RESEARCH ARTICLE

Lung Cancer in Women: A Single Institution Experience with 50 Patients

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Abstract

    <u>Background</u>: Lung cancer is the most common cause of cancer-related death worldwide. The incidence of lung cancer is aproximately 7-8 thousand percent in Turkish women. In this study, we aimed to evaluate the clinical, pathological properties and survival data of female patients with lung cancer who were treated in our center. <u>Materials and Methods</u>: From 2007 to 2012, 50 women with lung cancer were enrolled. Patient data were evaluated retrospectively. <u>Results:</u> The median age was 61 (40-81). Forty patients (80%) were diagnosed with non small cell lung cancer (NSCLC), 10 patients (20%) were small cell carcinoma (SCC). Twelve (24%) patients were smokers and 13 of 16 non-smokers had a history of exposure to asbestos. The most common histologic subtype was adenocarcinoma (46%) and this accounted for 71% in patients with exposure to asbestos. The most common initial Eastern Cooperative Oncology Group (ECOG) performance score was 1 (24 patients, 48%) and initial stage was IV (25 patients, 50%) in the study group. During the median 15 months (1-96 months) followup period: 1 year overall survival (OS) was 68%, 2year overall survival was 36% and the median survival time was 19 months. According to univariate analysis, poor ECOG performance status, advanced stage, anemia and weight loss at time of diagnosis were negative prognostic factors. However, adenocarcinoma sub-type was a positive prognostic factor. <u>Conclusions</u>: In this study NSCLC sub-type, poor ECOG performance score, advanced stage, anemia and weight loss were prognostic factors in Turkish women with lung cancer.

Keywords: Chemotherapy - female gender - prognosis - lung cancer - survival - Turkey

Introduction

    Lung cancer is the most common cause of cancer related death in men worldwide and it is the second leading cancer type after breast cancer in women (Jemal et al., 2010). Depending on the geographical region, incidence of lung cancer in women ranges from 0.6 to 35.6 thousand percent (Parkin et al., 2005, Nakamura et al., 2011). In the last two decades as a result of anti smoking campaigns, the mortality of lung cancer decreased among men meanwhile there is a significant increase in the mortality among women (Kamangar et al., 2006, La Vecchia et al,. 2010).

    Many features like the etiology, histological types or survival rates of lung cancer in women differ from men. Smoking is the major risk factor for both genders. Other risk factors that can cause lung cancer among non smokers are passive smoking, radon, exposure to asbestos, occupational exposures, hormones and genetic factors (Brownson et al., 1992, Taioli 1994, Darby et al., 2001, Grupta et al., 2001, Lissowska et al., 2005, Darby et al.,

2006, Ganti et al., 2006, Schrump et al., 2008, Ferlay et al., 2010, Bouchardy et al., 2011, Raùl Barrera-Rodriguez 2012). In this study, we present the clinical, pathological and survival datas of 50 female patients with lung cancer who were treated in our center.

Materials and Methods

    The medical data of female patients who admitted to the Oncology Unit of Cumhuriyet University Faculty of Medicine between 2007-2012 are retrospectively analysed. Patients' clinical, pathological features and survival data were recorded. The survival data of the patients were obtained from hospital records and unfollowed patients had been called in order to obtain information about their conditions.

    Patients' performance status before the treatment was evaluated by using performance scoring of Eastern Cooperative Oncology Group (ECOG). The stages were determined according to American Joint Committee on

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Cancer (AJCC) TNM (7th edition) staging.

Significant weight loss was defined as > 10% weight loss (in last 6 months) at the time of daignosis. Biochemical evaluation of patients was done by routine blood count and biochemical tests before the treatment. The results were evaluated statistically. Statistical analysis of frequency tests, Chi square test, Kaplan Meier survival analysis and Cox regression analysis were used.

Results

The median age of 50 patients was 61 (40-81). 40 patients (80%) were diagnosed with non small cell lung cancer (NSCLC) and 10 patients (20%) were small cell carcinoma (SCC). Histopathologically, 23 (46%) cases were adenocarcinoma, 6 (12%) cases were squamous cell carcinoma and 11 (22%) cases subtype analises were not applied. Fifteen (30%) patients had positive family history of cancer. Significant weight loss was found in 19 (38%) patients. Twelve (24%) patients were smokers. Only 21 patients (42%) information of asbestos exposure was obtained. Fourteen (67%) of these patients have a history of asbestos exposure (all of these patients have lived in houses that plastered with white clay.) The median exposure period was 30 years (8-60). Thirteen (81%) of 16 non-smoker patients presented with the history of asbestos exposure meanwhile 1 of 5 (20%) smoker patients (p= 0.025). In the group with exposure to asbestos, the most common histological type was adenocarcinoma (10 patients, 71%). The median survival of asbestos related lung cancer patients was 41 months, while the median survival of non asbestos related lung cancer patients was 19 months however, this difference was not statistically significant (p=0.958).

Comorbidity was present in 21 (42%) patients. These were: hypertension in 18 (36%) patients, diabetes mellitus in 8 (12%) patients, and coronary artery disease in 6 (12%) patients. Initial ECOG performance scores were 0 in 16 (32%) patients, 1 in 24 (48%) patients, 2 and above in 10 (20%) patients. Eight (16%) of NSCLC patients were stage 1, 4 (10%) of them were stage 2, 8 (14%) were stage 3 and 20 (40%) were stage 4; while in SCLC group 5 (%11) patients were diagnosed at limited stage, 5 (11%) at extensive stage.

In 16 patients (32%) brain metastases, in 12 (24%) liver metastases, 15 (30%) bone metastases and in 11 (22%) patients metastases were detected in the opposite lung involvement. During the clinical course, 4 (8%) patients developed superior vena cava syndrome and 4 (8%) patients developed deep vein trombosis.

As a treatment, chemotherapy was applied to 19 (38%) patients, undergone surgery in 4 (8%) patients, 4 (8%) patients received radiotheraphy, 9 (18%) patients received chemoradiotherapy and 6 (12%) patients only provided with palliative care support. Twenty-one patients (44%) received palliative radiotherapy: in 13 (50%) patients to the brain, and in 8 (38%) to the bone. The treatment related side effects were, nausea and vomiting occurred in 35 (76%) patients, anemia in 27 (59%) patients, neutropenia in 12 (26%) patients, esophagitis in 9 (20%) patients, thrombocytopenia in 8 (17%) patients, neutropenic fever

Table 1. Univariate Analysis

	No. patients (%)	Univariate analysis			
		1-year overall survival (%)	2-year overall survival (%)	The median survival (month)	p value
Histopathology					
SCLC*	10(20)	90	20	17	0.39
NSCLC**	40(80)	61	40	20	
Histopathology					
SCC***	6(15)	22	-	7	0.043
Adenocarsinoma	23(58)	69	59	40	
NSCLC	11(27)	52	-	17	
Stage					
Stage I	6(12)			96	<0.001
Stage II	4(8)			51	
Stage III	8(16)			15	
Stage IV	20(40)			6	
Limited stage	5(10)			22	
Extensive stage	5(10)			13	
ECOG					
ECOG 0	24(48)	91	52	34	<0.001
ECOG 1	16(32)	56	24	13	
≥ECOG 2	10(20)	-	-	3	
Weight loss					
No	31(62)	81	54	29	0.001
Yes	19(38)	45	6	11	
Comorbidity					
No	29(58)	71	34	20	0.665
Yes	21(42)	56	35	13	
Cisplatin					
No	18(36)	39	26	6	0.06
Yes	31(62)	86	41	22	
Hemoglobin					
<12 mg/dL	19(38)	56	-	13	0.001
>12 mg/dL	18(36)	88	65	34	
Age					
<65 age	30(60)	79	34	20	0.677
≥65 age	20(40)	49	37	11	

in 8 (17%) patients and radiation pneumonitis occurred in 3 (7%) patients, respectively.

During the median 15 months (1-96 months) follow up period: 1 year overall survival (OS) was 68%, 2 year overall survival was found to be 36% and the median survival time was 19 months. According to univariate analysis, the factors affecting the survival were NSCLC subtype, low ECOG performance score, advanced stage, low hemoglobin level, and weight loss at time of diagnosis (Table 1). Multivariate analysis was not done due to the small number of cases.

Discussion

It is estimated that about 1.3 million new cases will be diagnosed each year worldwide and 1.17 million will die of the disease. Unfortunately 58% of these patients will be diagnosed from developing countries (Brownson et al., 1992, Taioli 1994, Darby et al., 2001, Grupta et al., 2001, Lissowska et al., 2005, Darby et al., 2006, Ganti et al., 2006, Schrump et al., 2008, Ferlay et al., 2010, Bouchardy et al., 2011, Raùl Barrera-Rodriguez 2012). Although lung cancer is more frequent among men, it is a major threat to women today. In the case of our country, Turkey, according to the data of obtained from the Department of Cancer of the Ministry of Health, lung cancer is the 5th most common cancer in women (Cancer statistics, 2013). According to the International Agency for Research on Cancer (IARC) data, lung cancer represents about 4.5%

of all neoplasms and is ranked 4th in all cancer deaths in females in Turkey (Globacan, 2013). Recent studies in tumor research provide clear evidence that lung cancer in females is different than in males (Raùl Barrera-Rodriguez 2012).

Smoking is the most important etiologic factor of lung cancer in both men and women. As it is known, more than 85% of all lung cancer patients have a history of smoking and 20% of smokers develop lung cancer (Raùl Barrera-Rodriguez 2012). According to the data of 2012 from the Turkish Statistical Institute, female smoking prevalence in our country is 13.1% and the rate increases interestingly with the level of education (TurkStat, 2012). A study published by Seyfikli et al. in 2001, reported that the rate of smoking among housewives in Sivas was %19 (Seyfikli et al. 2001). In this study, collected data revealed that 24% of our patients had a history of smoking. According to the literature, the rates of non-smoker patients who were diagnosed with lung cancer were 10% in men and 20% in women (Sasco et al., 2004). In our study, non smoking female ratios have been found higher (76%) than what the literature suggests. We think that, along with passive smoking, other environmental exposures also contributed to this high rate. Indoor air pollution is an example of these environmental exposures. Studies have shown that factors such as poor in house ventilation conditions, cooking with using coal or wood, re using burnt cooking oil are increasing chance of having lung cancer in non-smoker women (Wu et al., 1985, Grupta et al., 2001, Lissowska et al., 2005). Exposure to passive smoking, radon and heavy metals are other environmental factors that can contribute to the risk of lung cancer (Brownson et al., 1992, Darby et al., 2001, Darby et al., 2006). Since the 1950s it is known that exposure to asbestos increases the risk of lung cancer for 7-10 times more frequent. All common types of asbestos are related to lung cancer. Smoking and exposure to asbestos are enhancing the carcinogen effect of each other. Lung cancer typically occurs after 30-35 years of exposure to asbestos (Schrump et al., 2008). All over the world along with industrial development, many countries have substantially reduced their asbestos usage; in some areas the exposure is still ongoing. Sivas is one of the provinces in the country where exposure to asbestos is very high. In our study, exposure to asbestos was found in 67% of patients, and these patients accounted for 81% of non smoker patients. In this group, the most common histological subtype was adenocarcinoma (71%). Our findings may indicate that asbestos exposure is an important etiologic factor for lung cancer in women of the area. However, more extensive studies are needed in this regard.

When histological subtypes were evaluated it appeared that small cell lung cancer comprises 17-34% of lung cancers among women in literature (Olak and Colson, 2004). In our study, SCLC rates are 20% and consistent with the literature findings. It is known that adenocarcinoma is the most common NSCLC subtype seen in women, and occurs in approximately 60% of cases (Olak and Colson, 2004). Squamous cell lung cancer that is highly related with smoking occurs in 10 30% of female lung cancers and this rate is lower than in men

(Olak and Colson, 2004, Raùl Barrera-Rodriguez 2012). In our NSCLC cases, 57.5% had adenocarcinoma, 15% of these cases were consisted of squamous cell carcinoma and pathological subtypes of NSCLC were not defined in 27.5% of patients.

Many studies suggest that the survival data is better in women than in men (Schiller et al., 2002, Wakelee et al., 2006, Albain and Gotay, 2007). This finding may be related with women's better response to platinum based chemotherapies and this response is more significant in adenocarcinoma sub-group (Visbal et al., 2004, Cerfolio et al., 2006, Wheatly-Price et al 2010). Southwest Oncology Group (SWOG) had investigated the influenced of gender in 2349 patients of whom 34% were female. The median overall survival was 11 months, 1-year survival was 46%, 2 years survival was 19% in women lung cancer patients (Albain and Gotay, 2007). In our study overall survival was 15 months, 1-year survival was 68%, 2 years survival was 36% in patients.

The most important unfavorable prognostic factors for lung cancer patients are advanced stage, weight loss, poor performance status non surgical treatment and male gender (Mould and Wiliams, 1982, Ramalingam et al., 1998, Radzikowska et al., 2002, Yang et al., 2001, Pitz et al., 2013). Caldarella et al. reported that, among women, survival was significantly better for adenocarcinoma patients than for those with squamous cell carcinoma. Compatible with the literature, the survival of the patients with adenocarcinoma subtype in our study was longer than other NSCLC cases.

Anemia is associated with shorter survival times for patients with many cancers (Caro et al., 2001, Berardi et al., 2005, Boehm et al., 2007). The risk of death is increased 19% in lung cancer patients presented with anemia (Caro et al., 2001). Baseline performance status, weight loss and the stage of the cancer are known to be independent and unfavourable prognostic factors for lung cancer patients (Stanley 1980, Sculier et al., 2008, Reck et al., 2012, Inal et al., 2012, Pirker et al., 2012). This study demonstrates that anemia, advanced stage, and weight loss are negative prognostic factors for the female patients with lung cancer.

In conclusion, lung cancer in females is one of the major health issues for our country. Despite of the low number of cases, squamous cell lung cancer, low ECOG performance score, advanced stage, low hemoglobin level, and weight loss at diagnosis have been identified as risk factors that affecting the survivals and also asbestosis may be important etiological factor for non-smoker patients in our study. For this patient group, large scale studies are needed to investigate the prognostic factors and etiologic factors other than smoking in our country.

References

Albain KS UJ, Gotay CC (2007). For the Southwest Oncology Group Lung Committee: Toxicity and survival by sex in patients with advanced non-small cell lung carcinoma (NSCLC) on modern Southwest Oncology Group (SWOG) trials. *J Clin Oncol*, **25**, 7549.

Berardi R, Brunelli A, Tamburrano T, et al (2005). Perioperative anemia and blood transfusions as prognostic factors in

patients undergoing resection for non-small cell lung cancers. *Lung Cancer*, **49**, 371-6.

Boehm DU, Lebrecht A, Schmidt M, et al (2007). Prognostic impact of haemoglobin levels in breast cancer. *Anticancer Res*, **27**, 1223-6.

Bouchardy C, Benhamou S, Schaffar R, et al (2011). Lung cancer mortality risk among breast cancer patients treated with anti-estrogens. *Cancer*, **117**, 1288-95.

Brownson RC, Alavanja MC, Hock ET, Loy TS (1992). Passive smoking and lung cancer in nonsmoking women. *Am J Public Health*, **82**, 1525-30.

Caro JJ, Salas M, Ward A, Goos G (2001). Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*, **91**, 2214-21.

Cerfolio RJ, Bryant AS, Scott E, et al (2006). Women with pathologic stage I, II, and III non-small cell lung cancer have better survival than men. *Chest*, **130**, 1796-802.

Darby S, Hill D, Doll R (2001). Radon: a likely carcinogen at all exposures. *Ann Oncol*, **12**, 1341-51.

Darby S, Hill D, Deo H, et al (2006). Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scand J Work Environ Health*, **32**, 1-83.

Demirci E, Daloglu F, Gundogdu C, et al (2013). Incidence and clinicopathologic features of primary lung cancer: a North-Eastern Anatolia region study in Turkey (2006-2012). *Asian Pac J Cancer Prev*, **14**, 1989-93.

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.

Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A (2006). Hormone replacement therapy is associated with decreased survival in women with lung cancer. *J Clin Oncol*, **24**, 59-63.

Gupta D BP, Gaborieau V, Jindal SK (2001). Risk factors of lung cancer in Chandigarh, India. *Indian J Med Res*, **113**, 142-50.

Inal A, Kaplan MA, Kucukoner M, Karakus A, Isikdogan A (2012). Prognostic factors in elderly patients with advanced non-small cell lung cancer treated with first-line cisplatin-based chemotherapy: a retrospective analysis of single institution. *J Buon*, **17**, 533-6.

Jemal A, Center MM, DeSantis C, Ward EM (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*, **19**, 1893-907.

Kamangar F, Dores GM, Anderson WF (2006). Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*, **24**, 2137-50.

La Vecchia C, Bosetti C, Lucchini F, et al (2010). Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. *Ann Oncol*, **21**, 1323-60.

Lissowska J, Bardin-Mikolajczak A, Fletcher T, et al (2005). Lung cancer and indoor pollution from heating and cooking with solid fuels: the IARC international multicentre case-control study in Eastern/Central Europe and the United Kingdom. *Am J Epidemiol*, **162**, 326-33.

Mould RF, Williams RJ (1982). Survival of histologically proven carcinoma of the lung registered in the North West Thames Region, 1975-1979. *Br J Cancer*, **46**, 999-1003.

Nakamura H, Ando K, Shinmyo T, et al (2011). Female gender is an independent prognostic factor in non-small-cell lung cancer: a meta-analysis. *Ann Thorac Cardiovasc Surg*, **17**, 469-80.

Olak J, Colson Y (2004). Gender differences in lung cancer: have we really come a long way, baby? *J Thorac Cardiovasc Surg*, **128**, 346-51.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin* **55**, 74-108.

Pirker R, Pereira JR, Szczesna A, et al (2012). Prognostic factors in patients with advanced non-small cell lung cancer: data from the phase III FLEX study. *Lung Cancer*, **77**, 376-82.

Pitz MW, Musto G, Navaratnam S (2013). Sex as an independent prognostic factor in a population-based non-small cell lung cancer cohort. *Can Respir J*, **20**, 30-4.

Radzikowska E, Glaz P, Roszkowski K (2002). Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. *Ann Oncol*, **13**, 1087-93.

Ramalingam S, Pawlish K, Gadgeel S, et al (1998). Lung cancer in young patients: analysis of a Surveillance, Epidemiology, and End Results database. *J Clin Oncol*, **16**, 651-7,

Raúl Barrera-Rodriguez JM-F: (2012). Lung cancer in women. *Targets Therapy*, **3**, 79-89,

Reck M, Thatcher N, Smit EF, et al (2012). Baseline quality of life and performance status as prognostic factors in patients with extensive-stage disease small cell lung cancer treated with pemetrexed plus carboplatin vs. etoposide plus carboplatin. *Lung Cancer*, **78**, 276-81.

Sasco AJ, Secretan MB, Straif K (2004). Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer*, **45**, 3-9.

Schiller JH, Harrington D, Belani CP, et al (2002). Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*, **346**, 92-8.

Schrump DS, Giaccone G, Kelsey CR, Marks LB (2008). Non-small cell lung cancer. In 'Cancer: Principles & Practice of Oncology', 8th Edition, eds DeVita VT, Lawrence TS, Rosenberg, SA. Lippincott Williams & Wilkins, Philadelphia. pp:896-946.

Sculier JP, Chansky K, Crowley JJ, Van Meerbeek J, Goldstraw P (2008). The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol*, **3**, 457-66.

Seyfikli Z, Gonlugur U, Sumer H, Topcu S (2001). Sivas'ta Ev Kadinlarinda Sigara Aliskanliklari (Smoking habits housewiwes in Sivas). *Tuberkuloz ve Toraks Dergisi*, **49**, 37-40,

Stanley KE (1980). Prognostic factors for survival in patients with inoperable lung cancer. *J Natl Cancer Inst*, **65**, 25-32.

Taioli E WE (1994). Endocrin factors and adenocarcinoma of the lung in women. *J Natl Cancer Inst*, **86**, 869-70.

TurkStat, global adult tabacco survey, 2012.

Visbal AL, Williams BA, Nichols FC, et al (2004).Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. *Ann Thorac Surg*, **78**, 209-15.

Wakelee HA, Wang W, Schiller JH, et al (2006). Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. *J Thorac Oncol*, **1**, 441-6.

Wheatley-Price P, Blackhall F, Lee SM, et al (2010). The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. *Ann Oncol*, **21**, 2023-8,

Wu AH HB, Pike MC, Yu MC (1985). Smoking and other risk factors for lung cancer in women. *J Natl Cancer Inst*, **74**, 747-51.

Yang R, Cheung MC, Pedroso FE, Byrne MM, Koniaris LG, Teresa AZ (2011). Obesity and weight loss at presentation of lung cancer are associated with opposite effects on survival. *J Surg Res*, **170**, 75-83.