

# Survival Outcomes in Patients With Locally Advanced NSCLC Converted to Resectable Disease by Neoadjuvant Therapy

ECE DUYGU GULSEN<sup>1</sup>, RASHAD ISMAYILOV<sup>2</sup>, AYDAN FARZALIYEVA<sup>2</sup>, MEHMET NEZIR RAMAZANOGLU<sup>2</sup>, ARZU OGUZ<sup>2</sup>, DALOKAY KILIC<sup>3</sup>, ZAFER AKCALI<sup>2</sup> and OZDEN ALTUNDAG<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Baskent University Faculty of Medicine, Ankara, Türkiye;

<sup>2</sup>Department of Medical Oncology, Baskent University Faculty of Medicine, Ankara, Türkiye;

<sup>3</sup>Department of Thoracic Surgery, Baskent University Faculty of Medicine, Ankara, Türkiye

## Abstract

**Background/Aim:** Neoadjuvant therapy enables disease conversion to resectability in selected patients with locally advanced non-small-cell lung cancer (NSCLC) but real-world survival outcomes in this setting are not well defined. This study aimed to evaluate survival outcomes and prognostic factors in patients with initially unresectable, non-metastatic NSCLC in whom complete resection was achieved following neoadjuvant therapy.

**Patients and Methods:** This retrospective cohort study included 35 patients with initially unresectable NSCLC who underwent R0 resection after neoadjuvant therapy. Demographic, clinical, radiological, and pathological characteristics, treatment details, and survival outcomes were collected. Factors associated with event-free (EFS) and overall (OS) survival were analyzed.

**Results:** The mean age at diagnosis was 67.6 years, and 85.7% of patients were male. Patients received a median of 3 (range=2-6) neoadjuvant therapy cycles (77% with carboplatin and paclitaxel). Postoperative pathology revealed mediastinal lymph node involvement in 37.1% and angiolymphatic invasion in 25.7% of patients. Adjuvant treatment was administered to 51.4% of patients, with no factor significantly associated with this decision. During a median follow-up of 40.6 months, the recurrence rate was 37.1%, and the mortality rate was 40%. The median EFS was 25.4 months, while the median OS was not reached. Two-year EFS and OS rates were 53.9% and 66.3%, respectively. Univariate analysis identified mediastinal lymph node involvement, angiolymphatic invasion, and receiving  $\geq 3$  neoadjuvant cycles as significant predictors of shorter EFS, while only mediastinal lymph node involvement significantly affected OS. Multivariate analysis did not reveal independent predictors, likely due to collinearity.

*continued*

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Rashad Ismayilov (ORCID: 0000-0002-7093-2722), MD, Department of Medical Oncology, Baskent University Ankara Hospital, Yukarı Bahçelievler, Mareşal Fevzi Çakmak Cd. 10. Sk. No. 45, 06490 Bahçelievler Ankara, Türkiye. Tel: +90 5070331995, e-mail: rismayilov@baskent.edu.tr

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*Conclusion:* Complete resection after neoadjuvant therapy yields favorable long-term survival in selected patients with initially unresectable NSCLC. Postoperative mediastinal lymph node status remains a critical prognostic factor.

**Keywords:** Non-small-cell lung cancer, neoadjuvant therapy, surgical resection.

## Introduction

Non-small-cell lung cancer (NSCLC) constitutes the majority of lung cancer diagnoses and remains a leading cause of cancer-related mortality worldwide (1). Approximately 20% to 30% of patients present with stage III, locally advanced disease at diagnosis, characterized by substantial heterogeneity in tumor size, lymph node involvement, and patient comorbidities (2). The management of locally advanced NSCLC requires multidisciplinary evaluation to determine the optimal therapeutic approach, balancing disease extent, resectability and patient fitness (3). For unresectable stage III NSCLC, concurrent chemoradiation followed by consolidation immunotherapy has become the standard of care, based on the PACIFIC trial results demonstrating significant survival benefits (4).

However, in selected cases, neoadjuvant therapy offers the potential to downstage tumors and achieve resectability, introducing surgery as a critical component of multimodal therapy. Recent trials have demonstrated the potential of neoadjuvant therapy to improve surgical outcomes and survival in resectable stage III NSCLC by reducing tumor burden and eradicating micrometastases (5-9). Despite growing interest in neoadjuvant strategies, prospective trials and real-world data on survival outcomes in patients with locally advanced NSCLC converted to resectable status by neoadjuvant therapy remain limited. Furthermore, factors influencing long-term survival following successful surgical resection are not fully understood (10, 11).

This study aimed to evaluate the real-world survival outcomes of patients with non-metastatic, initially unresectable locally advanced NSCLC who underwent complete resection following neoadjuvant therapy. Understanding survival patterns and prognostic factors in

this unique patient group may help refine patient selection, optimize multimodal treatment strategies, and improve long-term outcomes in unresectable locally advanced NSCLC.

## Patients and Methods

*Study population.* This retrospective cohort study included patients aged 18 years and older who were diagnosed with locally advanced NSCLC at our tertiary care center between January 2003 and December 2023. The study protocol was approved by the Institutional Ethics Committee (Decision No: KA23/356). The study specifically focused on patients initially deemed inoperable who became eligible for surgery following neoadjuvant therapy. Treatment decisions for all patients were made in a multidisciplinary tumor board comprising medical oncologists, radiation oncologists, thoracic surgeons, radiologists, and nuclear medicine specialists. Only patients who underwent complete (R0) resection were included, while those with microscopically (R1) or macroscopically (R2) positive surgical margins were excluded. Additional exclusion criteria included: diagnosis of metastatic disease or small-cell lung cancer; failure to receive or complete neoadjuvant therapy; insufficient pulmonary, renal, or hematological reserve for surgery; lack of regular follow-up in the Oncology Clinic; and incomplete medical records. Of the 163 patients screened, 35 met the inclusion criteria and were enrolled in the final analysis.

*Data collection.* Patient data were retrospectively retrieved from the hospital's electronic health records. Collected variables included demographic characteristics (age, sex, smoking history, date of diagnosis); tumor-related features (histological subtype, presence of driver mutations,

expression of programmed death-ligand 1 (PD-L1), T- and N-stage according to the American Joint Committee on Cancer, eighth edition), and treatment-related parameters (type and number of neoadjuvant therapy cycles, preoperative radiotherapy, date of surgery, postoperative mediastinal lymph node status, and adjuvant therapies). Outcomes assessed included recurrence status and site, treatment received at recurrence, survival status, date of death, and cause of death.

**Statistical analysis.** All statistical analyses were conducted using IBM® SPSS Statistics version 27 (IBM, Armonk, NY, USA). Descriptive statistics were reported as frequencies and percentages for categorical variables, and as the mean  $\pm$  standard deviation or median (range) for continuous variables, depending on data distribution. Group comparisons were performed using chi-square test or Fisher's exact test for categorical variables, and Student's *t*-test or Mann-Whitney *U*-test for continuous variables. Overall survival (OS) was defined as the time from surgery to death from any cause, and event-free survival (EFS) as the time from surgery to recurrence or death. Survival outcomes were assessed using the Kaplan-Meier method and compared using the log-rank test. To identify predictors of EFS and OS, univariate and multivariate Cox proportional hazards regression analyses were performed, and results are reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). A two-sided value of  $p < 0.05$  was considered statistically significant.

## Results

A total of 35 patients (85.7% male) with a mean age at diagnosis of 67.6 $\pm$ 8 years were included in the study. Baseline characteristics, neoadjuvant treatments, and surgical procedures are detailed in Table I. Excluding the patient who underwent surgery after 4 months of afatinib treatment, the median number of neoadjuvant treatment cycles among the remaining 34 patients was 3 (range=2-6).

Postoperative pathology revealed mediastinal lymph node involvement in 13 patients (37.1%) and angiolymphatic

Table I. Baseline characteristics of the study patients (n=35).

Characteristic	Value
Age, mean $\pm$ SD, years	67.6 $\pm$ 8.0
Male sex, n (%)	30 (85.7)
Smoking status, n (%)	34 (97.1)
Histological type, n (%)	
Squamous cell carcinoma	28 (80.0)
Adenocarcinoma	7 (20.0)
Driver mutations, n (%) (n=4)	
Negative	2/4 (50.0)
EGFR mutation	2/4 (50.0)
PD-L1 $\geq$ 1, n (%), n=9	4/9 (44.4)
T Stage, n (%)	
T1	4 (11.4)
T2	10 (28.6)
T3	9 (25.7)
T4	12 (34.3)
N Stage, n (%)	
N0	1 (2.9)
N1	2 (5.7)
N2	24 (68.6)
N3	8 (22.9)
Clinical stage, n (%)	
II B	1 (2.9)
III A	11 (31.4)
III B	19 (54.3)
III C	4 (11.4)
Neoadjuvant therapies, n (%)	
Carboplatin and paclitaxel	27 (77.1)
Cisplatin and gemcitabine	4 (11.4)
Cisplatin and pemetrexed	1 (2.9)
Cisplatin	1 (2.9)
Pembrolizumab	1 (2.9)
Afatinib*	1 (2.9)
NAT cycles, median (range)	3 (2-6)
Preoperative radiotherapy, n (%)	2 (5.7)
Surgical procedure, n (%)	
Lobectomy	21 (60.0)
Pneumonectomy	11 (31.4)
Segmentectomy	3 (8.6)

EGFR: Epidermal growth factor receptor; NAT: neoadjuvant therapy; PD-L1: programmed death-ligand 1; SD: standard deviation.

\*Eligible for surgery after 4 months of treatment.

invasion in 9 (25.7%). The median tumor diameter was 3 cm (range=0-9 cm), with 12 patients (34.3%) having tumors  $\geq$ 4 cm. Visceral pleural involvement was identified as pleural invasion in 2 (5.7%), pleural contact in 10 (28.6%), and no contact or invasion in 23 patients (65.7%). Cartilage invasion was present in 2 cases (5.7%). Mediastinal lymph node involvement was observed in 77.8% of patients with

angiolympathic invasion (7/9 patients) compared to only 23.1% of those without (6/26 patients) ( $p=0.006$ ). None of the patients whose disease became operable after two cycles of neoadjuvant therapy had angiolympathic invasion or mediastinal lymph node involvement, whereas among those who underwent surgery after three or more cycles, angiolympathic invasion was observed in 33% (9/27 patients) and mediastinal lymph node involvement in 48.1% (13/27 patients) ( $p=0.151$  and  $p=0.029$ , respectively).

Eighteen patients (51.4%) received adjuvant therapy following surgery. Among them, 10 received carboplatin plus paclitaxel, 3 received carboplatin plus gemcitabine, 3 received cisplatin plus vinorelbine, 1 received cisplatin plus pemetrexed, and 1 received afatinib. Postoperative radiotherapy was administered to 2 patients (5.7%). Baseline and pathological features did not significantly differ between patients who did and did not receive systemic adjuvant therapy (Table II).

During a median follow-up of 40.6 months (95% CI=29.0-52.2), recurrence occurred in 13 patients (37.1%), and 14 patients (40%) died. The median EFS was 25.4 months (95% CI=0.0-56.1 months), while the median OS was not reached. The 2-year EFS and OS rates were 53.9% (95% CI=36.5-71.3%) and 66.3% (95% CI=49.8-82.8%), respectively. In univariate analyses, receiving  $\geq 3$  cycles of neoadjuvant therapy (HR=6.43, 95% CI=1.31-31.5;  $p=0.022$ ), mediastinal lymph node involvement (HR=3.25, 95% CI=1.21-8.72;  $p=0.020$ ), and angiolympathic invasion (HR=3.13, 95% CI=1.18-8.34;  $p=0.022$ ) were significantly associated with shorter EFS (Table III). Regarding OS, only mediastinal lymph node involvement demonstrated a significant impact on mortality risk (HR=3.50, 95% CI=1.18-10.4;  $p=0.024$ ), whereas angiolympathic invasion (HR=2.65, 95% CI=0.88-7.99;  $p=0.084$ ) and receiving  $\geq 3$  neoadjuvant cycles (HR=6.94, 95% CI=0.85-56.9;  $p=0.071$ ) did not reach statistical significance (Figure 1). Multivariate analysis revealed that these three interrelated parameters were not independent predictors of EFS or OS (Table IV). Additionally, receiving adjuvant therapy was not associated with EFS or OS among the 13 patients with mediastinal lymph node involvement ( $p=0.985$  and  $p=0.723$ , respectively).

Table II. Comparison of patients with and without adjuvant therapy.

Parameter	Adjuvant therapy		p-Value
	Yes (n=18)	No (n=17)	
Age, mean $\pm$ SD, years	65.3 $\pm$ 8.0	69.9 $\pm$ 7.6	0.089
Male sex, n (%)	16 (88.9)	14 (82.4)	0.658
Histological type, n (%)			
Squamous cell carcinoma	16 (88.9)	12 (70.6)	0.228
Adenocarcinoma	2 (11.1)	5 (29.4)	
T Stage, n (%)			
T1/T2	6 (33.3)	8 (47.1)	0.407
T3/T4	12 (66.7)	9 (52.9)	
N Stage, n (%)			
N0/N1	2 (11.1)	1 (5.9)	0.859
N2	12 (66.7)	12 (70.6)	
N3	4 (22.2)	4 (23.5)	
Clinical stage, n (%)			
IIB/IIIA	7 (38.9)	5 (29.4)	0.555
IIIB/IIIC	11 (61.1)	12 (70.6)	
Median NAT cycles (range), n	3 (2-5)	3 (2-6)	0.079
Surgical procedure, n (%)			
Lobectomy	11 (61.1)	10 (58.8)	0.801
Pneumonectomy	6 (33.3)	5 (29.4)	
Segmentectomy	1 (5.6)	2 (11.8)	
Mediastinal LN involvement, n (%)	9 (50.0)	4 (23.5)	0.105
Median maximum tumor diameter (range), cm	2.5 (0-9)	3.5 (0-6.5)	0.483
Maximum tumor diameter $\geq 4$ cm, n (%)	5 (27.8)	7 (41.2)	0.404
Angiolympathic invasion, n (%)	4 (22.2)	5 (29.4)	0.711
Pleural contact or invasion, n (%)	5 (27.8)	7 (41.2)	0.404
Cartilage invasion, n (%)	0 (0.0)	2 (11.8)	0.229

LN: Lymph node; NAT: neoadjuvant therapy; SD: standard deviation.

## Discussion

This study evaluated the real-world survival outcomes of patients with initially unresectable, non-metastatic, locally advanced NSCLC who achieved complete surgical resection following neoadjuvant therapy. Our findings demonstrate that conversion to resectability and subsequent surgery in this highly selected cohort resulted in favorable long-term survival, with a 2-year OS rate of 66.3% and a median OS not reached during a median follow-up of over 40 months. However, postoperative pathological factors, particularly mediastinal lymph node involvement, significantly

Table III. Analysis of potential predictors of 2-year event-free (EFS) and overall survival (OS). Kaplan–Meier estimates of survival rates with standard error values are reported.

Parameter	Groups	EFS (%)	<i>p</i> -Value*	OS (%)	<i>p</i> -Value*
Age	<65 Years	53.3±16.1	0.938	74.1±12.9	0.825
	≥65 Years	52.5±11.0		62.0±10.6	
Sex	Male	58.0±9.3	0.517	68.1±8.8	0.779
	Female	40.0±21.9		60.0±21.9	
Histological type	SCC	53.8±9.9	0.381	69.4±9.1	0.766
	Adenocarcinoma	57.1±18.7		53.6±20.1	
T Stage	T1/T2	60.2±14.0	0.385	68.8±13.1	0.245
	T3/T4	50.8±11.2		65.2±10.7	
N Stage	N0/N1	66.7±27.2	0.517	66.7±27.2	0.815
	N2	47.3±11.5		62.1±10.8	
	N3	62.5±17.1		75.0±15.3	
Clinical stage	IIB/IIIA	52.4±15.7	0.949	62.9±14.9	0.600
	IIIB/IIIC	55.4±10.5		68.5±9.9	
NAT cycles	2	85.7±13.2	<b>0.022</b>	100.0±0.0	<b>0.037</b>
	3	48.6±13.1		67.5±12.1	
	≥4	33.3±15.7		33.3±15.7	
Surgical procedure	Lobectomy	53.5±11.5	0.937	58.8±11.3	0.511
	Pneumonectomy	54.5±15.0		72.7±13.4	
	Segmentectomy	66.7±27.2		100.0±0.0	
Mediastinal LN involvement	Absent	67.6±10.1	<b>0.013</b>	81.6±8.3	<b>0.017</b>
	Present	27.1±14.8		36.3±15.4	
Maximum tumor diameter	<4 cm	57.6±10.9	0.475	67.2±10.3	0.571
	≥4 cm	46.3±15.0		64.2±14.4	
Angiolymphatic invasion	Absent	65.4±9.3	<b>0.015</b>	76.7±8.3	0.071
	Present	15.6±14.2		31.1±17.9	
Pleural contact or invasion	Absent	62.4±10.7	0.369	71.6±9.9	0.482
	Present	37.5±15.3		56.3±14.8	
Adjuvant therapy	No	45.3±12.4	0.523	57.4±12.3	0.395
	Yes	60.4±13.1		74.4±11.4	

LN: Lymph node; NAT: neoadjuvant therapy; SE: standard error; SCC: squamous cell carcinoma. \*Log-rank test. Statistically significant *p*-values are shown in bold.

influenced prognosis, emerging as the sole significant predictor of OS.

Management of unresectable stage III NSCLC remains a major therapeutic challenge. The PACIFIC trial established concurrent chemoradiotherapy followed by durvalumab consolidation as the standard of care (12). Notably, the updated PACIFIC analysis demonstrated a 24-month OS rate of 66.3% (95% CI=61.7-70.4%) with durvalumab *versus* 55.6% (95% CI=48.9-61.8%) with placebo, setting a contemporary benchmark for this population (13). Interestingly, our surgical cohort achieved a comparable 2-year OS rate of 66.3%, despite representing a subgroup with disease initially deemed

unresectable. While direct comparisons must be made cautiously due to inherent selection biases, these findings suggest that for carefully selected patients, surgical conversion after neoadjuvant therapy can yield survival outcomes on a par with those achieved by consolidation immunotherapy in unresectable disease.

Recent phase II studies explored neoadjuvant strategies aiming to downstage tumors and facilitate resection in initially unresectable NSCLC. Zhou *et al*. demonstrated a 25% surgical conversion rate with neoadjuvant SHR-1701 plus chemotherapy, achieving an 18-month EFS rate of 74.1% in patients who underwent resection (14). Similarly, Xia *et al*. reported R0 resection rates of 50.0% and 42.9%

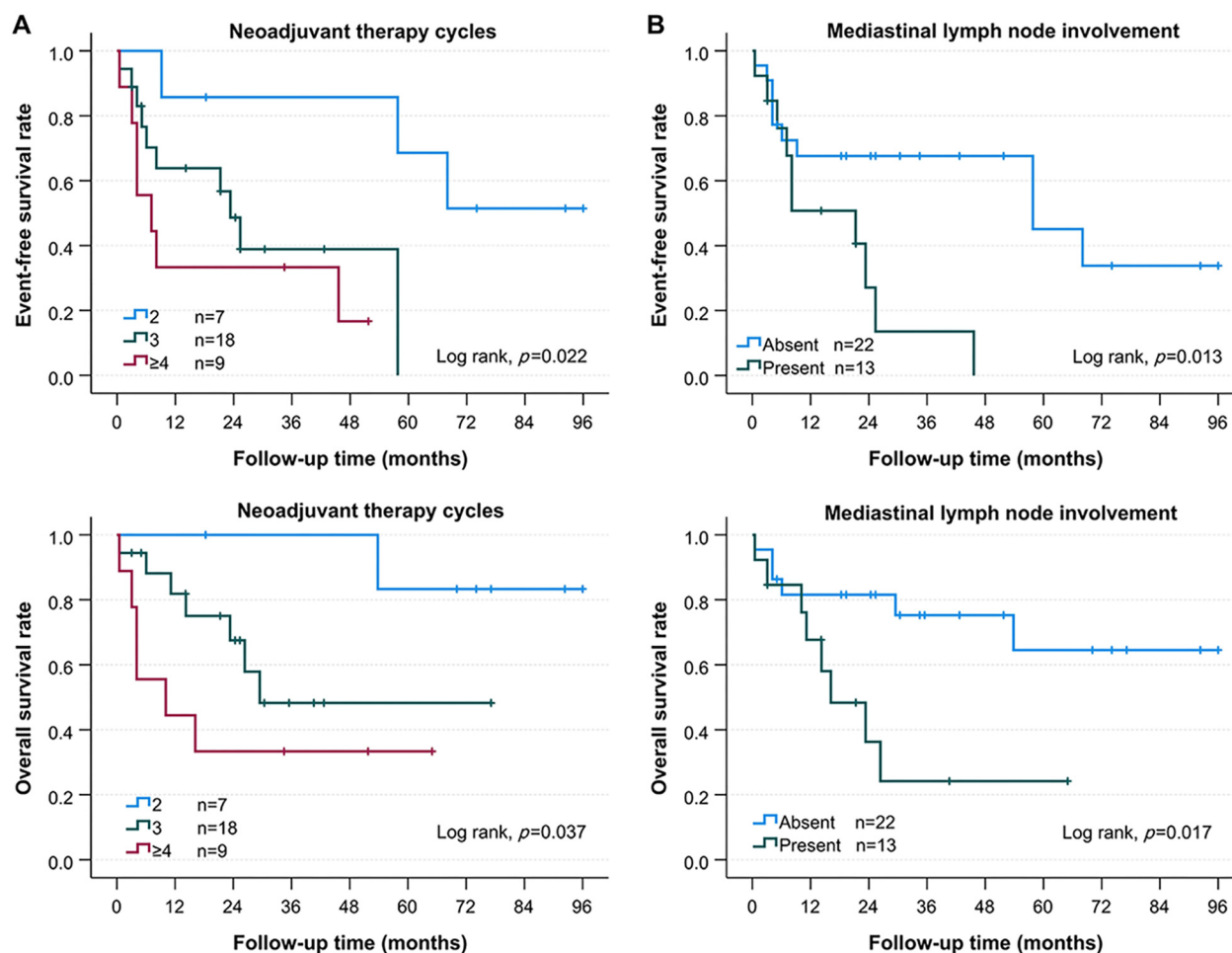


Figure 1. Continued

after neoadjuvant camrelizumab-based regimens, with favorable pathological responses (15). Zeng *et al.* achieved a 74.4% surgical conversion rate and high major pathological response/pathological complete response rates (65.6%/42.2%) with neoadjuvant chemoimmunotherapy (16). Targeted approaches have also shown promise, with Bian *et al.* reporting a 45.1% surgical conversion rate using neoadjuvant aumolertinib in patients with epidermal growth factor receptor-mutated NSCLC (17). Collectively, these studies highlight the evolving feasibility of surgical conversion strategies in locally advanced disease, aligning with the principle demonstrated by our findings that R0

resection after neoadjuvant therapy can confer substantial survival benefits.

In our cohort, postoperative mediastinal lymph node involvement was the strongest negative prognostic factor for both EFS and OS. Patients with residual nodal disease had a significantly higher risk of recurrence and mortality, consistent with prior observations across NSCLC surgical series (18, 19). Angiolymphatic invasion and the requirement for  $\geq 3$  cycles of neoadjuvant therapy were also associated with worse EFS, suggesting that less profound or delayed responses to induction therapy may predict residual disease burden and inferior outcomes. Although multivariate analysis

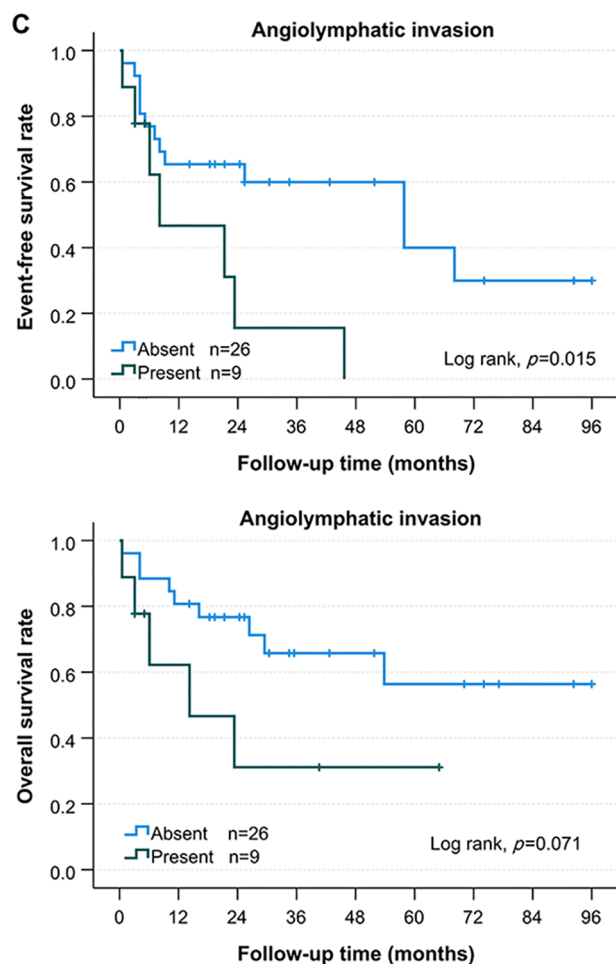


Figure 1. Kaplan–Meier curves for event-free survival (upper panel) and overall survival (lower panel) by number of neoadjuvant therapy cycles (A), mediastinal lymph node involvement (B), and angiolymphatic invasion (C).

did not identify independent predictors, likely due to sample size limitations and collinearity among variables, the observed trends underscore the critical prognostic role of achieving pathological nodal clearance (ypN0).

Regarding postoperative management, the inability to demonstrate a survival benefit from adjuvant therapy in the subgroup with mediastinal lymph node involvement highlights the need for close surveillance, stronger predictive biomarkers, and novel therapeutic approaches for this group. Only a minority of our patients received postoperative radiotherapy, reflecting evolving practice

patterns. The Lung ART trial demonstrated no significant improvement in disease-free survival with modern conformal postoperative radiotherapy compared to observation in completely resected N2-positive NSCLC (19), supporting a selective approach to postoperative radiotherapy use, particularly in patients with complete resection and pathological downstaging.

For many years, there has been discussion on the role of surgery after induction therapy in stage III NSCLC. Surgical resection and definitive chemoradiotherapy following induction chemotherapy were compared in early randomized trials, such as the European Organisation for Research and Treatment of Cancer study (20) and the Intergroup 0139 study (18). Although progression-free survival seemed to be enhanced in certain surgical subgroups, especially those undergoing lobectomy as opposed to pneumonectomy, neither trial found a statistically significant OS benefit with surgery *versus* definitive chemoradiotherapy. In our cohort, all patients underwent complete (R0) resection, and pneumonectomy was avoided, potentially contributing to the favorable survival outcomes observed.

Our study supports the evolving view that selected patients with initially unresectable NSCLC can achieve long-term survival with neoadjuvant therapy followed by surgery. However, appropriate patient selection remains critical. Recent evidence, particularly from the CheckMate-816 trial, highlight the importance of integrating biomarker-driven strategies into patient selection. In its updated analysis, CheckMate-816 became the first and only neoadjuvant-only immunotherapy phase III study to demonstrate a statistically and clinically significant 5-year OS benefit in patients with resectable solid tumors (21). Patients achieving a complete pathological response with nivolumab plus chemotherapy had a remarkable 5-year OS rate of 95%, compared to 56% in those without complete pathological response (HR=0.11, 95% CI=0.04-0.36). Notably, in patients with PD-L1 expression less than 1%, the unstratified HR for OS was 0.89, indicating that potential benefits of chemotherapy alone should not be ignored in low PD-L1-expressing subgroups. In our cohort,

Table IV. Predictive factors for event-free and overall survival by multivariate Cox regression analysis.

Factor	Event-free survival			Overall survival		
	HR	95% CI	p-Value	HR	95% CI	p-Value
≥3 Cycles of NAT	4.891	0.894-26.743	0.067	4.559	0.499-41.622	0.179
Mediastinal LN involvement	1.566	0.487-5.037	0.452	2.024	0.531-7.718	0.302
Angiolymphatic invasion	1.668	0.531-5.239	0.381	1.157	0.304-4.405	0.831

CI: Confidence interval; HR: hazard ratio; LN: lymph node; NAT: neoadjuvant therapy.

PD-L1 expression data were largely unavailable, limiting direct comparisons; nonetheless, this variable warrants consideration in future studies of neoadjuvant immunotherapy and surgical conversion. Furthermore, exploratory analyses from CheckMate-816 showed that presurgical circulating tumor DNA clearance was associated with improved OS in both treatment arms (nivolumab plus chemotherapy: HR=0.38, 95% CI=0.15-1.00; chemotherapy alone: HR=0.39, 95% CI=0.14-1.11). These findings suggest that PD-L1 expression and circulating tumor DNA clearance may help identify patients most likely to benefit from neoadjuvant strategies. As Moghanaki *et al.* emphasized, the lack of standardized criteria for resectability and reliable biomarkers for treatment response complicates clinical decision-making (22). Future research may improve selection procedures by using consistent definitions of resectability and perhaps by incorporating biomarkers such as PD-L1 expression, circulating tumor DNA clearance, tumor mutational burden, and copy-number variation status (6, 16, 23).

Limitations of our study include its retrospective design, a small sample size limiting statistical power for multivariable analyses, potential heterogeneity in neoadjuvant regimens over the study period, and incomplete biomarker data precluding detailed correlative analyses. Moreover, inherent selection bias exists, as only patients with R0 resection were included. Despite these limitations, our study has notable strengths, including its focus on a specific and challenging patient subset, the use of consistent multidisciplinary evaluation, and a relatively long follow-up period enabling mature survival data.

## Conclusion

In conclusion, our real-world data support that, in carefully selected patients, neoadjuvant therapy followed by complete surgical resection offers favorable long-term survival comparable to that achieved with contemporary immunotherapy-based standards in unresectable NSCLC. Postoperative nodal status remains a key prognostic determinant. This approach may be especially valuable in low- and middle-income countries where access to immunotherapy is limited, providing a viable and potentially cost-effective alternative when implemented within a multidisciplinary framework. Future research should focus on optimizing neoadjuvant regimens, developing reliable predictors of surgical conversion and pathological response, and standardizing surgical and pathological reporting to refine patient selection for this promising multimodal approach.

## Conflicts of Interest

The Authors declare that they have no conflicts of interest.

## Authors' Contributions

Conceptualization: OA; methodology: RI, AO and OA; formal analysis: RI, ZA and OA; investigation: EDG, RI, AF, MNR, AO, DK ZA and OA; data curation: RI, AO and ZA; resources: DK and OA; writing—original draft: EDG and RI; writing—review and editing: EDG, RI, AF, MNR, AO, DK ZA and OA; supervision: OA; Project administration: OA; visualization:

RI; validation: AO and OA; funding acquisition: OA. All Authors have read and agreed to the published version of the manuscript.

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During the preparation of this manuscript, a large language model (ChatGPT 4o, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine-learning-based image enhancement tools.

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