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Lung Cancer in Individuals Less Than 50 Years of Age

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Abstract The aim of this study was to compare the epidemiologic, clinical, and laboratory characteristics and survival rates of younger and older patients with lung cancer. We studied 1340 patients who were histopathologically diagnosed as having lung cancer from 1990 to 2005. Based on prior reports, we defined "younger" as individuals less than 50 years old. The patients were classified into two groups: <50 years (the younger group) and ≥50 years (the older group). Of the 1340 patients, 179 (13.4%) were in the younger group and 1161 were in the older group. In the younger group, exposure to occupational risk factors was a risk factor for lung cancer, while in the older group, smoking was a risk factor. At the time of diagnosis, chest pain was more common in the younger group, while in the older group, cough, dyspnea, and hilar enlargement on chest X-ray were more frequent. The incidence of adenocarcinoma and small-cell carcinoma was greater in the younger group, while squamous cell carcinoma was more common in the older group. Metastasis rates were significantly different between the two age groups: 52.0% of the younger group presented with stage IV disease compared with 43.5% of the older group. Although fewer younger than older patients were not able to receive or rejected anticancer therapy, the overall survival was similar in both groups. These data indicate that lung cancer had different etiopathogenetic characteristics in younger patients, which may have clinical implications. By planning preventive measures based on these characteristics, more efficient use of resources can be achieved.

Keywords Lung cancer · Age · Epidemiology · Survival

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Introduction

Lung cancer is the leading cause of cancer-related mortality in the world. The incidence of lung cancer increases with age; the frequency peaks in the sixth and seventh decades. Lung cancer is relatively rare among young adults. The percentage of cases under the age of 50 varies between 9% and 14% [1–3]. It is thought that the clinical characteristics and the disease course of younger patients with lung cancer may differ from those of older patients; this study was done to identify these differences. Previous studies have provided conflicting data about the clinical presentation and prognosis of young patients [1–3, 6, 7]. Most previous studies found more females and more adenocarcinoma among young lung cancer patients [1, 2, 4, 5]. Young patients have been reported to have a more advanced stage of the disease than old patients [3, 5] for which they received more aggressive treatment. Some studies have reported that young patients have a poor prognosis [6, 7], others have reported that young patients' prognosis is similar to that of old patients [3, 5, 8], while some have reported that young patients have a better prognosis than old patients [1, 2]. It is possible to explain these different prognoses based on various interpretations or the use of significant prognostic factors such as stage,

Karnofsky performance status, histopathology, and approaches to therapy that were used in these studies that were carried out in different geographical regions.

Despite the fact that previous studies do not reach the same results because of methodologic differences, the properties that have been determined by previous studies for the young age group, such as the different histologic types that are seen more often, being male or female, being in late stage when diagnosed, lead to the opinion that there may be differences between younger and older patients regarding etiology and tumor progression. For example, the etiologic factors for lung cancer at a younger age may be different from those for the older group. Thus, there may be differences in both the histologic type of tumor derived from possible specific etiologic factors and in the course of the tumor clinically. If so; differences in the tumors' clinic course between the young age group and others should be expected. Because of this, the target groups and methods for early diagnosis and preventive studies may be changed. Therefore, there is no consensus among the previous studies' results about this issue and more studies must be done.

Because of the issues mentioned above, the aim of the present study was to compare the epidemiologic, clinical, pathologic, and radiologic characteristics and the survival rates of young (<50 years old) and old (≥50 years old) lung cancer patients.

Materials and Method

Epidemiologic and clinical parameters and laboratory, monitoring, diagnosis, treatment, and prognostic data have been collected for all lung cancer patients diagnosed at our clinic since January 1990. This study retrospectively examined the data of 1340 lung cancer patients who had a histopathologic diagnosis and were seen in our clinic between January 1990 and December 2005. The patients were classified into two groups according to their age at the time of diagnosis: <50 years (the younger group) and ≥ 50 years (the older group). Based on prior reports, we defined "younger" as individuals less than 50 years old [1–4]. Of the 1340 lung cancer patients, 179 were in the younger group and 1161 were in the older group. The patients in the younger group were matched with the patients in the older group for gender, smoking history, family history of cancer, asbestos exposure, occupational risk, comorbidities, performance status based on the Karnofsky performance score (KPS), mean duration of symptoms, symptoms, physical examination findings, tumor histology, radiologic findings, tumor location, metastasis rates, metastasis sites, anticancer therapy status, and survival.

Patients were assigned a current smoking status depending on whether they had never smoked (never smokers), had not smoked for more than 1 year (former smokers), or were smoking at the time of the study (current smokers). Those who had quit smoking less than 1 year before were classified as current smokers. Pack-years of cigarette smoking were calculated as the product of the duration of smoking (in years) and the average number of cigarettes smoked per day. Exposure to second-hand smoke could not be assessed because this information was not documented in the charts that were reviewed. Cases of lung or nonlung cancer among first degree relatives of patients were considered as family history.

The time between the onset of a patient's complaints and his/her referral to our clinic was taken as the duration of symptoms. Symptoms were classified as being intrapulmonary (cough, chest pain, dyspnea, hemoptysis), extrapulmonary intrathoracic (hoarseness, dysphagia, and complaints related to particular syndromes, including superior vena cava syndrome and Horner's syndrome), paraneoplastic syndromes (clubbing, hypertrophic osteoarthropathy, inappropriate antidiuretic hormone secretion, hypercalcemia, leukocytosis, thrombocytosis excluding other causes, thrombophlebitis), metastatic (bone, liver, and cerebral complaints), and systemic (weight loss, fatigue). Physical examination findings were classified as local, intrathoracic, and metastatic.

Plain chest X-ray findings were classified based on the presence of a mass, hilar enlargement, mediastinal enlargement, pleural effusion, atelectasis, pneumonia, nodule, and a cavity.

Tumor location was defined as follows: The lungs were divided into upper, middle, and lower zones by two horizontal lines drawn through the upper and lower borders of the hilum. The lungs were also divided into central (perihilar) and peripheral (subpleural) regions. The peripheral region is the 4-cm-wide parenchymal zone located at the periphery of the lobes that is devoid of radiologically visible vessels [9]. In addition, to determine whether the tumor was centrally or peripherally located, the following findings were taken into consideration. The tumor was considered to be centrally located if one or more of the following X-ray findings was present: increased hilum size, laterally convex hilar shadow, strands radiating into the lung from the hilum, carcinomatous pleuritis, distal hyperinflation, paradoxical hilum sign, small hyperlucent lung (Fraser's sign), atelectasis, distal pneumonia, bronchial stenosis or amputation, filling defect, superior vena cava compression, diaphragmatic paralysis, or esophageal stenosis. If none of the preceding X-ray findings was present, then the tumor was considered to be peripherally located [9].

Disease was staged according to the new TNM staging system on the basis of history, physical examination, complete blood counts, chest X-rays, thoracic CT,

abdominal CT or ultrasonography, cerebral CT or magnetic resonance imaging, bone scintigraphy, and, when necessary, the results of invasive procedures carried out for mediastinal lymphadenopathy or suspicious areas [10].

Survival was defined as the time between the date of diagnosis and the date of death or date that the patient was last known to be alive.

Statistical Methods

Statistical software (SPSS version 10.0, SPSS Inc., Chicago, IL) was used for all analyses. Differences between the groups were tested using the χ^2 test for categorical data and Student's t test for continuous data. Multivariate analysis was performed using those factors that achieved $p < 0.10$ on univariate analysis as possible risk factors for cancer. The survival rates were estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival rates. A $p < 0.05$ was considered significant.

Results

The age distribution of the 1340 patients evaluated in the study is presented in Figure 1. Most patients were between 50 and 79 years of age; 13.4% of the patients were under the age of 50 years and 1.3% were above 80 years of age.

First, distribution of gender was evaluated by dividing the study into five equal time periods for the consideration of changes in epidemiology of lung cancer. Female patients made up 4.6% during the first 5-year period, 8.3% during the second 5-year period, and 9.5% during the last 5-year period. We observe that the proportion of female patients in our series has increased with time and the ratio of female patients has doubled during the 15-year period.

The demographic characteristics of the patients by age group are presented in Table 1. As expected, the

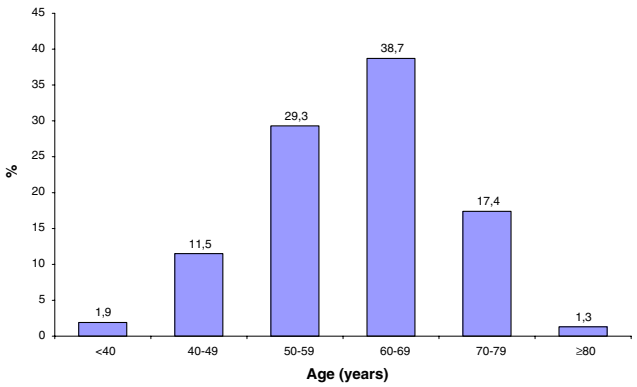

Fig. 1 The distribution of patients by age group

percentage of former smokers and cumulative number of pack-years were higher in older patients. However, smoker and never smoker ratios were similar in both groups. The comorbidity rate was higher in older patients.

Table 2 presents the results of the multivariate analysis of variables achieving $p < 0.10$ on the univariate analysis of factors that could be related to the risk of cancer in the younger age group shown in Table 1. Based on the results of the multivariate analysis presented in Table 2, exposure to occupational risk factors was a risk factor for lung cancer in the younger age group; occupational risk factors increased the risk of lung cancer 1.539 times more in the younger group than in the older group. Table 2 shows that smoking was a significant risk factor for lung cancer in the older group.

The performance status, symptoms, and physical examination findings of the two groups are shown in Table 3. The younger group had a better performance status than the older group (80.3 ± 0.8 vs. 77.6 ± 0.3; $p = 0.001$). Of the 1340 patients, 10 were asymptomatic (0.7%). With respect to the symptoms and physical examination findings, chest pain was more common in younger patients, while cough and dyspnea were more common in older patients.

The distribution of histologic subtypes was examined again by dividing the study into five equal time periods before determining whether there was any difference among age groups in terms of histologic subtypes. The ratios of squamous cell carcinoma and adenocarcinoma were 46.4% and 12.7% during the first 5-year period, 43.2% and 16.8% during the second 5-year period, and 39.3% and 21.6% during the last 5-year period, respectively. It is observed that there has been a significant increase adenocarcinoma over time. In younger patients the distribution of histologic subtypes was significantly different from that in older patients. The incidence of adenocarcinoma and small cell carcinoma was greater in younger patients, while squamous cell carcinoma was more common in older patients ($p = 0.003$) (Fig. 2).

The plain chest X-rays of 5 of 1340 patients were considered normal. When the two groups were compared in terms of the radiographic appearance of the lung cancer, hilar enlargement was more prevalent in the older group than in the younger group (Table 4).

The lesion location could not be clearly assessed in seven patients. Two patients in the older group had synchronous tumors; in both patients one tumor was centrally located and the other was peripherally located. Tumor location did not differ between younger and older groups (Table 5).

Fifty-three patients could not be staged for various reasons. Information on the clinical stage of the tumor was available in 97.8% of the younger group and 95.8% of the

Table 1 Demographic characteristics of patients by age group

Characteristics	Age at diagnosis (years)		*p* value
	<50	≥50	
No. patients, *n* (%)	179 (13.4)	1161 (86.6)	
Median age (range) (years)	45 (28–49)	63 (50–86)	
Gender, *n* (%)			
Male	165 (92.2)	1064 (91.6)	0.809
Female	14 (7.8)	97 (8.4)	
Smoking status, *n* (%)			
Current smoker	148 (82.7)	835 (71.9)	0.001
Never smoker	16 (8.9)	99 (8.5)	
Former smoker	15 (8.4)	227 (19.6)	
Pack-years	32.4 ± 1.8	51.4 ± 1.0	<0.001
Family history, *n* (%)	30 (16.8)	141 (12.2)	0.085
Asbestos exposure, *n* (%)[a]	83 (46.4)	626 (53.9)	0.060
Occupational risk, *n* (%)[b]	32 (18.4)	153 (13.3)	0.090
Comorbidity, *n* (%)	10 (5.6)	300 (25.8)	<0.001

[a] Twelve patients had occupational and the rest had environmental exposure to asbestos

[b] Of 12 occupational exposure cases, 3 were electricity isolation workers, 5 were brake-lining workers in automotive industry, and 4 were workers in locomotive industry

Table 2 Results of the logistic model consisting of factors that could be related to the risk of developing lung cancer in the younger age group

Variable	OR	95% CI	*p* value
Smoking	0.607	0.437–0.843	0.003
Family history	1.363	0.873–2.131	0.173
Asbestos exposure	0.765	0.554–1.055	0.103
Occupational risk	1.539	1.003–2.360	0.048

older group. Metastasis rates were significantly different between the age groups ($p = 0.035$): 52.0% of the younger group had stage IV disease compared with 43.5% of the older group. The most common site of metastatic involvement among younger patients with stage IV disease at presentation was bone (26.9%), followed by liver (14.3%), brain (12.0%), and contralateral lung (10.3%). Among the various metastatic sites, only the bone metastasis rate was significantly higher in younger patients than in older patients (26.9% vs. 16.4; $p = 0.001$) (Figs. 3 and 4).

The evaluation of therapy showed that fewer younger patients were not able to receive or rejected anticancer therapy for any reason (younger, 11.5% vs. older, 21.8%; $p < 0.001$). The median survival was 7.83 ± 0.63 (95% CI: 6.54–9.13) months in the younger group and 7.13 ± 0.36 (95% CI: 6.44–7.83) months in the older group; overall survival was similar in both groups ($p = 0.97$).

Discussion

The literature offers no clear definition of what constitutes a "young patient." Thus, various cutoff values have been used to evaluate the characteristics of lung cancer patients. Lung cancer is most frequently seen in patients between 60 and 70 years of age. Age 50 has also been referred to as a limit in some similar studies [1–4]. Thus, in this study, a young patient was defined as under the age of 50 years, and characteristics of these patients were determined.

In our study patients under 50 years of age at the time of diagnosis were 13.4% of the study population; this result is consistent with previous studies [1–3].

Various female-to-male ratios have been reported in this group of patients. Some studies reported a high female-to-male ratio [1, 2, 4, 5, 8, 11], which is likely because women are known to have a high sensitivity to lung carcinogens, while other studies have concluded that there is no gender difference [3, 12]. Our study also showed that there is no difference in the female-to-male ratio among the age groups. As expected, results of our study indicate that rate of quit smoking and cumulative amount of smoked cigarettes are higher in older patients. However, smoker and never smoker ratios were similar in both groups.

Our study concurred with previous studies that found that the performance status of younger patients with lung cancer is better than that of older patients [1, 12]. This may be due to the lower comorbidity rate of younger patients, since the prevalence of certain diseases such as cardiovascular disease, diabetes mellitus, COPD, cerebrovascular diseases, and hypertension increases with age.

Some studies have reported that compared with older patients, younger patients have a shorter duration of symptoms [12]. However, other studies found that younger patients had a longer duration of symptoms, were referred to hospitals long after the onset of symptoms, and, as a result, were diagnosed at a more advanced stage [5, 13].

Table 3 Performance status, symptoms, and physical examination findings of patients by age group

Characteristics	Age at diagnosis (years)		*p* value
	<50	≥50	
Performance status	80.3 ± 0.8	77.6 ± 0.3	0.001
Duration of symptoms (days)	102.9 ± 9.1	92.2 ± 2.8	0.177
Symptoms, *n* (%)			
Intrapulmonary			
Cough	122 (68.2)	965 (83.1)	<0.001
Chest pain	133 (74.3)	750 (64.6)	0.011
Dyspnea	91 (50.8)	701 (60.4)	0.016
Hemoptysis	58 (32.4)	448 (38.6)	0.110
Extrapulmonary intrathoracic			
Syndrome complaints[a]	12 (6.7)	56 (4.8)	0.287
Hoarseness	36 (20.1)	198 (17.1)	0.318
Dysphagia	2 (1.1)	20 (1.7)	0.552
Paraneoplastic syndrome complaints	56 (31.3)	354 (30.5)	0.836
Metastatic complaints			
Bone pain	13 (7.3)	50 (4.3)	0.082
Liver complaints	3 (1.7)	14 (1.2)	0.602
Cerebral complaints	3 (1.7)	50 (4.3)	0.093
Systemic complaints			
Weight loss	89 (49.7)	597 (51.5)	0.664
Fatigue	113 (63.1)	805 (69.4)	0.093
Physical examination, *n* (%)			
Local	114 (63.7)	790 (68.1)	0.240
Intrathoracic spread	55 (30.7)	295 (25.5)	0.139
Metastasis	61 (34.1)	381 (32.8)	0.744

[a] Superior vena cava syndrome, Horner's Syndrome, etc.

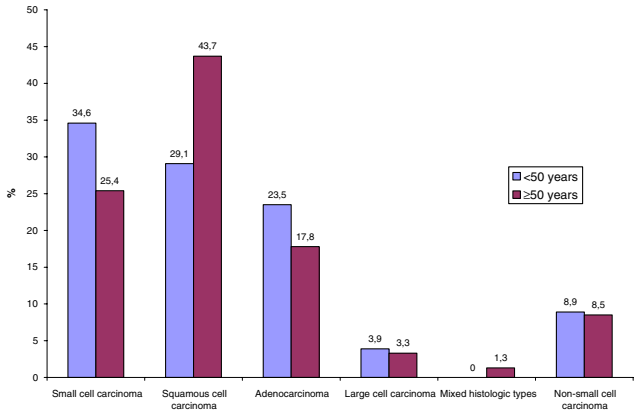

Fig. 2 Histopathologic characteristics of patients by age group

The mean duration of symptoms tended to be longer in younger than in older patients in our study; however, this difference was not statistically significant (102.9 ± 9.1 vs. 92.2 ± 2.8; $p = 0.177$). Only ten patients in our study were asymptomatic at the time of diagnosis, and two of these were in the younger group. In our study chest pain was more common among the younger patients, which is in line with previous studies [6, 14]; on the other hand, cough and dyspnea were more common among the older patients. Therefore, although lung cancer is a disease of advanced age, lung cancer should be suspected in young individuals who are at risk and are complaining of chest pain.

The ratio of female lung cancer patients has increased recently in developed Western countries due to changes in sociocultural and economic status, and adenocarcinoma has taken the lead in terms of frequency. In our study we examined the distribution of gender and cell type by dividing the 15-year period that our study covered into 5-year time periods to learn about the situation in Turkey. This data obtained from our series indicates that the ratio of female patients and adenocarcinoma cases has changed in recent years. However, this change is not as evident and as fast as in developed Western countries because Turkey is not as urbanized and there are not as many women in professional life compared to Western countries. The data of our series reflect behavior that occurred 20–30 years before the emergence of cancer, and changes in urbanization and smoking behavior actually became evident in 1980s in our country. Therefore, it is normal to note that the most frequent histopathologic type is squamous cell carcinoma and the ratio of female patients is low in our 15-

Table 4 Radiologic characteristics of patients by age group

Findings, n (%)	Age at diagnosis (years)		*p* value
	<50	≥50	
Mass	85 (47.5)	507 (43.7)	0.338
Hilar enlargement	60 (33.5)	512 (44.1)	0.008
Mediastinal enlargement	31 (17.3)	183 (15.8)	0.597
Pleural effusion	25 (14.0)	169 (14.6)	0.835
Atelectasis	26 (14.5)	183 (15.8)	0.671
Pneumonia	20 (11.2)	152 (13.1)	0.475
Nodule	9 (5.0)	67 (5.8)	0.689
Cavity	10 (5.6)	39 (3.4)	0.139

Table 5 Tumor location characteristics of patients by age group

Lesion locations	Age at diagnosis (years)		*p* value
	<50	≥50	
Location of tumor (%)			
Central	118 (66.3)	807 (70.3)	0.279
Peripheral	60 (33.7)	341 (29.7)	
Location of tumor (%)			
Upper zone	58 (32.6)	316 (27.5)	0.463
Middle zone	85 (47.8)	561 (48.8)	
Lower zone	26 (14.6)	204 (17.7)	
Multiple zones	9 (5.1)	69 (6.0)	

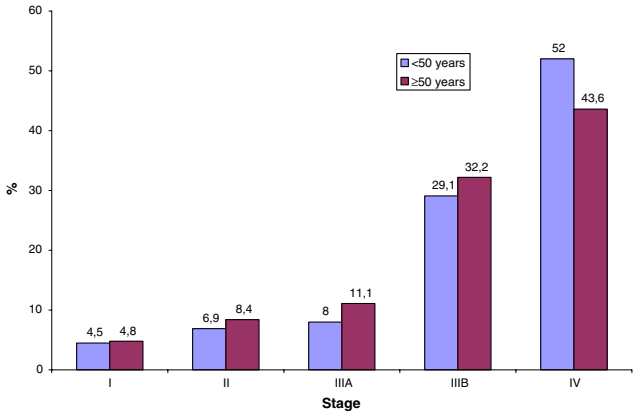

Fig. 3 Stage of patients according by age group

year series. However, sociocultural changes following 1980s have led to the start of expected changes in female-to-male patient ratio and cell types during the 5-year periods. In other words, epidemiologic changes in developed Western countries have also been experienced in our country. We believe that the real change will take place within the following 30 years.

Most previous studies have concluded that the distribution of histopathologic types differs between young and

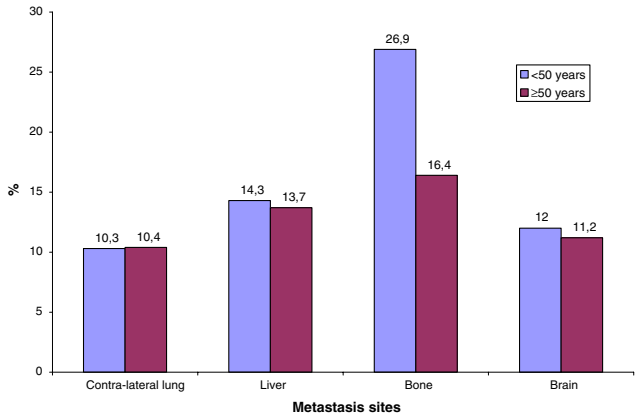

Fig. 4 Metastasis sites by age group

old lung cancer patients. While adenocarcinoma [1–5, 8, 12, 13, 15–17] and small cell carcinoma [1, 12] have been reported to be more prevalent in the younger group, squamous cell carcinoma [4, 5] has been found to be more common in the older group.

Although smoking is the most significant risk factor in the development of lung cancer, only 10–15% of all smokers develop lung cancer [18], and 10–15% of all lung cancers occur among nonsmokers. Thus, there are individual differences in susceptibility to lung carcinogens. Previous studies dealing with a family history of cancer concluded that younger patients are more likely to have a positive family history of cancer than older patients [1, 19]. In our study occupational risk factors were found to be a causal risk factor for developing lung cancer in the younger group, while smoking was identified as a risk factor for lung cancer in the older group. In our study younger patients had significant exposure to occupational risk factors, which partly explains the prevalence of small cell and adenocarcinoma cell types in this age group, as there have been some reports that adenocarcinoma and small-cell carcinoma are more prevalent in patients exposed to occupational risks [20, 21]. However, other yet unknown factors may be related to the higher prevalence of adenocarcinoma and small-cell carcinoma among young patients. On the other hand, smoking was found to be a causal risk factor in the older group, which is in line with the prevalence of squamous cell carcinoma in this group.

Other than hilar enlargement, no other differences in the radiologic findings were observed between the groups. Hilar enlargement was more common in the older group. There was no difference in tumor location between the two groups; this is in contrast to the findings of previous studies [4, 6]. However, the prevalence of small-cell carcinoma in the younger group and of squamous cell carcinoma in the older group is consistent because cancers of both cell types are usually located centrally.

The majority of previous studies has found that younger patients have more advanced-stage lung cancer than older patients [3, 5–7, 13, 15, 16, 22]. Nevertheless, there are other studies showing that the severity of the disease does not differ between the two groups [1, 14]. In our study, the metastasis rate (stage IV disease) was higher in the younger group than in the older group (52.0% vs. 43.5%; $p = 0.035$). In addition, bone metastasis was more prevalent in the younger group than in the older group. Taking into account the clinical courses of patients with the different histopathologic types, this may be due to the higher prevalence of small-cell carcinoma and adenocarcinoma, which are more aggressive in younger patients.

Stage IV disease is more common at presentation in the younger group and that a younger patient is more likely to be offered some form of anti cancer treatment than an older patient [1–3, 14]. In our study, the various types of therapy were not examined in detail; nevertheless, the rate of receiving anticancer therapy was higher in the younger group with advanced-stage disease than in the older group ($P < 0.001$). In our study, the higher co-morbidity rates in the older group may have affected the type of therapies that the patients received.

Conflicting results have been reported by previous studies dealing with survival rates of younger and older patients. Some studies reported that younger patients had lower survival rates than older patients [15], others reported similar survival rates for both [3, 5, 8, 12, 13, 17, 22, 23], and still others reported that younger patients had higher survival rates than older patients [1, 2, 14, 24]. In the present study, the overall prognosis was poor, and despite the many differences between the two groups, there was no difference in survival rates between younger and older patients. It may be that the differences between the two groups in terms of stage, histopathologic type, performance status, comorbidities, and receiving anticancer therapy, all of which significantly contribute to survival rates, were balanced in such a way that it resulted in similar survival rates. In the older group the incidence of stage IV disease was lower, the performance status was poor, the comorbidity rate was higher, and the rate of receiving anticancer therapy was lower. On the other hand, the young group had a higher rate of stage IV disease, with a higher rate of small-cell carcinoma and adenocarcinoma, which are known to be more aggressive, but their performance status was better, their comorbidity rate was lower, and the rate of receiving anticancer therapy was higher. Thus, these differences may have led to similar overall survival in the two groups.

It should be noted that our study has two limitations. First, occupational risk factors were not evaluated separately; occupations known to result in exposure to risks were evaluated as a single group and environmental smoke exposure was not evaluated separately either. Second, the various anticancer therapies that the patients received were not analyzed in detail.

In conclusion, the presence of occupational risk factors, chest pain, good performance status, adenocarcinoma, small-cell carcinoma, advanced stage of disease, bone metastasis, and the use of anticancer therapy were more frequent in the younger group than in the older group. Despite these differences, overall patient survival was poor, with no difference between the two groups. These data indicate that lung cancer may be etiopathogenetically different in the younger age group, which has clinical implications. Therefore, age should be considered a separate component when implementing preventive measures against lung cancer. Identifying the etiology in young and old patients more clearly and planning preventive measures according to the different etiologies would avoid wasting resources, which would result in more efficient use of existing resources. Different symptoms may be observed, metastasis rates may be higher, and cell types may be different, but the prognosis may be the same or worse among young patients. Therefore, younger individuals who are at risk for lung cancer due to their occupational history should have routine radiologic examinations.

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