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Original Article

Survival Effect of Surgery in Patients with Stage IIIB/N2 Non-small Cell Lung Cancer: A Comparative Study with Definitive Chemoradiotherapy

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Abstract

OBJECTIVE: We compared the survival outcomes of surgery within multimodality treatment regimens with the outcomes of definitive chemoradiation treatments in patients diagnosed with clinical (c) IIIB/N2 non-small cell lung cancer (NSCLC). We investigated whether surgery within multimodality treatment provides a survival advantage at this stage.

MATERIAL AND METHODS: Data from 79 patients with cIIIB/N2 between 2009 and 2016 were analyzed retrospectively. While the surgery was performed after neoadjuvant therapy in 51 cases (IIIB/Surgery Group), definitive chemotherapy ± radiotherapy was applied in 28 cases (IIIB/Definitive Group).

RESULTS: In cIIIB/N2 cases, the 5-year overall survival (OS) was 27.4%, with a median OS of 24.6 months. The 5-year OS of the IIIB/Surgery Group was 27.3% (median survival 22.5 months), while it was 28.6% (median survival 29.1 months) in the IIIB/Definitive Group (P = .387, HR = 0.798, 95% CI, 0.485-1.313). Although there was a survival advantage in the group with a pathological complete response (PCR) after surgery (n = 14) compared to the group that did not (n = 37), the observed difference was not statistically significant. (5-year OS; 42.9% vs. 18.5%, P = .104). Additionally, there was no statistically significant difference between the survival of PCR patients and the IIIB/Definitive Group in terms of OS (P = .488).

CONCLUSION: Surgery performed within multimodality treatment regimens in selected cIIIB/N2 cases did not provide a survival advantage over definitive chemoradiation treatments.

KEYWORDS: Stage IIIB, N2, neoadjuvant treatment, definitive therapy, lung cancer
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INTRODUCTION

Approximately 20%-30% of NSCLC cases are diagnosed at stage III.[1] In the eighth edition of tumor-node-metastasis (TNM), stage III, non-small cell lung cancer (NSCLC) is divided into 3 different stages. Stage IIIB constitutes a highly heterogeneous group, as T3-4/N2 and T1-2/N3 cases are represented at this stage. In contrast to N3 cases, surgery can be considered as an option in multimodal treatments in highly selective T3-4/N2 cases.[2] It is recommended that neoadjuvant chemotherapy (CT) or concomitant chemoradiotherapy (CRT) is followed by surgery in stage IIIA/N2 cases with single and non-bulky (<3 cm) N2 lymph node (LN) involvement, for which complete resection is feasible.[2] Although the current treatment approach in stage IIIB/N2 cases is immunotherapy and CRT, surgery is offered as a treatment option within multimodal regimens in very highly selected cases such as non-invasive T3/N2.[2] As durvalumab treatment is not routinely used in many countries, surgery is widely preferred in stage IIIB/N2 cases, and very promising survival results have been reported with multimodal treatment regimens, including surgery in selected stage IIIB/N2 cases where complete resection is possible.[3]

There are not many studies on the outcomes of surgery in stage IIIB/N2 NSCLC cases classified according to the eighth edition of TNM staging system. In this study, we compared the survival outcomes of stage IIIB/N2 patients not receiving immunotherapy and receiving only definitive CT ± radiotherapy (RT) treatment with the survival outcomes of selected cIIIB/N2 patients undergoing surgical treatment. We aimed to investigate whether surgery provides a survival advantage in selected clinical (c) IIIB/N2 NSCLC patients.

MATERIAL AND METHODS

The study received approval from the Ethics Committee at Yedikule Hospital with the number 329-5 on August 24, 2022 and was conducted following the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patients.

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The data of 79 patients included in the study with a diagnosis of cIIIB/N2 between 2009 and 2016 were evaluated retrospectively. The patients' staging was determined based on the eighth edition of TNM staging. Patients were divided into 2 groups: those who underwent surgery within multimodality treatment regimens (IIIB/Surgery Group) and those who received definitive treatment only (IIIB/Definite Group).

In all cIIIB/N2 patients, involvement of mediastinal LNs was proven by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or cervical mediastinoscopy. Extent mediastinoscopy or video-assisted thoracoscopic surgery was performed for a biopsy of aortopulmonary window (APW) LNs. The clinical diagnosis of T3-T4 was made by positron emission chemotherapy (PET-CT) and/or contrast-enhanced thorax CT. Patients with pathological involvement of a second nodule in the same lobe in PET-CT examination (confirmed preoperative or postoperative pathological examination), cases with tumor diameter between 5 cm and 7 cm, and cases with the suspected invasion of the chest wall, mediastinum, or pericardium were evaluated as T3.

Cases with suspected carina, vena cava superior, and atrium invasion, and cases >7 cm without invasion in which complete resection could be achieved, were considered selected T4 cases. Patients that were deemed unresectable due to invasion of the heart, great vessels, recurrent laryngeal nerve, esophagus, and vertebral body, as well as cases with cN3, bulky N2, multiple N2, and persistent N2 after neoadjuvant therapy, were excluded from the study and referred to oncology clinics for definitive treatment. Cases with incomplete resection (R1-2) were also not included.

In the PET-CT examination, mediastinal LN with a high standardized uptake volume-maximum (SUVmax) value before neoadjuvant therapy, a value of <2.5 after induction therapy was evaluated as radiological mediastinal downstage. In clinical restaging, mediastinoscopy was used to reevaluate the mediastinum after neoadjuvant therapy in cases diagnosed with N2 by EBUS, while re-evaluation was generally performed with PET-CT in cases undergoing mediastinoscopy in the initial staging. Endobronchial ultrasound and/or mediastinoscopy were used for restaging in cases with mediastinal LN >2.5.

When choosing a multimodality treatment regimen, including surgery or definitive CRT in stage IIIB/N2 cases where complete resection can be achieved, the patient's age, general condition, accompanying comorbidities, unfitness for multimodality treatment, insufficiency in respiratory function capacity, or cardiac risk were evaluated at the multidisciplinary tumor board conference. Moreover, patient preference was one of the most important selection criteria. Multidisciplinary councils consisted of a thoracic surgeon, radiation/medical oncologist, and pulmonologist, as recommended in the guidelines of the American Society of Clinical Oncology.[4] Surgery was performed in patients with mediastinal downstage after neoadjuvant CT or CRT in the IIIB/Surgery Group. In the IIIB/Definitive Group, where complete resection could be achieved but no resection decision was made, definitive CT ± RT was performed.

Platinum-based agents are preferred as neoadjuvant CT, and although there is no standardization, we applied them in the form of at least 2 cycles. There is currently no established standardization for deciding whether to perform CRT (60-66 Gray, 30-33 days) or CT alone for neoadjuvant therapy.

Posterolateral or anterolateral thoracotomy approaches were applied to the surgical group of patients. Although lobe-specific LN dissection/sampling may be preferred in the early stages, we en bloc remove the LNs in the ipsilateral mediastinum along with the surrounding adipose tissue in patients who have received neoadjuvant therapy for N2 disease. Therefore, in all patients, regardless of tumor size and location, systematic mediastinal nodal dissection was performed. Mediastinal LN stations (5-6-7-8-9 on the left side and 2R-4R-7-8-9 on the right side) and hilar LN stations (stations 10 and 11) were dissected en bloc as determined intraoperatively by the surgeon. The number of N2 stations dissected intraoperatively was 3.2 ± 1.2 (range: 3-5 stations), and the overall reported total N2+N1 stations were 6.5 ± 1.1 (range: 5-10 LNs). The resected tissues and lymph nodes were histopathologically evaluated by the same pathologists. In pathological reports, the overall N2+N1 LNs were reported as 18.5 ± 8.1 (10-75 LNs) (Table 1).

As a definitive chemoradiation treatment regimen, 6 cycles of platinum-based agents were given together with concomitant RT (60-66, Gray 30-33 days).

Clinical follow-up was conducted once every 3 months during the first year and once every 6 months between the first and fifth years. Patients were evaluated with a non-contrast chest CT every 6 months. In cases of suspected recurrences

Table 1. Description of Lymph Node Stations and Nodes Reported

Assessed and reported	Lymph Node Stations and Lymph Nodes ± SD (minimum–maximum)
Number of N2 station dissected	3.2 ± 1.2 (3-5)
Number of N1 station reported	3.0 ± 1.1 (2-5)
Number of N2 lymph nodes	9.3 ± 5.0 (6-33)
Number of N1 lymph nodes	10.6 ± 5.7 (6-54)
Overall total N2+N1 stations reported	6.5 ± 1.1 (5-10)
Overall total N2+N1 lymph nodes reported	18.5 ± 8.1 (10-75)

Main Points

- Treatment strategies are controversial in patients with stage IIIB/N2 non-small cell lung cancer.
- In selected stage IIIB/N2 cases where complete resection is possible, multimodality treatment regimens including surgery can be applied.
- Surgery performed within multimodality treatment regimens in selected cIIIB/N2 cases did not provide a survival advantage over definitive chemoradiotherapy treatments.

or metastases, PET-CT was requested, and cranial magnetic resonance imaging was conducted when deemed necessary.

Overall survival (OS) was defined as the duration from the date of surgery to the date of death from any cause.

Statistical Analysis

The data were inputted into the Statistical Package for the Social Sciences Statistics for Windows, Version 23.0 (IBM Inc., Armonk, NY, USA) software for analysis. Descriptive statistics were employed to characterize the variables, utilizing measures such as mean, maximum, and minimum values, while percentages were utilized for qualitative variables. By Kolmogorov–Smirnov analysis, whether the distributions were normal or not was determined. For variables that followed a normal distribution, the mean was reported, and to compare groups, the Student's *t*-test was utilized. The analysis of qualitative variables was conducted using the Pearson chi-squared test. However, if the sample size of a group was small, the Fisher's exact test was used instead. Nonparametric continuous variables were documented as the median and assessed using Mann–Whitney *U*-tests for comparison. Survival was estimated using the Kaplan–Meier method, and survival was compared between the groups with a log-rank analysis. A *P*-value less than .05 was considered to be statistically significant.

RESULTS

There were 79 patients included in the study with a diagnosis of cIIIB/N2. Surgery was performed in 51 (64.5%) patients within the multimodality treatment regimens (IIIB/Surgery Group). In 28 cases (35.5%), surgical resection was not performed, and definitive CT ± RT was administered (IIIB/Definite Group).

Demographic and clinicopathological characteristics of the patients are summarized in Table 2. There were 51 patients in the IIIB/Surgical Group and 28 patients in the IIIB/Definitive Group. There was no statistical difference between the groups in terms of age, gender, side, radiological tumor diameter, anatomical localization of positive LN, and clinical T subtype. There was a trend toward statistical significance in terms of histological tumor type ($P = .06$). A statistical difference was found between the 2 groups in terms of the mediastinal staging method ($P = .02$). In mediastinal staging, EBUS was performed at a statistically higher rate in the IIIB/Surgery Group (31.4% vs. 7.1%).

Lobectomy was performed in 41 patients in the IIIB/Surgery Group and pneumonectomy in 10. Chest wall resection was performed in 7 of them. While PET-CT was used most frequently for restaging of the patients (n = 32, 62.7%), mediastinoscopy was performed in 16.5% (n = 13) of the remaining patients and EBUS (n = 6) in 7.6%.

In the IIIB/Surgery Group, pathological complete response (IIIB/Surgery-PCR) was detected in 14 cases (27.4%), while viable tumors were present in 37 cases (72.6%) (IIIB/Surgery-non-PCR). Considering the postoperative pathology results, 40 (78.4%) of the patients developed downstage of N2 (IIIB/Surgery-Non persistent N2), while 11 patients (21.6%) had persistent N2 (IIIB/Surgery-Persistent N2).

Survival Analysis

The 5-year OS rate for all patients was 27.4%. (median survival time: 24.6 months, 95% CI, 18.2-30.9). The 5-year OS rate for the IIIB/Surgery Group was 27.3% (median survival time 22.5 months, 95% CI, 11.8-33.1), while it was 28.6% (median survival time 29.1 months, 95% CI, 18.9-39.2) for the IIIB/Definitive Group. The observed difference was not statistically significant ($P = .387$, HR = 0.798, 95% CI, 0.485-1.313) (Figure 1).

Subgroup Analysis

Among the patients in the IIIB/Surgery Group, the 5-year OS was 42.9% (median survival time: 27.0 months, 95% CI, 0-116.4) in patients with pathological complete response (n = 14), while it was 18.5% (median survival time: 15.6 months, 95% CI, 3.6-27.5) in non- or partial responders (n = 37). However, the observed difference was not statistically significant. ($P = .104$) (Figure 2).

There was also no statistical difference in terms of survival between patients with the pathological complete response and the IIIB/Definitive Group ($P = .488$).

Among the patients in the IIIB/Surgery Group, the 5-year OS was 29.8% (median survival time 23.1 months, 95% CI, 18.6-27.7) in those with downstage mediastinal LN (n = 40), while the 3-year survival rate in those with persistent N2 was 18.2% (median survival time 13.9 months, 95% CI, 3.3-24.5). Nonetheless, this difference was not statistically significant ($P = .113$, Figure 3).

The 5-year OS was also not affected by age ($P = .083$), gender ($P = .842$), histological type ($P = .978$), tumor diameter (0.866), whether surgery was within the treatment protocol ($P = .387$), mediastinal staging methods ($P = .294$), location of N2 ($P = .232$), and resection type ($P = .589$).

Comparisons of variables that may affect survival are listed in Table 3.

DISCUSSION

Lung cancer is one of the most important causes of cancer-related death in both genders worldwide.[5] In early-stage NSCLC cases, direct surgery option is a generally accepted approach. However, treatment strategies change significantly as the stage progresses, and the indication for surgery and its impact on survival become controversial. In current guidelines, surgery is not recommended in stage IIIB/N2, except for T3N2 patients who do not have clinical and radiological signs of an invasion.[2] The results of the phase III PACIFIC trial on nonsurgical stage III patients were striking. Cases that did not show progression after CRT were administered the PD-L1 antibody durvalumab, and the 5-year OS rate was reported to be 42.9%.[6] On the other hand, since immunotherapy is still an expensive treatment in many countries, its use in routine practice is limited.[7] The treatment strategy in cases at this stage may be, therefore, limited to definitive CRT. The sociocultural and economic conditions of the patients affect the treatment choice.[8] The patients included in our study were patients receiving treatment between 2009 and 2016, and none of these patients had a chance for definitive treatment, including

Table 2. Demographic and Clinicopathological Characteristics of the Patients

Variable	Total (n = 79)	Stage IIIB/Surgery (n = 51)	Stage IIIB/Definitive (n = 28)	*P*
Age, mean ± SD	57.6 ± 0.7	57.3 ± 0.9	58.0 ± 1.3	.825
Gender, n (%)			5 (17.9)	.180
Female	9 (11.4)	4 (7.8)	23 (82.1)	
Male	70 (88.6)	47 (92.2)		
Side, n (%)				.219
Left	35 (44.3)	20 (39.2)	15 (53.6)	
Right	44 (55.7)	31 (60.8)	13 (46.4)	
Histological subtype, n (%)				.067
Squamous cell	32 (40.5)	24 (47.1)	8 (28.6)	
Adenocarcinoma	34 (43.0)	22 (43.1)	12 (42.9)	
Other[#]	13 (16.5)	5 (9.8)	8 (28.6)	
Radiological tumor diameter, median cm, (IQR)	6.0 (1.9)	6 (1.7)	6.1 (2.2)	.955
Mediastinal staging type, n (%)				.02
Mediastinoscopy	61 (77.2)	35 (68.6)	26 (92.9)	
EBUS	18 (22.8)	16 (31.4)	2 (7.1)	
Positive LN, n (%)				.486
4R	33 (41.8)	22 (43.1)	11 (39.3)	
7	20 (25.3)	15 (29.4)	5 (17.9)	
4L	19 (24.1)	9 (17.6)	10 (35.7)	
APW	7 (8.9)	5 (9.8)	2 (7.1)	
Clinical T subtype, n (%)				.120
T3	55 (69.6)	36 (70.6)	19 (67.9)	
T4	24 (30.4)	15 (29.4)	9 (32.1)	
Resection type, n (%)*			—	N/A
Lobectomy	41 (80.4)	41 (80.4)		
Pneumonectomy	10 (19.6)	10 (19.6)		
ypN status, n (%)*			—	N/A
ypN0	35 (68.6)	35 (68.6)		
ypN1γ	5 (9.8)	5 (9.8)		
ypN2α	11 (21.6)	11 (21.6)		
ypT status, n (%)*			—	N/A
T0	14 (27.5)	14 (27.5)		
T1	13 (16.5)	13 (16.5)		
T2	18 (22.8)	18 (22.8)		
T3	4 (5.1)	4 (5.1)		
T4	2 (2.5)	2 (2.5)		

APW, aortopulmonary window; EBUS, endobronchial ultrasound; IQR, interquartile range; LN, lymph node; n, number; na, nonapplicable; yp, new pathological stage.
*These ratios were based on 51 patients undergoing surgery after neoadjuvant therapy. Unblock chest wall resection was also performed in 7 (13.7%) of these patients. While four of the patients with ypN1 were N1a, one patient was found to be N1b. While three of the patients with α ypN2 were found N2a1, five were ypN2a2, and three of them were N2b.
[#]Adenosquamous cell carcinoma and large cell carcinoma.

immunotherapy. Nevertheless, in our study, even in highly selective cIIIB/N2 patients who can achieve complete resection, surgery within multimodality regimens was found not to provide a survival advantage compared to definitive CRT.

In terms of survival outcomes of stage IIIB/N2 cases, quite different results are presented in the literature. These differences may be due to the use of different editions of TNM.

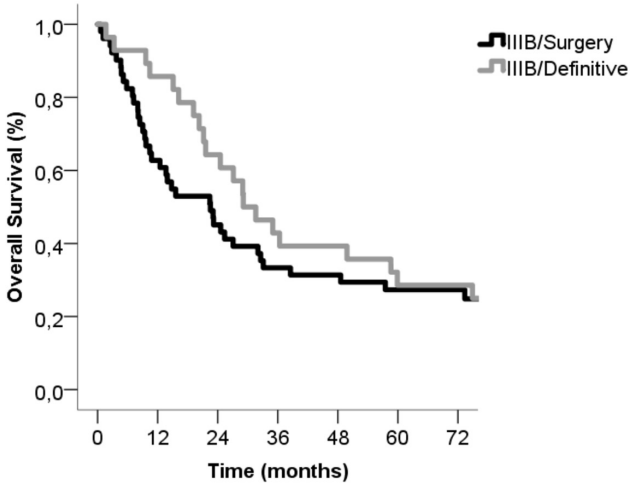

Figure 1. Overall survival of IIIB/Surgery Group and IIIB/Definitive Group.

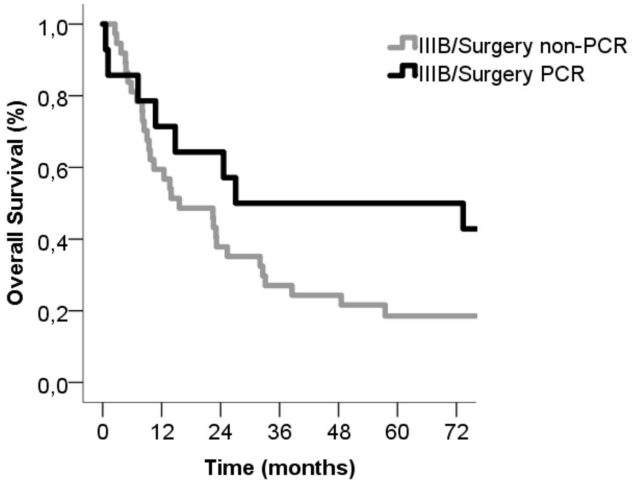

Figure 2. Overall survival of the IIIB/Surgery-nonPCR Group and the IIIB/Surgery-PCR group. PCR, pathological complete response.

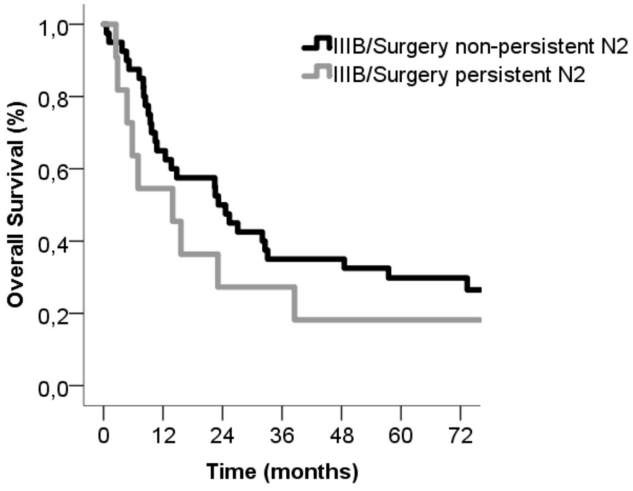

Figure 3. Overall survival of IIIB/Surgery-non Persistent N2 Group and IIIB/Surgery-Persistent N2.

The 5-year survival rate was reported as 25% in cN0-1 pathological (p) IIIB/N2 (unexpected N2) patients who were staged according to the eighth8th edition of the TNM system, and did not receive neoadjuvant therapy, whereas it was reported as 39% in cN2/N3 stage IIIB cases staged considering the seventh7th edition of the TNM system.[3,9] The authors attributed successful survival outcomes obtained from IIIB/N2-N3 patients, above the literature rates, to the selection of optimal surgical candidates and low postoperative mortality.[3]

The largest study on this subject is the ESPATURE Phase III study.[10] In selected IIIB NSCLC and resectable stage IIIA/N2 patients, according to the sixth edition of TNM staging,

Table 3. Comparison of Variables that May Affect Survival

Variable	5-year Overall Survival (%)	Median Survival Time (Months)	*P*
Age, n (%)			.083
<65	30.1	27.1	
≥65	15.4	15.6	
Gender, n (%)			.842
Female	26.9	24.5	
Male	33.3*	29	
Histological type			.978
Adenocarcinoma	30.9	22.4	
Non-adenocarcinoma	25.5	29	
Tumor diameter,			.866
≤7 cm	27	24.5	
>7 cm	25	25.3	
Treatment type, n (%)			.387
Neoadj+S ± Adj	27.3	22.5	
Adj	28.6	29.1	
Mediastinal staging type, n (%)			.294
Mediastinoscopy	30.9	24.5	
EBUS	16.7	24.6	
Mediastinal LN metastasis location			.232
Subcarinal	15	15.1	
Paratracheal or APW	32	24.6	
Resection type, n (%)			.589
Lobectomy	29.1	22.4	
Pneumonectomy	20.0*	23.1	
Response to treatment			.104
Pathological complete response	42.9	27	
Partial response or no response	18.5	15.6	
ypN status			.113
Downstage	29.8	23.1	
Persistent	18.2	13.9	

APW, aortopulmonary window; Adj, adjuvant treatment; EBUS, endobronchial ultrasound; LN, lymph node; Neoadj, neoadjuvant treatment; n, number; S, surgery; yp, new pathological stage.
*Three-year survival results.

surgeries after induction treatment regimens were compared with definitive treatment modalities, and there was no difference in survival between the groups. However, a survival advantage was seen in the surgical group, T3N2 cases, and T4N0-1 subgroups. Contrary to this study, in the analysis of the National Cancer Database data, including T4/N2 and N3 patients, patients treated with radiotherapy, chemotherapy, and surgery in any sequence group showed a statistically significant survival advantage compared to the definitive chemoradiation treatment group.[11]

The most important point to be considered in similar studies in the literature is the use of different editions of the TNM, and this probably affects survival outcomes.[12,13]

Using the eighth TNM staging system instead of the sixth and seventh editions of TNM and focusing only on the IIIB/N2 (T3-T4/N2) patient group in our study were thought to make our study a more successful design in questioning the role of surgery regarding the IIIB/N2 patient group.

We think that the 5-year survival rate of patients in the cIIIB/N2 group is similar to the latest International Association for the Study of Lung Cancer (IASLC) group data, which is a valuable parameter for our selection of appropriate patients (IASCL vs. the current study; cIIIB 5-year OS: 26%, median 19 months vs. 27.3%, median 22.5 months).[14] It was stated that the patients who would prefer surgery among the multimodality regimens in N2 cases should be patients in whom complete resection is feasible and whose 90-day perioperative mortality expectation should be ≤5%. Another point underlined in the same guidelines is that patients and their relatives should be included in the treatment decision process and that a surgical opinion must be received in non-surgical treatment decisions.[14] In the cases included in the study, the final decisions were evaluated in multidisciplinary tumor councils, and the preferences of the patients and their relatives were taken into account.

The mediastinal downstage after neoadjuvant therapy and the complete pathological response in the postoperative examination are known to be associated with good survival.[15,16] Conversely, 5-year survival rates of 30-47.3% have been reported in persistent single N2 cases that cannot achieve mediastinal downstage.[17] In our IIIB/Surgery Group, although the median survival difference was 10 months between persistent N2 cases and those with mediastinal downstage, this difference could not reach statistical significance (5-year OS: 29.8% vs. 18.2%). Likewise, although there was a median survival difference of approximately 11 months in the patient group with a complete response compared to the group with a non-complete response, this difference did not reach statistical significance against both the non-complete response and definitive treatment groups.

Mediastinal downstage can also be evaluated with EBUS and PET-CT, but mediastinoscopy is still the gold standard.[2,18] All 3 methods were used for restaging in the cIIIB/N2 patient group. In evaluating the best staging algorithms, EBUS is recommended as the minimally invasive method in the first step, and mediastinoscopy is for restaging.[2]

The PACIFIC study has led to the questioning of the surgery to be performed at this stage. Although surgery does not provide any survival advantage at this stage among multimodal treatment strategies, we think that applications for cancer immunotherapy in IIIB/N2/N3 patients bring new surgical indications. In the following years, surgery may have a new indication within neoadjuvant CT + immunotherapy and definitive CRT + immunotherapy regimens in stage IIIB/N2 cases.[19,20] Again, salvage surgery is a new indication in stage IIIB patients receiving definitive CRT + durvalumab and being completely respected with good condition, and there is not enough data on this subject yet.[21]

The current study has some limitations, primarily attributed to its retrospective design. It does not claim to determine treatment strategies in stage IIIB/N2 due to the limited sample size and limited single-center setting, which reduces generalizability to broader clinical practice. Therefore, the view that surgery does not provide a survival advantage at this stage should be interpreted with caution as it is a single-center study. However, our study is one of the largest studies in the IIIB/N2 patient group using only the eighth TNM staging system. We think that our similarity with IASLC survival results is indicative of our selection of the clinically appropriate stage IIIB patient group. Currently, EBUS/endoscopic ultrasound (EUS)-guided fine needle aspiration is the first-choice method for sampling mediastinal lymph nodes due to its minimally invasive nature and high diagnostic value. However, we could not apply for EUS because there was no equipment in our center during the years of the study. Therefore, we could not sample stations 8 and 9. Since the diagnosis of T3-4 disease is made only based on radiological findings, there may be disagreements among radiologists. The T4 patient group within the cIIIB/Surgery Group consists of a highly selected group of patients. In addition, the number of patients with PCR and mediastinal downstage is very small and may affect the outcomes of the study in terms of statistical significance. Therefore, the results of this study should be interpreted with caution in terms of surgical outcomes in stage IIIB/N2 NSCLC patients.

Complete resections performed within multimodality treatment regimens in highly selective cIIIB/N2 patients did not provide an advantage over definitive chemoradiation treatments in terms of OS. Although a survival advantage was observed in cases with a complete response to induction treatment regimens, this difference did not reach statistical significance compared to the definitive treatment group. Even though there was a difference in survival between cases with and without mediastinal downstage after induction treatment regimens, it was not statistically significant. Large phase III studies are needed on the application and benefit of surgery after neoadjuvant chemotherapy + immunotherapy or salvage surgery after definitive treatment in stage IIIB/N2 cases.

Ethics Committee Approval: This study was approved by Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval No: 329-5, Date: August 24, 2022).

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – V.E., Y.A.; Design – M.V.D., N.Ç.; Supervision – M.M., L.C.; Resources – N.Y.; Materials – V.E., N.Y.; Data Collection – N.Y., Y.A.; Analyses – N.Ç.; Literature search – C.B.S.; Writing – V.E., N.Ç.; Critical review – M.M.

Declaration of Interests: The authors have no conflict of interest to declare.

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