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***Original Article** / Özgün Makale*

Comparative evaluation of staging algorithms proven N2 non-small cell lung cancer treated by lung resection after neoadjuvant therapy

Kanıtlanmış N2 nedeniyle neoadjuvan tedavi sonrası akciğer rezeksiyonu ile tedavi edilen küçük hücreli dışı akciğer kanserinde evreleme algoritmalarının karşılaştırmalı değerlendirmesi

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ABSTRACT

Background: In this study, we aimed to compare the performances of clinical methods, minimally invasive methods, mediastinoscopy, and re-mediastinoscopy used in the restaging of patients receiving neoadjuvant therapy for pathologically proven N2. Our secondary objective was to determine the most optimal algorithm for initial staging and restaging after neoadjuvant therapy.

Methods: Between April 2003 and August 2017, a total of 105 patients (99 males, 6 females; mean age: 54.5±8.2 years; range, 27 to 73 years) who were diagnosed with pathologically proven Stage 3A-B N2 non-small cell lung cancer and received neoadjuvant therapy and subsequently lung resection were retrospectively analyzed. Staging algorithm groups (Group 1=first mediastinoscopy-second clinic, Group 2=first mediastinoscopy-second minimally invasive, Group 3=first mediastinoscopy-second re-mediastinoscopy, and Group 4=first minimally invasive-second mediastinoscopy) were created and compared.

Results: In the first stage, N2 diagnosis was made in 90 patients by mediastinoscopy and in 15 patients by minimally invasive method. In the second stage, 44 patients were restaged by the clinical method, 23 by the minimally invasive method, 23 by re-mediastinoscopy, and 15 by mediastinoscopy. The false negativity rates of Groups 1, 2, 3, and 4 were 27.2%, 26.1%, 21.8%, and 13.3%, respectively. The most reliable staging algorithm was found to be the minimally invasive method in the first step and mediastinoscopy in the second step. The mean overall five-year survival rate was 46.3±4.4%, and downstaging in lymph node involvement was found to have a favorable effect on survival (54.3% ***vs.*** 21.8%, respectively; p=0.003).

Conclusion: The staging method to be chosen before and after neoadjuvant therapy is critical in the treatment of Stage 3A-B N2 non-small cell lung cancer. In re-mediastinoscopy, the rate of false negativity increases due to technical difficulties and insufficient sampling. As the most optimal staging algorithm, the minimally invasive method is recommended in the first step and mediastinoscopy in the second step.

Keywords: Neoadjuvant therapy, non-small lung cancer, radiotherapy, surgery, downstaging.

ÖZ

Amaç: Bu çalışmada patolojik olarak kanıtlanmış N2 nedeniyle neoadjuvan tedavi almış hastaların yeniden evrelemesinde klinik yöntemler, minimal invaziv yöntemler, mediastinoskopi ve yeniden mediastinoskopinin performansları karşılaştırıldı. İkincil amacımız, ilk evreleme ve neoadjuvan tedavi sonrası yeniden evreleme için en uygun algoritmanın belirlenmesi idi.

Çalışma planı: Nisan 2003 - Ağustos 2017 tarihleri arasında patolojik olarak kanıtlanmış Evre IIIA-B N2 küçük hücreli dışı akciğer kanseri tanısı konmuş ve neoadjuvan tedavi almış ve ardından akciğer rezeksiyonu yapılmış toplam 105 hasta (99 erkek, 6 kadın; ort. yaş: 54.5±8.2 yıl; dağılım 27-73 yıl) retrospektif olarak incelendi. Evreleme algoritma grupları (Grup 1=birinci mediastinoskopi-ikinci klinik, Grup 2=birinci mediastinoskopi-ikinci minimal invaziv, Grup 3=birinci mediastinoskopi-ikinci yeniden mediastinoskopi ve Grup 4=birinci minimal invaziv-ikinci mediastinoskopi) oluşturuldu ve karşılaştırıldı.

Bulgular: Birinci evrelemede 90 hastaya mediastinoskopi ve 15 hastaya minimal invaziv yöntem ile N2 tanısı kondu. İkinci evrelemede 44 hasta klinik yöntem, 23 hasta minimal invaziv yöntem, 23 hasta yeniden mediastinoskopi ve 15 hasta mediastinoskopi ile yeniden evrelendirildi. Grup 1, 2, 3 ve 4'ün yanlış negatiflik oranları sırasıyla %27.2, %26.1, %21.8 ve %13.3 idi. En güvenilir evreleme algoritmasının ilk basamakta minimal invaziv yöntem ve ikinci basamakta mediastinoskopi olduğu belirlendi. Genel ortalama beş yıllık sağkalım oranı %46.3±4.4 iken, lenf nodu tulumunda evre azalmasının sağkalımı iyi yönde etkilediği saptandı (sırasıyla %54.3'e kıyasla %21.8; p=0.003).

Sonuç: Evre IIIA-B N2 küçük hücreli dışı akciğer kanseri tedavisinde neoadjuvan tedavi öncesi ve sonrasında seçilecek evreleme yöntemi kritiktir. Yeniden mediastinoskopide teknik zorluk ve yetersiz örnekleme nedeniyle yanlış negatiflik oranı yükselmektedir. En iyi evreleme algoritması olarak ilk basamakta minimal invaziv yöntem ve ikinci basamakta mediastinoskopi önerilir.

Anahtar sözcükler: Neoadjuvan tedavi, küçük hücreli dışı akciğer kanseri, radyoterapi, cerrahi, evre küçülmesi.

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Surgery after neoadjuvant chemotherapy or chemoradiotherapy is a therapeutic option used in patients with resectable Stage 3A-B N2 non-small cell lung cancer (NSCLC). The optimal treatment of these patients is still under investigation. Downstaging and complete resection of the mediastinal lymph nodes yield successful results.[1-3] However, the role of surgery in patients with persisted N2 in the resected lung after neoadjuvant therapy is controversial.[4,5] Mediastinal staging is the most important prognostic factor for long-term survival. Restaging is technically difficult due to adhesion from previous staging procedures and fibrosis after neoadjuvant therapy. It is controversial which procedure to use at this stage. There are various restaging techniques which are computed tomography (CT), positron emission tomography (PET)/CT, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), video-assisted thoracoscopic surgery (VATS), mediastinotomy, mediastinoscopy, and re-mediastinoscopy. In restaging, preventing false negativity and determining the most optimal method are the keys for treatment.

Currently, only CT, which has a sensitivity of 57% in a prospective study, is not recommended for restaging.[6] The PET scan is successful in initial mediastinal staging, but the success rate has been decreasing in recent results after neoadjuvant therapy. In a multi-center, prospective study, the sensitivity of PET in detecting persistent N2 disease after neoadjuvant therapy was found to be only 50%.[7]

Mediastinoscopy and EBUS-TBNA provide the advantage of pathological proof. Success rates differ in studies performed with restaging with EBUS-TBNA. Sensitivity rates have been detected in the range of 50 to 82%.[8-10]

Re-mediastinoscopy is technically challenging due to fibrosis and adhesions developed after previous mediastinoscopy and neoadjuvant therapy. To date, only a few centers have reported their experience with re-mediastinoscopy. A sensitivity between 70 and 73% is achieved.[11,12]

Mediastinal restaging after neoadjuvant therapy in NSCLC continues to be a difficult and controversial issue. Conditions of restaging are significantly affected by the first staging method. In the present study, we aimed to compare the performances of clinical methods (CT, PET), minimally invasive methods (EBUS-TBNA), mediastinoscopy, and re-mediastinoscopy used in the restaging of patients receiving neoadjuvant therapy for pathologically proven N2. Our secondary objective was to determine the most optimal algorithm for initial staging and restaging after neoadjuvant therapy.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at University of Health Sciences, Yedikule Chest and Diseases and Thoracic Surgery Training and Research Hospital, Department of Thoracic Surgery between April 2003 and August 2017. A total of 105 patients (99 males, 6 females; mean age: 54.5±8.2 years; range, 27 to 73 years) who were diagnosed with pathologically proven Stage 3A-B N2 NSCLC and received neoadjuvant therapy and subsequently lung resection were included. Exclusion criteria were as follows: receiving N3-caused neoadjuvant therapy (n=6), microscopic incomplete resection (R1) (n=8), macroscopic incomplete resection (R2) (n=1), those who could not complete treatment due to chemotherapy toxicity (n=13), and having progressive disease (T, N, or M factor-caused) (n=9). Only patients with multi-station N2 were included in the study.

First staging

Stage 3A-N2 staging was performed by standard cervical mediastinoscopy or minimally invasive methods (EBUS-TBNA). Examination and sampling of the left and right upper paratracheal nodes (2L and 2R levels on the Mountain-Dressler map), left and right lower paratracheal nodes (4L and 4R levels), and subcarinal (level 7) nodes were performed.[13] The EBUS-TBNA in 15 patients and mediastinoscopy in 90 patients were performed. Standard mediastinoscopy was performed in 56 of 90 patients who underwent mediastinoscopy at the first staging, and video mediastinoscopy was performed in 34 of them. Extended mediastinoscopy was performed in nine patients with metastasis in the aortopulmonary window.

Neoadjuvant therapy

Since the oncological treatment protocols of the patients were performed by different oncology clinics and the study group was spread over a long time, it was not standard. Two to six rounds of platinum-based chemotherapy and 45-50.4 Gy radiotherapy were used for treatment. Sixty patients received chemoradiotherapy, and 45 patients received chemotherapy.

Restaging

Thoracic CT and cranial magnetic resonance imaging (MRI) were performed in each patient four to

six weeks after the last day of treatment. The surgical decision was made for the patients re-evaluated by the Multidisciplinary Oncology Council, predicting complete resection after restaging.

The re-mediastinal staging was performed in 44 patients (Group 1) by clinical method (CT, PET), in 23 patients (Group 2) by minimally invasive method (EBUS-TBNA), in 23 patients (Group 3) by re-mediastinoscopy, and in 15 patients (Group 4) by mediastinoscopy. The first and restaging steps were classified and compared among the four groups (Figure 1).

As a disadvantage, there is no pathologist in the field during TBNA in our hospital. In addition, there is the advantage of consulting a pathologist during mediastinoscopy.

Nine of the mediastinoscopies performed in restaging were video-assisted and 10 of the re-mediastinoscopes were video-assisted (Figure 2).

Clinical restaging was performed based on the standard of accepting the radiologically suspicious lymph node above 1 cm in CT or lymph node above 3.5 in the maximum standard uptake value (SUV_{max}) in PET/CT.

In re-mediastinoscopy, after the first mediastinoscopy, dense adhesions may occur between the trachea and pre-tracheal vessels, making re-mediastinoscopy much more difficult. To avoid injury to the brachiocephalic artery, the first dissection was performed sharply on the left side of the trachea. A left paratracheal tunnel was created, until the origin of the left main bronchus was visualized. Pre-tracheal and paratracheal spaces were entered through this tunnel with a combination of blunt and sharp dissection. The goal was to reach all accessible lymph node stations and perform a complete re-mediastinoscopy with re-biopsy. Extended re-mediastinoscopy was not performed in any case, predicting adhesions to major vascular structures.

Surgical procedure

Patients who were found to be downstaging as a result of re-mediastinal staging were prepared for surgery approximately two weeks later (six to eight weeks after the last treatment). Due to the pathological difficulties of the post-neoadjuvant staging,[14] pathologists of our hospital make detailed pathological evaluations due to inaccuracies that may occur in the frozen-section. Therefore, mediastinoscopy and lung resection were performed in separate sessions. This period showed variations, since the cardiac and/or pulmonary examinations of patients may be prolonged after neoadjuvant therapy or additional preoperative problems. Sublobar lung resections were not applied in patients with local-advanced stage lung cancer, as they were not considered eligible from an oncological point of view. Systematic mediastinal lymph node dissection was performed in all cases. In the left upper lobe lesions, Stations 5 and 6 were removed, and after lower lobectomy Stations 8 and 9 were dissected. During resection, adhesions due to neoadjuvant

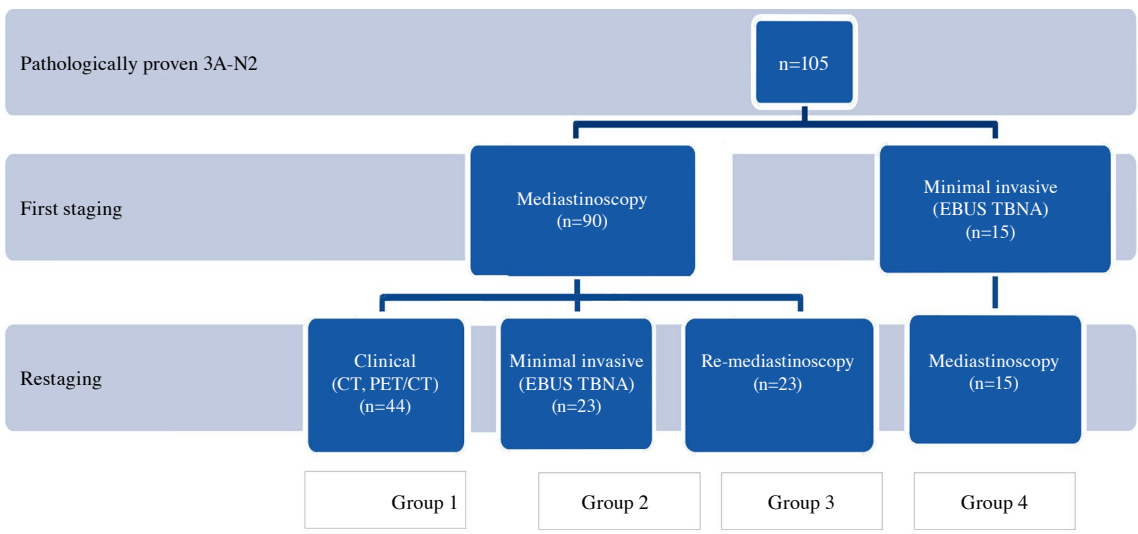

Figure 1. Initial and restaging methods and algorithm groups.
EBUS/TBNA: Endobronchial ultrasound/transbronchial needle aspiration; PET/CT: Positron emission/computed tomography.

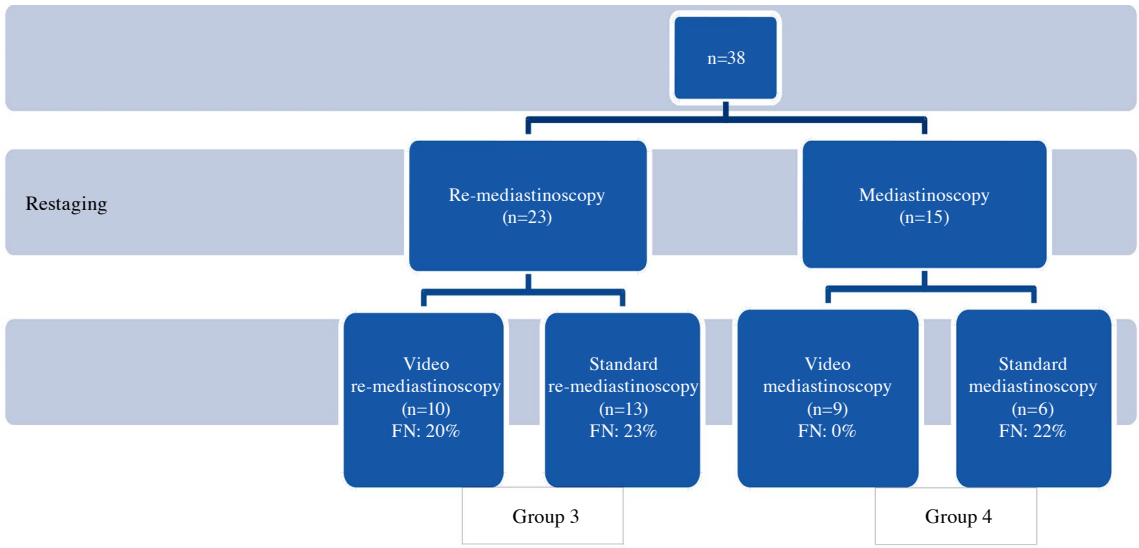

Figure 2. Comparison of video-assisted and standard methods in mediastinoscopy and re-mediastinoscopy used in restaging.

FN: False negativity.

therapy can be confused with tumor invasion, and frozen-section was used in suspicious areas and complete resection (R0) was confirmed. Pathological examination was performed using standard techniques and immunohistochemical staining was performed, when appropriate. The clinical staging of the cases whose pathological staging was performed using the 8th staging system was also updated considering the same staging system.[15] Based on the decision of the Multidisciplinary Oncological Council, 36 (34.3%) patients received adjuvant treatment after the operation. Regarding surgical and pathological characteristics, the size of resection, pathological staging, completeness of resection, mediastinal stations involved, number of lymph nodes removed, and both morbidity and mortality data were recorded.

Statistical analysis

Statistical analysis was performed using the SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The chi-square test was used to compare proportions. Survival was estimated by the Kaplan-Meier method, and survival comparison between the groups was performed by using the log-rank analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients are shown in Table 1. Most of the tumors (n=65; 61,9%) were located on the right side. Based on the examination of histological types, squamous cell carcinoma and adenocarcinoma were found in equal proportions. In the first staging step, 90 (85.8%) patients were diagnosed with Stage 3A-B N2 by the mediastinoscopy, and the remaining 15 were diagnosed by the minimally invasive method (EBUS-TBNA). The most common metastasis was detected in paratracheal lymph nodes with a rate of 55.2% (n=58; single paratracheal station involvement in 51 cases, multiple paratracheal station involvement in seven cases), while the subcarinal lymph node metastasis rate was 28.5%. A diagnosis of aortopulmonary window (No: 5-6) metastasis was made by performing extended mediastinoscopy in nine patients. The majority of patients had single-station N2 disease (85.8%). Fifteen patients benefited from neoadjuvant therapy, although pathologically multiple N2 was detected.

Restaging and surgery

A total of 41.9% (n=44) of the patients were restaged with the clinical method (PET/CT). While the minimally invasive method (EBUS-TBNA) was used in 23 patients, re-mediastinoscopy was performed in 23 patients (Table 2).

Complete resection (R0) was performed in all patients in the study group. Pneumonectomy was performed in a total of 19 patients, four of which were right and 15 were left. Mortality rate in the pneumonectomy group was 5.2%. Right pneumonectomy was performed in this case. A total of four (3.8%) patients developed mortality throughout the study, including respiratory failure in one, renal failure in one, and mortality due to pneumonia in two.

Surgical complication rate was 36.1% (n=38). While the most common complications were pleural

Table 1. Baseline characteristics of patients

	n	%	Mean±SD
Total number	105	100	
Age (year)			54.5±8.2
Sex			
Male	99	94.3	
Female	6	5.7	
Smoking status			
Never smoked	24	22.8	
Ex-smoker	60	57.2	
Active smoker	21	20	
Tumor side			
Right	65	61.9	
Left	40	38.1	
Histological subtype			
Squamous cell carcinoma	48	45.7	
Adenocarcinoma	48	45.7	
Adenosquamous carcinoma	9	8.6	
Clinical T-stage			
1	3	2.8	
2	57	54.2	
3	24	22.8	
4	13	12.3	
Neoadjuvant therapy type			
Chemoradiotherapy	60	57.1	
Chemotherapy	45	42.9	
Baseline mediastinal staging			
Mediastinoscopy	90	85.8	
Minimally invasive (EBUS/TBNA)	15	14.2	
Baseline mediastinal involvement zone			
Paratracheal (single)	51	48.6	
Subcarinal	30	28.5	
Aortopulmonary window	9	8.5	
Paratracheal plus subcarinal	8	7.6	
Paratracheal (multiple)	7	6.7	
Baseline mediastinal involvement			
Single	90	85.8	
Multiple	15	14.2	

SD: Standard deviation; EBUS/TBNA: Endobronchial ultrasound/transbronchial needle aspiration.

Table 2. Clinical characteristics after neoadjuvant therapy

	n	%
Staging algorithm		
1st: Mediastinoscopy-2nd: Clinical (Group 1)	44	41.9
1st: Mediastinoscopy-2nd: Minimally invasive (Group 2)	23	21.9
1st: Mediastinoscopy-2nd: Re-mediastinoscopy (Group 3)	23	21.9
1st: Minimally invasive-2nd: Mediastinoscopy (Group 4)	15	14.3
Operation type		
Lobectomy	65	64
Bilobectomy	19	18
Pneumonectomy	19	18
Pathological T-stage		
T0	38	36.1
T1	31	29.5
T2	28	26.6
T3	5	4.7
T4	3	2.8
Pathological N-stage		
N0	62	59
N1	18	17.1
N2	25	23.9
Pathological N2 involvement		
Single	12	11.4
Multiple	13	12.3
Pathological stage		
PCR (T0N0)	36	34.2
1A	12	11.4
1B	13	12.3
2B	14	13.3
3A	27	25.7
3B	3	2.9
Complication		
Yes	38	36.1
Mortality		
Yes	4	3.8
Recurrence		
Yes	33	31.4
Adjuvant therapy		
Yes	36	34.3
No	69	65.7

PCR (T0N0): Pathological complete response, no viable tumor left in the primary tumor and lymph nodes.

Table 3. Comparison of staging algorithms

	Group 1		Group 2		Group 3		Group 4	
Algorithm	n	%	n	%	n	%	n	%
NPV		72.8		73.9		78.2		86.7
False-negativity		27.2		26.1		21.8		13.3
ypN2	12		6		5		2	

NPV: Negative predictive value; ypN2: Persistent N2 patients after neoadjuvant therapy; Group 1= 1st: mediastinoscopy-2nd: clinical, Group 2= 1st: mediastinoscopy-2nd: minimally invasive, Group 3= 1st: mediastinoscopy-2nd: re-mediastinoscopy, Group 4= 1st: minimally invasive-2nd: mediastinoscopy.

complications that were prolonged air leaks and pleural space (n=11), the second most common complication was pneumonia (n=10). In cases of pleural space and prolonged air leak, discharge was performed with a Heimlich valve on postoperative Day 10. Drainage was completed, when the air leak disappeared in ambulatory monitoring. The bronchopleural fistula was observed in four patients. The right pneumonectomy was performed in one of these patients, and the right lower bilobectomy was performed in the other three. In the right pneumonectomy case with a bronchopleural fistula, debridement with thoracostoma and fistula closure with an omentum flap was performed after the regression of the infection. In three right lower bilobectomy cases who developed a bronchopleural fistula, the fistulas were at the subscentimetric level and healed after prolonged tube thoracostomy drainage.

Table 4. Factors affecting survival

	5-year survival	
	%	*p*
Age (year)		0.814
<65	46.7	
≥65	45.0	
Sex		0.334
Male	44.3	
Female	51.0	
The type of neoadjuvant treatment		0.687
CHT alone	57.6	
CHT/RT combined	45.7	
Operation type		0.211
Lobectomy	49.5	
Pneumonectomy	38.2	
Down-staging		0.003
No	21.8	
Yes	54.3	

CHT: Chemotherapy; RT: Radiotherapy.

Downstaging was detected after neoadjuvant therapy in 80 (76.1%) cases. Sixty-two of these cases were staged as persistent N0 patients after neoadjuvant therapy (ypN0) and 18 as ypN1. Based on the decision of the Multidisciplinary Oncological Council, 36 (34.3%) patients received adjuvant treatment after the operation.

Pathological complete response (ypT0N0) was detected in 36 patients. This patient group was the most common in pathological staging (34.2%). While no viable tumor cells were seen in the primary lesion in two cases, persistent N2 was detected (ypT0N2). More than half of the patients in the ypN2 group (n=13) had multiple station involvement.

During clinical follow-up, a total of 33 (31.4%) patients developed recurrence. The majority of them (n=24) were distant organ metastases and the most common type was brain metastasis (n=9). Local recurrence was detected in nine patients.

Comparative accuracy: Persistent N2 disease after neoadjuvant therapy

ypN2 was detected in 25 (23.9%) patients. When these cases were examined, 12 were restaged by clinical methods (PET/CT), six by minimally invasive method (EBUS, TBNA), five by re-mediastinoscopy, and two by mediastinoscopy.

The first and restaging steps were classified into four groups, and the algorithms of the groups were compared (Figure 1). The false negativity rates of Groups 1, 2, 3, and 4 were 27.2%, 26.1%, 21.8%, and 13.3%, respectively. The most reliable staging algorithm was found to be the minimally invasive method (EBUS-TBNA) in the first step and mediastinoscopy in the second step (Table 3). The negative predictive value of clinical methods (Group 1) was found to be lower than that of invasive methods (Groups 2, 3, 4). (72.8% *vs*. 78.6%, respectively).

In restaging patients who underwent mediastinoscopy, the rate of false negativity was found to be 0% versus 22%, when the video-assisted versus standard method was compared (p=0.05). In patients who underwent re-mediastinoscopy, false negativity rates were 20% *vs*. 23% in standard mediastinoscopy versus video-assisted (p=0.806) (Figure 2).

Survival

The mean overall five-year survival rate was 46.3±4.4%. Age (p=0.414), sex (p=0.334), type of operation performed (p=0.211), and neoadjuvant therapy type (p=0.687) did not affect the five-year survival, while downstaging after neoadjuvant therapy significantly affected survival (54.3% *vs*. 21.8%, respectively; p=0.003) (Table 4).

DISCUSSION

Primary surgical results in pathologically proven Stage 3A-B N2 NSCLC are poor, and the five-year survival rate is less than 10% in previous studies.[16] Small-scale randomized studies have suggested that adding cisplatin-based induction chemotherapy can improve prognosis.[17,18] In particular, in the case of lymph nodes, positive results have been demonstrated in patients, when downstaging and complete resection were performed.[1-3] Besides, poor prognosis and both increased surgical mortality and morbidity are observed in persistent N2 conditions.[4,6] In our study, we found that the most important factor affecting long-term survival is downstaging. The five-year survival was 21% in the group with downstaging and 54% in the ypN2 group (p=0.003). However, the detection of downstaging has technical difficulties due to the changes caused by chemotherapy and radiotherapy in the tissues.

The main goal of mediastinal staging is to identify patients with mediastinal metastases with the highest precision and lowest morbidity. The European Society of Thoracic Surgeons (ESTS) study group reported an acceptable rate of unpredictable mediastinal nodal disease at 10%.[19] It can be predicted that this rate would increase in patients who undergo resection after N2-caused neoadjuvant therapy. As expected, the false negativity rate in restaging after neoadjuvant was 23.9% in our study.

In the first staging, CT scanning has proven to have low accuracy. It is not surprising that the accuracy of the CT scan is also low in restaging. Mateu-Navarro et al.[11] compared CT scan and re-mediastinoscopy in 24 patients who received neoadjuvant chemotherapy for local-advanced NSCLC. The CT scan had 41% sensitivity, 75% specificity, and 58% accuracy. In a prospective study involving 93 patients who were restaged with PET after neoadjuvant therapy, PET was found to be more accurate than CT alone.[20] However, 20% false-negative and 25% false-positive cases were detected. In the present study, using the clinical method (PET/CT) in the restaging step had the highest false-negative rate. In particular, the accuracy of PET has increased in parallel with technological developments. However, considering that chemoradiotherapy consists of complex inflammatory and oncological processes, it seems to be difficult to increase this level of accuracy.

In our study, clinical restaging was performed based on the standard of accepting the radiologically suspicious lymph node above 1 cm in CT or lymph node above 3.5 in the SUV-max value in PET/CT. Different cut-off values of 2.5[21,22] or 3.5[23] can be used to detect metastatic lymph nodes. In addition, there are studies suggesting that a SUV_{max} higher than 3.95 indicates metastatic lymph nodes.[24] High cut-off values are used in the evaluation of mediastinal lymph nodes due to the high incidence of tuberculous in Türkiye and the fact that tuberculous lymphadenitis causes false positivity in PET/CT. Therefore, nodal biopsy and pathological evidence have been recommended in persistent N2 suspicion.[25] In a single-center, prospective study comparing re-mediastinoscopy and PET after neoadjuvant therapy for N2 disease, the sensitivity and specificity of mediastinoscopy were found to be 77% and 88%, respectively.[6]

Technically much more difficult than the first procedure, re-mediastinoscopy offers the advantage of detecting histological evidence of response after neoadjuvant therapy. Although some centers have achieved good results,[11] most surgeons would agree that re-mediastinoscopy is technically difficult and often insufficient. De Leyn et al.[6] compared PET and re-mediastinoscopy in the restaging step in their prospective study. In this study, re-mediastinoscopy was disappointing due to adhesions and fibrosis. The sensitivity of re-mediastinoscopy was 58.3% and the accuracy was only 28.6%. In the current study, the negative predictive value of the first mediastinoscopy was found to be higher than re-mediastinoscopy (Group 3 *vs*. Group 4; 86.7% *vs*. 73.9%, respectively). Considering the results of these two groups evaluated in terms of technical competence, the mean number of stations sampled was low in patients who underwent re-mediastinoscopy (Group 3 *vs*. Group 4; mean: 3.9 stations *vs*. 2.2 stations, respectively). This situation explained the false negativity rate. The station of

mediastinal staging that had the most important prognostic impact was the subcarinal area. While subcarinal station samples were collected from all patients in Group 4, it could not collect from four patients (26.6%) in Group 3 due to fibrotic adhesions. In patients who underwent re-mediastinoscopy (Group 4), the most frequent persistent lymph node station was subcarinal (two out of five patients). We do not recommend re-mediastinoscopy for restaging, due to insufficient sampling and high false negativity.

In recent years, the dominant role of cervical mediastinoscopy has been questioned by the EBUS and transbronchial biopsy series. The former is successful in accessing mediastinal nodal stations 4R, 4L, and 7. However, it cannot access prevascular nodes (station 3a), subaortic and paraaortic nodes (stations 5 and 6), as well as paraesophageal and pulmonary ligament nodes (stations 8 and 9). Some of these nodes (stations 8 and 9) can be accessed by endoscopic ultrasonography (EUS) through the esophagus. In the study of Herth et al.,[26] restaging after N2-caused neoadjuvant therapy in 124 patients was performed with EBUS-TBNA. The sensitivity was 76%, but the negative predictive value was as low as 20%. The largest series in the literature was reported by Szlubowski et al.[27] They used EBUS-EUS FNA together to restaging N2 disease in 106 patients. The sensitivity was 67%, and its negative predictive value was 73%. Our clinic has no experience with EUS staging. We believe that the combined use of EBUS would be useful in central and lower lobe tumors, particularly in the evaluation of stations 8-9, where the staging methods we use are insufficient. In the current study, restaging with EBUS-TBNA was found to be more reliable than the clinical method and re-mediastinoscopy.

One of the limitations of the study is its retrospective nature. In addition, patients with progressive disease were not referred for surgery during neoadjuvant therapy. Another limitation is that patients who underwent excessive dissection and biopsy from multiple lymph node stations in the initial staging were referred to the clinical staging group for restaging by the Multidisciplinary Oncology Council. Since the study was not randomized, it cannot be ignored to patient selection bias. Also, selection was made with the opinion of the Oncology Council in accordance with the algorithms, and bias in this regard was not excluded. In our observational study, different staging methods were not attempted in a single patient.

The main strengths are that the treatment of the cases was administered in a single center by a team experienced in lung cancer surgery and pathology. The cases were prepared for surgery by performing more invasive restaging (mediastinoscopy, re-mediastinoscopy) than many studies in the literature.

In conclusion, the staging method to be chosen before and after the neoadjuvant therapy is critical in the treatment of Stage 3A-B N2 NSCLC. In re-mediastinoscopy, the rate of false negativity is high due to technical difficulty and insufficient sampling. Re-mediastinoscopy should be avoided in restaging. As the most optimal staging algorithm, it is recommended to use the clinical method (positron emission tomography/computed tomography) in the first staging and mediastinoscopy after neoadjuvant therapy.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (date/no: 18.01.2021/2021/24). 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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