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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Long-term outcomes of surgery in resectable single-station N2 non-small cell lung cancer patients

Rezeke edilebilir tek istasyon N2 küçük hücreli dışı akciğer kanserli hastalarda uzun dönem cerrahi sonuçları

Bahar Agaoglu Sanli, Serkan Yazgan, Ahmet Ucvet, Esra Yamansavci Şirzai, Yunus Turk

Department of Thoracic Surgery, University of Health Sciences, Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, İzmir, Türkiye

ABSTRACT

Background: This study aims to examine the factors influencing prognosis and long-term survival outcomes in pathological single-station N2 (pN2a) patients undergoing surgical treatment for non-small cell lung cancer.

Methods: Between January 2012 and June 2021, a total of 144 patients (125 males, 19 females; mean age: 60.5±8.4 years; range, 48 to 78 years) who underwent anatomical resection for non-small cell lung cancer and were identified with pN2a disease were retrospectively analyzed. Factors influencing prognosis were analyzed. Survival analysis was performed.

Results: Forty-nine (34%) patients received neoadjuvant therapy and 87 (60.4%) patients underwent lobectomy. In terms of staging, 95 (66%) patients were classified as Stage 3A, while 49 (34%) patients were categorized as Stage 3B. Analysis of N2 subtypes revealed that 77 (53.5%) patients were classified as known N2, whereas 67 (46.5%) patients were identified as incidental. Histopathological evaluation revealed that 58 (40.3%) patients had adenocarcinoma, while 86 (59.7%) patients had non-adenocarcinoma histology. N2 disease was categorized as skip metastasis (pN0N2a) in 61 (42.4%) patients and non-skip metastasis (pN1N2a) in 83 (57.6%) patients. Adjuvant therapy was administered to 126 (87.5%) patients, with treatment modalities determined by the oncology clinics and patient characteristics. Among these, 46 (31.9%) patients received chemotherapy, 15 (10.4%) patients underwent radiotherapy, and 65 (45.1%) patients were treated with chemoradiotherapy. The five-year overall survival rate was 33.9% with a median duration of 37.1±5.0 months. The disease-free survival rate was 24.9% with a median duration of 18.2±2.3 months. Adenocarcinoma histology, non-skip N2 disease, lack of adjuvant therapy, and advanced age (>65 years) were found to be significant factors affecting the prognosis of pN2a disease.

Conclusion: The findings of this study indicate that adenocarcinoma histology, advanced age, absence of adjuvant therapy, and the presence of pN1N2a are significant prognostic factors in pN2a patients undergoing curative resection for non-small cell lung cancer.

Keywords: Adenocarcinoma, adjuvant therapy, elderly, lymph node, non-small cell lung cancer, single station N2, skip N2, surgery.

ÖZ

Amaç: Bu çalışmada küçük hücreli dışı akciğer kanseri nedeniyle cerrahi yapılan patolojik tek istasyon N2 (pN2a) hastalarda prognozu ve uzun dönem sağkalım sonuçlarını etkileyen sonuçlar değerlendirildi.

Çalışma planı: Ocak 2012 - Haziran 2021 tarihleri arasında küçük hücreli dışı akciğer kanseri nedeniyle anatomik rezeksiyon uygulanan ve pN2a hastalığı belirlenen toplam 144 hasta (125 erkek, 19 kadın; ort. yaş: 60.5±8.4 yıl; dağılım, 48-78 yıl) retrospektif olarak incelendi. Prognoza etki eden faktörler analiz edildi. Sağkalım analizi yapıldı.

Bulgular: Kırk dokuz (%34) hastaya neoadjuvan tedavi uygulanırken, 87 (%60.4) hastaya lobektomi uygulandı. Evreleme açısından 95 (%66) hasta Evre 3A olarak sınıflandırılırken, 49 (%34) hasta Evre 3B olarak sınıflandırıldı. N2 alt tiplerinin analizi, 77 (%53.5) hastanın bilinen N2 olarak sınıflandırıldığını, 67 (%46.5) hastanın ise tesadüfi olarak tanımlandığını ortaya koydu. Histopatolojik değerlendirmede 58 (%40.3) hastada adenokarsinom ve 86 (%59.7) hastada adenokarsinom dışı histolojiye rastlandı. N2 hastalığı 61 (%42.4) hastada atlanan metastaz (pN0N2a) ve 83 (%57.6) hastada atlanmayan metastaz (pN1N2a) olarak sınıflandırıldı. Tedavi yöntemleri onkoloji kliniğine ve hasta özelliklerine göre belirlenen 126 (%87.5) hastaya adjuvan tedavi uygulandı. Bunlardan 46 (%31.9) hastaya kemoterapi, 15 (%10.4) hastaya radyoterapi ve 65 (%45.1) hastaya kemoradyoterapi uygulandı. Beş yıllık genel sağkalım oranı %33.9 olup, medyan süre 37.1±5.0 ay idi. Hastalıksız sağkalım oranı %24.9 olup, medyan süre 18.2±2.3 ay idi. Adenokarsinom histolojisi, atlanmayan N2 hastalığı, adjuvan tedavi eksikliği ve ileri yaş (>65 yaş), pN2a hastalığının prognozunu etkileyen önemli faktörler olarak bulundu.

Sonuç: Bu çalışmanın bulguları, küçük hücreli dışı akciğer kanseri nedeniyle küratif rezeksiyon yapılan pN2a hastalarında adenokarsinom histolojisi, ileri yaş, adjuvan tedavinin olmaması ve pN1N2a varlığının önemli prognostik faktörler olduğunu göstermektedir.

Anahtar sözcükler: Adenokarsinom, adjuvan tedavi, yaşlı, lenf nodu, küçük hücreli dışı akciğer kanseri, tek istasyon N2, atlanan N2, cerrahi.

Corresponding author: Bahar Ağaoğlu Şanlı.
E-mail: drbaharagaoglu@hotmail.com

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Non-small cell lung cancer (NSCLC) represents one of the primary causes of cancer-related mortality globally.[1] At the time of diagnosis, approximately 30% of NSCLC cases are classified as locally advanced.[2]

Klastersky et al.[3] were the first to define single-station N2 disease (N2a) without intranodal spread as "minimal N2". Mediastinal lymph node metastasis is recognized as the most critical prognostic factor in patients undergoing complete resection with no evidence of distant metastasis.[4] The five-year survival rates of NSCLC patients in pathological Stages 1a, 1b, 2a, and 2b following complete resection are significantly lower compared to those observed in other solid organ tumors.[5] This outcome is thought to stem from insufficient invasive staging prior to resection or inadequate dissection of mediastinal lymph nodes.[6] In a prospective study conducted by Cerfolio et al.,[7] N2 disease was identified in 2.9% and 3.7% of patients with Stage 1 and Stage 2 NSCLC, respectively, despite the absence of mediastinal lymph node metastases detected through routine mediastinoscopy, endobronchial ultrasonography (EBUS), or positron emission tomography-computed tomography (PET-CT).[7] Resectable N2 disease represents a heterogeneous group, as evidenced by survival analyses reporting outcomes ranging from 6 to 35%.[8]

The standard approach for early-stage NSCLC involves complete surgical resection, with lobectomy remaining the gold standard for eligible patients.[9] Mediastinal lymph node dissection is recommended in all cases. The identification of pN2 in patients undergoing surgery for NSCLC is associated with a worse prognosis. Based on the presence of pathological N1 (pN1), pN2 disease may manifest as skip metastases (pN0N2) or non-skip metastases (pN1N2).[10] The optimal treatment strategy and prognostic factors for patients with pN2A remain subjects of ongoing debate.[10] Among these subgroups, pN2A and pN0N2 are particularly significant from a prognostic perspective.[9-11]

In the present study, we aimed to examine the factors influencing prognosis and long-term survival outcomes in pN2A patients undergoing surgical treatment for NSCLC.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at University of Health Sciences, Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, Department of Thoracic Surgery between January 2012 and June 2021. Among 159 consecutive patients who underwent anatomical resection for NSCLC, pathological examination confirmed the presence of pN2A. Fifteen patients were excluded from the study due to histological diagnoses other than NSCLC, a history of concurrent malignancies or prior primary cancers, distant metastases, microscopically positive surgical margins, or operative mortality. Finally, 144 patients (125 males, 19 females; mean age: 60.5±8.4 years; range, 48 to 78 years) who met the inclusion criteria were included. Survival rates of the patients were assessed, and factors influencing prognosis were analyzed. Data regarding age, histopathology, lymph node metastasis, tumor size, T status, comorbidities, neoadjuvant therapy, and adjuvant therapy were collected from hospital records, surgical reports, patient charts, and the national survival database. A written informed consent was obtained from each patient. The study protocol was approved by the University of Health Sciences, Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital Clinical Research Ethics Committee (date: 21.06.2023, no: CREC 2023/40-41). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Preoperative assessment

The preoperative evaluation protocol included posteroanterior chest radiography, thoracic CT, fiberoptic bronchoscopy, PET-CT, cranial magnetic resonance imaging (MRI) or CT, pulmonary function tests, and blood gas analysis as standard procedures. Patients showing involvement on PET-CT underwent EBUS and/or mediastinoscopy for staging. Those diagnosed with N2 disease were referred for neoadjuvant therapy, and invasive staging (EBUS and/or mediastinoscopy) was performed in patients with suspected N2 disease on PET-CT following the completion of neoadjuvant treatment.

Follow-up

Discharged patients were monitored through regular follow-up visits in the outpatient clinic, with all complications and deaths recorded. Follow-up evaluations were conducted at three, six, nine, and 12 months during the first postoperative year, at six-month intervals over the subsequent two years, and annually thereafter. Throughout the study period, the final status of each patient was verified using data from the national population registry system. All recorded deaths were included in the survival analysis. Survival time was calculated as the interval between the date of surgery and either the date of death or the date of the most recent record update.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 29.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Group comparisons were made using the Pearson chi-square test or Fisher exact two-tailed test, and the mean age and tumor size were made using the Student t-test. Kaplan-Meier method was

Table 1. Patient characteristics

Characteristics	n	%	Mean±SD
Age (year)			60.5±8.4
Sex			
Male	125	86.8	
Female	19	13.2	
Tumor size (cm)			4.2±2.2
Survival (month)			39.6±30.6
Disease free period (month)			
Conclusion			
Alive	47	32.6	
Exitus	97	67.4	
Incision			
VATS	9	6.3	
Thoracotomy	135	93.8	
Direction			
Right	75	52.1	
Left	69	47.9	
Operation			
Lobectomy	87	60.4	
Bilobectomy	26	18.1	
Pneumonectomy	31	21.5	
Neoadjuvant treatment			
Yes	49	34.0	
No	95	66.0	
Sleeve resection			
Yes	17	11.8	
No	127	88.2	
Chest wall resection			
Yes	4	2.8	
No	140	97.2	
Pericardial resection			
Yes	44	30.6	
No	100	69.4	
Tumor size group (cm)			
0	2	1.4	
<3	51	35.4	
3-7	76	52.8	
>7	15	10.4	
Lymph node station			
2	2	1.4	
4	40	27.8	
5	23	16.0	
6	17	11.8	
7	30	20.8	
8	22	15.3	
9	10	6.9	

Characteristics	n	%	Mean±SD
Conclusion			
Disease free survivor	34	23.6	
Recurrence or exitus	110	76.4	
Lymph node on PET-CT			
Positive	77	53.5	
Negative	67	46.5	
N2 Subtype			
Random	67	46.5	
Known	77	53.5	
Invasive intervention			
None	93	64.6	
EBUS	38	26.4	
Mediastinoscopy	12	8.3	
EBUS + MS	1	0.7	
Adjuvant treatment			
None	18	12.5	
Chemotherapy	46	31.9	
Radiotherapy	15	10.4	
Chemoradiotherapy	65	45.1	
Age group			
≤65	101	70.1	
>65	43	29.9	
Histology			
Adenocarcinoma	58	40.3	
Other	86	59.7	
pT			
1	40	27.8	
2	55	38.2	
3	33	22.9	
4	16	11.1	
Stage			
3a	95	66.0	
3b	49	34.0	

SD: Standard deviation; VATS: Video-assisted thoracoscopic surgery; PET-CT: Positron emission tomography-computed tomography; EBUS: Endobronchial ultrasonography; MS: Mediastinoscopy; pT: Tumor size.

used for survival calculations and survival rates were compared with log-rank and Cox regression analysis. A p value of ≤0.05 was considered statistically significant.

RESULTS

Based on age groups, 101 (70.1%) patients were under 65 years of age, while 43 (29.9%) patients were 65 years or older. The mean tumor size was 4.2±2.2 cm. Among the surgical approaches, nine (6.3%) patients underwent video-assisted thoracoscopic surgery (VATS), whereas 135 (93.8%) patients underwent thoracotomy; surgeries were performed on the right side in 75 (52.1%) patients and on the left side in 69 (47.9%) patients. Regarding the type of surgical procedure, 87 (60.4%) patients underwent lobectomy, 26 (18.1%) underwent bilobectomy, and 31 (21.5%) underwent pneumonectomy.

Staging revealed that 95 (66%) patients were classified as Stage 3a and 49 (34%) patients as Stage 3b. Among the N2 subtypes, 77 (53.5%) patients were classified as known N2, while 67 (46.5%) patients were classified as incidental N2. Histopathological evaluation identified adenocarcinoma in 58 (40.3%) patients and non-adenocarcinoma histology in 86 (59.7%) patients. Positivity for lymph nodes on PET-CT was observed in 77 (53.5%) patients, while 67 (46.5%) patients showed negative results. Invasive lymph node evaluation was not performed in 93 (64.6%) patients; however, 38 (26.4%) patients underwent EBUS, 12 (8.3%) patients underwent mediastinoscopy, and one (0.7%) patient underwent both EBUS and mediastinoscopy. Neoadjuvant therapy was administered to 49 (34%) patients.

Of 20 patients who underwent left pneumonectomy, number 5 lymph node was detected positive in four, number 6 lymph node in five, number 7 lymph node in five, number 8 lymph node in four, and number 9 lymph node in two patients. Of the 28 patients who underwent left upper lobectomy, lymph node number 4 was positive in three, number 5 in 14, and number 6 in 11 patients. Of 21 patients who underwent left lower lobectomy, lymph node number 5 was detected positive in five, number 6 in one, number 8 in four, and number 9 in five patients. Of 11 patients who underwent right pneumonectomy, lymph node number 2 was detected positive in two, number 4 in five, number 7 in two, number 8 in one, and number 9 in one patient. Of 28 patients who underwent right upper lobectomy, lymph node number 4 was positive in 26 and number 7 was found to be positive in two patients. Of 10 patients who underwent right lower lobectomy, lymph node number 4 was detected in one, lymph node number 7 in five, and number 8 in four patients. Of the 26 patients who underwent bilobectomy, lymph node number 4 was found positive in five, number 7 in 10, number 8 in nine, and number 9 in two patients.

Considering the metastases in lymph node stations, metastases were detected in lymph node number 2 in two (1.4%) patients, number 4 in 40 (27.8%) patients, number 5 in 23 (16.0%) patients, number 6 in 17 (11.8%) patients, number 7 in 30 (20.8%) patients, number 8 in 22 (15.3%) patients and number 9 in 10 (6.9%) patients. N2 disease was classified as skip (pN0N2) in 61 (42.4%) patients and non-skip (pN1N2) in 83 (57.6%) patients. Adjuvant therapy was administered to 126 (87.5%) patients, with treatment modalities varying based on the oncology clinic and patient-specific characteristics: 46 (31.9%) patients received chemotherapy (CR), 15 (10.4%) patients received radiotherapy (RT), and 65 (45.1%) patients underwent chemoradiotherapy (CRT) (Table 1).

Five-year overall survival (OS) rate and median OS were 33.9% and 37.1±5.0 months, respectively (Figure 1). Disease-free survival (DFS) rate and DFS time were 24.9% and 18.2±2.3%. The five-year survival rate in patients not receiving neoadjuvant therapy was 31.5%, while it was similar to 37.9% in patients receiving neoadjuvant therapy. The factors which negatively affected pN2A prognosis were adenocarcinoma histology, pN1N2, absence of adjuvant treatment and advanced age (>65 years) (Table 2, Figure 2). In the multivariate Cox analysis, age, histology, skip and non-skip N2, adjuvant and neoadjuvant treatment were included. (Table 3).

DISCUSSION

Studies on NSCLC patients have shown that surgical treatment provides significant benefits for patients with Stage 1a to 3a disease, whereas it is not superior to oncological treatments in patients with Stage 3b and 4 (a-b) disease.[12] Consequently, accurately determining the N and T stages-key components of TNM staging-through thoracic CT and PET-CT is critical prior to surgery. Among imaging modalities, PET-CT remains the most reliable non-invasive diagnostic tool, with reported sensitivity ranging from 74 to 85% and specificity between 70 and 92%.[13-16] Nevertheless, studies have reported pN2 rates of up to 15.3% in patients with PET-CT-negative findings, highlighting the necessity of additional invasive mediastinal staging.[17] This discrepancy may, in part, be attributed to the limited ability of PET-CT imaging to detect carcinoid tumors

Table 2. Survival analyses

Variables	Overall survival					Disease free survival				
	5-year survival (%)	Mean±SD	Median survival	Median survival 95% CI	*p*	5-year survival (%)	Mean±SD	Median survival	Median survival 95% CI	*p*
General	33.9	37.1±5.0		27.1-47.1	-	24.9	18.2±2.3		13.6-22.7	-
Sex					0.417					0.960
Male	32.9		22.3-46.4	22.3-46.4		24.8		13.8-23.4	13.8-23.4	
Female	40.9		19.5-64.6	19.5-64.6		26.3		5.6-24.7	5.6-24.7	
Direction					0.194					0.549
Right	36.0		37.7-54.1	37.7-54.1		25.9		12.2-29.9	12.2-29.9	
Left	31.9		16.3-40.3	16.3-40.3		24.1		12.4-22.9	12.4-22.9	
Neoadjuvant treatment					0.425					0.744
Yes	31.5		19.2-66.9	19.2-66.9		23.8		9.1-25.7	9.1-25.7	
No	37.9		19.7-54.2	19.7-54.2		25.4		12.9-24.3	12.9-24.3	
N2 subtype					**0.05**					0.106
Skip N2	43.7		26.9-68.8	26.9-68.8		32.1		19.7-33.4	19.7-33.4	
Non-skip N2	26.4		13.0-42.4	13.0-42.4		19.5		10.8-18.9	10.8-18.9	
N2 disease					0.156					0.78
Random N2	41.3		21.9-43.3	21.9-43.3		31.2		4.3-49.2	4.3-49.2	
Known N2	27.1		36.4-59.9	36.4-59.9		19.5		13.1-21.0	13.1-21.0	
Adjuvant treatment					**0.008**					**0.002**
None	13.3		7.0-28.2	7.0-28.2		5.6		1.1-13.6	1.1-13.6	
Chemotherapy	44.3		27.2-69.2	27.2-69.2		35.9		16.2-36.3	16.2-36.3	
Radiotherapy	38.9		0-63.9	0-63.9		20.0		3.1-23.2	3.1-23.2	
Chemoradiotherapy	32.2		29.5-54.6	29.5-54.6		24.7		6.1-38.6	6.1-38.6	
Adjuvant treatment					**0.002**					**0.002**
Yes	36.8		30.9-54.6	30.9-54.6		27.8		13.7-28.4	13.7-28.4	
No	13.3		7.0-28.2	7.0-28.2		5.6		1.1-13.6	1.1-13.6	
Age group (year)					**<0.001**					**0.003**
≤65	42.6		30.2-59.7	30.2-59.7		31.1		13.2-28.9	13.2-28.9	
>65	10.9		10.1-31.0	10.1-31.0		7.8		5.1-18.0	5.1-18.0	
Operation					0.198					0.671
Lobectomy	35.6		32.2-51.9	32.2-51.9		25.7		14.1-23.1	14.1-23.1	
Pneumonectomy	28.2		13.3-34.8	13.3-34.8		21.2		0-28.6	0-28.6	
Histology					0.490					**0.035**
Adenocarcinoma	28.7		22.4-42.9	22.4-42.9		16.2		12.4-20.7	12.4-20.7	
Other	37.2		29.6-55.9	29.6-55.9		30.8		14.7-30.8	14.7-30.8	
pT					0.703					0.926
1	34.6		3.1-65.7	3.1-65.7		24.8		8.4-26.3	8.4-26.3	
2	31.1		22.5-58.4	22.5-58.4		20.3		16.1-29.6	16.1-29.6	
3	39.9		10.2-63.9	10.2-63.9		29.4		8.6-19.5	8.6-19.5	
4	28.6		0-53.2	0-53.2		30.0		0-21.2	0-21.2	
Stage					0.785					0.674
3A	32.8		26.1-54.8	26.1-54.8		22.1		16.9-28.6	16.9-28.6	
3B	35.6		13.1-55.3	13.1-55.3		29.5		7.5-20.4	7.5-20.4	

SD: Standard deviation; pT: Tumor size.

and adenocarcinomas.[18] In our study, 32 (52.5%) of 61 skip N2 patients had pathological lymph node involvement in PET-CT. There was lymph node involvement in 46 (55.4%) patients in the non-skip group. Few studies have reported on skip N2 disease based on the results of modern radiological examinations, including PET-CT. Kim et al.[19] investigated the surgical outcomes in c-skip N2 and non-skip N2 patients based on the results of modern radiological examinations. As a criterion for lymph node positivity, the authors showed that the accuracy of PET-CT in detecting mediastinal lymph node metastasis was 74.4%, assuming that the shortest nodal diameter was ≥10 mm on CT or had higher metabolic activity than normal mediastinal and soft tissue on PET-CT. Our study, in parallel

Table 3. Cox analysis

			95% CI for Exp(B)	
	p	HR	Lower	Upper
OS Cox				
Age	0.004	1.923	1.226	3.016
Histology	0.348	1.217	0.807	1.835
N2	0.357	1.239	0.785	1.955
Non N2	0.147	1.368	0.896	2.087
Neoadjuvant	0.388	1.215	0.781	1.890
Adjuvant	0.014	2.027	1.154	3.563
DFS Cox				
Age	0.050	1.550	1.001	2.402
Histology	0.016	1.607	1.093	2.363
N2	0.297	1.258	0.817	1.938
Non N2	0.213	1.291	0.864	1.931
Neoadjuvant	0.802	1.053	0.704	1.574
Adjuvant	0.004	2.234	1.288	3.875

N2a : N2 disease; HR: Hazard ratio.

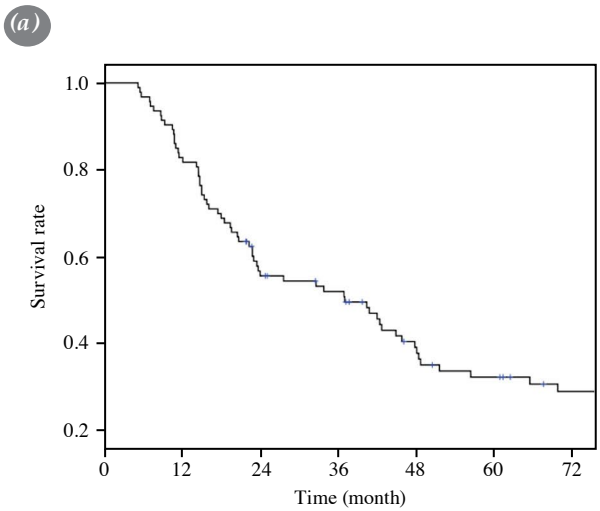
with other studies, showed that PET-CT was useful in evaluating mediastinal lymph node metastasis. However, Craig et al.[37] emphasized that it should be aware that one-third of patients with Stage 3-ssN2 did not actually have skip N2 according to CT, PET-CT and staging EBUS, and that the use of this criterion in defining treatment recommendations was questioned.

Patients with N2 or N3 disease identified through mediastinal staging are typically directed to oncological treatments rather than surgery, as surgical resection does not significantly improve survival or reduce recurrence rates. The PET-CT imaging has demonstrated that the prognosis of patients with single-station, known N2 disease who underwent surgical resection and mediastinal lymphadenectomy is similar to that of patients with single-station incidental N2 disease.[14] Kim et al.[19] reported that the OS rate for patients with negative findings on preoperative CT and PET-CT imaging was 54%, with a mean survival time of 74 months. Moreover, no significant survival difference was observed between patients with positive and negative preoperative CT and PET-CT imaging.

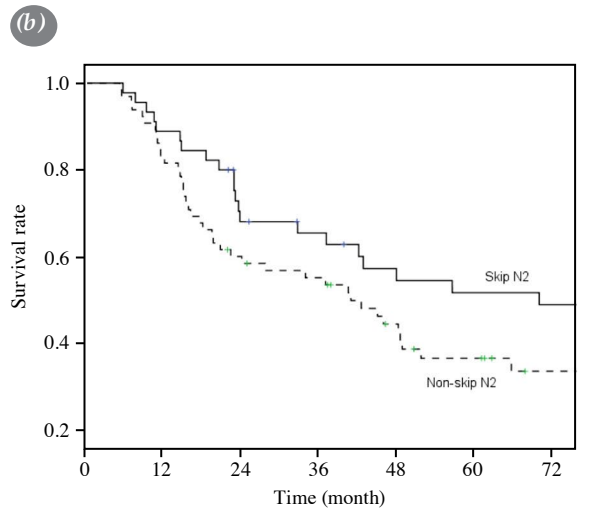
The results of the randomized ASTER trial conducted by Annema et al.[20] supported invasive mediastinal staging with both endosonography and mediastinoscopy. However, a recent meta-analysis by Bousema et al.[21] reported similar rates of N2 disease when staged by endosonography EBUS or EBUS+endoscopic ultrasound [EUS]) independent of confirmatory mediastinoscopy (9.6% *vs*. 9.9%) and highlighted a higher risk of complications in performing more invasive mediastinoscopy. A secondary observation emerging from the ASTER study was that despite a significant difference in the N2 rate (6.9% *vs*. 14.3%), five-year survival remained exactly 35%.

The prognosis of patients who undergo resection for the treatment of NSCLC but have histopathological evidence of lymph node involvement remains complex and controversial. The pN2 is an important prognostic factor for NSCLC, with survival outcomes varying significantly depending on the extent of nodal involvement within the same stage. Consequently, further studies are required to better delineate the prognostic implications of pN1 and pN2 lymph node involvement.[22] Studies have indicated that N2 disease is present in approximately 20 to 40% of all operated NSCLC patients.[23]

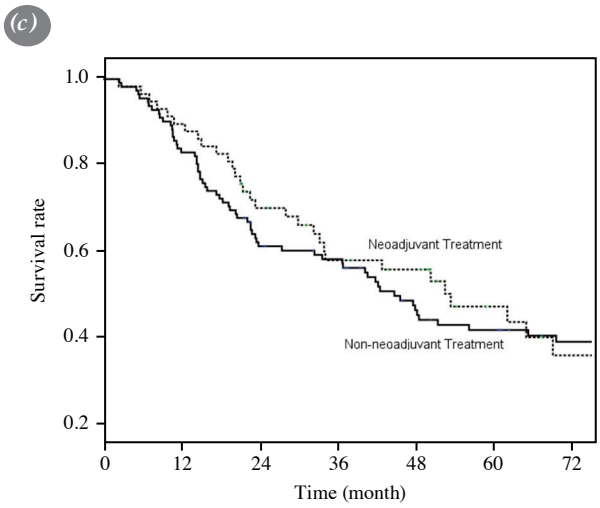
The anatomical proximity of N1 and N2 lymph nodes has led to the hypothesis that their prognostic implications may be similar. Indeed, studies have reported similar survival outcomes between patients with N1 disease involving hilar nodes and those with N2A disease.[24] In a recent study conducted in our clinic, it was observed that the five-year OS rate



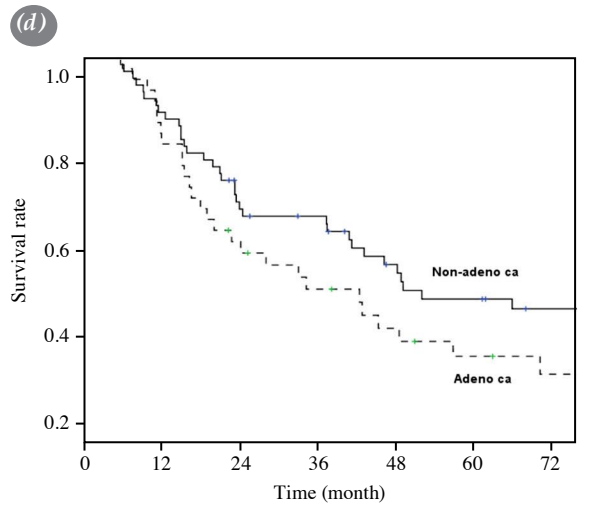
Number of risk by time	144	120	79	64	47	32	22



Skip	61	53	39	31	24	20	16
Non-skip	83	67	40	33	23	12	6



Number of risk by time							
Neoadjuvant	49	43	29	21	18	9	5
Non neoadjuvant	95	77	50	43	29	23	17

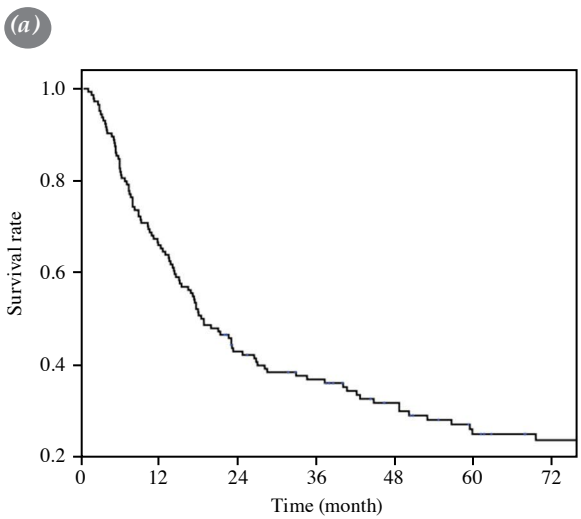


Number of risk by time							
Adenocarcinoma	58	49	30	22	17	10	7
Non adenocarcinoma	86	71	49	42	30	22	15

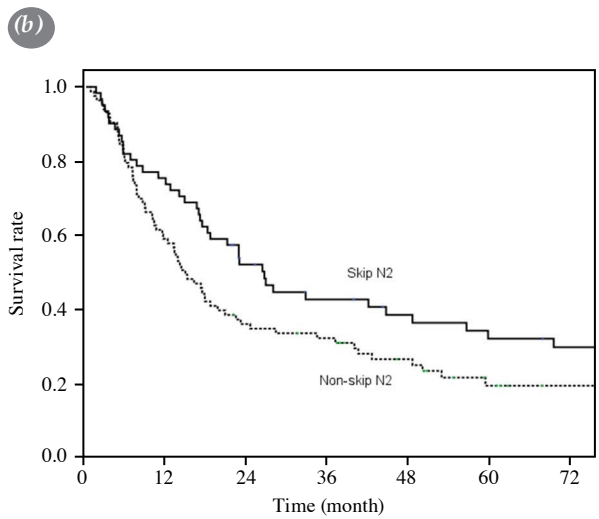
Figure 1. (a) Overall survival assessment (Kaplan-Meier analysis). **(b)** Skip N2 - non-skip N2 survival (Kaplan-Meier analysis). **(c)** Survival by neoadjuvant treatment and non-neoadjuvant treatment. **(d)** Histological subtypes (Kaplan-Meier analysis)

for patients with pN1 was similar to that of patients with pN0N2, both of which were significantly better than the OS rate for patients with pN1N2.[25] Our findings demonstrated that a favorable prognosis was consistent with the pN2A subgroup. Research focusing on skip metastases has suggested that the primary lung tumors associated with skip metastases are predominantly located in the upper lobe, facilitated by direct lymphatic drainage pathways.[26] Building on this, some studies have explored whether lymph node stations 5 and 6 should be considered as N1 nodes in the context of left upper lobe tumors.[27-29]

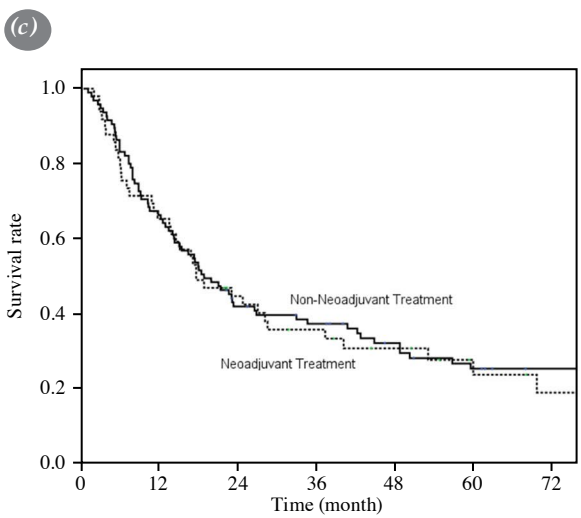
Goldstraw et al.[30] reported that anterior mediastinotomy or extended mediastinoscopy was the gold standard for tumors located in the central or



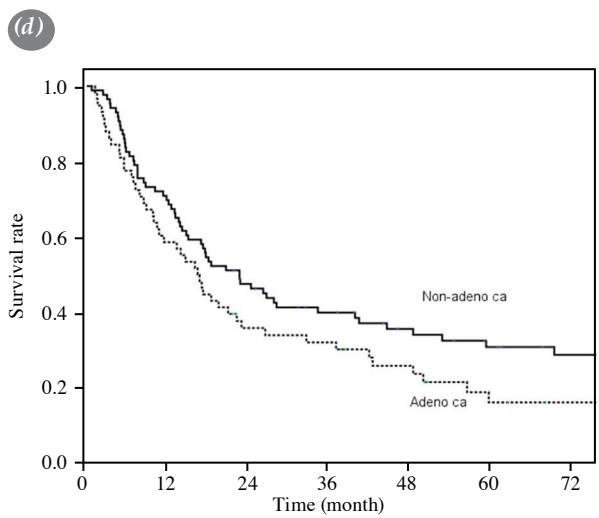
Number of risk by time	144	95	58	47	35	24	18



Skip	61	46	29	22	18	15	13
Non-skip	83	49	29	25	17	9	5



Number of risk by time							
Neoadjuvant	49	32	24	15	11	6	4
Non neoadjuvant	95	63	38	32	24	18	14



Number of risk by time							
Adenocarcinoma	58	34	19	17	12	6	4
Non adenocarcinoma	86	61	39	30	23	18	14

Figure 2. Disease free survival. **(a)** Overall survival assessment (Kaplan-Meier analysis). **(b)** Skip N2 - non-Skip N2 Survival (Kaplan-Meier analysis). **(c)** Survival by neoadjuvant treatment and non- neoadjuvant treatment. **(d)** Histological subtypes (Kaplan-Meier analysis).

upper lobe, given the poor survival outcomes when N2 was detected preoperatively. The pN2 can be single or multi-station, with or without pN1 involvement. In the literature, five-year survival rates of patients with pN2 disease vary between 20 and 35%. In the study conducted by Zhu et al.,[31] the patients in the group with high survival rate were patients with pN2A who underwent complete resection, had no preoperative proven N2, had a pathological stage of T1,2 N2, M0, had micro metastatic N2 lymph node metastasis and no lymph node 7 metastasis. Our study also showed that particularly some pN2A subgroups had a good prognosis. Carter et al.[32] also reported that there was no significant difference in survival between hilar pN1 disease and pN2A disease in patients undergoing lung resection. However, the appropriateness of direct

surgical resection for one of these groups remains a topic of ongoing debate.

In the light of these discussions, the International Association for the Study of Lung Cancer (IASLC) has proposed that skip N2 should be considered a new pN subclassification due to its association with better survival outcomes.[33] Recently, the IASLC proposed a new definition of N that combines the location of metastatic lymph nodes, N (single-station and multi-station), and omits N2 lymph node metastasis (SKN2), and also divided the N stage into multiple subgroups.[34] However, these new N classifications have yet to be validated. The clinical significance of skip metastasis in approximately 17.2 to 42.3% of resected pN2 NSCLC patients remains unclear.[35,36] In a recently published study, Craig et al.[37] showed that one-third of patients with Stage 3-single station N2 according to CT, PET-CT and EBUS performed for staging purposes did not actually have single station N2. This study emphasized the accuracy of clinical staging, the presence of micro-metastases and inadequate staging. Based on the results of this study, more detailed mediastinal staging should be performed in patients with suspected N2 or neoadjuvant treatment may be recommended to patients even with single N2.

In terms of histology, adenocarcinoma is an important histological subtype of NSCLC and its incidence has increased rapidly, accounting for almost half of all lung cancers in recent years. In the literature, the risk of lymph node metastasis and histological and molecular heterogeneity was higher in adenocarcinoma compared to squamous cell carcinoma.[38] The subgroup analysis of our study showed that histology of adenocarcinoma was one of the factors that negatively affected the prognosis.

Martini[39] reported that the survival of clinical T1 and T2 patients without significant mediastinal involvement was better than that of clinical T3 patients. This study also showed that the factors that adversely affected the prognosis of pN2A could be considered adenocarcinoma histology and pN1N2 stage, as we similarly found in our study.

Kim et al.[19] found that age less than 70 years, adenocarcinoma histology, clinical N1 disease and tumor size greater than 3 cm were independent risk factors for incidental N2.

The survival of patients who received and did not receive neoadjuvant treatment is similar. This suggests that the survival of patients who received neoadjuvant treatment due to known N2 is like that of patients with unexpected single station N2. According to the European Society of Thoracic Surgeons (ESTS), it has been argued that there is no difference between CT+RT+surgery and CT+surgery in resectable N2 (N2 station with short axis less than 25 mm, 30 mm that does not conglomerate or invade adjacent structures) patients. Albain et al.[40] evaluated 396 T1-3 cN2 patients who underwent induction CRT+surgery and CRT+RT±surgery; Radiological response was monitored in 202 patients who underwent etoposide+cisplatin+45Gc RT surgery and in 194 patients who continued RT (61 Gy), and N2 was detected at a single station in 76% of the operated patients. Post-hoc analysis showed that 90 patients who underwent lobectomy had a significant survival advantage compared to patients with similar demographics who received CRT (33.6 *vs*. 21.7 months, $p<0.002$).[40] In addition, Agbarya et al.,[41] based on the heterogeneous results in their survey study, argued that there were no standardized evidence-based decisions in NSCLC. Many factors influence the treatment pathway offered to patients with Stage 3 N2 NSCLC, including patient factors, the expertise of the team and local resources. Therefore, the role of multidisciplinary care in defining resectability and formulating an individualized treatment plan is crucial.[40] Studies have shown survival rates ranging from 34 to 48% in pN2A patients receiving adjuvant therapy, which is similar to the survival rates of those with N1 disease treated primarily with surgery.[19] A similar pattern was observed in a study by Macia et al.,[42] although it showed a lower five-year OS of 25% for pN0N2A. The survival rates of pN2A patients were similar to those of patients with multiple N1 (pN1B) (34%), in contrast to the five-year OS of patients with single N1 (pN1A) (73%). In a study by Nakagawa et al.[18] focusing on the potential benefit of adjuvant therapy specific to patients with only N2 disease, there were significant differences in long-term survival outcomes between patients who received only follow-up and patients who received adjuvant CR. The results were consistent with known studies supporting adjuvant CR in early-stage NSCLC with complete lymph node removal.[43] In our study, the absence of adjuvant therapy emerged as a significant negative prognostic factor for N2 disease.

Most studies have demonstrated that pN0N2 has a favorable impact on OS.[44,45] A prospective study by Abe et al.[46] reported that the five-year OS rates of the pN0N2 and pN1N2 groups were 81.3% and 37.5%, respectively, and the prognosis was significantly better in the pN0N2 group.

In conclusion, our study results indicated that adenocarcinoma histology, advanced age, absence

of adjuvant therapy, and the presence of pN1N2 were significant negative prognostic factors in pN2A patients who underwent curative resection. Based on these results, the recommendation of direct surgical treatment followed by adjuvant therapy in pN0N2A patients with non-adenocarcinoma histology in the younger age group can be further discussed. The new version of TNM staging would not immediately alter the treatment algorithm. To the best of our knowledge, the overall prognosis of these N2 subgroups is strongly dependent on a specific treatment; therefore, it would not be correct to assume that the revised staging automatically necessitates a change in therapeutic strategies. The results of our study need to be supported by prospective randomized studies on single station N2 with the introduction of the 9th TNM staging.

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

Author Contributions: Made substantial contributions to the design of the work, developed new software used in the work: B.A.S., S.Y.; Made the analysis of data: Y.T., E.Y.S.; Have drafted the work: B.A.S.; Revised: A.U., B.A.S.

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