RESEARCH ARTICLE

Prognostic Factors in Stage III Non-Small-Cell Lung Cancer Patients

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Abstract

Aim: The objective of this study is to investigate prognostic factors affecting survival of patients undergoing concurrent or sequential chemoradiotherapy (CRT) for stage III non-small-cell lung cancer (NSCL). **Methods and materials:** We retrospectively reviewed the clinical records of 148 patients with advanced, inoperable stage III NSCLC, who were treated between 2007 and 2015. **Results:** The median survival was found to be 19 months and 3-year overall survival was 27%. Age (<65 vs ≥65 years, p=0.026), stage (IIIA vs IIIB, p=0.033), dose of radiotherapy (RT) (<60 vs ≥60 Gy, p=0.024) and treatment method (sequential chemotherapy+RT vs concurrent CRT , p=0.023) were found to be factors affecting survival in univariate analyses. Gender, histological subtype, weight loss during CRT, performance status, induction/consolidation chemotherapy and presence of comorbidities did not affect survival (p>0.050). **Conclusion:** Young age, stage IIIA, radiotherapy dose and concurrent chemoradiotherapy may positively affect survival in stage III NSCL cases.

Keywords: Non-small lung cancer, prognostic factors, survival.

Asian Pac J Cancer Prev, **17 (10)**, 4693-4697

Introduction

According to the USA data, lung cancer is the most common cause of cancer death. NSCLC accounts for about 80% of all lung cancers (Siegel et al., 2015; Howlader et al.,2013 ;Wahbah et al.,2007). The 5 year survival rate is approximately %16 (Siegel et al., 2015; Howlader et al.,2013). About 80% of patients are diagnosed at stage III. The heterogeneity in this patients group makes it difficult to choose the optimal treatment and survival times of patients are quite variable on patient basis. Although surgical resection is treatment of choice for eligible patients in Stage III disease, other available treatment methods include surgery following induction chemo/radiotherapy or CRT.

It is extremely important to understand the progression of this disease which has low survival times despite the advancing treatment modalities. For this purpose, prognostic factors have been investigated and several prognostic factors have been described in a number of studies. The most well-known prognostic factors include diagnosis at early stage, good performance status, absence of significant weight loss and female gender (Finkelstein, 1986). Investigation of the additional prognostic factors that detemine survival outcomes and treatment options of Stage III patients may play an important role both in evaluation of optimal treatment options and increasing survival of patients. Several factors such as histopathological type of tumor, age, smoking status, presence of comorbidity, radiotherapy dose and treatment modality (chemoradiotherapy, radiotherapy or chemotherapy alone) may be the other indicators influencing treatment outcomes and survival (Gregory et al.,2003; Movsas et al.,1999; Auperin et al.,2010; Van Baardwijk et al.,2010; The objective of this study is to investigate prognostic factors affecting survival outcome of the patients undergone concurrent or sequential CRT with the diagnosis of stage III non-small-cell lung cancer.

Material and Methods

We retrospectively reviewed the clinical records of 148.0 patients with a diagnosis of advanced, inoperable stage 3A and 3B NSCLC, who were seen and treated at Cumhuriyet Univerity Medical Faculty Education and Research Hospital between 2007 and 2015. Data collected included patients gender, age, performance status, histology, stage, comorbidities, smoking status, weight loss , type of therapy and RT dose. Survival time was measured from the date of diagnosis to date of death from any cause or date of last patient contact.

Tumor staging was done according to the American Joint Committee on Cancer (AJJC) TNM 7. All patients were staged by computed tomography scan of the chest, abdomen, and pelvis. Positron emission tomography scan and brain imaging were used for staging in some patients upon the discretion of the treating physician if needed. Patients performance status was determined according

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to scoring system of the Eastern Cooperative Oncology Group (ECOG). Weight loss was defined as a weight loss of 5% during CRT or RT.

The Statistical Package for Social Sciences (SPSS) for Windows 14.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. For descriptive statistics, the mean, standard deviation, frequency, and median were used. The survival rates were calculated according to the Kaplan–Meier method. A multivariate analysis (Cox regression analysis) was used to evaluate the independent risk factors that affected survival. P values ≤0.05 were accepted as statistically significant.

Results

One hundred forty-eight locally advanced NSCLC patients who were treated with chemoradiotherapy were included in the study retrospectively. The clinical and pathological characteristics of these patients are shown in Table 1. The median age was found as 60 (range 31-81). Most of the patients were male (91%). Histopathologically, squamous cell carcinoma were observed in 100 (%68) patients and adenocarcinoma were diagnosed in 27.0 (%18) patients. 75 (51%) patients had comorbidity. At diagnosis, ECOG PS= 0-1 patients were %81 and none of the patients had ECOG PS= 4.

Twenty-six (17%) patients had received sequential chemotherapy+radiotherapy and 122.0 (83%) patients had received concurrent CRT. Of the patients in the concurrent CRT arm, 87 (71%) had received additional induction/ consolidation chemotherapy. A total of 66,6 Gy RT dose was planned in all patients, but 133 (90%) of these patients could received 60 Gy or higher RT doses.

In mean follow-up of 23±1.7 months, the median survival time was found as 19 months and 3-year OS rate as 27%. In univariate analysis; age (p=0.026), stage (p=0.033), type of treatment (p=0.023) and RT dose (p<0.001) were found as the prognostic factors affecting survival. The results of univariate analysis are shown in Table 1 and the survival curves of important prognostic factors are shown in Figure 1. Similarly; age (HR: 1.58; 95% CI: 1.03-2.43; p=0.034), stage (HR: 1.6; 95% CI:

Table 1. Prognostic factors that affect survival of patients

Subgroup	N (%)	3 year survival (%)	Median survival (months)	P
Age				
<65	100 (68)	33	22	0.026
≥65	48 (32)	21	16	
Sex				
Men	135 (91)	29	19	0.468
Women	13 (19)	24	21	
Histopathology				
1SCC	100 (68)	32	30	0.172
Adenocarcinoma	27 (18)	27	18	
2NOS	21 (14)	19	17	
Performance score				
3ECOG0	53 (39)	21	17	0.273
ECOG1	57 (42)	-	24	
ECOG2	25 (19)	-	13	
Stage				
3A	7 (49)	37	24	0.033
3B	75 (51)	21	14	
Treatment				
Sequential 4CT+5RT	26 (17)	15	15	0.023
Concurrent 6CRT	122 (83)	30	21	
Treatment				
CRT	35 (29)	43	29	0.791
7Ind/Cons+KRT	87 (71)	27	20	
RT dose				
<60 Gy	15 (10)	0	7	<0.001
≥60 Gy	133 (90)	30	21	
Weight lose				
No	96 (71)	20	10	0.573
Yes	39 (29)	25	18	

SCC, Squamous cell carcinoma; NOS, Not otherwise specified; ECOG, Eastern Cooperative Oncology Group; CT, Chemotherapy; RT, Radiotherapy; CRT, Chemoradiotherapy; Ind/Cons, Induction/Consalidation

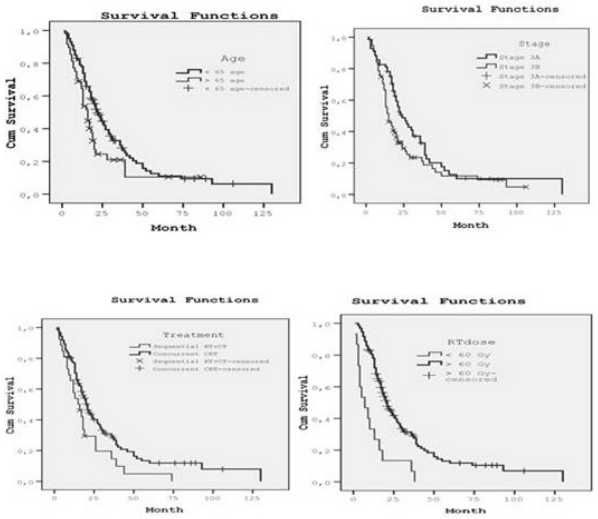

Figure 1. Survival Curves

Table 2. Independent Prognostic Factors

	HR1	%95 CI2	p value
Age			
>65	1		
≥65	1.6	1.0-2.4	0.034
Stage			
3A	1		
3B	1.6	1.1-2.4	0.018
Treatment			
SequentialCT+RT	1		
Concurrent CRT	0.5	0.3-0.9	0.025
RT dose			
<60 Gy	1		
≥60 Gy	0.3	0.1-0.5	<0.001

HR, hazard ratio; CI, confidence interval

1.1-2.4; p=0.018), type of treatment (HR: 0.5; 95% CI: 0.3-0.9; p=0.025), and radiotherapy dose (HR: 0.3; 95% CI: 0.1-0.5; p<0.001) were determined as the independent prognostic factors affecting survival in multivariate analysis. The results of multivariate analysis are given in Table 2.

At follow-up, 110 (74%) patients developed progression. In 62 (56%) of these patients, the primary tumor (and/or regional lymph nodes) was the only site of progression, while distant metastasis was found in 48 (44%) patients. Out of 62 patients who developed locoregional progression, 46 (74%) was squamous cell carcinoma.

Discussion

The prognostic factors for OS among non small cell lung cancer patients have been defined in many studies. Searching the literature, mean survival of locally advanced NSCLC patients is found to be 15-20 months and 5-year overall survival rate was 20.0-30.0% (Curran et al.,2011; Furuse et al.,1999; Furuse et al.,2000). These findings were similar to the results of our study.

One of the most important factor affecting survival in this study was primary treatment modality. OS and 3 year survival results show significiant differences according to the selected treatment (concurrent versus sequential chemoradiotherapy). Studies comparing sequental and concurrent CRT regimens in advanced inoperable NSCLC have shown significant survival advantage with concurrent regimens and thus, concurrent CRT constituted to the standart treatment (O'Rourke et al.,2010; Curran et al.,2011; Furuse et al.,1999; Furuse et al.,2000). Sequental chemotherapy/RT or RT alone may be only favorable in fragil patients who will not be able to tolerate concurrent treatment (Sause et al.,2000; Dillman et al.,1996). It has been shown that, chemotherapies before (induction) and after (consolidation) CRT do not affect overal survival (Tsujino et al.,2013; Vokes et al.,2007). In our study, similarly, survival times were shown to be superior in CRT group compared to RT group (3-year survival: 15% vs 30%, respectively). In addition, consistently with the literature no significant difference was found in the patients receiving induction/consolidation chemotherapy compared to those receiving CRT.

Approximately half of patients with NSCLC are 70-year-old or above at the time of diagnosis (Langer et al.,2000). In our study, the avarage age of the patients were 60. Looking to the studies, young age seems to be a better prognostic factor (Aslan et al.2006). Poorer prognosis in elderly patients might be resulted from lack of directing these patients to the standard curative treatment. Although the standard treatment is CRT in Stage III NSCLC, there are studies in the literature suggesting that, most of elderly patients are not directed to the standard curative treatment , resulting in high mortality and poor survival outcomes (Coate et al.2011; Piccirilo et al.,2004 ; Fentimen et al.,1990). In a meta-analysis of 6 studies conducted by Auperin et al., no correlation could be established between age and survival in NSCLC patients (Auperin et al., 2010). These results indicate that survival rates of elderly fit patients who are able to receive concurrent CRT are similar to those of younger patients. In our study, survival times of patients under 65 years of age were significantly longer than in patients above 65 years of age (median survival 22 months vs 16 months). Additionally, in multivariate analysis age was shown to be an independent prognostic factor.

Patients performance status and disease stages are important prognostic factors in NSCLC. A poor performance score and advanced disease negatively affect survival (Capewell et al.,1990; Brim et al.2006; Mutlu et al.,2013; Bradley et al.,2015; Langer et al.,2000; Arslan et al.,2014). In our study no correlation could be determined between ECOG PS and survival. But it has been demonstrated that, advanced stage was more negatively influence survival . Survival times of stage IIIB patients were shown to be worse by 1.6 folds compared to stage IIIA patients and the stage was found as an independent prognostic factor.

Several studies have shown female gender as a good prognostic factor (Wolf et al.,1991 ; Blanchon et al.,2015). In the present study, no significant difference was found between both sexes in terms of survival (3-year survival

29% vs 24%). Only a small portion of patients were woman and that might influenced the statistically results.

Several studies have shown that weight loss at the time of diagnosis is a poor prognostic factor (Finkelstein et al.,1986; Feld et al.,1994). Although in the present study no correlation could be established between weight loss and survival, patients' weight loss was defined as losing more than 5.0% of body weight during RT. No study was found in the literature investigating the relationship betwen weight loss during RT and survival.

Adenocarcinoma is the most frequently encountered histological type of NSCL, accounting for about half of the cases (Wahbah et al.,2007). Unlike the literature, in this study histological type was found as squamous cell carcinoma in 100 (68%) The reason for this dissimilarity is unknown. Some studies demonstrate that squamous cell cancers are associated with better prognosis and increased survival, while others not. (Brim et al.,2006; Vansteenkiste et al.,1997; Abbasi et al.,2011). In a meta-analysis of 6 studies including 979 patients, Movsas et al. demonstrated increased median survival times when patients with squamous cell carcinoma histology were treated with more aggressive combined treatment modalities (induction chemotherapy + CRT) (Movsas et al.,1999). In our study, median survival time was found as 30 months in patients with adenocarcinoma and 18 month in patients with squamous cell carcinoma, and there were no statistically significant difference. Some studies have shown that, patients with squamous cell carcinoma show rather local/locoregional progression, while adenocarcinoma subtype progresses more with distant metastasis (Perez et al.,1987; Gaspar et al.,2005). Unlike the literature, in this study both locoregional progression (74%) and distant metastasis (58%) were more frequently observed in patients with squamous cell carcinoma.

The most commonly used radiotherapy dose in the curative radiotherapy in Stage III NSCLC is 60-70 Gy. The minimum recommended radiotherapy dose is 60.0 Gy. In a RTOG study investigating whether a radiotherapy dose of 74 Gy is superior, raising the dose to 74 Gy did not improve the results and was shown to be potentially harmful (Bradley et al.,2015). In our study, compatible with the literature; survival of patients who had received 60 Gy or higher RT dose was shown to be better than the patients who received under 60 Gy doses .

The power of our study was that a relatively homogenous patient population with stage III NSCLC who treated with chemoradiotherapy was analyzed. Most of the previously published prognostic information on NSCLC is based on patients with heterougenous disease stage and variable combinations of therapy. Among the parameters; age, stage and treatment modality (concurrent chemoradiotherapy) were shown to be independent prognostic factors for overall survival. The current study has some limitations. First, the retrospective analysis of the study and second, the study could not determine which chemotherapy regimen is recommended for this group of patient. In this study, although the sequence and schedule of chemotherapy were heterogeneous, a platinum-based standart regimen was used most of the patients. Therefore, the results regarding the efficiacy of concurrent chemoradiotherapy rather than chemotherapy regimen is reliable.

In conclusion; in the locally advanced NSCLC patients treated with chemoradiotherapy, the prognostic factors affecting OS rate are diagnosis age, stage, primary treatment and RT dose. These results underline once again the importance of careful staging and the necessity of concurrent chemoradiotherapy in eligible patients. High locoregional progression rate seen in patients having histological subtype of squamous cell carcinoma raises the question of could higher RT doses be used in these patients in order to obtain intrathoracic tumor control.

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