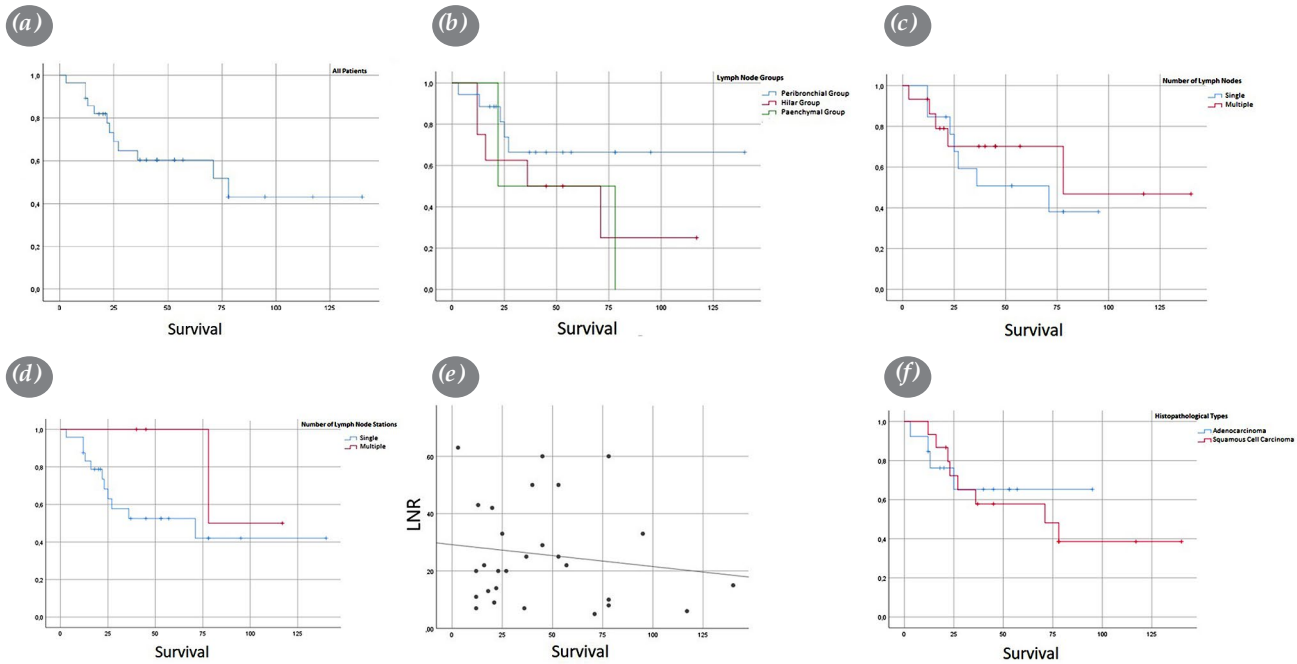

Figure 1. Survival analysis. **(a)** Survival of all patients. **(b)** Survival for lymph node groups. **(c)** Survival for the number of metastatic lymph nodes. **(d)** Survival for the number of metastatic lymph node levels. **(e)** Relationship between metastatic lymph node ratio and survival. **(f)** Survival for histopathological types.

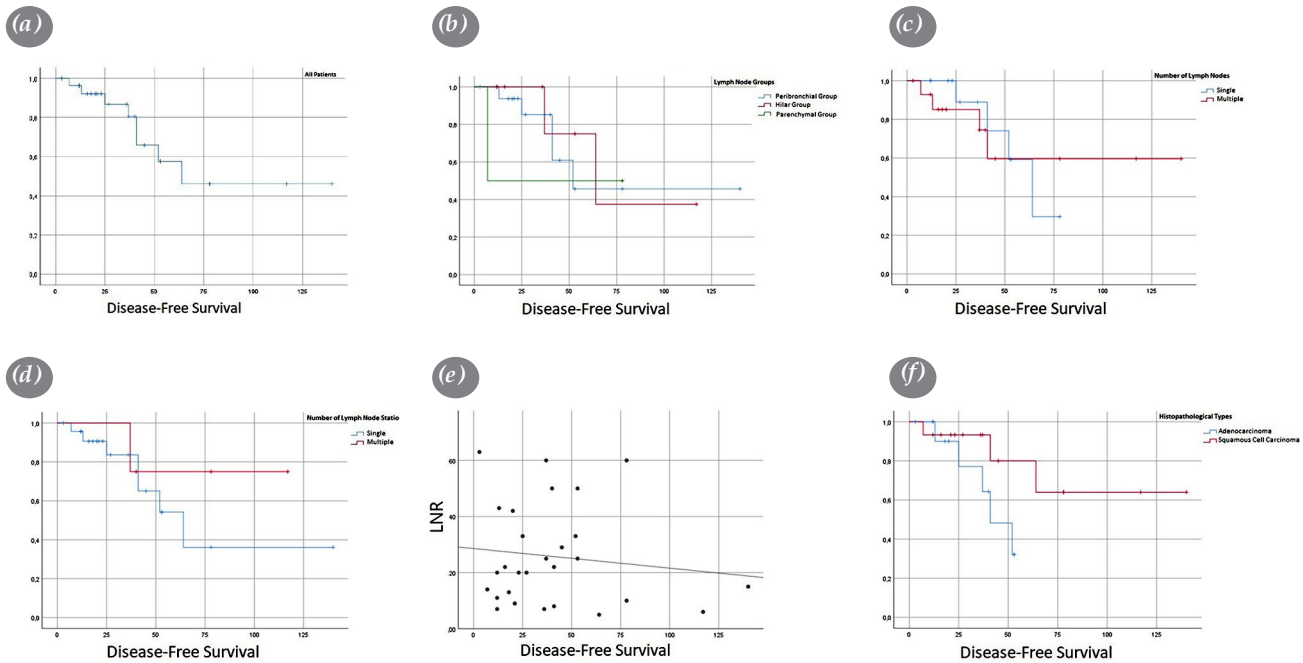

Figure 2. Disease-free survival (DFS). **(a)** DFS of all patients. **(b)** DFS for lymph node groups. **(c)** DFS for the number of metastatic lymph nodes. **(d)** DFS for the number of metastatic lymph node levels. **(e)** Relationship between metastatic lymph node ratio and DFS. **(f)** DFS for histopathological types.

Table 5. Survival and disease-free survival analysis results

	Total	Hilar group	Peribronchial group	
	%	%	%	p†
All patients				
5 year survival	62.75	52.3	67.2	0.302
5 year DFS	42.95	38,00	44.8	0.840
Lymph node number status		Single	Multiple	
5 year survival		62.23	63.33	0.616
5 year DFS		41.56	43.04	0.886
Lymph node station status				
5 year survival		62.70	60.58	0.360
5 year DFS		42.88	41.78	0.396
LNR				
Survival		Correlation coefficient: 0.084		0.645
DFS		Correlation coefficient: 0.042		0.866
Histopathological type		Adenocarcinoma	Squamous cell carcinoma	
5 year survival		69.03	56.48	0.844
5 year DFS		47.25	38.66	0.096
Hilar group				
5 year survival		57.53	47.07	0.842
5 year DFS		41.8	34.2	0.214
Peribronchial group				
5 year survival		73.92	60.48	0.468
5 year DFS		49.28	40.32	0.332

DFS: Disease-free survival; LNR: Lymph node ratio; † Kaplan-Meier method.

total recurrence-metastasis, recurrence-metastasis of nN1a-b groups and histopathological subtypes in terms of recurrence-metastasis in nN1a-b (Table 4).

The mean follow-up was 45.6±32.3 (range, 3 to 140) months. The five-year survival rate was 62.75%, and five-year DFS rate was 42.95% (Figures 1 and 2). There was no statistically significant difference among the groups in terms of survival and DFS for anatomical groups, nN1a-b groups, sN1a-b groups, total histopathological types, and histopathological types on the basis of lymph node groups (Table 5, Figures 1 and 2).

In the non-parametric correlation test, there was an inverse proportion among the LNR, and survival and DFS, although it did not reach statistical significance (cc: 0.084, p=0.645; cc: 0.042, p=0.866, respectively) (Table 5, Figures 1 and 2).

DISCUSSION

In NSCLC, N1 is defined as ipsilateral peribronchial, hilar, or intraparenchymal lymph nodes.[1,2,7] The N1 lymph nodes are located in five stations ranging from hilar (level 10) level to subsegmental (level 14) level.[7,16,17] In addition, N1 metastasis occurs in 11 to 18% of NSCLC.[18] In our study, it was seen in 14.29% of the patients undergoing lobectomy.

Defining the level of dissected lymph node mostly depends on the surgeon's experience and may be a difficult decision. Therefore, in some studies, this situation was attempted to be prevented by classifying lymph nodes as hilar (level 10), interlobar (level 11-12), segmental (level 13-14), or hilar/interlobar-peripherally.[15,17] In our study, N1 lymph nodes were classified as hilar, peribronchial, and intraparenchymal.

In NSCLC, a five-year survival rate of 7 to 67% has been reported in isolated N1 metastasis.[4,7,13,18-20] In the study of Liu et al.,[15] which included 163 patients, 80.4% of whom underwent lobectomy, the three-year and five-year survival rates were 62.1% and 43.5%, respectively. The five-year DFS rate was reported in patients with N1 metastasis at a rate of 50.1 to 52%.[7,17] In our study, the five-year survival rate was 62.75%, and the five-year DFS rate was 42.95%.

In many studies related to the subject, better prognosis is predicted in N1 metastases from hilar to peripheral level.[7,9,15,17,20] In the study of Liu et al.,[15] the five-year survival rate in the hilar/interlobar group was 37.1%, and this rate was 49.9% in peripheral N1 metastases. In the study of Eichorn et al.,[20] the five-year survival rate was 74.2% in hilar and 69.5% in peripheral N1 metastases, and the five-year survival rate was 59.9% in both hilar and peripheral N1 metastasis, and 68.2% in patients with metastasis in the hilar or peripheral group and no statistically significant difference was observed between the groups (p=0.849, p=0.068, respectively).

Lymph node metastases limited to intrapulmonary levels have been reported to show an intermediate prognosis between N0 and N1.[7,16] Similarly, in the study of Rena et al.,[17] the five-year survival rate and DFS rates of intraparenchymal N1 metastasis were found to be located between N0 and N1. Also, in the same study, the five-year survival and DFS rates of level 10 lymph node metastasis were reported to be between the level 11-12 lymph nodes and N2 lymph node metastases. In a study with 120 SCC-diagnosed N1 metastases conducted by Nakao et al.,[4] N1 lymph nodes were classified as direct and discrete groups according to the distance from the main tumor. They reported that the results of the discrete N1 group were almost as poor as N2, although the results of the N1 group were compared with N0 tumors.[4] According to these results, although direct N1 metastasis supports local discrete N1 metastasis to be systemic, both groups were classified as N1.[4] In our study, the five-year survival rate was 52.3% in the hilar group and 67.2% in the peribronchial group. Although the hilar group which was more central in the peribronchial group, a proportional superiority was observed. However, no statistically significant difference was observed between the groups (p=0.302). Similarly, the estimated survival time was longer in the peribronchial group. The five-year DFS rates were 38% in the hilar group and 44.8% in the peribronchial group. In the peribronchial group, although the estimated survival time was longer, no significant difference was observed between the groups (p=0.840).

The nN in operable lung cancer has been reported to be an independent prognostic factor.[10,12] There are studies reporting a better outcome of nNa than nNb.[6,7,17] In a study, the five-year survival rate was 67.6% in nNa group and 66.6% in nNb group.[20] In the same study, although there was a better survival tendency in nNa group, there was no significant difference between the groups (p=0.623).[20] Saji et al.[14] reported that a small number (1-3) of N1 metastasis was a better prognostic factor than a higher number of metastases. In this study, the five-year survival and DFS rates were 64.8% and 71.6% in the group with 1-3 number N1 metastases versus 39.2% and 32.9% in the group with four and more N1 metastases (p<0.0001, p=0.0002, respectively).[14] According to some authors, the nN for lung cancers may better express the N category prognosis than the currently used anatomical localization.[3,12,14] In our study, contrary to the literature, the five-year survival and DFS rates of nN1b group (63.33% and 43.04%, respectively) were better than nN1a group (62.23% and 41.56%, respectively). However, there was no statistically significant difference between the groups (p=0.567, p=0.886, respectively). This can be attributed to the high number of nN1b in the peribronchial lymph node group with better prognosis.

The long term outcomes have been reported to be better in patients with sN1a than in cases of sN1b.[7,13,20] In the study of Eichhorn et al.,[20] the five-year survival rate was 58% in sN1a group and 50% in sN1b group. In the study of Maeshima et al.,[7] the five-year DFS rate was 56.3% in sN1a group and 37.8% in sN1b group. Similar to the literature, in our study, the five-year survival and DFS rates were better in sN1a group (62.70% and 42.88%, respectively) than sN1b group (60.58% and 41.78%, respectively). However, there was no statistically significant difference between the groups (p=0.360, p=0.396, respectively).

The LNR is a poor prognostic factor.[7] Indeed, some studies have reported that LNR can be an independent predictor in operable N1 NSCC cases.[6] In the study of Wang et al.,[12] the worst five-year survival rate was found in the group with high LNR, compared to the lower group (p<0.0001). In daily practice, however, it may not be an ideal prognostic factor to use the number of lymph nodes directly or in combination, since there may not be enough N1 lymph node excision or examination in all patients due to different surgical experiences. In contrast, Wang et al.,[12] suggested that the prognostic impact of LNR would less affect the number

of dissected lymph nodes. In our study, as the LNR increased, estimated survival and DFS rates decreased, although no statistically significant difference was observed (p=0.645, p=0.866, respectively).

The five-year survival or DFS have been reported to be better in patients with SCC than in cases of adenocarcinoma.[7,9,15,17] In some studies, however, no significant difference was found between the histopathological types in terms of survival time.[15] In a study, central and nN1b had a worse prognosis in the group diagnosed with adenocarcinoma.[20] In this study, the effect of sN1b on survival was observed only in the histopathological type of adenocarcinoma. In our study, the five-year survival rate was 56.48% in SCC group and 69.03% in adenocarcinoma group. The five-year DFS rate was 47.25% in adenocarcinoma group and 38.66% in SCC group. However, there was no statistically significant difference between the two groups (p=0.844, p=0.096, respectively). There was no statistically significant difference in adenocarcinoma and SCC histopathological groups in both peribronchial and hilar LN groups for the five-year survival and DFS rates (p=0.842-0.214, p=0.468-0.332, respectively).

Another issue is that intrapulmonary lymph node metastasis rates have been reported between 12 and 37.5% in the literature, and there is no standard protocol for pathological examination of these metastases.[16] In our study, this rate was 7.69%. Other than routine, repeating gross tissue examination or performing this examination by a second physician (e.g., the surgeon) may increase the rate of pathological lymph nodes. It has been reported that the pathological stage may increase by 2.4% or 11% after a routine or careful pathological examination.[6,16]

According to the reports in the literature, N1 definitions are found to be insufficient in the last lung TNM classification. Evaluations in the form of nN, LNR, and combinations of these among themselves and localization are reported to reflect the prognosis more successfully.[9,14,15,18] Peribronchial station metastasis, nN1a, sN1a, direct invasion, and microscopic invasion are considered good prognostic factors for N1 metastases.[7,17] In our study, although not statistically significant, peribronchial station metastasis, sN1a, low LNR, and histopathological type of adenocarcinoma were good prognostic factors for prognosis.

The present study has some limitations. First, the study is retrospective and our final total number of patients is relatively low. Second, in the study, only patients who underwent resection were included, and there were no results for patients with unoperated N1 metastases. Third, while defining the lymph node localization, the definition of localization of the lymph nodes in the intermediate zones was dependent on the surgeon. In addition, at levels 10, 11, and 12, excision was surgeon-dependent, while 14 and 15 levels were mostly pathologist-dependent.

In conclusion, as in the last Tumor, Node, Metastasis classification, if N1 is considered only in terms of anatomical localization, it may be insufficient to reflect the prognosis accurately. In our study, we found no significant difference in the majority of the criteria analyzed; however, we observed a proportional difference in almost all of the criteria. With the contribution of larger studies in the future, the structure that would be formed by examining N1 in terms of parameters such as sub-levels, number of metastasis, number of metastatic stations, rate of metastasis or combinations of these would have a more impact on the decisions in the follow-up and treatment process of this patient population.

Ethics Committee Approval: The study protocol was approved by the Kocaeli University, Faculty of Medicine, Ethics Committee (Date: 15/06/2020, No: 2020/130). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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