Prognostic Factors in Patients with Clinic Locally Advanced T4 Lung Cancer: Surgical Considerations

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Abstract

Background Inclusion of surgery in the treatment of T4 lung cancer has been a debate for the last two decades. The aim of this study is to investigate the potential prognostic factors which could affect the outcome.

Methods Fifty-seven clinical T4 non-small cell lung carcinoma (NSCLC) patients out of 716 lung resections, who were operated at a single institution in 7 years period, were included in this study. Patients are grouped into three groups as patients with neoadjuvant treatment group (group 1 *n*: 16), salvage surgery group (surgery after 3 months of definitive chemotherapy and radiotherapy) (group 2 *n*: 14), and straightforward surgery group (group 3 *n*: 27) with adjuvant treatment. Groups were analyzed and compared in terms of postoperative complications, 30 days of mortality, disease free survival, and overall survival.

Results Mean overall survival (OS) was 48.43 ± 4.4 months and mean disease-free survival (DFS) 40.55 ± 4.46 months for all patients. Thirty days mortality was 5.2% and complication rates were 63.1%. Two years OS was 61.4 ± 6.4%, DFS was 58.1 ± 7.8%. Group 1, Group 2, and Group 3 patients had mean 39.14 ± 5.6, 44.7 ± 7.1, and 62.9 ± 4.8 months for OS (*p*: 0.09), and 29.6 ± 7.2, 38.4 ± 9.1, and 46.9 ± 6 months for DFS (*p*: 0.27). Patients who received blood transfusion showed significantly worse outcomes (*p*: 0.001 for DFS and *p*: 0.004 for OS).

Conclusion According to our outcomes, surgery should be included in the treatment of clinical T4 lung cancer when physiologically and oncologically possible with careful patient selection. This study demonstrates that patients receiving straightforward surgery have longer survival, in spite of higher perioperative mortality rate. Risks and benefits should be considered carefully.

Keywords
- non-small cell lung cancer
- TNM staging
- T4 tumor

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Introduction

T4 tumors are a subgroup of locally advanced tumors which are not homogeneous. Lately the International Association for the Study of Lung Cancer published the 8th edition of the tumor, node, and metastasis (TNM) classification of lung cancer.[1,2] The T4 category was defined as invasion of the heart, mediastinal fat tissue, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina and additional nodules in different ipsilateral lobes, solid component size of the tumors larger than 7 cm, and diaphragm invasion in the recent TNM classification.[1,2] In our retrospective cohort study we aimed to investigate the overall and disease-free survivals (DFS) of patients who underwent surgical resection for cT4 NSCLC, based on the 8th edition of the TNM classification, to define the related risk factors.

Patients and Methods

This study was approved by the Demiroglu Bilim University Institutional Review Board (date: April 19, 2022, reference number: 2022–08–03). We have retrospectively analyzed cT4 NSCLC patients who underwent anatomical resection with the aim of R0 resection at the Florence Nightingale Hospital between January 2013 and January 2020.

Preoperative Staging

Clinical staging of T4 can be described as a radiological staging at the initial presentation of the patient. At this study, patients' radiological staging was performed with contrast-enhanced chest computed tomography (CT), contrast-enhanced brain magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose positron emission tomography (PET CT), and mediastinoscopy after confirmation of pulmonary function tests and cardiac evaluations was performed. Patients who received preoperative therapy either at an induction or definitive setting were also included in the study. The study group consists of patients who were diagnosed with clinical locally advanced T4 N0–2 M0–1 diseases.

Operative Procedures

Invasive mediastinal staging was performed in all patients preoperatively. Systemic mediastinal lymph node dissection, as it is described by European Society of Thoracic Surgeons, was routinely applied to all cases.[3]

Extended resections were performed commonly in our cases. Atrium, pulmonary artery, aorta, vena cava superior, subclavian artery or vein were invaded in 27 cases. If tumors were found to be invading the vessels by simply abutting their adventitia, local resection of the adventitia was preferred. Tangential resections, closure of vessels, patch plasties, and tube graft interpositions were performed by the selection of the surgical team, on purpose of R0 resection, for each case. Tumors invading the aorta by simply abutting the aortic adventitia were treated by local resection of the adventitia. The involvement of the supra-aortic vessels, such as subclavian artery, vertebral artery, and carotid artery we evaluated of the circle of Willis by MRI may be required to assure a resection of one of the vertebral arteries with the subclavian vessels. In case a hypoplasia of the contralateral vertebral artery exists or in the absence of adequate posterior communicating arteries, reconstruction of the vertebral artery was considered to prevent a stroke. Esophagus, diaphragm, and vertebrae resections were the other indications. Laminectomy, decompression, and vertebrae resections were performed with spinal surgery team. 2 mm polytetrafluoroethylene graft was used for diaphragm grafting when primary repair of the defect was insufficient in diaphragm resection cases.

Data Collection

Age, gender, criteria for T4 disease, Charlson-Deyo comorbidity index, clinical nodal status, preoperative additional therapy status, surgical approach, type of histology, pathological nodal status and stage, rate of necrosis, postoperative complications, and types of the first recurrence were the demographic, clinical, surgical, radiological, and pathological data which were retrieved from medical records of our department. The basis of the Clavien–Dindo classification was used to evaluate postoperative complications. Long-term results were collected by outpatient visits.

Preoperative and Postoperative Treatment

Neoadjuvant treatment was typically administered to patients if there was a possibility of incomplete resection, or if the tumor was localized at the superior sulcus with the findings of a Pancoast tumor. Induction radiotherapy with chemotherapy was administered if there was cranial metastasis, N2 lymph node station metastasis, or if it was an unresectable tumor at the first diagnosis. In our population, the applied total radiation dose was 54 Gy or more for the neoadjuvant setting. Postoperative radiotherapy was chosen in patients who had R1 resection. In patients who underwent R0 resection, adjuvant therapy was typically administered if the ratio of necrosis at the pathological specimen was found to be low (>90%). The routine follow-up procedures included a physical examination and thorax CT control (first in postoperative third month, then twice in a year) and FDG-PET CT for once a year in our department. MRIs of the brain were not routinely performed in the postoperative follow-up. Patients are in the follow-up for at least 5 years after surgery. Local recurrence was accepted when tumor relapse at the same side even though R0 resection was performed. DFS was the time between the date of operation and detecting recurrence. Overall survival (OS) was accepted as the time from the date of surgery until the date of death from any cause. Information and follow-up data were obtained from the hospital database, office records, and by direct contact with the patients or patients' relatives. Informed consent was obtained from all patients. Two years follow-up was analyzed for all patients. Patients were divided into three groups. Patients with neoadjuvant treatment group (group 1 *n*: 16), salvage surgery group (surgery after 3 months of definitive chemotherapy and radiotherapy) (group 2 *n*: 14), and straightforward surgery group (group 3 *n*: 27) with adjuvant treatment were

evaluated in terms of postoperative complications, mortality, DFS, and OS.

Statistical Analysis

For statistical analysis, the IBM SPSS Statistics version 21 software package was used. Data were presented as median; range or interquartile range mean, and SD. Categorical variables were compared using Chi-square tests. The Mann-Whitney test was used to compare continuous variables. The Kaplan-Meier Method (log rank test) was used to calculate the unadjusted survival rate. A *p*-value of less than 0.05 was considered as the threshold for statistical significance.

Results

In total, 716 lung resections for NSCLC were retrospectively analyzed and 57 clinically T4 patients were included in our study. Our patient group consisted of 46 males and 11 females with median age of 61.77 ± 9.6 years. Indications for a T4 disease is shown in ►**Table 1**. The mean length of stay at hospital was 11.7 days (range 5–72 days). Fifteen patients (26.3%) underwent reoperation for complications. Five patients had brain metastasis (brain oligometastatic) which was spotted at the time of diagnosis or during follow-up period. Postoperatively, 12 patients were found to be N2 positive, and 17 patients N1 positive, 28 patients had no pathological lymph node metastasis (49.1%).

Table 1 Characteristics of patients, tumors, and operations

Characteristics	
Mean age	67.76 (96–40)
Sex	
Male	46
Female	11
Type of resections	
Right pneumonectomy	3
Left pneumonectomy	9
Right upper lobectomy	11
Middle lobectomy	4
Left upper lobectomy	16
Left lower lobectomy	2
Right lower lobectomy	4
Bilobectomy inferior	7
Bilobectomy superior	3
Histology	
Squamous cell carcinoma	29
Adenocarcinoma	13
Others	15
Pathologic *N* status	
N0	28 (49.1%)
N1	17 (29.8%)
N2	12 (21.05%)
N3	0
M1	5 (8.7%)
Complete resection	
R0	56 (98.2%)
R1	1 (1.7%)
R2	0

Table 2 Resection types of patients

Surgical technique	Number of operated patients	Number of patients with proved invasion pathologically
Pulmonary artery patchplasty	10	4
Partial atrium resection	6	5
Vertebra partial corpectomy	2	1
Segmental aortic wall resection	2	0
Superior vena cava patchplasty	4	2
Subclavian artery graft interposition	1	1
Subclavian artery patchplasty	1	0
Pulmonary artery sleeve	3	1
Diaphragm partial resection	2	1
Bronchial sleeve (2 carinal)	6	6
Total	**37**	**21**

Except one patient with vertebral invasion who had an R1 resection, all other patients received R0 resection. Detailed resection types and number are in ►**Table 2**. All patients were followed at the intensive care unit for at least 1 day after the surgery. Ten patients needed perioperative transfusion (17.6%). The most common complications were atrial fibrillation, pneumonia, and prolonged air leak. Thirteen patients developed distant metastasis (22.8%) and nine developed local recurrence (15.8%) during the follow-up period.

Mean OS was 48.43 ± 4.4 months and mean DFS: 40.55 ± 4.46 month for all patients (DFS was analyzed after exclusion of early mortality with no recurrences). Thirty days mortality was 5.2% and complication rates were 63.1%. According to Clavien–Dindo classification, 58.3% of patients were grade 1 and 2a. Charlson-Deyo comorbidity index score of all patients were 5.1. Two years OS was 61.4% ± 6.4% and DFS was 58.1% ± 7.8%.

Patients with different histological type had similar survival and DFS (*p*: 0.629, *p*: 0.736). OS of patients with major (mediastinum and vessel) invasion was 33.4 ± 7.3 months and patients with no invasion was 51.57 ± 4.9 months (*p*: 0.16). However, DFS were 37.94 ± 4.4 months and 44.12 ± 10.44 months (*p*: 0.82).

Patients were categorized into three groups: patients with neoadjuvant treatment (group 1 *n*: 16), salvage surgery (after 3 months definitive chemotherapy + radiotherapy) (group 2 *n*: 14), and straightforward surgery (group 3 *n*: 27) with adjuvant treatment. Median necrosis rate was 61% among group 1 and 2 (55.2% in group 1, 68% in group 2). Relations between age, gender, mortality, Charlson-Deyo comorbidity index, Clavien–Dindo index and OS and DFS were analyzed for all series and for these three groups as shown in ►**Table 3**.

The mean OS of three groups were 39.14 ± 5.6, 44.7 ± 7.1, 62.9 ± 4.8 months, respectively (*p*: 0.09) (►**Fig. 1**). The mean DFS were 29.61 ± 7.2, 38.44 ± 9.1, 46.9 ± 6 months (*p*: 0.27) (►**Fig. 2**).

Mortality rates were 0%, 7.1 versus 12.5% (*p*: 0.54) and complication rates were 50, 57, and 44.3% (*p*: 0.74). Adjacent organ invasion was detected in six patients in group 1 (37.5%), four patients in group 2 (28.6%), and nine patients in group 3 (33.3%). Patients' need of blood transfusion showed significantly worse results in our series. Survival was 48.1 ± 1.2 months for no transfusion group, 29.2 ± 3.4 months with transfusion group (*p*: 0.004), DFS results were 46.27 ± 4.2 versus 7.1 ± 1.19 months (*p*: 0.001).

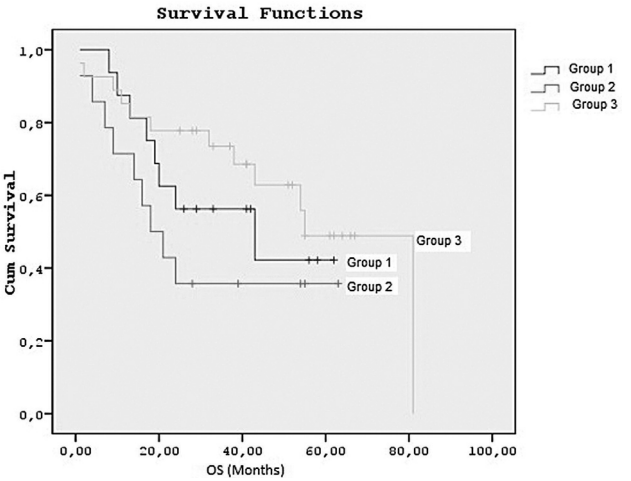

Fig. 1 Overall survivals of groups by using Kaplan–Meier method.

Discussion

Therapeutic strategy of clinical T4 lung cancer varies according to oncological criteria, lower potential of its resectability, and its natural openness to severe morbidities. From a surgeon's perspective, we aimed to clarify the prognostic factors that may affect the therapy results of the patients having surgery. To begin with, 30-day mortality was 5%, and the complication rate was found as 63.1% in our study. Among groups I-II-III, mortality rates were 0, 7.1, and 12.5% (*p*: 0.54). Yıldızeli et al's study, including 271 surgically treated T4 NSCLC cases, came out with 4% mortality and 35% morbidity.[4] Similarly, Aksoy et al's study with 284 T4 NSCLC cases who had surgery found 5.6% mortality and 23.9% morbidity rate.[5] Yamanashi et al's study investigating results of 93 cases stated 30-day mortality as 0%, with a complication rate of 56%.[2] Comparing with these studies' mortality and morbidity rates, it is possible to say that our mortality rate is similar, but a higher morbidity rate was observed. This may be related with high age-adjusted Charlson comorbidity index of our study's cases.[6] Considering the preoperative condition of the population we performed surgery upon, higher postoperative morbidity was an expected result.

Rendina et al evaluated T4 cases with induction therapy, 42 patients (73%) underwent surgery with a 4-year survival of 25.9%; 36 patients were found to have complete resection, with a 4-year survival of 30.5%.[7] Eberhardt et al's phase III study comparing 5-year OS of cases who received surgery after induction chemoradiotherapy and cases with definitive chemoradiotherapy stated OS rates of 44% for induction chemoradiotherapy and 40% for definitive chemotherapy, and DFS of 32% for induction chemoradiotherapy and 35% for definitive chemoradiotherapy.[8] One of our previous studies have showed that patients can undergo salvage lung resection with acceptable mortality and high morbidity

Table 3 Characteristics of subgroups

Subgroup of T4 category					*p*-Value
Characteristics	**Overall**	**Group 1**	**Group 2**	**Group 3**	
Number of patients	57	16 (28.07%)	14 (24.56%)	27 (47.36%)	
Median age (y)	67.76	59.25	59.14	64.62	0.101
Sex					0.7
Male	46 (80.7%)	14 (87.5%)	11 (78.57%)	21 (77.7%)	
Female	11 (19.29%)	2 (12.5%)	3 (21.42%)	6 (22.2%)	
Mean OS	48.43 ± 4.4	39.14 ± 5.6	44.7 ± 7.1	62.9 ± 4.8	0.09
Mean DFS	40.55 ± 4.46	29.61 ± 7.2	38.44 ± 9.1	46.9 ± 6	0.21
Charlson-Deyo comorbidity index	5.1	4.75	5	5.37	0.44
Postoperative mortality	3 (5.26%)	0	1 (1.75%)	2 (3.5%)	0.74
Clavien–Dindo (stage IIIA or high)	13 (36.5%)	2 (15.38%)	5 (38.46%)	6 (46.15%)	0.053

Abbreviations: DFS, disease-free survival; Group 1, neoadjuvant treatment group; Group 2, salvage surgery (after 3 mo definitive chemotherapy + radiotherapy); Group 3, straightforward surgery group; OS, overall survival.

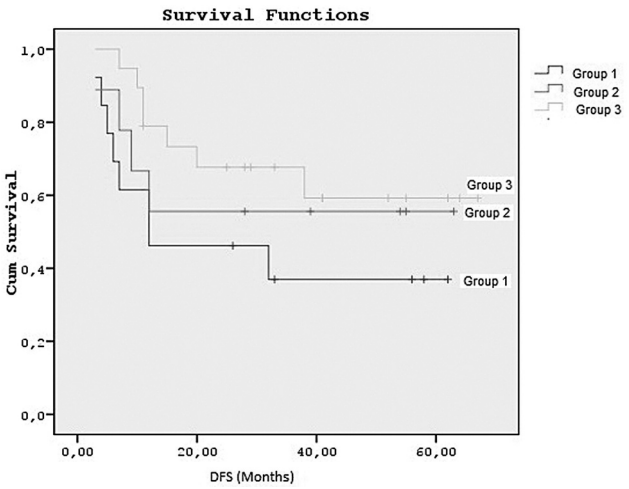

Fig. 2 Disease free survivals of groups by using Kaplan–Meier method.

rate. Mean disease free and OS were 14 ± 12 months and 19 ± 13 months in this study.[9] Sun et al's study, including The National Cancer Database's cases who underwent surgery with >7 cm NSCLC between years 2010 and 2015, compared the groups with induction chemotherapy and straightforward surgery. 5-year OS were found similar between groups (induction chemotherapy 53.5% vs. straightforward surgery 62.2%). Induction chemotherapy was not found significantly correlated with survival.[10] In our study, mean OS was 48.43 ± 4.4 months and 2-years survival was 61.4 ± 0.64%. Group I, group II, and group III cases' OS were 39 months, 44 months, and 62 months accordingly (p: 0.09). Longest survival was observed in straightforward surgery group. The main take-home message we suggest here is that if a T4 tumor is considered to require neoadjuvant treatment at the time of diagnosis, it is a difficult tumor case and there is a greater chance that things may not go as well as expected in terms of survival. We ended up with the result that our straightforward surgery group could have consisted of "easier" and "more naive" tumors.

In addition to this topic, another important question to answer for the highly heterogeneous T4 NSCLC group is "who has better survival among reasons for a patient to be staged as T4?" From this aspect, Misthos et al's study divided T4 cases into two groups. Cases with aorta invasion had 30.7% 5-years survival, and vena cava superior invasion cases had 11%.[11] Yang et al's study stated that pulmonary great vessel involvement had improved survival compared with patients with another mediastinal organ invasion.[12] Dartevelle et al's study stated the 5-years survival results after surgery for tumor invasions including carina, superior vena cava, and thoracic inlet invasion cases as 47, 46.6, and 41.5% accordingly.[13] In our study, vascular or mediastinal invasion cases found to have worse survival with OS of 38.9 ± 4.3 months and DFS of 42.44 ± 5.1 months. Despite this statistically insignificant comparison, we advocate that radical surgical resection of locally advanced T4 NSCLC is worth being performed in selected patients. With recent 8th revision of TNM staging in place, the new T4 group now includes previous T3 tumors >7 cm in size. It is necessary to re-evaluate this particular group for the choice of treatment. We found that our T4 cases without invasion, who benefited from treatment had better survival with OS of 56 ± 7.5 months and DFS of 56.31 ± 8.1 months. In contrast with our findings, Li et al's study showed that patients with only T4 extension showed better survival than patients with only tumor size > 7 cm.[14]

Ilıonen and Jones stated that the most important determinants of a successful outcome after surgery are achieving an R0 resection and avoiding incidental pathologic N2 disease in their 2018 study.[15] Assessing the pN stage's effect on survival, 12 of our cases (21%) were found to have occult N2 disease. According to pN stage, OS periods were found as 36.6 ± 4.9 months for N0, 50.43 ± 4.9 months for N1, and 44.11 ± 11 months for N2 cases (p:0.13). Surprisingly, our longest survival among N groups was observed in N1 patients; and N2 patients happened to survive longer than N0 patients. Usual literature results were like Watanabe et al's study results including 215 patients which stated 5-year survival results of 45.0, 27.0, and 25.0% accordingly for pN0, pN1, and pN2.[16] The reason for this lower survival rate among N0 cases may be inclusion of surgically treated oligometastatic T4 cases in this group.

T4 NSCLC invading the main mediastinal structure were historically accepted as unresectable, and usually treated with palliative chemotherapy or radiation. Advances in surgery have been challenging this dogma for a long time. Studies prove that complete, en bloc resection offers better chance of long-term survival. R0 resection was stated by many studies as one of most important prognostic factors for T4 NSCLC surgery.[6,13] Our R1 resection ratio was 1.75%. To achieve an R0 resection, the use of cardiopulmonary bypass (CPB) is controversial. It is notorious for its potential of causing bleeding diathesis, acute respiratory distress syndrome, and tumor dissemination. According to the available literature, planned use of CPB for carefully selected patients in experienced centers can be safe, and is associated with similar oncologic outcomes as in patients in whom CPB is not used.[17] Our CPB usage ratio for an R0 resection was 3.5% among all patients. Langer et al's study did not find any significant survival difference between T4 patients who were operated using CPB, and patients without[18]; as in De Perrot et al's study which confirms the safety of CPB for NSCLC invading the great vessels and/or the left atrium in well-selected patients.[19] Similar arguments can be made about using blood transfusion during the surgical period. In contrast with CPB usage, our study showed that cases who received blood transfusion had significantly worse survival results. DFS was 25 months for cases who received transfusion, 46 months for who did not. OS was 29 months and 48 months accordingly (p: 0.004).

Our study has also several limitations, mostly due to its retrospective nature and limited sample size. Surgical results may not be generalizable to all thoracic centers since the type of surgical procedures required to resect T4 NSCLC needs experience, and every clinic may have its own preferences during patient selection and surgery. Our experience on

selecting candidates for surgery includes a detailed radiological evaluation with our thoracic radiology team. Also we got assistance from experienced cardiovascular surgery and orthopaedic surgery teams for needed cases. This may also bring a selection bias and relatively good results.

In an update from PACIFIC trial, a Phase 3, placebo-controlled trial of patients with unresectable, stage III NSCLC without disease progression after chemoradiotherapy, consolidative durvalumab had significantly better results in the primary end points of OS and progression-free survival (PFS).[20] Rate of 4 years survival was 49.6% in durvalumab group, PFS was 35.3%. These rates were respectively 36.3 and 19.5% in placebo group.[20] Recent update of the same trial with the fifth year results was demonstrated. Updated analyses also demonstrated preferable OS and PFS benefit with durvalumab after chemoradiotherapy. Remaining alive rates at 5 years were 42.9% in patients randomly allocated to durvalumab treatment. 33.1% of durvalumab patients remain alive and free of disease progression.[21] We believe, salvage surgery and surgery for T4 will eventually need to be reassessed in the next decade including administration of immunotherapy. However, our study may be a benchmark to demonstrate the outcomes without use of immunotherapy. That is why our study may have an important place in the literature.

Conflict of Interest
None declared.

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