RESEARCH ARTICLE

Survival Results and Prognostic Factors in T4 N0-3 Non-small Cell Lung Cancer Patients According to the AJCC 7th Edition Staging System

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Abstract

Background: The American Joint Committee on Cancer (AJCC) published a new staging system (7th edition) in 2009. In our study, we evaluated the survival results and prognostic factors among T4 local advanced non-small cell lung cancer (LA-NSCLC) patients in a large heterogeneous group, in accordance with this new system. Materials and Methods: We retrospectively evaluated the files of 122 T4 N0-3 M0 LA-NSCLC patients, identified according to the new staging system, treated at two centers between November 2003 and June 2012. Variables correlating with univariate survival at p<0.20 were later included in multivariate Cox regression analysis. Here, selection of relevant predictors of survival was carried out in accordance with the likelihood ratio formula with p<0.05 regarded as significant. Results: The median age was 60 and the median follow-up period was 17.4 months. Median overall survival (OS) was 18.3 months, the 1 year overall survival (OS) rate was 72%, and the 5 year OS rate was 28%. Statistically significant predictors of survival were (p<0.20) ECOG-PS (Eastern Cooperative Oncology Group Performance Status), age, T4 factor subgroup, stage and primary treatment in OS univariate analysis. On multivariate analysis for OS ECOG-PS (p=0.001), diagnostic stage (p=0.021), and primary treatment (p=0.004) were significant. In the group receiving non-curative treatment, the median OS was 11.0 months, while it was 19.0 months in the definitive RT group and 26.6 months in the curative treatment group. There was a significant difference between the non-curative group and the groups which had definitive RT and curative operations (respectively p<0.001 and p=0.001) in terms of OS, but not between the groups which had definitive RT and curative operations. The median event free survival (EFS) rate was 9.9 months, with rates of 46% and 19% at 3 and 5 years, respectively. On univariate analysis of EFS rate with ECOG-PS, weight loss and staging, statistical significance was found only for thorax computerized tomography (CT)+18F-fluorodeoxy-glucose positron emission tomography-CT (PET-CT) use, stage and primary treatment (p<0.20). In multivariate analysis with EFS, only the primary treatment was statistically significant (p=0.001). In the group receiving non-curative treatment, the median EFS was 10.5 months while in the curative operation group it was 14.7 months. When all the primary treatment groups were taken into consideration, grade III/IV side effect swas observed in 57 patients (46.6%). Esophagitis was most prominent among those that received definitive radiotherapy. Conclusions: Independent prognostic factors among these 122 heterogeneous LA-NSCLC T4 N0-3 M0 patients were age at diagnosis, ECOG-PS, stage and primary treatment, the last also being a significant prognostic indicator of EFS. Our findings point to the importance of appropriate staging and a multidisciplinary approach with modern imaging methods in this patient group. In those with T4 lesions, treatment selection and the effective use of curative potential should be the most important goal of clinical care.

Keywords: T4 local advanced non-small cell lung cancer - primary treatment - non-curative treatment - curative approach

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Introduction

An estimated 1.6 million new lung cancer cases are seen throughout the world every year. Lung cancer ranks first in deaths caused by cancer among men and second among women (Globocan, 2008). The 5 year survival rate of lung cancer in Europe and the USA (United States of America) is approximately 16%, in spite of all the recent improvements in diagnosis and treatment (Jemal et al., 2010). Almost 85% of lung cancers fall within the non-small cell (NSCLC) subgroup and many of these are staged as stages IIIA, IIIB or IV during diagnosis

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(Bulzebruck et al., 1992; Bhaskarapillai et al., 2012; Maliuk et al., 2013).

The American Joint Committee on Cancer (AJCC) published a revised 7th edition of lung cancer staging system in 2009. With the new staging system in local advanced NSCLC (LA-NSCLC), a satellite nodule on the same lobe was revised as T3 from T4, a nodule in different lobes was revised as T4 from M1, and malign pleural and pericardial effusion was revised as M1a from T4 (Detterbeck et al., 2009).

In lung cancer, local advanced disease is defined by the degree of T and N status. T4 LA-NSCLC is a large heterogeneous group. The T4 lung cancer group with no distant organ metastasis includes T4 N0-3 M0. In LA-NSCLC patients, effective management of the disease is very difficult despite all the new treatment models Albain (Albain et al., 1991; Paesmans et al., 1995). In T4 tumors, surgical treatment is not typically recommended as the probability of invasion into mediastinal vital structures is high and therefore R0 resection change (R0; no residual tumor, R1; microscopic residual tumor, R2; macroscopic residual tumor) is low. But, surgery can be carried out on selected T4 cancers in cases of complete resection of the pulmonary artery or limited invasion of structures such as the superior vena cava, left atrium, and carina (DiPerna et al., 2005). While the preferred treatment for eligible T4 N0-1 M0 (Stage IIIA) patients is surgical resection, other treatment options include chemotherapy before tumor resection or concurrent chemo-radiotherapy. For T4 N0-1 M0 patients who cannot be operated upon, the contemporary treatment is chemotherapy after concurrent chemo-radiotherapy. For T4 N2-3 M0 (Stage IIIB) patients, surgical resection is not usually recommended. If full dosage chemotherapy cannot be administered, chemotherapy after concurrently chemo-radiotherapy is recommended (Belani et al 2005; Gandara et al 2006; Hana et al., 2007; Albain et al., 2009; Curan et al., 2011).

In many previous studies, survival extension was shown in a selected group of T4 NSCLC patients who had been operated on (Watanabe et al., 1991; Martini et al., 1994; Izbicki et al., 1995; Hsu et al., 1996; Bernard et al., 2001; Osaki et al., 2003; Pitz et al., 2003).

Due to unequal case volume and different evaluation criteria, the reported risk factors and prognostic parameters that are related to survival differ in T4 NSCLC patients. For example, whether the treatment is curative or palliative, T4 diagnosis, the state of lymph nodes, the pathological subgroup type of the tumor, the age at diagnosis, smoking status, co-morbidity, ECOG-PS (Eastern Cooperative Oncology Group Performance Status), and weight loss can all be factors that affect treatment results and survival rates (Watanabe et al., 1991; Martini et al., 1994; Izbicki et al 1995; Hsu et al 1996; Bernard et al., 2001; Osaki et al., 2003; Pitz et al., 2003; Gregory et al., 2012). Therefore it is important to identify the factors that affect overall survival (OS) rate and event free survival (EFS) rates for the selection of treatments and differentiation of patients in this heterogeneous group of LA-NSCLC (T4 N0-3 M0) cases.

The limited amount of randomized studies related to LA-NSCLC patients increases the importance of retrospective studies (Kazuhiko et al., 2012). In this retrospective study, we aimed to evaluate the factors that affect survival by presenting OS rate and EFS rate results in T4 N0-3 M0 LA-NSCLC patients.

Materials and Methods

We retrospectively examined the files of patients with a diagnosis of NSCLC who were treated between November 2003 and June 2012 in the hospitals of Antalya Akdeniz University and Konya Selçuk University.

The patient with lobe satellite nodule who were classified as T4 according to the AJCC 2002 staging system, were reclassified as T3 according to the AJCC 2009 staging system. Patients with malign pleural or patients with pericardial effusion or pleural nodules are classified as M1a in the new staging system and were also not included in the study (Detterbeck et al., 2009). Patients with superior sulcus tumor (pancoast tumor) were not included in the study. One hundred twenty two T4 N0-3 M0 LA-NSCLC patients whose histological diagnosis were made according to World Health Organization (WHO) guidelines were included in this study. The data were primarily obtained from hospital files and electronic data, as well as from patients and patient relatives directly.

Clinical staging was carried out using computerized tomography (CT) of the upper abdomen and thorax, magnetic resonance (MR) of brain, whole body bone scintigraphy, fiber-optic bronchoscopy, and in some patients by using mediastinoscopy and intraoperative observations. MR was used in suspected invasions of the chest wall, large vein, and vertebrae. From June 2007 on, 18F- fluorodeoxy-glucose positron emission tomography-CT (PET-CT) was used in some selected patients.

The TNM status of all patients was determined in accordance with the standard radiological guidelines. Tissue samples obtained from mediastinoscopy and or surgical treatments together with and cytological samples obtained from pleural and/or pericardial fluids were also used in staging.

Applied treatments

The following treatments were applied to patients included in this study group: Definitive radiotherapy, definitive concurrent chemo-radiotherapy, palliative radiotherapy, curative surgery, palliative surgery, induction chemotherapy and palliative chemotherapy, as well as various combinations of these treatment regimes according to the unique needs of individual patients.

Statistical analysis

Univariate and multivariate survival analysis were carried out for OS rate and EFS rate. For EFS, recurrence or progression or second primary or death were taken into consideration as the 'Events'. Univariate Cox regression analysis was applied to univariate survival rates. Variables analyzed by the univariate method and having a $p<0.2$ were then included in the subsequent multivariate Cox regression analysis. In the multivariate analysis, the selection of variables was carried out in accordance with the likelihood ratio formula with $p<0.05$ as significant.

Results

The characteristics of patients

One hundred twenty two LA-NSCLC T4 N0-3 M0 patients, who were treated between November 2003 and June 2012, were included in the study retrospectively. The clinical and pathological characteristics of these patients can be seen in Table 1. The median age was 60 (range 42-80). Most of the patients were male (95.9%). Smoking frequency was 97.5% and the average consumption was 52.4 packages/year (range: 9-160 packages-year). The proportion of patients who had experienced weight loss at the time of diagnosis was 8.2%. 45 patients had co-morbidities (36.9%). When the histological subtypes were examined, squamous epithelium cell carcinoma was observed in 63.1%, of patients. Adenocarcinoma (23%), large cell carcinoma (9%) and not otherwise specified (NOS) (4.9%) were diagnosed relatively lower frequencies. At diagnosis, ECOG-PS=1 patients were in majority 70.5% and none of the patients had ECOG-PS=4. There were 45 patients (36.9%) for whom only thorax CT+PET-CT was used in staging of the tumor. In the staging of other patients, additional imaging methods were also used CT/PET.

Twenty six different therapies were applied to the patients. We found it suitable to classify the treatments into three main categories. These were the group without curative treatment, groups with definitive radiotherapy, and definitive surgery (Table 2).

In induction, adjuvant and palliative chemotherapy protocols using platinum (cisplatin, carboplatin), docetaxel, gemcitabine, etoposide, paclitaxel, vinorelbin or pemeterexed were administered. Cisplatinum resistant patients single agent chemotherapy (docetaxel, gemcitabine, etoposide, paclitaxel, vinorelbin or pemeterexed) were given as a palliative treatment. Two patients, who were not suitable for curative treatment, also had palliative surgery. For patients who received definitive radiotherapy, platinum (cisplatin, carboplatin) was usually the single agent in chemotherapy given concurrently as a sensitizer. The total classical or hyperfractionated dosage recommended in definitive radiotherapy was 60-70 Gy. In the curative surgery group, all patients had postero-lateral thoracotomy and systemic mediastinal lymph node dissection.

Various methods of evaluating response during follow up were carried out. Patients who received palliative chemotherapy, radiological and clinical evaluation at 2-3 months or at the end of 6 months were applied. Patients who had definitive radiotherapy were evaluated clinically and with biochemicaland pathological tests and radiological methods. Radiological responses were classified into four categories of stable disease (SD), partial response (PR), complete response (CR), and progressive disease (PD) according to WHO criteria (a total of 7 patients were clinically responsive or progressive) (Miller et al., 1981).

Toxicity scores were also calculated according to WHO criteria. The toxicity evaluation was done at the beginning and end of each chemotherapy cycle, with weekly biochemical tests and physical examinations during radiotherapy (World Health Organization, 1979).

Patient examinations were carried out before each chemotherapy cycle, on a weekly basis for patients

Table 1. Clinical and Pathologic Characteristics

Features		Patient No	(%)
Age:			
Median (Mean±SD*)	59.8±9.1 (60%)		
Range (42-80)	≤60 age	64	(52.4%)
	>60 age	58	(47.6%)
Gender:	Man	117	(95.9%)
	Woman	5	(4.1%)
Smoking history	Yes	119	(97.5%)
	Never	3	(2.5%)
	Amount (packet/years)	52.4	
Range (9-160)			
Weight loss:	Yes	10	(8.2%)
	No	112	(91.8%)
Co-morbidity:	Yes	45	(36.9%)
	No	77	(63.1%)
Histological sub-type:	Adenocarcinoma	28	(23.0%)
	Squamous cell carcinoma	77	(63.1%)
	Large cell carcinoma	11	(9.0%)
	Not otherwise specified	6	(4.9%)
ECOG-PS**	0	10	(8.2%)
	1	86	(70.5%)
	2	24	(19.7%)
	3	2	(1.6%)
For staging			
Thorax CT+PET-CT§ used only:			
	Yes	45	(36.9%)
	No	77	(63.1%)
T4 Factor (AJCC 7th edition, 2009):			
	Large vascular invasion	40	(32.8%)
	Mediastinal invasion	18	(14.8%)
	Total of other invasions,	25	(20.5%)

*Standart deviation; **Performance status

Table 2. Primary Treatment Methods and Response

Primer treatment	Patient No (%) & Stage		Response	Death (%)
Without curative treatment:	31 (%25.4)			18 (%58.0)
		Stable disease	2	
Stage IIIA;		Progressive disease	9	
T4 N0 M0	7	Complete response	0	
T4 N1 M0	5	Partial response	15	
Stage IIIB;		Clinic benefit	3	
T4 N2 M0	12	Clinic progress	0	
T4 N3 M0	7	Unknown	2	
Definitive RT:	78 (%63.9)			43 (%55.1)
		SD	16	
Stage IIIA;		PR	36	
T4 N0 M0	11	CR	11	
T4 N1 M0	15	PD	11	
Stage IIIB;		Clinic benefit	1	
T4 N2 M0	48	Clinic progress	3	
T4 N3 M0	4	Unknown	0	
Curative Surgery:	13 (%10.7)	SD	0	4 (%30.7)
Pneumonectomy	6	PR	3	
Stage IIIA;		CR	10	
T4 N0 M0	2	PD	0	
T4 N1 M0	2	Clinic benefit	0	
Stage IIIB;		Clinic progress	0	
T4 N2 M0	2	Unknown	0	
Lobectomy	7			
Stage IIIA;				
T4 N0 M0	2			
T4 N1 M0	3			
Stage IIIB;				
T4 N2 M0	2			

receiving radiotherapy and in the first postoperative month for the patients who received surgical treatment. Follow up evaluations included physical examination, blood tests and radiological methods when needed. Subsequent evaluations were carried out in periods of usually once every 3 months during the first 2 years, once in 6 months over the next 3 years, and the subsequent annually during5 years with physical examination, radiological imaging and biochemical tests.

Treatment responses

PD (15 patients) rate was high in the patient group that did not receive curative treatment. Incontrast, PR (36 patients) rate was high among the patient group receiving definitive radiotherapy, and the CR (10 patients) rate was high in the patient group receiving curative surgery (Table 2). Among 13 patients who had curative surgery, 10 had R0 resections and 3 had R1 resections.

Univariate and multivariate analysis results of overall survival

For all patients, the median overall survival was 18.3 months, 1 year OS rate was 72%, and 5 year OS rate was 28% (Figure 1). 65 (53.3%) patients had died at the time of analysis (Table 3). 18 (58%) of the patients who did not receive curative treatment, 43 (55.1%) of the patients who had definitive radiotherapy, and 4 (30.7%) of the patients who had curative surgical treatment had died (Table 2).

In univariate analysis of OS (Table 3), a statistically significant relationship with survival was found for ECOG-PS at diagnosis, age, T4 factor subgroups, stage and primary treatment (p<0.20). Incontrast no statistical significances were found for weight loss at diagnosis,

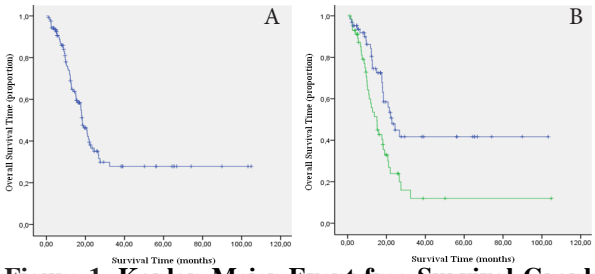

Figure 1. Kaplan-Meier Event-free Survival Graph. A) T4 N0-3 M0 patients; **B)** according to primary treatment condition

Table 3. Overall Survival, (Univariate and Multivariate Analysis)

	Univariate					Multivariate			
	HR	95.0% CI for HR Lower	Upper	Wald	p	HR	95.0% CI for HR Lower	Upper	Wald
Performance status at diagnosis	2.36	1.46	3.83	12.2	0.001	1.92	1.2	3.2	6.43
Age at diagnosis	1.05	1.02	1.08	11.56	0.001	1.04	1.01	1.07	7.33
T4 invasion category (T4X)				4.93	0.18				3.64
Other invasion spaces versus Mediastinal invasion	1.88	0.85	4.15	2.43	0.12				2.05
Major vascular invasion versus Mediastinal invasion	1.06	0.49	2.3	0.02	0.88				1.8
Multiple space invasion versus Mediastinal invasion	1.76	0.82	3.78	2.14	0.14				0.5
Clinical stage	0.68	0.41	1.14	2.14	0.14	0.52	0.3	0.9	5.35
Primer treatment				13.73	0.001				11.23
Curative without - treatment versus Curative surgery	4.81	1.61	14.34	7.96	0.005	2.87	0.92	8.92	3.33
Definitive radiotherapy versusCurative surgery	1.88	0.67	5.23	1.45	0.23	1.04	0.35	3.04	0.005
weight loss <5%	1.03	0.95	1.12	0.52	0.47				
Co-morbidity	1.21	0.73	1.99	0.54	0.46				
Cigarette amount	1	0.99	1.01	0.02	0.88				
Pathologic sub-type§				4.34	0.36				
Stage Thorax-CT + PET-CT*	0.74	0.45	1.22	1.36	0.24				
Nodal statusβ	0.89	0.7	1.14	0.84	0.36				

*18F- fluorodeoxy-glucose positron emission tomography

Table 4. Event Free Survival (Univariate and Multivariate Analysis)

	Univariate					Multivariate				
	HR	95.0% CI for HR Lower	Upper	Wald	p	HR	95.0% CI for HR Lower	Upper	Wald	p
Performance status at diagnosis	1.77	1.15	2.71	6.8	0.009				3.24	0.072
Clinical stage	0.75	0.49	1.14	1.76	0.184				3.44	0.064
weight loss <5%	1.05	0.98	1.13	1.8	0.178				3.24	0.072
Stage Thorax-CT+PET-CT**	0.73	0.48	1.12	2.07	0.15				0.13	0.715
Primary treatment				23.16	0.001				23.16	0.001
Curative without - treatment versus Curative surgery	4.52	2.015	10.14	13.4	0.001	4.52	2.01	10.14	13.4	0.001
Definitive radiotherapy versus Curative surgery	1.55	0.74	3.26	1.36	0.243	1.55	0.74	3.26	1.36	0.243
Age at diagnosis	1.01	0.99	1.03	1.15	0.283					
Co-morbidity	1.01	0.72	1.68	0.19	0.663					
Cigarette amount	1	0.99	1.01	0.011	0.916					
Pathological subtype§				3.6	0.461					
Lymph Node Status	0.92	0.76	1.19	0.67	0.412					
T4 invasion category (T4X)				4.5	0.214					
Other invasion at spaces versus Mediastinal invasion	1.71	0.89	3.31	2.56	0.109					
Major vein invasion versus Mediastinal invasion	0.98	0.52	1.85	0.01	0.957					
Multiple space invasion versus Mediastinal invasion	1.23	0.65	2.3	0.4	0.526					

*18F- fluorodeoxy-glucose positron emission tomography

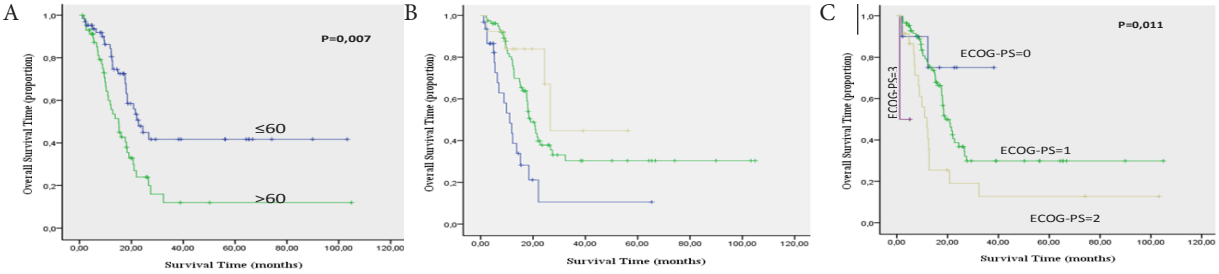

Figure 2. Kaplan-Meier Graph of Overall Survival According to A) ECOG-PS Diagnosis; B) Stage at Diagnosis and C) Kaplan-Meier Overall Survival Graph of Patients According to Primary Treatment

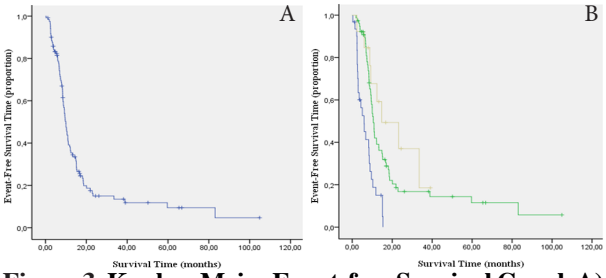

Figure 3. Kaplan-Meier Event-free Survival Graph A) T4 N0-3 M0 Patients and; B) According to Primary Treatment Condition

co-morbidities, smoking history, mediastinal lymph nodeinvasion , thorax-CT+PET-CT usage in staging, or pathological subtype situation (p>0.20).

With multivariate analysis, the statistically significant variables affecting OS rate were age (p=0.007), ECOG-PS at diagnosis (p=0.001), stage (p=0.021), and primary treatment (p=0.004) (Figure 1 and Figure 2). The median OS rate was 22.7 months in the ≤60 patient age group, and 15.0 months among patients more than 60 years old (Figure 2A). For stage IIIA patients, the median OS rate was 21.5 months, for stage IIIB patients it was 17.6 months. For the patient group who did not have curative treatment, the median OS was 11.0 months, The same figures was 19 months for definitive radiotherapy patients, and 26,6 months for patients who had curative treatment In OS, while there was a statistically significant difference between the group that did not have curative treatment and the groups that were treated with definitive radiotherapy and curative surgery (Table 3) (p<0.001 and p=0.001 respectively), no significant differences were found between the groups which had definitive radiotherapy and curative surgery (p=0.22).

Event-free survival rate univariate and multivariate analysis results

Among all patients, median EFS was 9.9 months, 1 year EFS rate was 46%, 3 year rate was 19% and 5 year rate was 15% (Figure 1). Twenty six patients (21.3%) were living without event (relapse, progression, second primary or death) at the time of analysis.

In univariate analysis of EFS, ECOG-PS at diagnosis, weight loss, only thorax-CT+PET-CT usage in staging, stage and primary treatment were statistically significant factors (p<0.20). No statistical relationship with EFS was found for diagnosis age, co-morbidity situation, smoking amount, T4 factor subgroups, N factor situation and pathological subtype situations (p>0.20).

With multivariate analysis, only primary treatment type had a statistically significant impact on EFS (p=0.001) (Figure 3). In the patient group that did not receive curative treatment, the median EFS was 5.9 months. Among patients treated by definitive radiotherapy, EFS was 10.5 months, and for patients treated with curative surgery, EFS was 14.7 months.

Toxicity

When all the primary treatment groups are taken into consideration, grade III/IV side effects were observed in 57 patients (46.6%). The most common side effect was nausea/vomiting, which was seen in 60 patients (49.1%), and the least common side effect was diarrhea, which occurred in 4 patients (3.2%). Esophagitis mainly affected the patient group who received definitive radiotherapy.

Discussion

The prognostic factors for OS and EFS among T4 N0-3 M0 LA-NSCLC patients have been defined in many studies using the new AJCC staging system (Vansteenkiste et al., 1997; Necla et al., 2005; Birim et al., 2006; Sibel et al., 2010). Upon examination of the literature, the median GSR for LA-NSCLC patients is found to be 15-20 months; 5 year OS rate was 20-30%. Event free survival of %. 8-10 months and 5 year EFS rate around 10-20%, were also observed in these patients. These figures were similar to the results of our study (Bulzebruck et al., 1992; Martini et al., 1994; Sibel et al., 2010) .

One of the most important factors affecting survival in our study was primary treatment. OS and EFS results show differences according to the selected primary treatment (no curative treatment, definitive radiotherapy, curative surgery) in many studies that have been carried out on LA-NSCLC patients. It is reported that the patients treated by curative surgery have a better median OS rate than those who received radiotherapy and chemotherapy (Buccheri et al., 1991; Marino et al., 1994; Pierre et al., 2005; Jian et al., 2009; Hao-xian et al., 2009; Akira et al., 2010; Sibel et al., 2010; Benedict et al., 2011; Filippo et al., 2012). In our study, we have found that there is a significant statistical relationship between primary treatment and both OS rate and EFS rate. Although a difference was detected between the patients treated with curative surgery and the patients who received definitive radiotherapy, this difference was not statistically significant. The reason behind this could be the low number of patients treated with curative surgery in our study group. In addition to this, we cannot exclude the existence of a patient subgroup in which radiotherapy could be as beneficial as surgery.

Examining T4 factor status, it was reported that the survival rate of patients with large vascular invasions was better than patients with invasions into other mediastinal structures. It was also reported that the survival rates of T4 NSCLC patients with aortic and esophagus invasions are decreased (DiPerna et al., 2005; Shen et al., 2007). In contrast to these studies, in a study where T4 factor status was examined according to mediastinal organ involvement no significant difference was found in terms of prognosis and survival (Maruf et al., 2009). In our study, we could not identify a statistically significant difference in multivariate analysis of T4 status, although the effect of T4 factor subgroups on OS rate seemed to be important in univariate analysis. Furthermore There was no significant difference between EFS and T4 factor status. Since we were unable to demonstrate a relationship between T4 subgroup and survival, we propose that all T4 patients should be approached curatively in the absence of other contraindications.

Lung cancer occurs most commonly in the 6th decade of life (Prager et al., 2000). In our study, the average age of the patients is 59±9.1. When studies that evaluate the relationship between age and OS rate are examined, the 2 year survival rate of patients who are younger than 65 is higher than among patients who are over 65 (Wigren et al., 1997). In another study, the prognosis of patients >70 age was better than the other group (Albain et al., 1991). In our study, we have found that the median OS rates of patients ≤60 age is longer.

Many researchers have evaluated the relationship between performance and survival. Poor performance affects survival negatively in NSCLC patients (Feld et al., 1980; Stanley et al., 1980; Ruchdeschel et al., 1986; Capewell et al., 1990; Feld et al., 1994; Takigawa et al., 1996; Martins et al., 1999; Necla et al., 2005; Sibel et al., 2010; Inal et al., 2012). In our study, ECOG-PS was an important prognostic factor among the T4 tumor patient group and enhanced median OS rates were achieved for patients with good ECOG-PS situations.

It has been determined that the weight loss at the time of diagnosis is an important factor that affects OS and EFS (Feld et al., 1980; Stanley et al., 1980; Sibel et al., 2010). In some studies, no statistically significant relationship was found between weight loss and OS rate (Necla et al., 2005; Sibel et al., 2010; Zuleyha et al., 2011). In our study, we could not identify a statistically significant difference between weight loss and EFS or OS in multivariate analysis, however, the effect of weight loss on EFS rate seemed to be important in univariate analysis. Therefor it is safe to conclude that this study demonstrated for general survival weight loss in the patient group with T4 did not have any prognostic importance.

Smoking and co-morbidity status affects both survival and postoperative morbidity in NSCLC patients (Anne, 2006; Birim, 2006; Sibel, 2010). However in our study, we could not find any statistically significant relationship between smoking status or co-morbidity presence and OS rate and EFS rate.

Many studies have examined the effect of histopathological cell subtype on the tumor behavior and prognosis in NSCLC patients. In some studies, squamous histology has been correlated with better prognosis and increased survival rates when compared with non-squamous histology (Vansteenkiste, 1997; Birim, 2010). Conversely, other studies have reported that non-squamous subtype correlated with better prognosis and survival rate (Charloux et al., 1997; Sibel et al., 2010; Zuleyha et al., 2011). In some studies, including our own, histopathological subtype had no effect on patient prognosis and did not correlate with any statistically significant difference in OS rate and EFS rate (Taha et al., 2006; Sibel et al., 2010).

It has been shown that PET-CT is superior to traditional CT in staging NSCLC patients (Dwamena et al., 1999; Cerfolio et al., 2003; Reed et al., 2003). The inclusion of PET-CT with other known prognostic indicators while evaluating tumor characteristics, prognosis, and survival would be useful (Nael et al., 2008). In this report, when thorax-CT+PET-CT was used in staging, there was no relationship with the use of additional staging methods and survival (OS and EFS) rates. In our opinion, additional imaging methods other than thorax-CT, PET-CT and cranial imaging are unnecessary in this patient group.

It is generally assumed that N factor status is an important factor in NSCLC patients. Some data has demonstrated that T4 NSCLC N2 positive patients have a poor prognosis (Lucchi et al., 2007; Hao-xian et al., 2009; Akira et al., 2010). Also, in a study on NSCLC patients who were treated surgically, it was found that N0 or N1 cases lived longer than N2 and N3 cases (Okamato, 2005). In contrast to these information, in other studies N2 positivity was not a prognostic factor in T4 patients because T4 status was a more significant factor in determining survival rate (Hao-xian et al., 2003). Morever, there were no significant differences between pathological N0 and N1-2 in terms of survival among T4 patients (Maruf et al., 2009). In our study, we could not find a significant difference correlation between N factor status and OS rate and EFS rate in univariate analysis and we propose that N factor does not play an important role in the determination of prognosis in this group of NSCLC patienths.

It has been previously determined that stage is an important prognostic factor for NSCLC patients (Capewell et al., 1990; Parkin et al., 1990; Feld et al., 1994; Takigawa et al., 1996; Feld et al., 1997; Sugiura et al., 1997; Birim et al., 2006; Mutlu et al., 2013). This study demonstrated a statistically significant relationship between OS rate and stage in multivariate analysis. Although a significant correlation could be seen between EFS rate and stage in univariate analysis, no statistically significant relationship was found in multivariate analysis. These findings show that stage is a dependent prognostic factor. Careful patient selection and curative potential should not be disregarded.

In conclusion, in the heterogeneous group of T4 N0-3 M0 122 NSCLC patients, the prognostic factors affecting OS rate are diagnosis age, ECOG-PS, stage and primary treatment. Primary treatment is also a significant prognostic factor in EFS rate. Our findings confirm the importance of careful staging and a multidisciplinary approach, along with the use of modern imaging methods in this patient group. In T4 patient group, suitable patient

selection and efficient utilization of curative potential should be the primary focus of clinical treatment.

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