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Neoadjuvant Treatment Is Not Associated with Better Survival in T4 Non-Small Cell Lung Cancer

Gizem Özçıbık Işık[1], İsmail Sarbay[2], Halil İbrahim Bulut[1], Burcu Kılıç[1], Ezel Erşen[1], H. Volkan Kara[1], M. Kamil Kaynak[1], Akif Turna[1]

[1]Department of Thoracic Surgery, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[2]Department of Thoracic Surgery, Sinop Atatürk State Hospital, Sinop, Türkiye

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Abstract

Objective: The best treatment strategy for T4 non-small cell lung cancer (NSCLC) has yet to be defined. However, studies have shown that surgical resection benefits selected patients without N2/N3 disease. We aimed to determine the effect of neoadjuvant chemotherapy and/or radiation therapy on survival in patients with T4N0-1 NSCLC.

Methods: Between January 2002 and December 2020, 107 T4 patients who were operated on for NSCLC in our clinic were analyzed. Nine patients (8.3%) with T4N2 disease were excluded. Eighty-six patients (87.8%) received neoadjuvant high-dose radiation therapy and/or chemotherapy before resection. Twelve (12.2%) patients underwent surgical resection without induction chemotherapy or radiotherapy. Demographic characteristics, laboratory values, respiratory parameters, and pathological characteristics were recorded. Survival of the neoadjuvant + surgery and upfront surgery groups was calculated using the Kaplan–Meier test, while they were analyzed using both the log-rank test and Cox proportional-risk models.

Results: In the neoadjuvant and upfront surgery groups, 10-year survival rates were 58.3% and 45.0%, respectively (hazard ratio: 1.39; 95% CI: 0.519-3.302; $P = .567$). Median survival times were 58, respectively. After adjustment for potential confounding variables, no statistically significant difference was found between the 2 groups in terms of survival (hazard ratio: 1.26; 95% CI: 0.49-3.21, $P = .631$) compared with the surgery-alone group. In addition, N1 disease was not found to be an independent prognostic factor (hazard ratio: 1.26; 95% CI: 0.49-3.21, $P = .631$).

Conclusion: Aggressive treatment of T4N0 NSCLC with neoadjuvant chemotherapy and/or radiotherapy did not seem to prolong survival. Additionally, we did not find N1 to be a significant prognosticator. A prospective multicenter trial should evaluate these results.

Keywords: Advanced non-small cell lung cancer, neoadjuvant therapy, survival, T4 non-small cell lung cancer

Introduction

Lung cancer is responsible for the most deaths from cancer, with 1.8 million deaths worldwide, and it also constitutes the most common cancer group together with breast cancer and prostate cancer, with 2.2 million new cases every year.[1] The determination of the right strategy in the treatment of non-small-cell lung cancer is of paramount importance to the survival of lung cancer patients. Therefore, the TNM system, which classifies the disease according to tumors' features such as tumor burden, lymph node metastasis, and distant metastasis, is used worldwide.[2] In light of the experience gained in the last few decades, optimum and standard treatment strategies for each stage of lung cancer have emerged.[3]

T3 and T4 non-small cell lung cancer (NSCLC) have been grouped as diverse groups of locally advanced cancer. T4 tumors may invade main vessels such as the intrapericardial portion of the main pulmonary artery, aorta, vertebral body, esophagus, or carina.[4,5] Many of the patients with T4 tumors were deemed inoperable due to poor survival.[6] On the other hand, many T4 tumors were evaluated as unresectable.[7] However, surgical resection of T4 NSCLC is worth being performed in selected N0-N1 patients when a complete resection is possible.[7,8]

Despite many improvements in thoracic surgery and oncology, discussions continue about treatment strategies for T4 disease, which is also known as locally advanced lung cancer.[3] Dartevelle et al demonstrated that resection of T4 NSCLC is feasible and oncologically beneficial in well-selected patient groups such as T4N0-1M0.[7] Yamanashi et al emphasized the significance of the correct determination of lymph node status, such as excluding N2 patients and performing a complete resection.[9]

In our study, we aimed to determine the effect of neoadjuvant chemotherapy and/or high-dose radiation therapy on survival in patients with T4N0-1 NSCLC.

Methods

Written informed consent was obtained from patients who participated in this study. The İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine ethics committee (Approval no: 2022/787592, Date: March 3, 2022) gave us permission to study. We retrospectively evaluated a series of 107 patients with

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Corresponding author: Gizem Özçıbık Işık Department of Thoracic Surgery, İstanbul Universitesi-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
e-mail: ozcibikgizem@gmail.com
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pathological T4 NSCLC who were surgically treated between January 2002 and December 2020. Eighty-six patients (87.8%) received curative radiotherapy (61.2-64.0 Gy in 32-33 fractions) over 6 weeks and/or chemotherapy (carboplatin; AUC2; paclitaxel; 40-50 mg/m^2 weekly). 50 patients received concurrent chemoradiotherapy treatment. 36 patients received chemotherapy treatment. We determined the disease stage using the 7th edition of the TNM Classification for Lung and Pleural Tumors.[3] The patients with multiple-station N2 or N3 or T4 disease and superior sulcus tumors were excluded from the analyses (Figure 1).

All patients received weekly platinum–taxane combination chemotherapy concurrently with definitive radiotherapy. Radiotherapy was performed using the 3D-conformal radiotherapy or intensity-modified radiotherapy (IMRT) technique in order to minimize toxicity to nearby structures.

The preoperative workup included routine blood tests, postero-anterior and lateral chest radiographs, bronchoscopy, pulmonary function tests, the diffusion capacity of the lung for carbon monoxide, a ventilation–perfusion lung scan in select patients, and blood gas analysis. Computed tomographic scans of the thorax, cranial magnetic resonance imaging, and positron emission tomography computed tomography (PET-CT) analysis were performed on patients.

Almost all patients underwent mediastinal lymph node sampling through cervical mediastinoscopy at stations 2, 4, (both left and right), and 7. After definitive CRT, we reevaluated the patients radiologically. Figure 1 displays the study's flowchart. We evaluated the response to definitive CRT using the Response Evaluation Criteria in Solid Tumors (RECIST) using CT or PET-CT and included patients who showed "no progression" on PET-CT, as per the RECIST criteria.[10] We deemed patients operable if they showed no progression after CRT and no mediastinal lymph node involvement, as confirmed by EBUS, mediastinoscopy, or video-assisted mediastinoscopy lymphadenectomy (VAMLA). Patients were re-evaluated in a multidisciplinary tumor board comprising a thoracic radiologist, experienced thoracic oncologic surgeon, medical oncologist, radiation oncologist, pulmonary physician, and nuclear medicine specialist to establish that (1) the tumor was potentially technically resectable, (2) pulmonary function criteria were mandated (predicted post-resectional forced expiratory volume in 1 s (FEV1) of at least 40% of predicted on quantitative perfusion scan if post-CRT FEV1 was less than 2000 mL (standard formula specified in protocol), and (3) the Karnofsky performance status (KPS) was at least 80. We also offered surgery to the patients who showed a complete response, either by CT or PET.

The time elapsed between the completion of CRT and surgery was 6-9 weeks. Surgical resection was performed after it was pathologically proven that mediastinal lymph node involvement was not observed. Patients underwent a muscle-sparing anterior thoracotomy or posterolateral thoracotomy. The bronchial stump was closed with parietal pleura or pericardial adipose tissue in patients who had a thoracotomy.

A complete resection was defined as the surgeon's removal of all detectable disease and histologic confirmation of tumor-free resection margins.

Every patient underwent a systematic dissection of the mediastinal lymph nodes, in addition to anatomic lung resection. Lymph nodes 2, 4, 7, 8, 9, 10, and 11 on the right side and 5, 6, 7, 8, 9, 10, and 11 on the left side were dissected. The mean number of resected N2 lymph nodes was 4.9 (between 4 and 12), and the mean number of resected N1 lymph nodes was 13.3 (between 5 and 49).

We evaluated post-surgery complications in 2 groups: major and minor.[11] Major complications were identified as patients

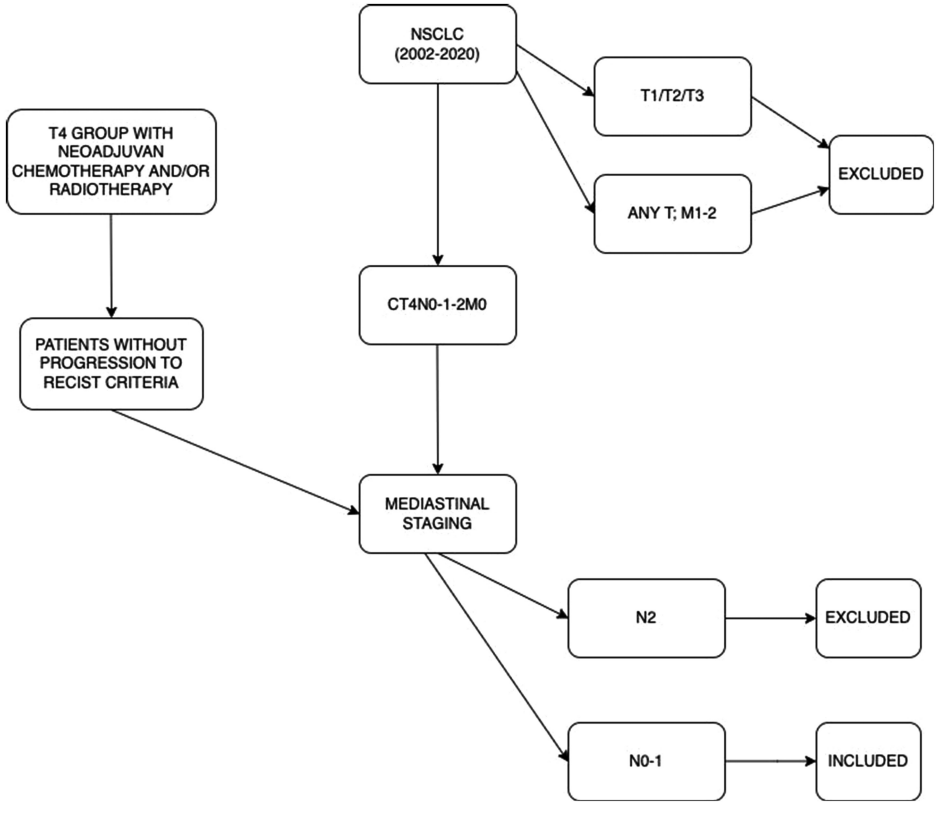

Figure 1. The CONSORT diagram of the study.

requiring intensive care unit monitoring or requiring revision (such as bleeding, prolonged air leak, fistula, pneumonia, or ARDS).[11] Minor complications were the postoperative adverse events that do not require intensive care monitoring, such as temporary atrial arrhythmias, atelectasis, and minimal air leaks.[11] Perioperative mortality was defined as death occurring within 90 days of surgery. The Institutional Review Board has approved the study.

Recorded clinical variables were age, gender, and presence of comorbid factors, smoking, FEV1, FVC values, FEV1%, FVC%, FEV1/FVC, DLCO percentages, location of computed tomography, type of resection, clinical stage before and after treatment, pathological stage after surgery, histological type, clinical and pathological response, recurrence, presence of complication, duration of hospital stay, and duration of clinical follow-up. The mean follow-up duration was 66.8 months (11-220 months).

Statistical Methods

The characteristics of patients were compared with the Fisher's exact test for categorical variables. The length of survival was defined from the date of surgery to the date of last contact or death. Survival curves were plotted using the Kaplan–Meier method, and a log-rank test was used to assess differences in survival between groups. All statistical analyses were performed using the Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA).

Results

The postoperative 90-day mortality occurred in 6 patients (6.1%). There was no statistically significant difference in demographic characteristics (age, gender) between the group of patients who underwent surgery only and the group that underwent surgery after neoadjuvant treatment (respectively, $P = .514$; 0.812) (Table 1). There were no statistically significant differences between the 2 groups in terms of respiratory parameters [Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), %FVC, %FEV1, FEV1/FVC, Diffusing capacity of the lungs for carbon monoxide (DLCO), %DLCO] (Table 1). A comparison of the 2 groups' clinical comorbidities revealed no statistically significant difference (Table 1). The operations performed are shown in Table 2. Lobectomy was the most commonly performed procedure.

Five-year survival was 58.3% in the group receiving neoadjuvant therapy and surgery. Median survival in the group receiving neoadjuvant therapy and surgery was 117 months (95% CI: 67.3-168.2 months). Five-year survival in the surgery group was 46.9%. Median survival in the surgery group was 136.2 months (95% CI: 90.9-136.2 months) (hazard ratio, 1.309; 95% CI, 0.519-3.302) (Figure 2). After adjustment for potential confounding variables of gender, age, tumor size, and nodal involvement in the (N0 or N1) neoadjuvant + surgery group, there was no statistically significant difference in terms of survival (hazard ratio, 1.26; 95% CI, 0.49-3.21, $P = .631$) compared with the surgery-alone group. N1 disease was not found to be an independent prognostic factor (hazard ratio, 1.26; 95% CI, 0.49-3.21, $P = .631$).

The most common complication was prolonged air leaks (air leaks lasting 5 or more days) (41.5%, Table 3), with pneumoderma being the second most common complication (26.5%, Table 3).

There was no patient reported as R2 after surgery; additional resections, such as rib resection and chest wall resection, were added when necessary. Preoperative and preoperative evaluation provided the current resection status and the balance of the resectable margins. All patients targeted R0 resection. However, 31 patients (31.6%) were identified as R1 in the final pathology report; these patients were evaluated for adjuvant therapy.

Discussion

In our study, we found that patients with T4N0-1M0 NSCLC can be operated on safely with a high long-term survival rate. We also disclosed that neoadjuvant chemotherapy or radiotherapy in those patients did not seem to provide a survival benefit. In addition, N1 did not seem to be a statistically significant prognosticator in these patients.

Studies reporting the outcomes of T4 NSCLC patients showed inconsistent results.[12] The survival of patients with T4N2 tumors has invariably been shown to be poor.[7,8,12] T4 patients with N0-N1 disease showed a 5-year survival rate of more than 40%.[7,8,12] Also, Yildizeli and colleagues showed that complete resection is of great importance in providing better survival in T4 NSCLC patients.[8] They showed that the 5-year survival of patients undergoing complete resection was 40% vs. 16% in those with positive surgical margins.[8] The NCCN guidelines also recommend that "T4 local extension tumors require en bloc resection of the involved structure with a negative margin."[13] In a large multicenter database study, Towe and colleagues showed that the use of neoadjuvant therapy was associated with a great reduction in the rate of

Table 1. Preoperative Clinical Characteristics of the Patients

Variable	Surgery (n = 12)	Neoadjuvant Therapy + Surgery (n = 86)	*P*
Age	60 ± 8	61 ± 9	.514
Gender			
Male	2 (16.4%)	11 (12.8%)	.812
Female	10 (83.3%)	75 (87.2%)	
Pulmonary function test			
FVC (mL) (SD)	3260 ± 110	3000 ± 175	.893
FEV1(mL) (SD)	2400 ± 115	1950 ± 120	.116
FVC (%) (SD)	89 ± 2	88 ± 3	.172
FEV1 (%) (SD)	80 ± 3	75 ± 3	.627
FEV1/FVC (SD)	90 ± 2	85 ± 3	.656
DLCO (mLCO/min/mm)	20 ± 1,6	19 ± 1,5	.109
DLCO (%) (SD)	74 ± 5,6	73 ± 6	.256
Comorbidities (Presence of at least 1 comorbidity) (%)	5 (41.6)	20 (23.2)	.17
Diabetes mellitus (%)	1 (8)	6 (6)	.24
Hypertension	8 (66.6)	44 (51.1)	.31
Coronary arterial disease	3 (25)	28 (32.5)	.6
Chronic obstructive pulmonary disease	3 (25)	24 (27.9)	.83
Idiopathic thrombocytopenic purpura	1 (8)	0	.1

Table 2. Performed Operations

Lung Resection Types	n	%
Right resection	57	58.2
Left resection	41	41.8
Pneumonectomy	29	29.6
Lobectomy	69	70.4
Total	98	100

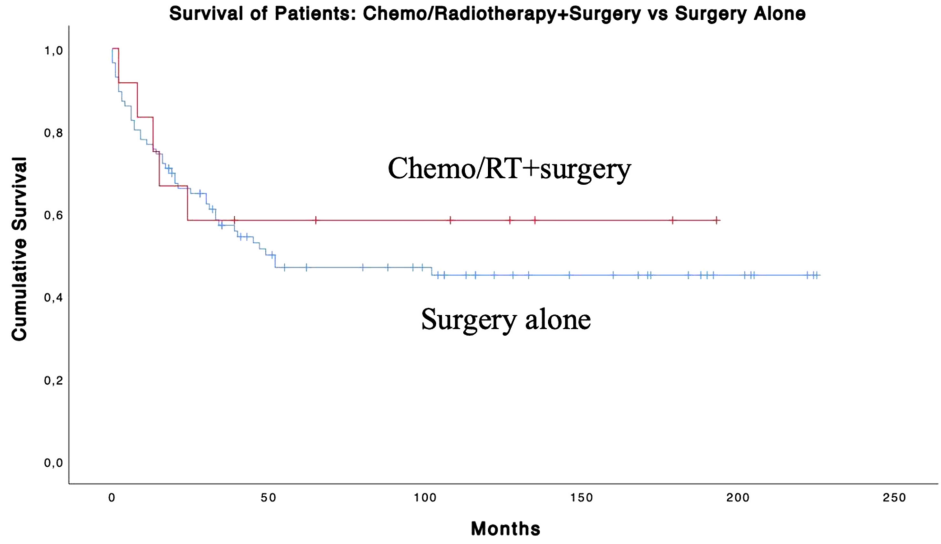

Figure 2. Survival Analysis.

positive margins as well as a better survival rate.[14] We have found that neoadjuvant therapy was associated with a better, although statistically not significant, survival.

It is strictly recommended that mediastinal lymph nodes be evaluated with PET/CT and, in most cases, mediastinoscopy since neoadjuvant chemoradiotherapy regimens have also been effective in treating patients with T4N2 NSCLC.[15-17] However, we excluded N2 patients and patients with 2 lung tumors in different lobes. Current guidelines support upfront resectional surgery and surgery after neoadjuvant treatment for resectable T4N0-1 NSCLC, but recommend that surgery is "preferred."[13] The NCCN guidelines also indicated that "T4 local extension tumors require en bloc resection of the involved structure with a negative margin."[13]

Although the most expected effect of neoadjuvant treatment might be on surgical margins, there may be benefits to tailoring neoadjuvant treatment to select patients. The likelihood of performing a complete resection was reported to be higher in patients with T4 NSCLC.[14] It was reported that 79% of patients with T4 NSCLC undergoing neoadjuvant therapy were downstaged.[14] It is plausible to suggest that neoadjuvant treatment might have an additional advantage in controlling "locoregional" disease progression as well.

Immune checkpoint inhibitor durvalumab, an anti-PDL1 monoclonal antibody, showed progression-free and overall survival benefits compared to placebo after definitive CRT in locally advanced NSCLC patients in a randomized phase III PACIFIC trial, setting the new standard of care in this stage.[10] It is important to note that we are required to downstage all patients (i.e., N0-1) before planned surgery.

There are limitations to our study. Our series includes patients from a single thoracic surgery unit. The study is a retrospective analysis of prospectively recorded patients. In addition, the operated patients were selected according to their negative N2/N3 status as well as their better performance status and pulmonary function test. Furthermore, the difference in numbers between the 2 groups was large, and the number of patients was small. By increasing the number and diversity of patients in the future, we can reduce the limitations of the study.

In conclusion, surgery for T4 lung cancer is challenging but seems to provide promising survival. Preoperative staging should aim to exclude patients with N2 disease. Aggressive treatment of T4N0-1 NSCLC with neoadjuvant chemotherapy and/or radiotherapy did not seem to prolong survival. Furthermore, we did not find N1 to be a significant prognosticator. A prospective multicenter trial should evaluate these results.

Table 3. Complications Developed Following Surgical Resections

Complication	n	%
Prolonged air leak	22	41.5
Pneumonia	5	9.4
Pleural effusion necessitating drainage	2	3.7
Dysrhythmia affecting hemodynamic status	0	0
Pneumothorax necessitating tube insertion	0	0
Lobe atelectasis	3	5.7
Wound infection	5	9.5
Pneumoderma	14	26.5
Empyema	2	3.7
Hemorrhage requiring reoperation	0	0
Total	53	100

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (Approval no: 2022/787592, Date: March 3, 2022).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Materials – G.Ö.I., İ.S.; H.İ.B., Data Collection and/or Processing – G.Ö.I., İ.S.; H.İ.B., Analysis and/or Interpretation – G.Ö.I., İ.S.; H.İ.B., Literature Search – G.Ö.I., İ.S.; H.İ.B., Writing – G.Ö.I, A.T.; Critical Review – A.T., B.K., E.E., H.V.K., K.K.

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