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Prognostic factors in operated T_3 non-small cell lung cancer: A retrospective, single-center study of 129 patients

Ameliyat edilmiş T_3 küçük hücre dışı akciğer kanserinde prognostik faktörler: 129 hastalık retrospektif, tek merkezli çalışma

Ahmet Uluşan[1], Maruf Şanlı[2], Ahmet Feridun Işık[2], Miray Ersöz[3], Bülent Tunçözgür[4], Kemal Bakır[5], Seval Kul[6], Levent Elbeyli[2]

Institution where the research was done:
Medical Faculty of Gaziantep University, Gaziantep, Turkey

Author Affiliations:
[1]Department of Thoracic Surgery, Hitit University Erol Olçok Training and Research Hospital, Çorum, Turkey
[2]Department of Thoracic Surgery, Medical Faculty of Gaziantep University, Gaziantep, Turkey
[3]Department of Thoracic Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[4]Department of Thoracic Surgery, Private Güven Hospital, Ankara, Turkey
[5]Department of Pathology, Medical Faculty of Gaziantep University, Gaziantep, Turkey
[6]Department of Biostatistics, Medical Faculty of Gaziantep University, Gaziantep, Turkey

ABSTRACT

Background: This study aims to investigate the prognostic factors that affect survival rates and durations in patients with T_3 non-small cell lung cancer who underwent surgery.

Methods: A total of 129 patients with T_3 non-small cell lung cancer (125 males, 4 females; mean age 60±9.3 years; range 23 to 80 years) who were performed surgery in our clinic between January 1997 and December 2013 were evaluated retrospectively in terms of age, gender, type of resection, tumor histopathology, tumor, node and metastasis staging, lymph node invasion, chemotherapy and radiotherapy, and recurrence.

Results: During the evaluation, while 61 patients (47.3%) were alive, 68 (52.7%) had lost their lives. One-, two- and five-year survival rates of the study population were 79.8%, 56.9% and 23.2%, respectively. Mean duration of survival was 41.5±4.0 months (range 33.7-49.4 months). Patient's age or tumor histopathology did not affect the duration of survival. Overall duration of survival was significantly longer in patients of stage IIB, patients who had low stages of lymph node invasion, who were performed lobectomy, who received chemotherapy or radiotherapy or who were without recurrence ($p<0.05$ for each). Multivariate regression analysis revealed that lymph node invasion, presence of recurrence or pneumonectomy, or failure to have been administered chemotherapy increased mortality risk significantly (hazard ratios 0.217, 3.369, 2.791 and 2.254, respectively).

Conclusion: Our findings revealed that lymph node invasion, presence of recurrence or pneumonectomy, or failure to have been administered chemotherapy are poor prognostic factors in T_3 non-small cell lung cancer. Prognostic factors should be taken into consideration during treatment and follow-up periods of patients with T_3 non-small cell lung cancer.

Keywords: Prognosis; survival; T_3 non-small cell lung cancer.

ÖZ

Amaç: Bu çalışmada cerrahi geçiren T_3 küçük hücre dışı akciğer kanserli hastalarda sağkalım oran ve sürelerini etkileyen prognostik faktörler araştırıldı.

Çalışma planı: Kliniğimizde Ocak 1997 - Aralık 2013 tarihleri arasında cerrahi uygulanan T3 küçük hücre dışı akciğer kanserli 129 hasta (125 erkek, 4 kadın; ort. yaş 60±9.3 yıl; dağılım 23-80 yıl) yaş, cinsiyet, rezeksiyon tipi, tümör histopatolojisi, tümör, nod ve metastaz evresi, lenf nodu tutulumu, kemoterapi ve radyoterapi ile nüks durumu açısından retrospektif olarak incelendi.

Bulgular: Değerlendirme sırasında 61 hasta (%47.3) sağ iken 68'i (%52.7) hayatını kaybetmişti. Çalışma popülasyonunun bir, iki ve beş yıllık sağkalım oranları sırasıyla %79.8, %56.9 ve %23.2 idi. Ortalama sağkalım süresi 41.5±4.0 ay (dağılım 33.7-49.4 ay) idi. Hasta yaşı ve tümör histopatolojisi sağkalım süresini etkilemedi. Genel sağkalım süresi evre IIB hastalarında, düşük lenf nodu tutulum evresine sahip hastalarda, lobektomi uygulananlarda, kemoterapi veya radyoterapi alanlarda ve nüks olmayanlarda anlamlı olarak daha uzundu (her biri için $p<0.05$). Çok değişkenli regresyon analizi lenf nodu tutulumunun, nüks veya pnömonektomi varlığının ya da kemoterapi uygulanmamasının ölüm riskini anlamlı olarak artırdığını gösterdi (risk oranları sırasıyla, 0.217, 3.369, 2.791 ve 2.254).

Sonuç: Bulgularımız lenf nodu tutulumunun, nüks veya pnömonektomi varlığının ya da kemoterapi uygulanmamasının T_3 küçük hücre dışı akciğer kanserinde kötü prognostik faktörler olduğunu gösterdi. T_3 küçük hücre dışı akciğer kanserinde hastaların tedavi ve izlem sürecinde prognostik faktörler dikkate alınmalıdır.

Anahtar sözcükler: Prognoz; sağkalım; T_3 küçük hücre dışı akciğer kanseri.

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Correspondence: Ahmet Uluşan, MD. Hitit Üniversitesi Erol Olçok Eğitim ve Araştırma Hastanesi, Göğüs Cerrahisi Kliniği, 19100 Çorum, Turkey.
Tel: +90 364 - 223 03 00 e-mail: draulusan@gmail.com

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Worldwide, lung cancer is a major cause of cancer-related deaths in both males and females. In 2013, 1.6-million deaths were reported due to lung cancer.[1] In Turkey, the incidence of lung cancer in males and females in 2009 was reported to be 0.066% and 0.0081%, respectively.[2] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. As most cases are diagnosed in later stages, the prognosis is poor, with five-year survival rates varying between 2% and 50% according to the stage and extent of the disease at the time of the diagnosis.[3,4] Other than the stage of the disease, the type of surgery,[5] chemotherapy[6] and radiotherapy[7] were reported to influence survival rates. Accurate determination of the pathological and tumor, node and metastasis (TNM) staging and other factors that may influence the prognosis (evaluation of the risks) are crucial in treatment planning (surgery, chemotherapy, or radiotherapy) and follow-up.

The TNM classification system is commonly used in staging of lung cancer. The system was updated in 2009, with important changes made regarding the classification of the "T" component, which represents the dimensions and local extent of the tumor.[8-10] Regarding the new criteria in the updated classification system, there has been little research on the prognostic factors in patients with T_3 or advanced NSCLC with low survival rates.[11] Therefore, in this study, we aimed to investigate the prognostic factors that affect survival rates and durations in patients with T_3 non-small cell lung cancer who underwent surgery.

PATIENTS AND METHODS

This was a retrospective study of the medical records of 129 patients (125 males, 4 females; mean age 60±9.3 years; range 23 to 80 years) with a diagnosis of NSCLC who underwent surgery in Gaziantep University Medical School, Thorax Surgery Department of Şahinbey Research and Implementation Hospital between January 1997 and December 2013. Inclusion criteria were T_3 NSCLC tumors (tumors that were greater than 7 cm or invasion of the chest wall), including tumors of the superior sulcus; tumors of the diaphragm, phrenic nerve, mediastinal/parietal pleura, or parietal pericardium; tumors of the main bronchus that were <2 cm from the carina; and the presence of atelectasis or obstructive pneumonia of both lobes of the lung or different tumor nodules in a single lobe of the lung that were not diagnosed histopathologically as small cell lung cancer. For the evaluation of mediastinal lymph nodes, all the patients underwent positron emission tomography (PET) since 2006, when our hospital had PET.[12] According to the PET results, mediastinoscopy was performed on the basis of the criteria defined by Sanli et al.[13] Before 2006, mediastinal lymph nodes had been evaluated with computed tomography (CT), and mediastinoscopy was performed for patients without distant metastasis and having mediastinal lymph node with a short axis >1 cm. Patients having mediastinal lymph node with a short axis of 1 cm or less were surgically operated without mediastinoscopy. All patients underwent cranial magnetic resonance imaging and abdominal CT for detection of distant metastasis. The study was approved by the Ethical Committee of Gaziantep University Medical School (Approval Date; 20 March 2014, No. 97). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki and Directory for Patients' Rights.

Information on the demographics, surgery, postoperative histopathological diagnosis, and TNM stages of the study population was recorded. The surgical interventions performed were divided into the following subgroups: pneumonectomy, lobectomy, and other (i.e., modified resection, sleeve resection, and wedge resection).

The TNM classification was performed according to the invasion of regional lymph nodes. Patients without any regional lymph node invasion were classified as N_0. Those with ipsilateral peribronchial and/or ipsilateral hilar lymph node invasion or intrapulmonary lymph node invasion due to direct invasion of the tumor were classified as N_1; those with ipsilateral mediastinal and/or subcarinal lymph node invasion were classified as N_2; and those with contralateral mediastinal/hilar and ipsilateral scalene or supraclavicular lymph node invasion were classified as N_3. The surgical stages of the tumors were also recorded.

The number of patients who received chemotherapy and/or radiotherapy and recurrences during the postoperative period was recorded. Telephone interviews with the patients/their relatives were performed to obtain information on each patient's health status at the time of the study. If a patient was not alive, the cause of death was recorded. All the telephone interviews were completed within two weeks to prevent the effect of the timing on the findings.

For patients who died, the duration between the date of the surgery and death was determined as the survival time. For patients who were alive, the survival time was considered as the duration between the date of the surgery and the telephone interview and was recorded in months.

Table 1. Demographics and lung cancer related clinical features of 129 patients

	n	%
Gender		
Male	125	96.9
Female	4	3.1
Histopathologic diagnosis		
Squamous cell carcinoma	75	58.1
Adenocarcinoma	35	27.1
Other (adenosquamous, giant cell, sarcomatoid)	19	14.7
Stage		
IIB	74	57.4
IIIA	55	42.6
T_3 criteria		
>7 cm	66	51.2
Chest wall invasion	27	20.9
Other invasions	36	27.9
Lymph node invasion		
N_0	74	57.4
N_1	29	22.5
N_2	26	20.2
Type of operation		
Lobectomy	67	51.9
Pneumonectomy	48	37.2
Other (modified, sleeve, wedge)	14	10.9
Chemotherapy*		
Yes	90	69.8
No	38	29.5
Radiotherapy*		
Yes	63	48.8
No	65	50.4

* Data obtained from available patients.

The effects of variants, such as like age, gender, type of surgery, tumoral histopathology, surgical staging, lymph node invasion, chemotherapy and radiotherapy, and recurrence, on the survival duration were evaluated.

Statistical analysis

All the statistical analyses were performed using IBM SPSS for Windows version 22.0, (IBM Corp., Armonk, NY, USA) software. Patients' demographics and clinical features were summarized using descriptive statistical methods, including means, standard deviations, incidences, and percentages. Kaplan-Meier curves, with 95% confidence intervals were constructed to determine cumulative one year, two-year, and five-year survival rates. The log-rank test was used to evaluate whether clinical variants caused differences in general survival rates. Univariate and multivariate Cox regression analyses were conducted to determine the variants that had a significant influence on survival rates. The variants that were determined as significant in the univariate analysis ($p<0.05$) were included in the multivariate analysis. The results of the Cox regression analysis were presented, together with hazard ratios and 95% confidence intervals. The limit for statistical significance was set as $p<0.05$.

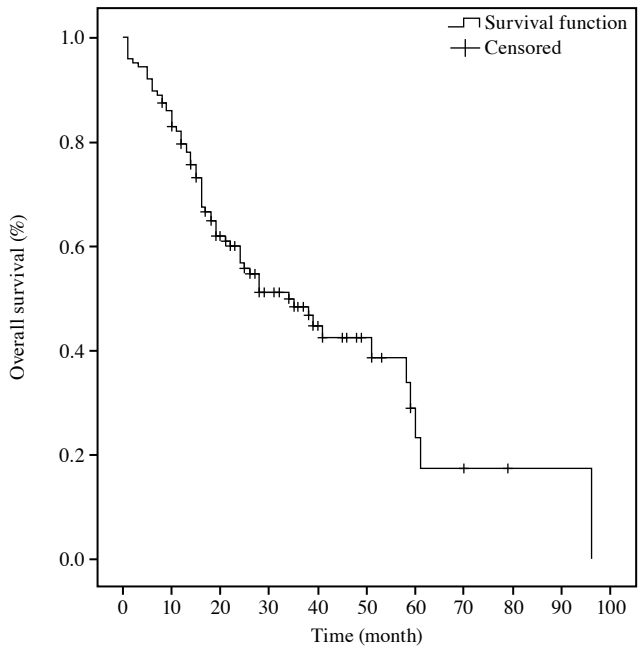

Figure 1. Kaplan-Meier curve for all patients.

RESULTS

The clinical characteristics of the patients were summarized in Table 1. The most common histopathological diagnoses were squamous cell carcinoma (58.1%) and adenocarcinoma (27.1%). Seventy-four (57.4%) patients were classified as stage IIB, and 54 (42.6%) were classified as stage IIIA. When T_3 criteria were taken into consideration, 27 patients (20.9%) had chest wall invasion, 36 patients (27.9%) had other types of invasion, and 66 patients (51.2%) had masses greater than 7 cm. Regarding the staging of

Table 2. Survival and recurrence rates of patients obtained with phone calls (n=129)

	%
Overall survival	47.3
One-year survival	79.7
Two-year survival	56.9
Five-year survival	23.2
Recurrence	35.7

the disease, 74 patients (57.4%) were classified as N_0, 29 (22.5%) were classified as N_1, and 26 (20.2%) were classified as N_2 (Table 1). The number of patients who underwent pneumonectomy and were found to have pathological N_2 disease was 13.

Sixty-one patients (47.3%) were alive at the time of the interview, and 68 (52.7%) were not (Figure 1). The one-, two-, and five-year survival rates of the study population were 79.8%, 56.9%, and 23.2%, respectively. Forty-six patients (35.7%) had recurrences, while 83 (64.3%) had no recurrences (Table 2).

The mean duration of survival was 41.5±4.0 months (range 33.7 to 49.4 months). Neither the patient's age nor tumoral histopathology/T_3 criteria affected the duration of survival (p=0.028 and p=0.695, respectively). However, the overall duration of survival was significantly higher in patients with stage IIB, lower stages of lymph node invasion, history of prior lobectomy, history of chemotherapy or radiotherapy, and no recurrences (p<0.05 for each of the variants, Table 3). The one-, two-, and five-year survival rates according to the evaluated clinical variants were presented in Table 4.

The multivariate Cox regression analysis, including the variants that had significant effects on survival rates, revealed that the risk of death was significantly higher in patients with the following: lymph node invasion, recurrences, no chemotherapy, and history of pneumonectomies (hazard ratios: 0.217, 3.369, 2.791, and 2.254, respectively) (Table 5).

Table 3. Effects of clinical variants on survival (months)

	n	Mean±SD	95%CI	*p**
Total	129	41.5±4.0	33.7-49.4	
Age (year)				0.982
<60	55	37.3±3.5	30.3-44.2	
≥60	74	43.2±5.9	31.5-54.8	
Histopathologic diagnosis				0.228
Squamous cell carcinoma	75	40.4±5.4	29.8-51.0	
Adenocarcinoma	35	44.4±4.4	35.7-53.1	
Other	19	27.6±4.3	19.3-35.9	
Stage				<0.001
IIB	74	50.0±5.0	40.2-59.8	
IIIA	55	23.0±2.6	18.0-28.0	
T_3 criteria				0.695
>7 cm	66	36.1±3.2	29.8-42.4	
Chest wall invasion	27	45.7±8.8	28.5-63.0	
Other invasions	36	39.6±5.9	28.0-51.2	
Lymph node invasion				<0.001†
N_0	74	50.2±5.0	40.4-60.1	
N_1	29	27.5±3.7	20.4-34.7	
N_2	26	16.3±2.6	11.3-21.3	
Type of operation				0.002‡
Lobectomy	67	47.9±5.4	37.4-58.4	
Pneumonectomy	48	29.0±4.6	20.0-38.1	
Other	14	36.0±5.0	26.3-45.6	
Chemotherapy				<0.001
Yes	90	46.0±4.5	37.2-54.9	
No	38	27.9±4.8	18.5-37.3	
Radiotherapy				0.028
Yes	63	49.4±6.2	37.1-61.6	
No	65	32.8±3.4	26.1-39.6	
Recurrence				0.003
Yes	47	23.6±2.3	19.2-28.1	
No	78	48.5±5.3	38.0-58.9	

SD: Standard deviation; CI: Confidence interval; * Log Rank (Mantel Cox); † p=0.012 for N_0 vs. N_1; p=0.001 for N_0 vs, N_2; p=0.047 for N_1 vs. N_2; ‡ p=0.001 for lobectomy vs. pneumonectomy; p=0.994 for lobectomy vs. other; p=0.045 for pneumonectomy vs. other.

Table 4. Effects of clinical variables on survival rates

	1-year survival	2-year survival	5-year survival
	Mean±SD	Mean±SD	Mean±SD
Age (year)			
<60	0.8±0.1	0.5±0.7	0.2±0.1
≥60	0.8±0.1	0.6±0.6	0.2±0.1
Histopathologic diagnosis			
Squamous cell carcinoma	0.8±0.1	0.7±0.1	0.2±0.1
Adenocarcinoma	0.9±0.1	0.7±0.1	0.4±0.1
Other	0.8±0.1	0.5±0.1	0.4±0.1
Stage			
IIB	0.9±0.0	0.7±0.1	0.3±0.1
IIIA	0.6±0.1	0.4±0.1	0.3±0.8
T_3 criteria			
>7 cm	0.9±0.0	0.6±0.1	0.1±0.1
Chest wall invasion	0.9±0.1	0.6±0.1	0.5±0.1
Other invasions	0.6±0.1	0.5±0.1	0.4±0.1
Lymph node invasion			
N_0	0.1±0.0	0.8±0.1	0.3±0.1
N_1	0.6±0.1	0.5±0.1	0.5±0.1
N_2	0.6±0.1	0.2±0.1	0.0±0.0
Type of operation			
Lobectomy	0.9±0.0	0.7±0.1	0.3±0.1
Pneumonectomy	0.7±0.1	0.4±0.1	0.1±0.1
Other	0.8±0.1	0.6±0.2	0.6±0.2
Chemotherapy			
Yes	0.9±0.0	0.7±0.1	0.2±0.1
No	0.5±0.1	0.3±0.1	0.3±0.1
Radiotherapy			
Yes	0.9±0.0	0.7±0.1	0.4±0.1
No	0.8±0.1	0.5±0.1	0.1±0.1
Recurrence			
Yes	0.8±0.1	0.3±0.1	0.0±0.0
No	0.8±0.1	0.7±0.1	0.3±0.1

SD: Standard deviation.

DISCUSSION

Post-treatment survival and prognosis expectations cannot be explained by any single parameter in complex diseases -such as lung cancer- which include multiple risk factors and pathophysiological mechanisms. Nonetheless, within the frame of present evidence-based risk parameters, an individualized approach to therapy should be adopted, with associated survival expectations that are specific to the patient. Large-scale trials in different geographical regions can increase knowledge of the number of parameters that have significant influence on the prognosis and consequently contribute to more accurate predictions of survival rates. With this in mind, the present study evaluated the effects of clinical variants on survival rates in patients with resected locally advanced NSCLC.

The mean survival rate for most patients with NSCLC, which constitutes the majority of lung cancers, was previously reported to be 50 months.[4] The same study reported that approximately 10-15% of NSCLC patients had T_3 or T_4 disease with low expected survival rate.[4] In our series of 129 patients with T_3 NSCLC, the mean duration of survival was 41.5±4.0 months (range 33.7 to 49.4 months), and the five-year survival rate was 23.2%. These findings are consistent with those in the literature.[3,4] Turna et al.[14] reported a mean survival rate of 49±9 months in 44 patients with resected T_3 NSCLC. The duration of survival of patients in their study was longer than that of our study population and longer than that reported in other studies.[14] We suggest that the discordance in the duration of survival may be due to differences in sample sizes.

Table 5. Effects of clinical variables on mortality rates by multivariate Cox regression analysis

	Hazard ratio	95%CI	*p*
Stage			
IIB	Referans		
IIIA	0.706	0.147-3.388	0.663
Lymph node invasion			
N_0	Referans		
N_1	0.239	0.110-0.522	<0.001
N_2	0.217	0.044-1.061	0.059
Type of operation			
Other	Referans		
Lobectomy	1.429	0.482-4.235	0.520
Pneumonectomy	3.369	1.137-9.976	0.028
Chemotherapy			
Yes	Referans		
No	2.791	1.383-5.631	0.004
Radiotherapy			
Yes	Referans		
No	0.607	0.302-1.221	0.161
Recurrence			
Yes	Referans		
No	2.254	1.275-3.986	0.005

CI: Confidence interval.

There have been various reports of the effects of age on survival rates. Suzuki et al.[15] found that the risk of death was 4.17 times higher in patients with T_3 NSCLC who were older than 80 years in their series of 168 patients. On the other hand, Sonobe et al.[16] found no difference in survival rates (p=0.2691) based on a retrospective analysis of 234 patients, in which they classified the patients into three groups according to age (≤70 years, between 71 and 75 years, and ≥76 years). Similarly, the present study did not demonstrate any effect of age on the survival rate. This finding may be explained by the limited number of elderly subjects-only one patient was older than 80 years in the study group, and that patient was alive during the study period. When we divided the population into two age groups (those younger and older than 60 years), there was no significant difference in the survival rates of these groups.

Many studies of parameters that influenced prognosis and survival rates in lung cancer revealed a sex-related difference.[16-18] In a retrospective analysis of 86 patients with advanced-stage NSCLC, Iyoda et al.[18] found that male gender was associated with a poor prognosis. However, in common with many similar studies, there were far fewer female than male patients in their population. The male bias in their population had negative influence on confidence intervals and influenced the statistical significance of the findings. In the present study, there were only four female patients, and all of these were alive at the time of the study. Thus, it was not possible to evaluate the effect of gender on the survival rate.

With regard to resection, the type of resection affects prognosis and survival rates in two different ways. Incomplete resection of a tumor contributes to an unfavorable quality of life and lower survival rates, and a decrease in total pulmonary capacity due to complete resection has a marked influence on postoperative mortality. A study that examined whether pneumonectomy resulted in better survival rates concluded that there was no statistically significant relationship between pneumonectomies and survival rates.[19] In the present study, the survival rates of patients who had lobectomy were significantly higher than those who had pneumonectomy.

Squamous cell carcinomas generally originate from areas that are close to the main bronchi. In contrast, adenocarcinomas and bronchoalveolar carcinomas occur in peripheral lung tissues. The most common types of NSCLCs are squamous cell carcinomas, adenocarcinomas, and bronchoalveolar carcinomas, and the prognosis and therapeutic approaches are similar.[3] Iyoda et al.[18] reported that the histopathological structure of a tumor did not

influence the prognosis. This was confirmed in the present study, which revealed no difference in the survival rates of patients who had adenocarcinomas versus squamous cell carcinomas.

The stage of the disease also plays an important role in prognosis and survival. In a recent study, Wang et al.[20] reported a five-year survival rate of 44.7% and 24.4% in patients with stage IIB and IIIB disease, respectively. Similarly, in the present study, the survival rates of the patients with stage IIB disease were significantly higher than those of patients with stage IIIA ($p<0.001$), but the stage of the disease did not influence survival rates according to a multivariate Cox regression analysis.

Other than its effects on prognosis and survival, lymph node invasion is used to determine appropriate therapeutic options. Suzuki et al.[15] reported a five-year survival rate of 26.5% in patients with lymph node invasion. The same rate was 53.3% in patients without lymph node invasion ($p<0.004$). In the present study, the mean duration of survival was 50.2 months in patients with N_0 disease, and the mean duration of survival in patients with N_1 and N_2 disease was 27.5 and 16.3 months, respectively ($p<0.001$). Consistent with the results of the current study, Takenaka et al.,[17] also showed that lymph node invasion was associated with a poor prognosis.

The benefits of chemotherapy and radiotherapy for patients with T_3 NSCLC need to be comprehensively assessed. Many reports have demonstrated long-term positive effects of both treatments on prognosis and survival.[20-23] On the other hand, higher mortality rates were reported in cases of postoperative chemoradiotherapy, particularly in patients who had undergone pneumonectomies.[19,24] Arriagada et al.[25] performed a prospective analysis of 1867 patients with NSCLC and found five-year survival rates of 44.5% and 40.4% in patients who did or did not receive chemotherapy, respectively ($p<0.03$). They concluded that chemotherapy had positive effects on long-term survival. In the present study, the mean duration of survival was 46 months and 27.9 months in patients who did or did not receive chemotherapy, respectively ($p<0.001$). Similarly, the mean duration of survival was 49.4 months and 32.8 months in patients who did or did not receive radiotherapy, respectively ($p=0.028$). These findings point to positive effects of chemotherapy and radiotherapy on prognosis and survival and are consistent with those in the literature. However, when considering candidates for postoperative chemotherapy and radiotherapy, the relationship between chemotherapy and radiotherapy and short-term increased morbidity and mortality should be kept in mind.

In the present study, although the mean duration of survival was 23.6 months in patients with recurrences, it was 48.5 months in those who did not have recurrences ($p=0.003$). This finding was consistent with that of the study by Sonobe et al.,[16] who reported that the risk of poor prognosis was 2.1 times higher in patients who had recurrences within one year and 1.8 times higher in patients who had recurrences within 1-2 years. Similarly, Choi et al.[26] reported five-year survival rates of 22.8% in patients with early recurrence, 57.3% in patients with late recurrence, and 82.1% in patients without recurrence.

The major limitations of the present study were its small sample size and retrospective design. Nonetheless, the findings are noteworthy, given that this was a relatively large study of factors contributing to the prognosis of Turkish patients with T_3 NSCLC.

In conclusion, lymph node invasion, recurrences, a history of surgery (pneumonectomy), and the absence of chemotherapy were poor prognostic factors in T_3 non-small cell lung cancer patients. These prognostic factors should be taken into consideration during treatment and follow-up periods of patients with T_3 non-small cell lung cancer.

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