RESEARCH ARTICLE

Lung Cancer in Women, a Different Disease: Survival Differences by Sex in Turkey

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Abstract

Purpose: In this study, we aimed to evaluate the effects of sex-based non-small cell lung cancer (NSCLC) varieties on survival rates. Materials and Methods: A retrospective study was performed in patients with NSCLC who were diagnosed by histological methods between the years 2000 and 2010. A chi-square test was used to compare variables. Overall survival (OS) was estimated by the Kaplan-Meier method. Results: Of the 844 patients, 117 (13.9%) were women and 727 (86.1%) were men. Adenocarcinoma was more common in women than in men (p<0.0001). There were more women non-smokers than men (p<0.0001). There was no statistically significant difference in ECOG PS, weight loss>10%, stage, LDH, albumin and treatment between women and men. Women younger than 65 years (17.0 *vs* 12.0 months; p=0.03), who had adenocarcinoma histology (15.0 *vs* 10.0 months; p=0.006) and who had a hemoglobin level ≥12g/dL (18.0 *vs* 12.0 months; p=0.01) were found to have a better median OS rate than men. Median OS rates were found to be 13.0 months in females and 12.0 months in males (p=0.14). Among metastatic patients, the median OS was 11.0 months in females and 8.0 months in males (p=0.005). Among stage IIIB and stage IV patients who had first line platinum-based chemotherapy, the median OS was 17.0 months in women and 11.0 months in men (p=0.002). The response rate of chemotherapy was higher in women than in men (p=0.03). Conclusions: In our study, we found that survival duration is longer and chemotherapy response is better in women with NSCLC who do not have anemia or comorbidities and who are mostly non-smokers with adenocarcinomas. Further studies regarding the causes of these differences may provide clarity on this subject.

Keywords: Non-small cell lung cancer - adenocarcinoma - sex differences - survival - Turkey

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Introduction

Lung cancer is the most common type of cancer in the world and is the leading cause of death in both women and men (Siegel et al., 2014). The incidences of lung cancer have increased dramatically in the last decades and this increase is especially evident in female patients (Gasperina and Rom, 2004; Thomas et al., 2005). The importance of differences in gender and histologic patterns of lung cancer patients has garnered more attention lately. Female patients are presented with younger ages and more advanced stages in diagnosis (Patel, 2005). In spite of this obvious disadvantage, female patients appear to fare better during the period after diagnosis (Caldarella et al., 2007). Adenocarcinoma histology occurs more often in women than in men (Gasperina and Rom, 2004; Thomas et al., 2005). Gender-specific genetic profiles have been found in tumor tissue and these profiles have correlated with clinical results (Mostertz et al., 2010). Many factors may affect the differences in survival rates between women and men. Cigarette smoking, passive smoking, diet, occupation, indoor exposure, and personal factors are among the issues that can prevent or facilitate the development of cancer. It is possible that many factors are effective in women and this condition increases the sensitivity to carcinogens. In the lung tissue, estrogen effects mediated through estrogen receptors, other receptors that stimulate cellular proliferation, epidermal growth factor receptor gene mutations, mutations of KRAS and EML4-ALK, and specific molecular aberrations may also play a role in gender-based survival rate differences (Gasperina and Rom, 2004; Patel, 2005; Thomas et al., 2005; North and Christiani, 2013). Epidermal growth factor receptor gene mutations are more common in women and women who carry this mutation benefit more from EGRF inhibitors (Shepherd et al., 2005).

In multiple studies, survival rates of women were found to be better than men. Women respond better to

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treatment and they seem to have longer survival durations. Better survival durations were found in women who had Stage I-III NSCLC and had the same treatment as men with the same stage of the disease (Batevik et al., 2005; Cerfolio et al., 2006). In three major studies conducted on patients with advanced stage NSCLC, female gender was found to be among the important independent prognostic factors (Finkelstein et al., 1986; Albain et al., 1991; Paesmans et al., 1995). As previously mentioned, it is clear that female gender is a positive prognostic factor in all the stages of NSCLC, but the clinical importance of these differences is still in question.

In this study, we aimed to evaluate the effects of sex-related differences on survival in NSCLC.

Materials and Methods

This study was conducted at the Department of Medical Oncology in Ankara Oncology Teaching and Research Hospital, Ankara, Turkey. The Ankara Oncology Teaching and Research Hospital Ethics Committee approved this retrospective study in May, 2009. The investigation was a retrospective and single center study. These patients received treatment and follow-up visits between June, 2000 and April, 2010 in our hospital.

The data from this study included demographic information, histological classification, clinical staging, hemoglobin (Hgb) level, serum albumin, and lactate dehydrogenase (LDH) levels. Age, gender, smoking history, weight loss (loss of more than 5% of body weight in the last 6 months), therapeutic modalities, and survival rates were registered based on the data obtained from the patients' charts. The patients' performance statuses were recorded according to the Eastern Cooperative Oncology Group (ECOG) performance score. A radiological assessment was performed on all patients. The inclusion criteria were: 1) patients who were histologically or cytologically diagnosed as primary NSCLC and staged according to the tumor-node-metastasis system (American Joint Committee on Cancer (AJCC) TNM 7th edition) and 2) patients with stage I, II, III and IV diseases. Patients were excluded if they had small cell lung cancer (SCLC) or if their primary cancer was not lung cancer (i.e., it began in another region of the body and spread to the lungs). The methods that were used for diagnosis were bronchoscopy (43%), transcutaneous needle biopsy of tumor (32.1%), mediastinoscopic biopsy (2.7%), lymph node biopsy (5.2%), and biopsy of metastases in 142 cases (17%). The initial treatment modalities included surgery, chemoradiotherapy, chemotherapy (CT) and palliative radiotherapy. Data on the type of CT regimen and number of CT cycles were collected. Therapeutic responses were evaluated using the criteria determined by the World Health Organization (Travis et al., 2004).

Statistical analysis

Chi-square or Fisher exact tests were used for a comparative analysis of categorical data. The primary outcome used in this analysis was survival following lung cancer diagnosis. The duration of overall survival (OS) was calculated from date of pathologic diagnosis until death or until the date of the last follow-up visit. Overall survival was estimated using the Kaplan-Meier method and the log-rank test was used for comparison of outcomes. All statistical analyses were performed using version 16.0 of the Statistical Package for the Social Sciences software program. A p-value<0.05 was considered as statistically significant.

Results

Patient characteristics

A total of 844 patients were analyzed; 117 (13.9%) were female and 727 (86.1%) were male. The median age of diagnosis was 59.1 in women and 57.4 in men (p=0.10). 56.7% of females and 66.9% of males were under the age of 65 (p=0.06). The majority of patients had a good performance status. There were no differences in performance statuses between women and men (p=0.26). Adenocarcinoma was more common in women than in men (53.8% *vs* 32.2%; p<0.0001). Squamous cell carcinoma (SCC) was the dominant histological type in men (38.5%). There were more female non-smokers than male (70.9% *vs* 5.6%; p<0.0001). The incidence of anemia was higher in female patients than in males. The frequency of comorbid conditions was also higher in women compared to men (p=0.002). The most common comorbidities in women were arterial hypertension (61.4%), diabetes (35.1%), chronic obstructive pulmonary disease (32.3%), cardiomyopathy (20.4%) and thyroid diseases (8.9%). Asbestosis (7.8%) and prior healed tuberculosis (5.4%) were common among women. Ten individuals were found to have secondary malignities, which were most commonly breast cancer and cervical cancer. The most common comorbidities of men were chronic obstructive pulmonary disease (35.9%), arterial hypertension (31.6%), cardiopathy (25.3%), diabetes (18.9%), and thyroid diseases (5.1%). Asbestosis was found in 12.6% and prior healed tuberculosis in 6.3% of men. Secondary malignities were found in 32 male patients, mostly larynx cancer and bladder cancer. The distribution of stages was similar between females and males (p=0.29). As expected, the majority of the patients presented with advanced stages III-IV disease. In both groups, the most common locations of metastases were bone, brain, and liver, in that order. The frequency of bone and liver metastasis and malign pleural effusion was higher in women than in men (44.7% *vs* 30.7%; p<0.05). The distribution of treatment modalities was similar between females and males. 13% of women and 11.9% of men underwent surgery, chemotherapy was administered to 72.3% of women and 76.0% of men, and radiotherapy was administered to 68.1% of women and 75.3% of men. Patient characteristics are displayed in Table 1.

Survival analyses

Median follow-up duration was recorded as 44.0 months (3-134). Median OS was 13.0 months (95% CI 8.0-17.9) in women and 12.0 months (95%CI 10.7-13.2) in men (p=0.14) (Figure 1). Among early stage patients, median OS was 23.0 months (95%CI 11.1-34.9) in women and 18.0 months (95%CI 15.5-20.4) in men, which was

not statistically significant (p=0.48). When a total of 451 patients (72 women and 379 men) that were metastatic in diagnosis were evaluated, the median OS was found to be 11.0 months (95%CI 5.5-13.2) in women and 8.0 months (95%CI 6.4-9.4) in men (p=0.005) (Figure 2). Based on the parameters that show differences between the two groups (including age of diagnosis, smoking, comorbidities, histopathology, hemoglobin level, and locations of metastases), the effect of sex on overall survival (OS) was evaluated.

In patients younger than 65 years old, the median OS was 17.0 months (95%CI 11.5-22.4) in women and 12.0 months (95%CI 10.6-13.3) in men (p=0.03). In patients aged ≥65, the median OS was 7.0 months in women and 11.0 months in men, which was not found to be statistically significant (p=0.56) (Figure 3). In spite of the fact that males with a history of smoking had shorter survival times than women, the difference was not statistically significant (12.0 months *vs* 14.0 months; p=0.71). In patients without a history of smoking, median OS was 14.0 months in women and 11.0 months in men (p=0.24). The median OS of patients with adenocarcinoma was 15.0 months (95%CI 6.9-17.1) in women and 10.0 months (95%CI 7.3-12.6) in men (p=0.006). Median OS of patients with non-adenocarcinoma was 14.0 months (95%CI 6.9-17.1) in women and 12.0 months (95%CI 10.8-13.2) in men; however, the difference was found to be statistically insignificant (p=0.15) (Figure 4). Median OS of patients with comorbidities was 10.0 months (95%CI 7.04-12.9) in women and 12.0 months (95%CI 9.7-14.3) in men (p=0.72). Median OS of women who did not have any comorbidities was 17.0 months and 12.0 months in men (p=0.02) (Figure 5). Median OS of patients who had a hemoglobin level below 12g/dL was 9.0 months (95% CI 5.8-12.2) in women and 9.0 months (95%CI 7.7-10.3)

Table 1. Clinicopathological Characteristics of Patients According to Sex

Characteristics	Female (n=117)		Male (n=727)		p
	n	%	n	%	
Mean Age ± SD	59.1±11.9		57.4±10.2		0.1
Age					
< 65	51	56.7	360	66.9	0.06
≥ 65	39	43.3	178	33.1	
ECOG					
0-1	51	43.6	369	50.8	0.26
2	47	40.2	271	37.3	
3	19	16.2	87	12	
Smoking					
Smokers	34	29.1	686	94.4	<0.0001
Non-smokers	83	70.9	41	5.6	
Weight loss **					
≥ 5%	17	32.1	125	41.8	0.22
< 5%	36	67.9	174	58.2	
Comorbidity					
Yes	65	55.6	294	40.4	0.002
No	52	44.4	433	59.6	
Stage					
I	4	3.4	27	3.7	0.29
II	3	2.6	27	3.7	
III	38	32.5	294	40.4	
IV	72	61.5	379	52.1	
Histology					
Adenocarcinoma	63	53.8	234	32.2	< 0.0001
Squamous cell carcinoma	19	16.2	280	38.5	
Large cell carcinoma	4	3.4	19	2.6	
Others*	4	3.4	36	4.9	
NSCLC-NOS	27	23.1	158	21.7	
Hemoglobin**					
< 12 g/dL	46	44.7	202	30.7	0.006
≥ 12 g/dL	57	55.3	456	69.3	
LDH**					
< 250 U/L	42	50	216	41.1	0.15
≥ 250 U/L	42	50	310	58.9	
Albumin**					
< 3.5 g/dL	43	45.3	299	47.3	0.74
≥ 3.5 g/dL	52	54.7	333	52.7	
Metastasis					
Bone	36	59	184	41.4	0.009
Liver	26	22.6	106	14.6	0.03
Brain	31	26.5	153	21	0.18
Surrenal	6	5.2	77	10.6	0.07
Opposite Lung	14	12.2	52	7.2	0.06
Pleural Effusion	21	18.3	58	8	<0.0001
Treatment					
Surgery	15	13	86	11.9	0.75
Radiotherapy	79	68.1	541	75.3	0.11
Chemoradiation	3	2.6	36	5.1	0.34
Chemotherapy	81	72.3	532	76	0.63

ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, Lactate dehydrogenase; ALP, Alkaline phosphatase; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; *These other rarer subtypes included adenosquamous carcinoma, anaplastic, sarcomatoid carcinoma, angiosarcoma and mucoepidermoid carcinoma; **Comparisons were made between patients whose data on weight loss, hemoglobin, LDH and albumin levels are present

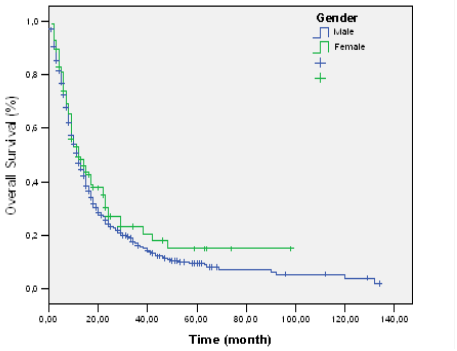

Figure 1. Overall Survival According to Sex (Includes All Patients)

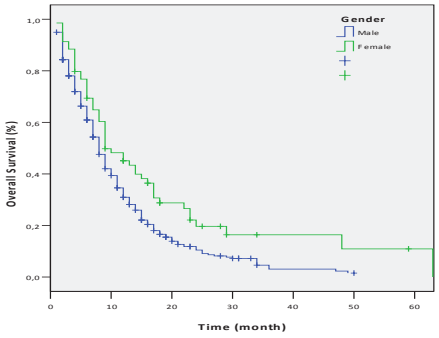

Figure 2. Overall Survival According to Sex in Patients who were Metastatic at the Time Of Diagnosis

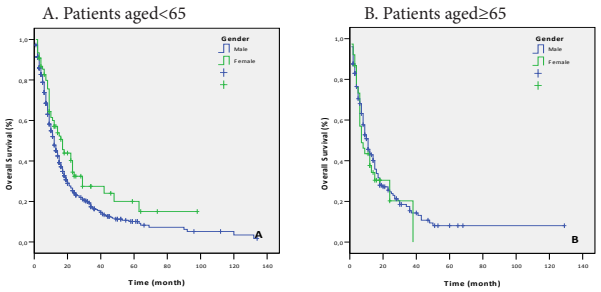

Figure 3. Overall Survival According to Sex in Patients Aged <65 (A) and ≥65 (B)

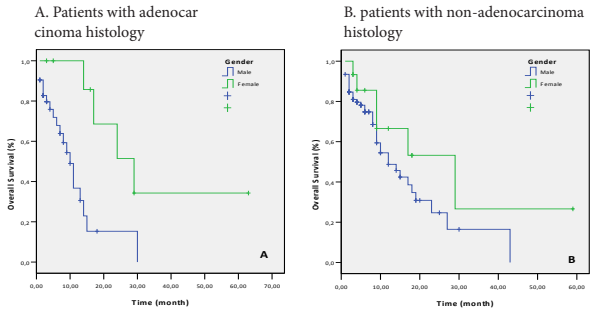

Figure 4. Overall Survival According to Sex in Adenocarcinoma (A) and Non-adenocarcinoma (B) Histological Subgroups

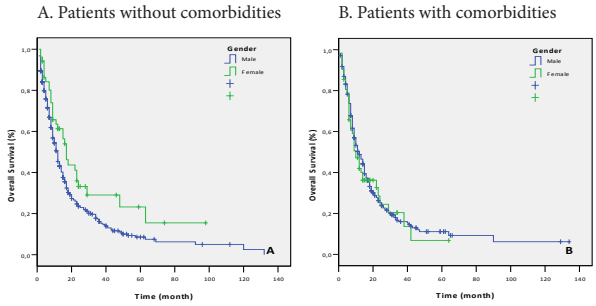

Figure 5. Overall Survival According to Sex in Patients With (B) and Without (A) Comorbidities

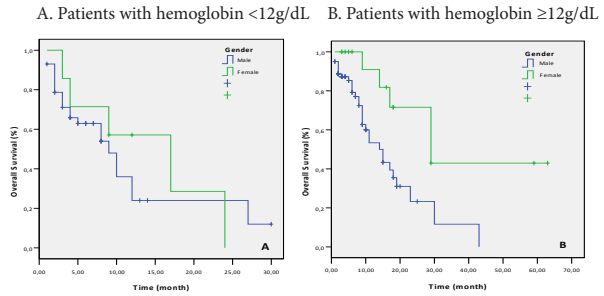

Figure 6. Overall Survival According to Sex in Patients with Hemoglobin <12g/dL (A) and Hemoglobin ≥12g/dL (B) Subgroups

in men (p=0.39). The median OS of patients who had a hemoglobin level ≥12g/dL was 18.0 months (95%CI 11.0-24.9) in women and 12.0 months (95%CI 10.4-13.6) in men (p=0.01) (Figure 6).

Evaluations of patients according to locations of metastases showed that the median OS of women with liver metastasis was 12.0 months (95% CI 9.3-14.6) while men was 7.0 months (95% CI 5.7-8.2) (p=0.005).

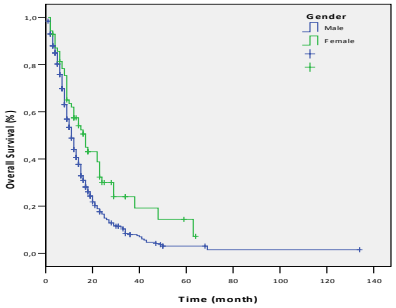

Figure 7. Overall Survival According to Sex in Stage IIIB and Stage IV Patients who were Administered First Line Platinum Based Chemotherapy

The median OS of patients who had brain metastasis was 15.0 months (95% CI 7.2-22.8) in women and 7.0 months (95% CI 5.8-8.1) in men (p=0.001). Metastases of bone, surrenal gland, opposite lung tissue, and malign pleural effusion showed no statistically significant differences between groups. Among metastatic cases, it was observed that women who had surgery for brain metastasis had significantly longer survival time than those who did not (16.0 months *vs* 7.0 months, respectively) (p=0.004).

The median OS of stage IIIB and IV patients who were administered first line platinum-based chemotherapy (442 male, 72 female) was 17.0 months in women and 11.0 months in men (p=0.002). Among these patients, the chemotherapy response rate was higher in women than in men (31.6% *vs* 17.7%, respectively) (p=0.03). 19 patients (15 female and 4 male) had been administered Erlotinib, a target-specific agent, as second-line treatment. They were all non-smokers with adenocarcinoma histologic type who had 0 and 1 performance scores. Their median age was 51 years old. Their response rates were 40% partial and 40% stable response. Their median OS was found to be 18.0 months (95%CI: 11.0-24.9).

Discussion

Lung cancer is more common in men all around the world, but its incidence is increasing faster in women than in men (Gasperina and Rom, 2004; Thomas et al., 2005). Based on survival rates, NSCLC appears to be a heterogeneous disease that has notable differences in prognosis between individuals. Gender may be one of the important factors having an effect on this heterogeneity. Many prior studies have sought an answer to the question of whether or not the biological behavior of NSCLC tumors is different based on the gender of the patient.

Of 844 patients with NSCLC who were followed in a single center, we analyzed male and female groups according to differences in age, smoking history, comorbidity, histopathology, hemoglobin level, and metastasis locations. In women with lung cancer, we found that survival duration was better in younger patients, those with adenocarcinoma histology, less comorbidity, and those with a basal hemoglobin level above 12g/dL. We found that response rates to chemotherapy and survival durations were better in women than in men when both were administered chemotherapy. Although

overall survival was longer in women than men, this was not statistically significant. However, in patients with metastases, women were found to have longer survival durations than men.

The incidence of lung cancer varies across countries. In our study, women patients of NSCLC were found to be 13.9%. In other study conducted in our country between 1994 and 1998 in which 11,849 patients were evaluated, 9.6% of the cases were women, while in a meta-analysis published in 2008, the rate of lung cancer in women was reported to be 7.5% (Goksel and Akkoclu, 2002; Gonlugur et al., 2008). When compared to these low percentages, our study (which took place over the last decade) shows that there has been a slight increase in cases of women with lung cancer in our country. In a study conducted in Spain that included 1,290 patients, the rate of lung cancer in women was found to be similar to our study (14.7%) (Parente et al., 2011). In a study of North America, the rate of lung cancer in female patients was 19%, while in Sweden it was reported to be 40% (De Perrot et al., 2000; Koyi, Hillerdal, and Branden, 2002). We believe that the reason that the incidence of lung cancer in women is still lower in our country than in others is because smoking is less popular among women in our country.

Age is an important indicator of the risk of cancer. In our study, the median age at the time of diagnosis was found to be similar in both male and female groups. However, the median survival duration in women under the age of 65 was found to better than both men in the same age group and women at and above the age of 65. In a study conducted on 20,561 lung cancer patients (which was similar to our study), 13.9% of the patients were females who were younger than male patients and had longer survival durations (Radzikowska, Glaz, and Roszkowski, 2002). According to SEER data, younger female patients had better OS than older patients (Subramanian et al., 2010). Hereditary risk factors which are possessed by young patients of lung cancer make them more sensitive to carcinogenic effects.

Today, all histological types of lung cancer are increasing among women while adenocarcinoma incidence is increasing in men (Devesa et al., 2005). Adenocarcinoma has replaced SCC and become the most common type of cancer in both women and men. Nevertheless, adenocarcinoma incidence is higher in women and SCC incidence is higher in men (Travis et al., 1996; Pinsky et al., 2013). In our study, patients with adenocarcinoma (which was found to be more common in women) had longer survival durations. Similar to our study, other studies have shown that the survival difference in women is more likely related to the histology in the medical literature (Visbal et al., 2004; Caldarella et al., 2007; Chang et al., 2009; Wheatley-Price et al., 2010). In another study, the survival advantage was found to be in non-squamous histology in stage II and IIIA cases (43 *vs* 25 months, $p<0.01$) (Keller et al., 2002). In a meta-analysis including 86,800 patients and 39 articles in which 37.7% of patients were female, the results were very heterogeneous and the percentages of patients with adenocarcinoma ranged from 17.3% to 100%. This meta-analysis showed that women had better overall survival than men and that the survival advantage is not just limited to stage I patients (Haruhiko Nakamura et al., 2011). In addition, there is a need for further studies in which adenocarcinoma cases are below 50% in order to show whether or not the survival advantage remains the same for women.

It is unclear why women are more predisposed to adenocarcinoma than men. The role of genetic, biologic, and hormonal factors is not yet fully understood (Patel, 2005). Some studies have claimed that women are more sensitive than men to the carcinogenic effects of cigarettes (Risch et al., 1993; Henschke et al., 2006). Because SCC cases are related to heavier smoking histories, low exposure to cigarettes but increased sensitivity to their carcinogens may explain why the incidence of adenocarcinoma is higher among women. Recently, it was found that activation of the gastrin-releasing peptide receptor gene, which is localized on the chromosome X, is related to a proliferative response in bronchial cells. In the absence of cigarettes, this gene was shown to be expressed less (Shriver et al., 2000). Another explanation is related to hormonal status. Estrogen may affect molecular and histological features of lung cancer and it may explain some of the differences between genders (Yang et al., 2011). Estrogen replacement therapy, short menstrual cycle and late menopause are shown to increase the risk of adenocarcinoma in women (Taioli and Wynder, 1994; Chlebowski et al., 2009).

In our study, 29.1% of the women and 94.4% of the men were smokers. 70.9% of the women were non-smokers, which is a higher rate than what is reflected in the literature (Sun, Schiller, and Gazdar, 2007). However, our results are similar to a previous Turkish study (Babacan et al., 2014). The link between smoking and histological types of lung cancer is stronger in squamous cell and small cell cancer and weaker in adenocarcinoma (Henschke et al., 2006; Yoshino et al., 2006; Sun et al., 2007). In our study, the ratio of smokers and frequency of SCC are both higher among men, which supports this link. Therefore, a higher rate of SCC among men may explain why their survival rate is lower than that of women. Because a biological characteristic of adenocarcinoma is presented with bronchioalveolar carcinomas (BACs), which are less aggressive and better prognosis. However, no survival difference was found between smoker and non-smoker male and female patients in our study. In several studies (Yoshino et al., 2006; Yano et al., 2008), an important survival advantage was statistically lost when adjusted for smoking status, while in some studies, this advantage continues (Kawai et al., 2005; Henschke et al., 2006). In a meta-analysis, it was found that female gender is a positive prognostic factor, independent from smoking status (Haruhiko et al., 2011).

Recently, it was reported that NSCLC patients who had never smoked had longer survival durations than smokers with NSCLC (Dresler et al., 2000; Bain et al., 2004; Wakelee, et al., 2007). Transversion mutations in the gender-dependent p53 gene also affect the carcinogenic risk of smoking in women (Kure et al. 1996; Dresler et al., 2000). In patients who never smoked, the etiology of lung cancer apart from cigarettes and its biology will be

important for explaining whether or not endocrine factors are effective. We think that whatever their gender is, adenocarcinoma and patients who never smoked must be evaluated separately and their treatment strategy should be re-shaped.

In addition to lung cancer, smoking habits induce many critical diseases such as coronary ischemic disease, chronic obstructive pulmonary disease, pneumonia, and non-pulmonary malignant tumors. The World Health Organization reported that at least 25% of women died because of cigarette-related diseases. In women, the most important smoking-related causes of death are cardiovascular diseases (41%), lung cancer (21%), and chronic obstructive pulmonary diseases (18%) (Chollat-Traquet, 1992). However, in our study, the frequency of comorbidity was higher in women than in men and survival was found to be shorter in women with comorbidities. Despite the smoking ratio being considerably lower in our female patients than in the males, the fact that diseases such as arterial hypertension, diabetes, and COPD are more common in women suggests the influence of genetic predisposition rather than environmental factors. In a recent study in Denmark that parallels ours, out of 9,369 lung cancer cases between the years 2000 and 2011, better survival rates were achieved in women without comorbidities. Comorbidity was found to be a negative prognostic factor in this study (Deleuran et al., 2013).

In addition to a higher rate of comorbidities, the incidence of anemia was found to be higher in women than in men. The survival rate of women without anemia was found to be longer than men without anemia. The presence of anemia clearly shortened survival in both genders. As discovered in earlier studies, the presence of anemia before treatment was reported to be an independent prognostic factor (Ferrigno and Buccheri, 2003). We think that the presence of both comorbidity and anemia caused survival to be shorter in men than in women. However, despite the fact that the survival duration of patients who had surgery in the early stages of their disease was longer in women than in men, this difference showed no statistical significance.

A population-based study conducted between 1985 and 2004, which included 10,908 patients, found that independent from age of diagnosis, treatment, histology, and smoking history, survival duration was better in women than in men (9.4 months *vs* 6.8 months; $p<0.001$) and survival was longer than 20 months in women who were treated surgically (Pitz et al., 2013). When survival rates are compared between genders after resection in patients with NSCLC, female gender was found to have a positive effect on survival (Batevik et al., 2005). In a wide-scale international study, women were found to have better prognoses in all stages, not just the early stages (Sculier et al., 2008).

In multiple randomized clinical trials, survival duration was found to be longer in women patients with unresectable stage IIIB-IV who were administered chemotherapy (Efficace et al., 2006; Wakelee et al., 2006). In a meta-analysis of 5 randomized trials involving 2,349 patients who were on a single platin-based chemotherapy, women were found to have longer overall survival than men (median 9.6 *vs* 8.6 months, HR 0.86). This meta-analysis also indicated that women in the adenocarcinoma sub-group were especially likely to benefit from chemotherapy to a greater extent than men (10.9 months *vs* 8.4 months, HR 0.70) (Wheatley-Price et al., 2010). In our study, among patients with stage IIIB and IV disease who were on first line platinum-based chemotherapy, both chemotherapy response rate and survival duration were found to be higher in women patients than in men. It is possible that the fact that most of our women patients have adenocarcinoma histology and are non-smokers impacted these results. However, positive differences were determined in small and important data regarding long-term survival and treatment response in lung cancer patients irrespective of histology and stage (Thomas et al., 2005). In order to obtain better responses to treatment, further research into the role of tumor biology in both genders is needed.

In our study, the most common locations of metastases in both men and women were bone, brain, and liver, respectively. Similar to the existing medical literature, our study showed that the presence of metastasis clearly reduces survival (Finkelstein, Ettinger, and Ruckdeschel, 1986). In many studies, the presence of hepatic metastasis is significantly correlated with shorter survival (Finkelstein et al., 1986; Albain et al., 1991; Paesmans et al., 1995). The presence of liver and/or brain metastasis significantly shortened survival in men as compared to women. In a study conducted on patients with brain metastasis, EGFR mutation, age <65, cranial radiotherapy history, good performance status, and administration of Erlotinib after diagnosis were reported to be positive prognostic factors (Sekine et al., 2014). It was observed that in metastatic cases, the survival durations of patients whose brain metastases were treated with surgery were significantly longer than those of patients who did not receive surgical treatment. The superior survival rates of women with brain metastasis can be explained by the higher adenocarcinoma frequency in the female group and the fact that the female group consisted of patients with solitary brain metastasis who were operated on and responded better to treatment.

Recently, it was reported that epidermal growth factor receptor tyrosine kinase inhibitors are effective on treatment of NSCLC patients who carry the EGFR gene mutation (harbor specific). These tumor mutations occur frequently in adenocarcinoma, people who have never smoked, women, and Asian-specific subgroups of patients (Mok et al., 2009). Female gender is a significant clinical prognostic factor for patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (Shepherd et al., 2005; Yano et al., 2008). Clinical trials showed that pure BAC patients responded very well to EGFR-TKIs (Miller et al., 2004). It appears that there is no difference between women and men regarding KRAS and EML4-ALK mutations (North and Christiani, 2013). Because our data were collected between 2000 and 2010, these drugs were not in routine use during the first phase of our study. In our study, there were patients who used these drugs in the 2nd and 3rd line treatment. We believe that the results we obtained were better than the response rates in the current literature because our group consisted

of a specific patient group (all of them were EGFR mutation positive and non-smokers). In patients with lung adenocancer, treatments which are personalized by adjustment to tumor histology produce significantly better results. Thus, understanding the relationship between gender, smoking history, and histology is important to the planning and evaluation of future studies.

The heterogeneous nature of the group and the fact that it was retrospective are among the limitations of this study. Another disadvantage is that EGFR mutation and ALK rearrangement were not tested for during the time period included in our study. A lack of packs-per-year data on smoker patients prevented us from answering the dose response question regarding smoking. A slight advantage may be that our study is a single center study, in which treatment approaches did not vary and patients with similar treatment protocols and certain reference values for laboratory data were included.

In conclusion, it was found that survival duration is longer and chemotherapy response is better in women with non-small cell lung cancer who do not have anemia or comorbidities and who are mostly adenocarcinoma and non-smokers. Decreased exposure to cigarettes indicates that women are more sensitive to the carcinogenic effect of smoking and environmental factors depending on a genetic basis. Our results indicate that gender is related to histology and impacts survival duration. The improved prognosis for women may not just be due to an increase in the adenocarcinoma ratio but also to hormonal, genetic, and molecular pathway differences between genders. The results of our study indicate that lung cancer is a different disease in women than in men. Further studies on the epidemiology and biology of lung cancer may lead to improved, patient-specific treatment in the future.

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