Non-Small Cell Lung Cancer in Women: A Distinct Entity?

Kadınlarda Küçük Hücreli Dışı Akciğer Kanseri: Farklı Bir Antite mi?

Umut Kefeli[1], Bala Basak Oven Ustaalioglu[2], Burcak Yilmaz[2], Dincer Aydin[3], Nur Sener[3], Mehmet Aliustaoglu[3]
Mahmut Gumus[4]

[1] Medeniyet University Goztepe Education and Training Hospital, Unit of Medical Oncology, Istanbul, Turkey
[2] Haydarpasa Numune Education and Training Hospital, Unit of Medical Oncology, Istanbul, Turkey
[3] Dr. Lutfi Kirdar Kartal Education and Training Hospital, Department of Medical Oncology, Istanbul, Turkey
[4] Bezmialem University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey

ABSTRACT

Aim: Lung cancer is one of the major causes of cancer-related deaths in both sexes and increasing worldwide. In many studies this increase in incidence and mortality was related to the sex, tumor type and clinical characteristics of the patients. The aim of this study was to evaluate the differences in clinical features and the prognostic factors in our female patients with NSCLC.
Methods: We retrospectively analyzed the records of our 893 patients with non-small cell lung cancer (NSCLC) from 2005 to 2012. Of these, 773 were male (86.5%) and 120 were female (13.5%) patients. The data included demographic information, histologic classification, clinical staging, presenting symptoms and treatment modalities. Survival was estimated by using Kaplan–Meier method and prognostic factors were evaluated with log-rank and Cox regression tests.
Results: The median age of the female patients was 60.6. The percent of the male and female patients that had a smoking history was 89.6% and 44.9%, respectively. Most common tumor type in female patients was adenocarcinoma (32.7%) and in male patients was squamos cell carcinoma (34.0%). The median survival time for female patients was 13.7 months and for the male patients it was 10.9 months (p>0.05). In univariate analysis, age, weight loss, combination therapy and PS correlated with a better OS for female patients. In multivariate analysis, only good PS showed consistency with survival for women.
Conclusion: NSCLC in women is different in women as compared with men. Women are more likely to develop adenocarcinoma of the lung and have more favorable prognosis. A more through understanding of the NSCLC in women may lead to new treatment and prevention strategies.

Key Words: Sex, lung cancer, women

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ÖZET

Amaç: Akciğer kanseri her iki cinsiyette de kanser ile ilişkili önde gelen ölüm nedenlerinden biridir ve tüm dünyada giderek artmaktadır. Birçok çalışmada insidans ve mortalitedeki bu artış cinsiyet, tümör tipi ve hastaların klinik karakteristikleri ile ilişkili bulunmuştur. Bu çalışmanın amacı kadın küçük hücreli dışı akciğer kanserli (KHDAK) hastalarda klinik özellik farklılıklarını ve prognostik faktörleri araştırmaktır.
Gereç ve Yöntem: 2005-2012 yılları arasında 893 KHDAK'lı hastanın verileri geriye yönelik incelendi. Hastaların 773'ü erkek (%86.5) ve 120'si (%13.5) kadındı. Hastaların demografik verileri, histolojik tipleri, klinik evreleri, semptomları ve tedavi modaliteleri incelendi. Sağkalım Kaplan-Meier metodu ve prognostik faktörler log-rank ve Cox regresyon testleri ile analiz edildi.
Bulgular: Kadın hastaların medyan yaşı 60.6 idi. Erkek hastalarda sigara öyküsü olanların oranı % 89.6 iken, kadın hastalarda bu oran % 44.9 olarak bulundu. Kadınlarda en sık tümör tipi adenokarsinom (%32.7),erkeklerde skuamöz hücreli karsinomdu (%34.0). Kadın hastaların medyan genel sağkalımı 13.7 ay, erkek hastaların 10.9 ay olarak saptandı (p>0.05). Tek değişkenli analizlerde kadın hastalarda yaş, kilo kaybı, kombinasyon tedavisi ve performans statüsü sağkalımı artıran faktörlerdi. Çok değişkenli analizlerde kadın hastalarda sağkalım ile ilşkili tek faktör iyi performans statüsüydü.
Sonuç: Kadınlarda KHDAK erkeklere göre farklıdır. Kadınlarda adenokarsinom daha sıktır ve KHDAK daha iyi prognozludur. Kadın KHDAK'nin daha detaylı anlaşılması yeni tedavi ve prevensiyon stratejelerinin geliştirilmesine olanak sağlayacaktır.

Anahtar Sözcükler: Cinsiyet, akciğer kanseri, kadın

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Address for Correspondence / Yazışma Adresi: Umut KEFELI, M.D. Medeniyet University Goztepe Education and Training Hospital, Unit of Medical Oncology, Istanbul, Turkey Phone: 0902165664000-9281 Fax: 090216442294 E-mail: ukefeli@yahoo.com

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INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths worldwide, with non–small-cell lung cancer (NSCLC) accounting for 85% of those deaths (1). A total of 228,190 new lung cancer cases and 159,480 deaths from cancer are projected to occur in the United States in 2013. It is estimated that 87,260 men and 72,220 women will die from lung cancer in the United States in 2013 (2). The rise in lung cancer-related mortality among women accompanied by a decrease among men has significantly altered the male/female ratio in this disease (3).

Smoking is the overwhelming cause for lung cancer in both men and women. Approximately 85 to 90 % of patients with lung cancer are smokers (3). Although smoking prevalence in men has decreased by one half since its peak in 1960s, smoking prevalence among women has decreased by only one quarter during the same period (4,5). There are also other risk factors and differences affecting susceptibility and survival of lung cancer like hormonal influences, genetic variations and sexes' different responses to therapy .(3,6). This study was planned to evaluate the differences in clinical features and the prognostic factors in our female patients with NSCLC.

METHODS

We retrospectively analyzed the records of the patients with NSCLC from January 2005 to March 2012 at the Dr. Lutfi Kirdar Education and Training Hospital Medical Oncology Department. All medical records were collected by a detailed review of the patients' charts. The data included demographic information, histologic classification, clinical staging, presenting symptoms and treatment modalities. The diagnosis of NSCLC was established mostly by bronchoscopic biopsy and then by transthoracic fine needle aspiration biopsy (TTIAB) or mediastinoscopy, respectively. Complete blood count, liver function tests, LDH value, renal function tests before the start of chemotherapy and before each cycle were all recorded. Toxicities and treatment side effects were obtained from patients' records that were all recorded before each chemotherapy cycle. All patients were staged according to the TNM classification (7th edition) based on the physical examination, chest X-ray, chest CT scans, abdominal ultrasound or CT, bone and brain scans. Performance status was recorded according to the Eastern Cooperative Oncology Group (ECOG) performance score.[7] Sites of distant metastases were recorded. Patients were treated according to the stage and performance status as chemotherapy, radiotherapy or combination modalities. Patients with stage IV NSCLC were treated with chemotherapy if the PS was ≤ 2. Radiotherapy was performed as concurrent therapy or as palliative therapy when needed. Data on the chemotherapy regimen, number of cycles, toxicity, objective response, second-line therapy, the time of disease progression and death were all collected. According to Response Evaluation Criteria in Solid Tumors (RECIST) criteria the response to therapy was assumed as partial when tumor size decreased 30% radiologically. If tumor size did not change after the treatment, it was defined as a stable disease and if tumor size increased by 20%, it was accepted as a progressive disease (8). The patients were followed until their death or the latest follow-up.

Statistical analysis

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software was used for the statistical analyses. A p value less than 0.05 was considered to be significant. Most values were expressed as mean ± SD. Median and minimum–maximum levels were used when data were not normally distributed. The variables considered were sex, PS, weight loss, smoking habitus, histology, stage of disease, chemotherapy regimens and number of cycles. Toxicity was classified according to the World Health Organization criteria at each cycle of chemotherapy (9). Kaplan–Meier method was used for the survival analysis. The univariate analysis of potential prognostic factors was assessed by using the log-rank test. The Cox regression model was used for the multivariate analysis. Overall survival (OS) was calculated from the diagnosis of patient to the date of death from any cause or of the last follow-up. Progression-free survival (PFS) was calculated from the diagnosis of patient to the date of the disease progression, recurrence or death from any cause.

RESULTS

A total of 893 patients with NSCLC were eligible including 773 male (86.5%) and 120 female (13.5%) patients. The median age of patients was 60.0 (range 26–89). Eighty-three percent of the patients had a smoking history. The percent of the male and female patients that had a smoking history was 89.6% and 44.9%,respectively (p<0.001). In histopathological examination, 291 (32.7%) of tumor were detected as squamous cell carcinoma and 215 (24.2%) of them were adenocarcinoma. Three hundred twenty-four patients (36.3%) had undefined-NSCLC. Most common tumor type in female patients was adenocarcinoma (32.7%) and in male patients it was squamos cell carcinoma (34.0%) (p>0.05). There was no statistical association between smoking and histopathology (p>0.05). A PS score of 0–1 was stratified in 78.5% and a PS score of 2–4 was recorded in 21.5% of the patients. The percent of the female and male patients that had a PS score of 0-1 was 73.0% and 70.4%, respectively (p>0.05). Fifty-five percent of patients (55.7%) had a weight loss of ≥ 5% in the last three months. There was no statistical difference between sexes and by weight loss (p>0.05). One hundred forty-eight patients (14.9%) patients had family history of cancer and of these, 33% of had a relative with a lung cancer. Twenty-four percent of the patients were clinically staged as stage III (males 26.3% vs. females 20.0%), and 61% of the patients were in stage IV (males 68.0% vs. females 59.9%) (p>0.05). Patient characteristics are shown in Table 1.

Table 1 Clinical characteristics of the patients

Characteristics	Patients (n=893)
Sex	
Men	773 (% 86.5)
Women	120 (% 13.5)
Age	
Men	60 (33-89)
Women	59.5 (26-87)
ECOG PS	
0-1	701 (% 78.5)
2-4	192 (% 21.5)
Weight loss	
< %5 in the last 3 months	454 (% 44.1)
≥ %5 in the last 3 months	577 (% 55.7)
Family history of cancer	
Yes	133 (% 14.9)
Lung cancer	44 (% 33)
Other	89 (% 65)
No	760 (% 85.1)
Stage	
3	214(24%)
4	544 (61%)
Smoking habitus	M/F (%)
Current or former	89.6 / 44.9
Never	10.4 / 55.1
Histology	M/F (%)
Squamous cell	34.0 / 24.3
Adenocarcinoma	22.8 / 32.7

Seven hundred and seventy-two patients (86.5%) received a combination of chemotherapy and 51 patients (5.8%) received single-agent chemotherapy. Seven-hundred-seventy (86.2%) of the patients were given platinum-based combination therapy mostly as carboplatin–paclitaxel (34.1%), cisplatin–docetaxel (21.6%), carboplatin–docetaxel (9.6%), cisplatin–gemcitabine (6.4%) and cisplatin-vinorelbine (6.1%). The percent of the female and male patients that received a combination therapy was 85.0% and 86.5%, respectively (p>0.05). Eighty-eight percent of the patients that received chemotherapy had ≥ 3 cycles of chemotherapy. There was no statistical difference between sexes (p>0.05). The percent of patients with a PS score of 0–1 that received ≥ 3 cycles was 75.8% and only 12 % of patients with a PS score of 2–4 received ≥ 3 cycles of chemotherapy without a statistical difference between sexes (p>0.05). The most frequent toxicities were the haematological (43.6%), nausea–vomiting (23.7%) and neurological (10.9%) toxicities. The most common grade 3/4 haematological toxicities were neutropenia (32.6% for females vs. 20.5% for males, p = 0.034) and anemia (20.3% for females vs. 12.4% for males, p = 0.046). There were no statistical differences for other side-effects between sexes (p>0.05). Treatment results are given in Table 2.

The overall response rate (sum of partial and complete response rates) was 35.8%. The response rate of the patients that received a combination chemotherapy was 36.4% (263 of 722) and this was 15.6% (8 of 51) for a single-agent chemotherapy (p=0.03) (Table 2). The percents of the female and male patients that responded to the therapy after 6 cycles were 36.4% and 35.7%, respectively (p>0.05).

Table 2. Treatment modalities and regimens of the patients

	Patients (n) (%)
Chemotherapy regimen	
Combination therapy	772 (86.5%)
Single agent therapy	51 (5.80%)
Best supportive care	70 (7.70%)
Combination therapy	
Female	102 (85.0%)
Male	668 (86.5%)
Chemotherapy cycles	
< 3	99 (12.0%)
≥ 3	724 (88.0%)
Response to therapy	
Yes (Partial or complete response)	
Female	44 (36.4%)
Male	235 (35.7%)
No	
Female	76 (63.6%)
Male	538 (64.3%)
Toxicities	
Haematological	357 (43.6%)
Nausea–vomiting	195 (23.7%)
Neurological	90 (10.9%)

The median survival for the entire group was 11.2 months (95% CI: 9.9–12.5, Fig. 1) with 1- and 2-year survival rates of 48.4% and 28.4%, respectively. The median survival time for female patients was 13.7 months, and for male patients it was 10.9 months (p>0.05, Fig. 2).

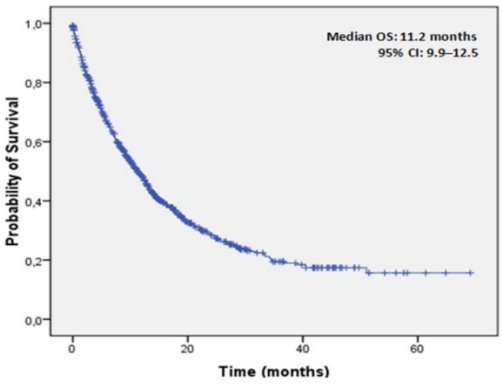

Figure 1. Median survival time of the patients.

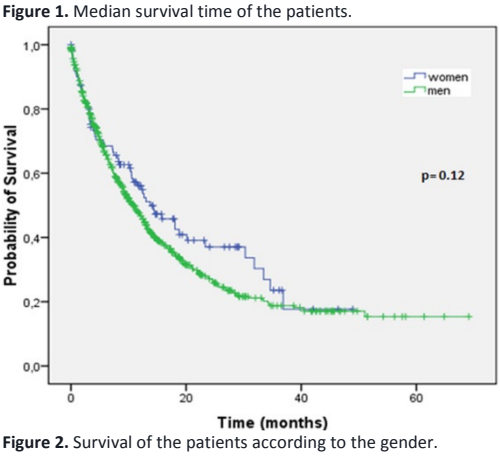

Figure 2. Survival of the patients according to the gender.

One- and two-year survival rates for female patients were 56.1% and 37.1, and for male patients they were 47.2% and 27.4% (p>0.05). In univariate analysis, age, weight loss, combination therapy and PS correlated with a better OS for 120 female patients (p<0.01). The median survival of the female patients who had a PS of 0–1 (33.6 vs. 5.8 months; p<0.01; Fig. 3) was longer than the patients who had a PS of 2–4. Female patients that were ≤ 60 year old showed better survival than the older female patients (23.3 vs. 10.5 months; P<0.01). There was no relationship between sex, LDH and hemoglobin values, histology of the tumor, stage, chemotherapy cycle and overall survival for female patients (p>0.05). These data are shown in Table 3. In multivariate analysis, only good PS showed consistency with survival (P<0.05).

Table 3. Univariate analysis of the prognostic factors for the female patients

Variable	Overall survival Median (months)	P value
Sex		0.12
Male	10.9	
Female	13.7	
Age		0.008
< 60	23.3	
≥ 60	10.5	
Performance status		0.002
0-1	34.6	
2-4	5.8	
Weight loss		0.006
≤ 5% in previous 3 months	19.7	
≥ 5% in previous 3 months	13.0	
Chemotherapy regimen		0.007
Combination	15.7	
Single agent	3.1	
Histology		0.13
Adenocarcinoma	13.0	
Squamous cell	18.0	

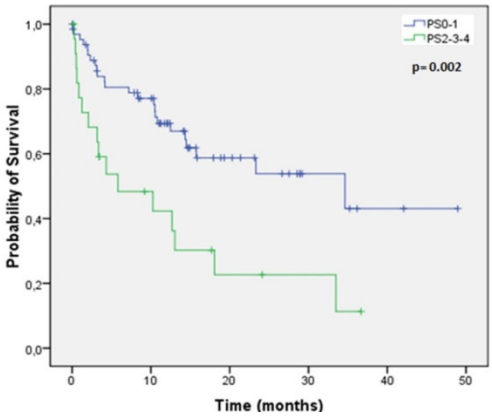

Figure 3. Survival of the female patients according to the performance status (PS).

The median PFS was 8.9 months (95% CI: 7.9–9.9). The median PFS for female patients was 10.3 months and for male patients it was 8.8 months (p>0.05). In univariate analysis, there was a statistical association between PS, weight loss and PFS for 120 female patients (P<0.05). The median PFS of the female patients who had a PS of 0–1 (12.4 vs. 4.6 months; p<0.05) was longer than the patients who had a PS of 2–4. The median PFS of the female patients who had a weight loss ≤ 5% (14.2 vs. 8.4 months; p<0.05) was longer than the patients that had a weight loss than ≥ 5% of the body weight. In multivariate analysis, only weight loss affected PFS (p<0.05).

DISCUSSION

Lung cancer is the major cause of cancer-related deaths in women. There are very clear differences between different biologies, natural history and sex-related responses to therapy (3). The Surveillance, Epidemiology and End Results Database of lung cancer have been analyzed for prognostic factors and the following ones were identifed as favorable prognostic factors: low-stage disease, surgical therapy, early age and female sex (10).

Since the late 1980s, lung cancer incidence in men was reported to decrease while it was reported to increase in women in many countries (11,12). Huhti et al. reported that women with lung cancer frequency have increased in a 20-year period from 6% to 15% (13).

Fry et al. reported in their study that median age of the cases with NSCLC has increased to become 67.4 in 1992 from a value of 66.2 in 1986. Also in another study it was found that patients with lung cancer were older as compared to those in previous decades (14,15). In our study, the percentage of female patients with NSCLC was found to be 13.4% which was in line with with the rise in frequency, but the median age of our female patients 59.5 was inconsistent with the results of these studies.

Increase in the incidence of female patients with lung cancer was explained by the rise in smoking women's ratio and exposure to environmental and occupational carcinogens (11,12). Women began smoking in significant numbers in the 1940s, with a peak incidence in the 1970s. Currently, 22% of women are smokers (3,16). There is considerable controversy over the RR for lung cancer in women vs men at any given level of tobacco exposure (3). A hospital-based, prospective, case-control study by Zang and Wynder found that women had a 1.2- to 1.7-fold higher risk for lung cancer than men (17). CT screening of an at-risk population (ie, _ 10 pack-years) yields an increased risk of lung cancer for women as compared to men (odds ratio [OR], 2.7) after adjusting for age and smoking history (18). Bain et al, however, recently analyzed the cohort data from the Nurses Health Study of women and the Health Professionals follow-up study of men, and failed to find a difference in risk. In addition, they reviewed six other cohort studies that also failed to demonstrate a difference (19). In our study, eighty-three percent of the patients were smokers. The percent of male and female patients who had a smoking history was 89.6% and 44.9%, respectively (p<0.001). Dramatic changes in the histology of non-small cell lung cancer have been recorded in the past two decades. The incidence of squamous cell carcinomas has decreased by 30%, while that of adenocarcinomas has risen in the US, Canada, Australia, the Netherlands and elsewhere (20). The SEER data in the US (2002-2006) show that of all lung cancers, 36.9% correspond to adenocarcinomas and 19.9% to squamous cell carcinomas. Similar trends have been observed in most developed countries (20,21). The reasons for this change in the histopathology of NSCLC seem to be related to tobacco consumption, which causes 90% of the diagnosed lung cancers. Changes in smoking habits, with Virginia tobacco gradually replacing dark tobacco and filtered cigarettes gradually replacing unfiltered ones, and changes in the composition of certain brands with a reduction in polycyclic aromatic hydrocarbons and an increase in N-nitrosamines seem to be the cause of this variation in the histopathology of lung cancer in such a short period (20,22,23). In our study 32.7% of tumor histology were detected as squamous cell carcinoma and 24.2% of them were adenocarcinoma. Three hundred twenty-four patients (36.3%) had undefined-NSCLC. Most common tumor type in female patients was adenocarcinoma (32.7%) and in male patients it was squamos cell carcinoma (34.0%) (p>0.05). There was no statistical association between smoking and histopathology (p>0.05). As in our study female smokers are more likely to develop adenocarcinoma of the lung than squamous cell carcinoma, which is more common in men (24,25). These results in our study may be explained by the differences in smoking habits in our country and the confounding effects of the passive smoking and to the genetic factors between sexes and nations.

Although the incidence of lung cancer is higher in women than in men and continues to rise, women show better responses to the therapy. This appears to be true regardless of the stage, therapeutic modality, or histology (3). A Polish population-based study of 20,561 cases of lung cancer between 1995 to 1998 revealed that female patients had a better prognosis than males regardless of the modality of therapy (26). The Southwest Oncology Group (SWOG) evaluated concurrent cisplatin/etoposide plus chest radiation followed by surgery for stages IIIA and IIIB NSCLC. A univariate analysis of prestudy factors revealed that the two best predictors of survival were substage and sex. The survival time for women was 21 months which was signficantly longer than that of men, which was 12 months (p=0.08) (3,27). A similar survival advantage for women is present in advanced-disease patients treated with chemotherapy. Albain et al. reviewed the 2,531 patients enrolled in 13 SWOG trials of therapeutic interventions in "extensive stage nonsmall cell lung cancer" conducted between 1974 and 1987. Female sex was a strong, independently favorable factor for survival with a risk ratio of 0.77. The median survival ratio for females/males was 5.7/4.8, with a 1-year survival rates of 19% vs 14% (p< 0.01 for survival comparisons within each category) (28). Almost identical results were noted by the European Lung Cancer Working Party (ELCWP) in a review of 1,052 patients with locally advanced or metastatic NSCLC treated with cisplatinum-based chemotherapy from 1980 to 1991 (29). In our study, 772 patients (86.5%) received a combination chemotherapy and 51 patients (5.8%) received a single-agent chemotherapy. Seven hundred and seventy patients were given a platinum-based combination therapy.

The percent of the female and male patients that received combination therapy was 85.0% and 86.5%, respectively (p>0.05). The median survival time for female patients was 13.7 months and for male patients it was 10.9 months (p>0.05). One- and two-year survival rates for female patients were 56.1% and 37.1, and for male patients they were 47.2% and 27.4%, respectively (p>0.05). In univariate analysis, age, weight loss, combination therapy and PS correlated with a better OS for 120 female patients (p<0.01). The median survival of female patients who had a PS of 0–1 (33.6 vs. 5.8 months; p<0.01) was longer than the patients who had a PS of 2–4. Female patients that were ≤ 60 year old showed better survival than the older female patients (23.3 vs. 10.5 months; P<0.01). In multivariate analysis, only good PS showed consistency with survival (P<0.05). Our data set is consistent with that of other studies in that female patients had relatively better outcomes related to NSCLC. The reasons for why women have better survival than men could be explained by biological differences, genetics , smoking habits and cultural factors (3,5).

CONCLUSION

It seems that NSCLC in female patients is a distinct entity as compared with men. Although still rising, women smokers' ratio is less than men. Women smokers are more likely to develop adenocarcinoma. Female patients with NSCLC have superior response rates to the therapy and better prognosis as compared with men. These differences are mostly explained by smoking habits, cultural, hormonal and genetic factors. A more thorough understanding of the NSCLC in women may lead to new treatment and prevention strategies. Future lung cancer trials should contain greater number of female patients to better understand these differences.

Conflict of Interest

No conflict of interest was declared by the authors.

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