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Research Article

Neoadjuvant chemotherapy with surgery versus concurrent chemoradiation in N2 non-small cell lung cancer: a retrospective comparative analysis of treatment outcomes

N2 lenf nodu tutulumu olan küçük hücreli dışı akciğer kanserinde neoadjuvan kemoterapi sonrası cerrahi ile eşzamanlı kemoradyoterapinin karşılaştırılması: Tedavi sonuçlarının retrospektif analizi

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Abstract

Aim: The most effective management approach for non–small cell lung cancer (NSCLC) patients presenting with mediastinal (N2) lymph node involvement has not yet been clearly established. This study compared clinical outcomes between neoadjuvant chemotherapy followed by surgical resection (NACTx-Surgery) and definitive concurrent chemoradiation (CRT) in patients with N2 disease.

Material and Methods: In this retrospective cohort analysis, we evaluated 61 individuals diagnosed with N2 stage NSCLC who received treatment at two high level tertiary care institutions. Thirty-one patients received NACTx-surgery, and 30 patients received definitive CRT. Overall survival (OS), event free survival (EFS), and prognostic factors were compared using Kaplan- Meier analysis and Cox proportional hazards modeling.

Results: The NACTx-surgery group achieved significantly superior median OS (37.9 months vs. 26.8 months; p = 0.031) compared with the CRT group. EFS showed a trend toward improvement with NACTx-surgery (median 21.4 months vs. 13.9 months; p = 0.052). TNM stage emerged as an independent predictor of EFS in multivariable analysis (HR 0.48; p = 0.03). Recurrence occurred in 54.8% of NACTx-surgery patients and 70.0% of CRT patients.

Conclusions: For appropriately selected patients with resectable N2 NSCLC, multimodal NACTx-surgery approaches achieved superior survival outcomes compared with definitive CRT. These findings support aggressive pursuit of resectability assessment and multimodal therapeutic planning. Future prospective randomized trials comparing contemporary NACTx- surgery with modern CRT plus consolidation immunotherapy are needed.

Keywords: N2 lymph node disease, mediastinal involvement, neoadjuvant chemotherapy, surgical resection, concurrent chemoradiation, overall survival, event free survival, prognostic factors

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Öz

Amaç: Mediastinal (N2) lenf nodu tutulumu olan küçük hücreli dışı akciğer kanseri (KHDAK) hastalarında optimal tedavi stratejisi henüz yeterince tanımlanmamıştır. Bu çalışma, N2 hastalığı olan hastalarda neoadjuvan kemoterapi sonrası cerrahi rezeksiyonu (NAKT-Cerrahi) ile definitif eşzamanlı kemoradyoterapiyi (KRT) karşılaştırmıştır.

Gereç ve Yöntemler: Bu retrospektif kohort çalışması iki onkoloji merkezinde tedavi gören N2 KHDAK'li 61 hastayı analiz etmiştir. Otuz bir hasta NAKT sonrası cerrahi aldı, 30 hasta ise definitif KRT aldı. Genel sağkalım (OS), nüks/progresyonsuz sağkalım (EFS) ve prognostik faktörler Kaplan Meier analizi ve Cox orantılı hazard modellemesi kullanılarak karşılaştırıldı.

Sonuçlar: NAKT Cerrahi grubu KRT grubuna kıyasla anlamlı şekilde daha yüksek median OS (37,9 ay'a karşı 26,8 ay; p = 0,031) elde etmiştir. Nüks/progresyonsuz sağkalım NAKT- Cerrahi yaklaşımında iyileşme eğilimi göstermiştir (median 21,4 ay'a karşı 13,9 ay; p = 0,052). Multivariable analizde TNM evresi EFS'nin bağımsız belirleyicisi olarak ortaya çıkmıştır (HR 0,48; p = 0,03). Nüks/progresyon NAKT-Cerrahi hastalarının %54,8'inde ve KRT hastalarının %70,0'ında görülmüştür.

Sonuçlar: Rezektabl N2 KHDAK'li uygun seçilmiş hastalar için multimodal NAKT-Cerrahi yaklaşımları definitif KRT'ye kıyasla daha iyi sağkalım sonuçları sağlamıştır. Bu bulgular rezektabilite değerlendirmesinin agresif şekilde takip edilmesini ve multimodal terapötik planlamayı desteklemektedir. Çağdaş NAKT-Cerrahi ile modern KRT artı konsolidasyon immünoterapisini karşılaştıran prospektif randomize çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: N2 lenf nodu hastalığı, mediastinal tutulum, neoadjuvan kemoterapi, cerrahi rezeksiyon, eşzamanlı kemoradyoterapi, genel sağkalım, olaysız sağkalım, prognostik faktörler

Introduction

Lung cancer is among the most commonly diagnosed malignancies worldwide and remains the foremost contributor to cancer related deaths across the globe. Despite substantial advances in therapeutic approaches over the past decade, clinical outcomes remain suboptimal, with a 5-year OS rate ranging from 25-30% across all disease stages. Notably, survival outcomes demonstrate an inverse correlation with disease stage progression, with considerably higher rates in early stage disease and markedly reduced rates in locally advanced or distant metastatic presentations. Within the diverse spectrum of lung cancer subtypes, NSCLC is the most frequent, comprising nearly 80% of diagnoses and constituting the principal histopathologic category [1].

According to the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system, N2 status refers to metastasis involving lymph nodes in the ipsilateral mediastinum or the subcarinal region. When presenting as bulky N2 disease, this classification typically reflects substantial mediastinal lymphadenopathy, characterized by nodal masses exceeding 3 cm in greatest dimension, evidence of central necrosis, or extensive abutment against adjacent mediastinal structures [2].

Despite the expanding evidence base, the optimal therapeutic sequencing for patients with N2 disease remains inadequately defined, and robust clinical criteria to distinguish candidates suitable for neoadjuvant chemotherapy from those warranting definitive concurrent chemoradiation have yet to be established.

Contemporary evidence based guidelines have substantially reshaped the therapeutic landscape for resectable stage III NSCLC, with a demonstrable shift toward multimodal perioperative treatment strategies. The American Society of Clinical Oncology (ASCO) guidelines for stage III NSCLC recommend that surgical candidates may receive neoadjuvant chemo immunotherapy as an alternative to conventional approaches, including neoadjuvant chemotherapy (NACTx) or neoadjuvant concurrent chemoradiation (CRT) [3]. Concordantly, the NCCN Guidelines (Version 3.2025) advocate for perioperative immunotherapy combined with neoadjuvant platinum based chemotherapy in patients with stage IB-IIIA NSCLC lacking actionable EGFR or ALK mutations, with particular emphasis on adjuvant immunotherapy consideration in appropriately selected patients following comprehensive multidisciplinary tumor board evaluation [4].

In patients presenting with substantial comorbidities, bulky N2 lymphadenopathy, medical inoperability, and absence

of distant metastatic disease, CRT remains a cornerstone therapeutic strategy, substantiated by pooled analyses and meta-analyses demonstrating superior OS outcomes compared with sequential treatment approaches [5].

The main aim of this investigation is to evaluate and contrast the clinical outcomes of stage III N2 NSCLC patients without distant metastases who receive neoadjuvant therapy followed by surgical resection with those treated with CRT. Particular attention is given to OS, EFS, and the prognostic variables associated with these endpoints.

Material and Methods

This retrospective cohort analysis was performed at two high volume tertiary referral centers in Ankara, Turkey. Individuals diagnosed with stage IIB, IIIA, or IIIB NSCLC accompanied by N2 lymph node involvement and lacking any radiologic or clinical evidence of distant metastasis between July 2011 and May 2025 were included in the assessment. The total study cohort comprised 61 patients with complete clinicopathological and follow up data.

Eligible patients included those aged 18 years or older at diagnosis with histologically confirmed NSCLC of adenocarcinoma, squamous cell carcinoma, or non-small cell carcinoma not otherwise specified (NSCLC NOS) histology, stage IIB to IIIB disease with N2 nodal involvement without distant metastasis, and complete medical records and clinical follow up data available at our institutions. Patients were excluded if they had a histological diagnosis of small cell lung cancer (SCLC) or large cell carcinoma, were lost to clinical follow up with incomplete medical records, were younger than 18 years at diagnosis, or had evidence of distant metastatic disease (stage IV). In addition, patients who underwent upfront surgery without neoadjuvant therapy and were found to have N2 disease only on postoperative pathology were not included in the analysis.

Comprehensive clinicopathological data were systematically collected and analyzed for each participant, including demographic characteristics (age at diagnosis, gender), smoking history (never smoker, former smoker, or current smoker), disease stage, pathological features, molecular and immunological markers, and treatment modalities. Tumor staging was performed according to the 8th edition of the AJCC TNM Staging Manual [6].

Immunohistochemical and Molecular Analysis

Immunohistochemical (IHC) assessment was carried out using a predefined marker panel that included thyroid transcription factor 1 (TTF 1) and p40. IHC findings were retrospectively extracted from archived postoperative pathology records, and each marker was classified as positive or negative according to the original interpretation of institutional pathologists. Staining of ≥10% of tumor cells was accepted as indicative of positivity.

Programmed death ligand 1 (PD L1) expression was stratified into three categories: 0% (negative), 1-25% (low expression), and >25% (high expression).

Molecular testing for predictive biomarkers was performed on tumor tissue specimens using standard institutional protocols. The following molecular alterations were systematically evaluated: epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, and proto oncogene tyrosine protein kinase ROS1 (ROS1) fusions.

Treatment Protocols

Patients received treatment according to contemporary evidence based guidelines and institutional protocols. The study cohort was divided into two principal treatment groups based on clinical assessment and therapeutic strategy.

In the cohort undergoing surgical management, patients were treated with platinum based NACTx, with or without the addition of immunotherapy, followed by surgical resection (lobectomy, pneumonectomy, or wedge resection) and systematic mediastinal lymph node dissection. In contrast, individuals assigned to definitive concurrent chemoradiation received platinum doublet chemotherapy administered simultaneously with thoracic radiotherapy as part of the CRT protocol.

Outcome Definitions and Follow Up

OS was characterized as the duration from the initial diagnosis to either death from any cause or the most recent clinical follow up, whichever occurred earlier. EFS was defined as the interval between diagnosis and the first documented event, including recurrence, disease progression, or death from any cause.

Clinical follow up data, including surveillance imaging, treatment responses, recurrence patterns, and vital status, were systematically recorded from institutional medical records. The

study protocol was reviewed and approved by the Ankara City Hospital Clinical Research Ethics Committee (Approval TABED 1-25-1579, 20/07/2025). Given the retrospective nature of the study and the use of archival specimens, the requirement for informed consent was waived in accordance with national regulations and institutional policy. All procedures complied with the principles of the Declaration of Helsinki and local data protection regulations.

Statistical Analysis

Statistical analyses were conducted using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA) and R (version 4.0 or higher). Categorical variables were summarized as frequencies and percentages, whereas continuous variables were described using median values with interquartile ranges (IQRs). Comparisons of continuous data between treatment groups were performed with the Mann–Whitney U test, while categorical variables were evaluated using Pearson's Chi square test or Fisher's exact test when required. Survival outcomes were analyzed through the Kaplan–Meier method, and differences between groups were examined using the log rank test. Survival curves for OS and EFS were created in R with appropriate graphical visualization. Multivariable analyses were carried out using Cox proportional hazards regression to determine independent predictors of OS and EFS. Adjusted hazard ratios (HRs), along with corresponding 95% confidence intervals (CIs) and p values, were calculated. A two sided p value below 0.05 was considered statistically significant.

Results

Patient Characteristics

From July 2011 to May 2025, a total of 61 individuals diagnosed with stage IIB–IIIB NSCLC exhibiting N2 lymph node involvement were enrolled in the study. The cohort was divided into two therapeutic subgroups: 31 patients (50.8%) underwent NACTx-surgery, whereas 30 patients (49.2%) were managed with CRT.

Median age was 65 (50–83) years for the entire cohort, with no significant difference between the NACTx-surgery group (median 62 years) and the CRT group (median 67 years, p = 0.23). The majority of patients were male (90.1%), with only 6 female patients (9.9%) enrolled, and gender distribution was comparable between treatment groups (p = 0.093). Active or former smokers comprised 90.1% of the cohort (n = 55), whereas never smokers represented 9.9% (n = 6), with no significant difference between groups (p = 0.093).

Regarding histological classification, squamous cell carcinoma was the most common subtype (49.2%, n = 30), followed by adenocarcinoma (44.2%, n = 27) and NSCLC NOS (6.6%, n = 4). Histological distribution did not differ significantly between treatment groups (p = 0.360). Primary tumor (T) classification showed a significant difference between groups (p = 0.006): T1 tumors were present exclusively in the NACTx-surgery cohort (14.8%, n = 9), while T4 tumors were more prevalent in the CRT group (18.0% vs. 6.6%, p = 0.006). Distribution of T2 and T3 tumors was relatively balanced between treatment groups.

Lymph node involvement showed a marked significant difference between treatment groups (p = 0.001). N2a disease predominated in the NACTx-surgery group (42.6% of total cohort), whereas N2b disease was more prevalent in the CRT group (34.4% of total cohort). Correspondingly, TNM stage distribution differed significantly between groups (p = 0.001). Stage IIB disease was observed exclusively in the surgical cohort (14.8%, n = 9), stage IIIA disease was more frequent in the NACTx surgery surgical group (26.2% vs. 9.8%), and stage IIIB disease predominated in the CRT group (39.3% vs. 9.8%).

Immunohistochemical analysis revealed TTF 1 positivity in 45.9% of patients (n = 28), with no significant between group difference (p = 0.154). p40 expression was positive in 54.1% of cases (n = 33), also showing no significant difference between groups (p = 0.591).

Molecular testing identified activating EGFR mutations in 3 patients (4.9%), ALK rearrangement in 2 patients (3.3%), and ROS1 rearrangement in 2 patients (3.3%), with no significant differences in the prevalence of these alterations between treatment groups (p = 0.210, 0.222, and 0.222, respectively). PD L1 expression was stratified as follows: negative (0%) in 26 patients (42.6%), low expression (1–25%) in 18 patients (29.5%), and high expression (>25%) in 7 patients (11.5%). PD L1 status could not be determined in 10 patients (16.4%) due to unavailable or inadequate tissue samples. PD L1 expression status did not differ significantly between treatment groups (p = 0.366). The baseline demographic and clinicopathological characteristics of the entire cohort and by treatment group are presented in table 1.

Table 1. Clinical and pathological characteristics of the patients.

Characteristics	All Patients	Neoadjuvant Chemotherapy + Surgery Group	Chemoradiotherapy Group	p value (Neoadjuvant CT + Surgery vs. Chemoradiotherapy)
	n (%)	n (%)	n (%)	
Number of Patients	61(100)	31 (50.8)	30 (49.2)	0.44
Age (years)*	65 (50 83)	62 (50 83)	67 (54 76)	0.23
Gender				
Female	6 (9.9)	5 (8.2)	1 (1.6)	0.093
Male	55 (90.1)	26 (42.6)	29 (47.5)	
Smoking Status				
Active / Former	55 (90.1)	26 (42.6)	29 (47.5)	0.093
Never Smoker	6 (9.9)	5 (8.2)	1 (1.6)	
Pathology				
Adenocarcinoma	27 (44.2)	16 (26.2)	11 (18)	0.360
Squamous Cell Carcinoma	30 (49.2)	14 (23)	16 (26.2)	
NOS	4 (6.6)	1 (1.6)	3 (4.9)	
Primary Tumor (T)				
T1	9 (14.7)	9 (14.8)	0 (0)	0.006
T2	15 (24.6)	8 (13.1)	7 (11.5)	
T3	22 (36.1)	10 (16.4)	12 (19.7)	
T4	15 (24.6)	4 (6.6)	11 (18)	
Pathological lymph node				
N2a	35 (57.4)	26 (42.6)	9 (14.8)	0.001
N2b	26 (42.6)	5 (8.2)	21 (34.4)	
TNM Stage				
IIB	9 (14.8)	9 (14.8)	0 (0)	0.001
IIIA	22 (36.1)	16 (26.2)	6 (9.8)	
IIIB	30 (49.1)	6 (9.8)	24 (39.3)	
TTF 1				
Positive	28 (45.9)	17 (27.9)	11 (18)	0.154
P40				
Positive	33 (54.1)	16 (26.2)	17 (27.9)	0.591
EGFR Mutation				
Present	3 (4.9)	2 (3.3)	1 (1.6)	0.210
ALK Rearrangement				
Present	2 (3.3)	1 (1.6)	1 (1.6)	0.222
ROS1 Rearrangement				
Present	2 (3.3)	1 (1.6)	1 (1.6)	0.222
PDL1				
0	26 (42.6)	11 (18)	15 (24.6)	0.366
1 25	18 (29.5)	11 (18)	7 (11.5)	
>25	7 (11.5)	5 (8.2)	2 (3.3)	
Unknown	10 (16.4)	4 (6.6)	6 (9.8)	

*n : number; %: percentage ; TNM : tumor node metastasis ; PD L1 : programmed death ligand 1. TTF 1: thyroid transcription factor 1, ALK: anaplastic lymphoma kinase, EGFR: epidermal growth factor receptor, ROS1: proto oncogene tyrosine protein kinase ROS1. *Age is presented as median values thyroid transcription factor 1 (TTF 1)*

Treatment Modalities and Clinical Outcomes

Neoadjuvant Chemotherapy Followed by Surgical Resection Group

All 31 patients in the NACTX-surgery group received neoadjuvant chemotherapy prior to surgical intervention. Carboplatin Paclitaxel was the predominant NACTx regimen, administered to 18 patients (58.1%), followed by Carboplatin Paclitaxel combined with Nivolumab in 5 patients (16.1%). Additional NACTx regimens included Cisplatin Gemcitabine (9.7%), Carboplatin Pemetrexed (6.5%), Cisplatin Pemetrexed with Nivolumab (6.5%), and Cisplatin Docetaxel (3.2%).

Following NACTx completion, all patients underwent surgical resection with mediastinal lymph node dissection. Lobectomy with lymph node dissection was performed in 16 patients (51.6%), representing the most common surgical procedure. Pneumonectomy with lymph node dissection was performed in 9 patients (29.0%), and wedge resection with lymph node dissection was performed in 6 patients (19.4%). Postoperatively, 21 patients (67.7%) received adjuvant chemotherapy, predominantly consisting of Carboplatin Paclitaxel (66.7%), followed by Cisplatin Vinorelbine (28.6%) and Carboplatin Pemetrexed (4.8%). Additionally, 7 patients (22.6%) received adjuvant radiotherapy.

During the follow up period, recurrence or disease progression occurred in 17 patients (54.8%). The most frequent site of recurrence was the lung and mediastinal lymph nodes (35.3%), followed by brain metastases (29.4%), multiple sites (23.5%), bone metastases (5.9%), and hepatic metastases (5.9%). Among the 17 patients with recurrent or progressive disease, first line salvage therapy was administered to all patients. Nivolumab monotherapy was the most frequently selected first line treatment (35.3%), followed by Carboplatin Paclitaxel (17.6%), Docetaxel monotherapy (11.8%), and single agent chemotherapy or targeted therapy regimens (Cisplatin Gemcitabine, Carboplatin Pemetrexed, Gemcitabine Docetaxel, Afatinib; (each 5.9%), as well as palliative radiotherapy (11.8%). Fourteen patients (82.4%) experienced further progression after first line treatment, with the majority (57.1%) receiving no additional systemic therapy. Second line treatment was administered to 6 patients (42.9%), including Nivolumab (14.3%), Osimertinib (7.1%), Docetaxel (7.1%), Vinorelbine (7.1%), and Cisplatin Pemetrexed (7.1%).

Concurrent Chemoradiation Therapy Group

All 30 patients in the CRT group, Carboplatin Paclitaxel was the predominant chemotherapy regimen, administered to 26 patients (86.7%), while Cisplatin Etoposide was used in 4 patients (13.3%). Following completion of CRT, 4 patients (13.3%) received consolidation therapy, comprising Carboplatin Paclitaxel (50.0%) and Durvalumab immunotherapy (50.0%). Recurrence or disease progression was documented in 21 patients (70.0%) during follow up. The predominant site of recurrence was the lung and mediastinal lymph nodes (42.9%), followed by brain metastases (19.0%), multiple sites (28.6%), bone metastases (4.8%), and hepatic metastases (4.8%). Among the 21 patients with recurrent or progressive disease, first line salvage therapy was administered to 17 patients (81.0%). Nivolumab monotherapy was the most frequently selected first line treatment (38.1%), followed by Nivolumab Ipilimumab dual immunotherapy (4.8%), Pembrolizumab (4.8%), and chemotherapy based regimens (Cisplatin Gemcitabine, Carboplatin Pemetrexed, each 4.8%) or targeted therapy (Alectinib, Erlotinib, each 4.8%), and palliative radiotherapy (9.5%). Four patients (19.0%) did not receive any first line salvage therapy. Fourteen patients (82.4%) experienced further progression after first line treatment. Second line treatment was administered to 5 patients (35.7%), including Docetaxel (14.3%), Nivolumab (7.1%), Vinorelbine (7.1%), and Gemcitabine (7.1%), while 9 patients (64.3%) did not receive additional systemic therapy. The detailed treatment modalities and clinical course for both groups are summarized in table 2.

Survival Outcomes

Overall Survival

OS analysis demonstrated a statistically significant difference between the two treatment groups (Log rank test, $\chi^2 = 4.66$, $p = 0.031$). The NACTx-surgery group exhibited a median OS of 37.9 months whereas the CRT group demonstrated a mOS of 26.8 months. In the NACTx-surgery group, 14 of 31 patients (45.2%) experienced death from any cause, with 17 patients (54.8%) remaining alive at the time of last follow up. In the CRT group, 20 of 30 patients (66.7%) died, while 10 patients (33.3%) were censored. The superior median OS in the NACTx-surgery group suggests a potential survival advantage of this multimodal approach compared with definitive CRT, though both groups demonstrated substantial variability in individual survival outcomes. The OS Kaplan Meier survival curves are presented in figure 1.

Table 2. Treatment modalities and clinical course of the patients.		
	Neoadjuvant Chemotherapy + Surgery Group	**Chemoradiotherapy Group**
	n (%)	n (%)
Neoadjuvant chemotherapy	31 (100)	0 (0)
Neoadjuvant chemotherapy regimen		
Carboplatin–Paclitaxel	18 (58)	
Carboplatin–Paclitaxel–Nivolumab	5 (16.1)	
Cisplatin–Gemcitabine	3 (9.7)	
Carboplatin–Pemetrexed	2 (6.5)	
Cisplatin–Pemetrexed–Nivolumab	2 (6.5)	
Cisplatin–Docetaxel	1 (3.2)	
Chemoradiotherapy	0 (0)	30 (100)
Chemoradiotherapy regimen		
Carboplatin–Paclitaxel		26 (86.7)
Cisplatin–Etoposide		4 (13.3)
Surgical procedure		
Pneumonectomy + Lymph Node Dissection	9 (29)	
Lobectomy + Lymph Node Dissection	16 (51.6)	
Wedge Resection + Lymph Node Dissection	6 (19.4)	
Adjuvant chemotherapy	21 (67.7)	
Adjuvant chemotherapy regimen		
Carboplatin–Paclitaxel	14/21 (66.7)	
Cisplatin–Vinorelbine	6/21 (28.5)	
Carboplatin–Pemetrexed	1/21 (4.8)	
Consolidation Therapy After Chemoradiotherapy		4 (13.3)
Carboplatin–Paclitaxel		2/4 (50)
Durvalumab		2/4 (50)
Adjuvant radiotherapy	7 (22.6)	
Recurrence / Progression	17 (54.8)	21 (70)
Site of Recurrence / Progression		
Lung / Mediastinal Lymph Node	6/17 (35.3)	9/21 (42.8)
Brain	5/17 (29.4)	4/21 (19)
Bone	1/17 (5.9)	1/21 (4.8)
Liver	1/17 (5.9)	1/21 (4.8)
Multiple Sites	4/17 (23.5)	6/21 (28.6)
First line Treatments		
Nivolumab	6/17 (35.3)	8/21 (38.1)
Nivolumab–Ipilimumab		1/21 (4.8)
Pembrolizumab		1/21 (4.8)
Carboplatin–Paclitaxel	3/17 (17.6)	
Cisplatin–Gemcitabine	1/17 (5.9)	1/21 (4.8)
Carboplatin–Pemetrexed	1/17 (5.9)	1/21 (4.8)
Gemcitabine–Docetaxel	1/17 (5.9)	
Docetaxel	2/17 (11.8)	
Gemcitabine		1/21 (4.8)
Afatinib	1/17 (5.9)	
Alectinib		1/21 (4.8)
Erlotinib		1/21 (4.8)
Palliative Radiotherapy	2/17 (11.8)	2 (9.5)
No Treatment		4 (19)
Progression After First Line Treatment	14/17 (82.4)	14/17 (82.4)
Second line Treatments		
Nivolumab	2 (14.3)	1 (7.1)
Osimertinib	1 (7.1)	
Docetaxel	1 (7.1)	2 (14.3)
Vinorelbine	1 (7.1)	1 (7.1)
Cisplatin–Pemetrexed	1(7.1)	
Gemcitabine		1 (7.1)
No Treatment	8 (57.1)	9 (64.3)

n : number; %: percentage

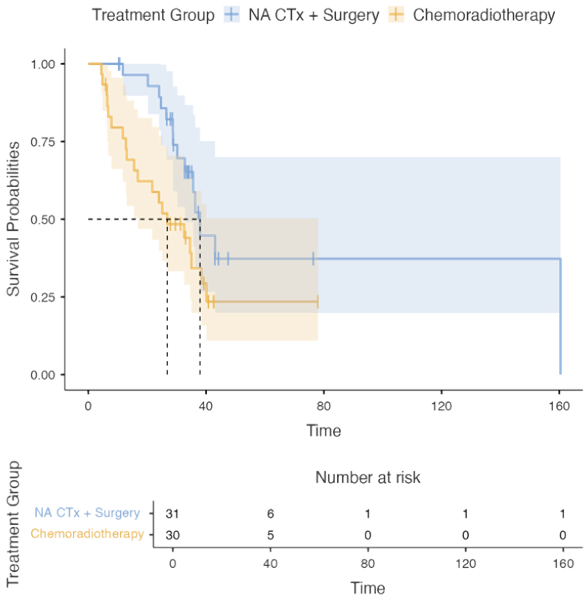

Figure 1. Kaplan Meier Analysis of Overall Survival by Treatment Modality.

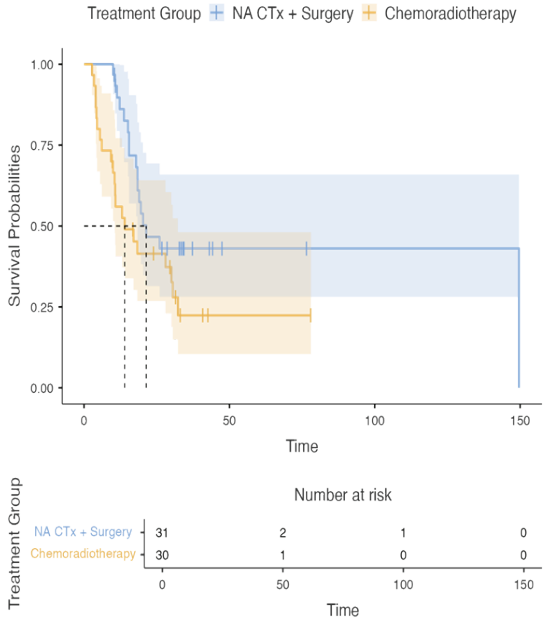

Figure 2. Kaplan Meier Analysis of Event Free Survival by Treatment Modality Prognostic Factors Analysis.

Event Free Survival

EFS analysis, defined as time from diagnosis to first documented recurrence, disease progression, or death from any cause, demonstrated a trend toward improved EFS in the NACTx-surgery group compared with the CRT group, approaching but not reaching statistical significance (Log rank test, χ^2 = 3.76, p = 0.052). The NACTx-surgery group achieved a mEFS of 21.4 months, whereas the CRT group demonstrated a mEFS of 13.9 months. In the NACTx-surgery cohort, 17 of 31 patients (54.8%) experienced an event (recurrence, progression, or death), with 14 patients (45.2%) remaining event free at last follow up. In the CRT group, 21 of 30 patients (70.0%) experienced documented events, while 9 patients (30.0%) remained event free. Although the EFS difference between groups did not achieve traditional statistical significance (p = 0.052), the numerical advantage in the NACTx-surgery group suggests a potentially clinically meaningful delayed time to disease progression or death. The EFS Kaplan Meier survival curves are presented in figure 2.

Univariate analyses were conducted to explore variables linked to OS and EFS across the full study population. Gender, age, smoking status, lymph node involvement classification (N2a vs. N2b), and PD L1 expression status did not demonstrate significant associations with OS or EFS. Histological type (adenocarcinoma vs. squamous cell carcinoma) showed a trend toward association with OS (p = 0.12), although this did not reach statistical significance.

TNM stage classification demonstrated significant prognostic value for both OS and EFS in univariate analysis. Stage IIB–IIIA disease was associated with superior mOS of 37.9 months compared with stage IIIB disease (30.2 months, p = 0.033). Similarly, stage IIB–IIIA disease predicted improved EFS with median of 25.9 months versus 17.0 months for stage IIIB (p = 0.030).

Multivariable Cox proportional hazards modeling was utilized to determine which factors independently influenced survival outcomes. In the analysis of overall survival, TNM stage did not retain statistical significance as an independent variable (p = 0.22), and treatment strategy likewise failed to demonstrate independent prognostic value (p = 0.209).

For event free survival, TNM stage emerged as an independent predictor of improved EFS, with stage IIB–IIIA disease associated with significantly prolonged time to progression or death compared with stage IIIB disease (HR 0.48, 95% CI 0.25–0.94, p = 0.03). Other variables including gender, age, smoking status, histological type, lymph node classification, PD L1 expression, and treatment modality did not achieve independent statistical significance in the multivariable models. The univariate and multivariable analyses for both OS and EFS are summarized in table 3.

Table 3. Univariate and Multivariable Cox Proportional Hazards Analysis for Overall Survival and Event Free Survival.

		Overall survival			Event free survival		
Variables		**Months**	**Univariate p value**	**Multivariate p value HR**	**Months**	**Univariate p value**	**Multivariate p value HR**
Gender	Male	26.4	0.89		18.3	0.21	
	Female	35.6			NR		
Age	< 65	35.6	0.38		20.3	0.55	
	≥ 65	32.5			18.9		
Smoking	Yes	35.0	0.67		18.9	0.68	
	No	24.6			21.3		
Pathology	AdenoCA	43.0	0.12		21.3	0.67	
	SCC	32.7			18.3		
Lymph node	N2a	37.9	0.17		21.4	0.14	
	N2b	32.5			17.0		
TNM Stage	IIB IIIA	37.9	**0.033**	0.22 HR:0.608	25.9	**0.030**	**0.03 HR:0.48**
				95%CI:0.27 1.35			**95%CI:0.25 0.94**
PDL1	Negative	32.5	0.21		18.9	0.86	
	Positive	36.3			18.3		
Treatment	NA CTx + Surgery	37.9	**0.031**	0.209 HR: 0.59	21.3	0.052	
	CRT			95%CI:0.26 1.33	13.9		

HR:Hazard Ratio, NR:Not reached

Discussion

The management of NSCLC with N2 lymph node involvement represents a significant clinical challenge, as these patients are potentially candidates for multimodal therapy but face heterogeneous clinical presentations and competing treatment options. While NACTx- surgery has become the preferred approach for resectable N2 disease, a substantial proportion of patients with N2 NSCLC are treated with CRT due to medical inoperability, significant comorbidities, extensive primary tumor burden, or patient preference. The primary objective of this retrospective analysis was to compare clinical outcomes and identify prognostic factors in patients with N2 involvement who received either NACTx-surgery or CRT in a real world clinical practice setting. This comparison addresses a practical clinical gap by providing outcome data that may inform treatment selection and counseling for patients with locally advanced N2 disease presenting with variable clinical circumstances.

This retrospective analysis of 61 patients with NSCLC-N2 lymph node involvement demonstrated that NACTx-surgery was associated with significantly superior OS compared with CRT. The NACTx-surgery group achieved a mOS of 37.9 m. compared with 26.8 m. in the CRT group (p = 0.031), representing an absolute survival advantage of approximately 11 months. EFS analysis demonstrated a trend toward improved outcomes with NACTx-surgery approach (21.4 m. vs. 13.9 m. p = 0.052). In multivariable Cox proportional hazards analysis, TNM stage classification (stage IIB-IIIA vs. IIIB) emerged as an independent predictor of EFS, whereas treatment modality did not achieve independent statistical significance, likely reflecting the influence of patient selection factors and disease extent on treatment assignment. These findings support the consideration of multimodal NACTx-surgery approaches for appropriately selected patients with resectable N2 disease while acknowledging that CRT remains an important treatment option for patients with medical contraindications to surgery or extensive disease burden.

Platinum based neoadjuvant chemotherapy has been established as the standard induction strategy for resectable locally advanced NSCLC, with multiple trials demonstrating significant survival improvements compared with surgery alone. The Southwest Oncology Group (SWOG) 9900 trial, a landmark randomized phase III study of 354 patients with clinical stage IB–IIIA resectable NSCLC, compared preoperative paclitaxel carboplatin followed by surgery with surgery alone. Although the trial closed prematurely due to emerging evidence supporting postoperative CTx, the preoperative CTx arm demonstrated a trend toward improved OS (62 m. vs. 41 m.; HR 0.79) and progression free survival (33 m.vs. 20 m.; HR 0.80). Major pathological response to chemotherapy was observed in 41% of patients, without unexpected toxicity.

These seminal data established the safety and feasibility of preoperative platinum doublet chemotherapy and provided the rationale for subsequent trials investigating neoadjuvant approaches in resectable locally advanced NSCLC [7].

In support of these observations, the phase III study led by Scagliotti compared preoperative gemcitabine–cisplatin followed by surgical resection with surgery alone in 270 patients with stage IB–IIIA NSCLC. The cohort receiving preoperative chemotherapy achieved significantly longer progression free survival (HR 0.70) and OS (HR 0.63) than the surgery only group, with the most notable benefit observed in the stage IIB–IIIA subset (3 year PFS: 55.4% vs. 36.1%). These findings reinforced the utility of platinum based NACTx across multiple regimen combinations and demonstrated the broader applicability of this treatment strategy for patients with resectable advanced NSCLC [8].

The CheckMate 816 trial, a landmark phase 3 study, evaluated the addition of nivolumab to platinum based NACTx in patients with resectable stage IB–IIIA NSCLC. In this trial, neoadjuvant nivolumab plus platinum based chemotherapy significantly improved EFS compared with chemotherapy alone (EFS: 31.6 m. vs. 20.8 m.; HR 0.63; p = 0.005). Notably, the pathological complete response rate was substantially higher with the addition of nivolumab (24.0% vs. 2.2%; p<0.001), suggesting enhanced tumor cytoreduction and improved mediastinal clearance with immunotherapy integration. At the interim analysis, the hazard ratio for OS favored the nivolumab containing arm (HR 0.57), although this did not reach prespecified significance [9].

In this study, NACTx-surgery group achieved a mOS of 37.9 months, which is lower than the SWOG 9900 preoperative chemotherapy arm (62 months) and the Scagliotti gemcitabine cisplatin arm (mOS not explicitly stated but with favorable HR 0.63), but comparable to the chemotherapy alone control arms in these trials. The predominantly use of carboplatin paclitaxel (58.1%) as the neoadjuvant regimen aligns with the SWOG 9900 backbone, while the modest integration of immunotherapy (16.1% received nivolumab containing regimens) reflects the limited adoption of checkpoint inhibitors during the study period. The inferior event free survival in our cohort (median 21.4 months) compared with the CheckMate 816 nivolumab plus chemotherapy arm (31.6 months) may be attributable to several factors: the composition of our cohort with exclusively N2 disease (a more advanced nodal category than the IB–IIIA populations in SWOG 9900, Scagliotti, and CheckMate 816), and the limited systemic incorporation of neoadjuvant immunotherapy. These findings underscore that while conventional platinum doublet neoadjuvant approaches achieve meaningful survival outcomes in N2 disease, the integration of checkpoint inhibitors into neoadjuvant strategies, as demonstrated by CheckMate 816, may yield superior outcomes compared with chemotherapy alone.

In our CRT cohort treated without routine consolidation immunotherapy, the mOS of 26.8 months and EFS of 13.9 months represent outcomes achievable with crt as monotherapy. These results are consistent with historical data from trials evaluating CRT in unresectable or medically inoperable stage III NSCLC, wherein mOS typically ranges from 15 to 30 months depending on patient selection, performance status, and treatment intensity [10,11]. The predominant use of Carboplatin Paclitaxel chemotherapy (86.7% of CRT patients) during concurrent radiation reflects standard practice. Notably, only 13.3% of our CRT cohort (n = 4) received consolidation therapy after CRT, with equal distribution between chemotherapy and durvalumab. This low utilization of consolidation immunotherapy reflects the practice patterns during the study period, prior to the widespread adoption of durvalumab consolidation based on PACIFIC trial results [12]. The substantially higher recurrence rate in the CRT group (70.0% vs. 54.8%) and the predominance of advanced stage IIIB disease (39.3% vs. 9.8%) may contribute to the inferior survival outcomes in this cohort compared with the NACTx-surgery group. These observations highlight the potential for improvement in CRT outcomes through the systematic implementation of consolidation immunotherapy strategies, as demonstrated by emerging evidence.

A contemporary retrospective analysis conducted by Qi and colleagues evaluated 308 patients with potentially resectable stage III NSCLC, comparing outcomes between those who underwent neoadjuvant chemoimmunotherapy followed by planned surgical resection and those treated with CRT followed by immunotherapy. Among these patients, 195 (63.3%) underwent neoadjuvant chemoimmunotherapy with surgery and 113 (36.7%) received concurrent CRT followed by immunotherapy. After propensity score matching, the neoadjuvant chemoimmunotherapy surgery group demonstrated significantly superior mPFS (not reached vs. 25.9 m in the CRT + immunotherapy cohort HR 2.91; p<0.001). Although mOS was not reached in either group,

the 3-year OS rate was numerically higher in the neoadjuvant chemoimmunotherapy surgery cohort (87.5% vs. 75.0%; p = 0.22). The safety profiles were comparable between groups, though grade 3/4 hematological toxicity was more frequent in the concurrent chemoradiation immunotherapy group [13]. These findings align with the present study, wherein the NACTX Surgery group achieved superior OS (and a trend toward improved EFS) compared with the CRT group. Collectively, these data suggest that for appropriately selected patients with resectable N2-NSCLC, multimodal NACTx-surgery approaches may offer survival advantages compared with definitive chemoradiation, particularly when coupled with modern chemotherapy regimens and consideration of immunotherapy integration.

Limitations of the study

This investigation carries several notable limitations. Foremost, it represents a retrospective analysis conducted at two institutions and involves a relatively small cohort, which inherently restricts statistical robustness and limits the extent to which the results can be generalized. Second, treatment assignment was not randomized, and the groups differed significantly in TNM stage distribution and nodal classification, introducing potential selection bias. Third, heterogeneity in chemotherapy regimens and the limited incorporation of adjuvant and consolidation therapies precludes detailed comparisons of specific drug combinations. Finally, this study does not provide direct evidence on the benefits of neoadjuvant or consolidation immunotherapy compared with chemotherapy alone, which are now emerging as important components of contemporary practice.

In conclusion, in this retrospective cohort of patients with NSCLC - N2 lymph node involvement, NACTx followed by surgical resection achieved significantly superior OS and a trend toward improved EFS compared with concurrent CRT. TNM stage emerged as an independent predictor of EFS, with stage IIB–IIIA disease associated with better outcomes. The superior outcomes achieved with NACTx-surgery compared with CRT monotherapy suggest that complete surgical resection, when technically feasible, offers survival advantages that should encourage aggressive pursuit of resectability assessment and multimodal therapeutic planning. These findings support the continued consideration of multimodal NACTx-surgery approaches for appropriately selected patients with resectable N2 disease. As immunotherapy based approaches become increasingly integrated into both neoadjuvant and consolidation settings, future prospective randomized trials comparing contemporary NACTx-surgery regimens with modern CRT plus consolidation immunotherapy approaches are essential to establish optimal treatment strategies for this challenging patient population.

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Ethics approval

The study protocol was reviewed and approved by the Ankara City Hospital Clinical Research Ethics Committee (Approval TABED 1-25-1579, 20/07/2025).

Author Contributions

Conceptualization,D.B, Ö.B.; Methodology, D.B, Ö.B and E.A; Data curation, B.K, E.H and Ö.F.K.,; Formal analysis and statistical analysis,D.B, İ.S and D.U; Writing original draft.D.B and M.D; Writing review and editing.D.B and E.H; Supervision.Ö.B; Project administration,D.B . All authors have read and agreed to the published version of the manuscript

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