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Research Article

Survival Evaluation in Patients Over 70 Years of Age With Advanced Stage Non-small Cell Lung Cancer

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Abstract

Objectives: Non-small cell lung (NSCLC) cancer is usually seen in elderly patients. The impact of over 70 age on the survival of patients with NSCLC has not been studied. This study aimed to evaluate the impact of demographic and clinical variables on survival in Stage IV the NSCLC elderly patient.

Methods: This study was a retrospective cohort analysis of 244 patients with advanced stage NSCLC, between January 2015 and December 2019. The patients were classified as the <70 years and ≥70 years. The primary and secondary outcomes were the overall survival and the impact of the demographics and clinical variables on survival, respectively.

Results: The numbers of patients who were <70 and ≥70 years were 136 (55.7%) and 108 (44.3%), respectively. Although the overall survival in patients aged 70 years or older was shorter than that of the younger patients, the difference was statistically insignificant (p=0.236). Weight loss, ≥2 comorbidities and TNM stage IV were significantly associated with shorter overall survival.

Conclusion: Weight loss, increased comorbidities and TNM stage IV are the independent risk factors for overall survival in patients with advanced stage of NSCLC. Older age did not found any impact on survival in the study.

Keywords: Non-small cell lung cancer, elderly

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Lung cancer is one of the most common and lethal cancers worldwide.[1-3] Non-small cell lung cancer (NSCLC) that accounts for 85% of all lung cancers is usually diagnosed at advanced stages.[4] It is known that 30 to 40% of lung cancer patients are older than 70 years.[1,4] So, the majority of the new cases of lung cancer are elderly NSCLC patients.[5]

Controversy remains about the cut-off point of age for the definition of elderly. Although medical oncologists have considered the age of 65 years for this purpose, it is speculated that a cut-off value of 65 years is not representative of the older population.[6] In the light of those explanations, 70 years have been accepted for the limit of senescence and the geriatric period in some studies.

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[4,7] Several studies found decreased survival rates in the elderly patients when the cut-off values of age starting from 60 years and over were used.[5,10,11,15] In advanced NSCLC patients with over 70 years has not been studied in detail.

Advanced age may be directly related to reduced use of the physiological reserve and increased number of comorbidities and medications.[8] Older patients with lung cancer have been usually under-represented or excluded by the clinical trials.[8-13] Moreover, the side effects of the treatment modalities for lung cancer and limited life expectancy in elderly cancer patients are critical issues that negatively impact lung cancer survival.[4] The ages of the patients might also be an effective factor for the selection of chemotherapeutic drugs.[4,14] The use of only first-line treatment in elderly patients rather than platinum-based doublets or immune checkpoint inhibitors has been reported to lead to a lack of an optimal treatment.[4]

This study aimed to evaluate the survival outcomes in advanced stage NSCLC patients with 70 over age and determine the demographic and clinical variables affecting survival.

Methods

Study

This study was a retrospective cohort analysis of consecutive 244 patients with non-small cell lung cancer who underwent medical treatment and follow-up for locally advanced and advanced-stage lung cancer (stage IIIB, stage IIIC, stage IVA, and stage IV B) in the Department of Medical Oncology and Center for Palliative Care, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey between January 2015 and December 2019. The local ethical committee approved the study (116.2017.124). All patients provided written informed consent for collecting their medical data for scientific purposes and publication. The study was conducted under the 2013 Declaration of Helsinki and later amendments.

Patients

The patients with NSCLC confirmed by cytology or histology were evaluated. Based on the World Health Organization (WHO) classification, squamous cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma were considered under the group of NSCLC.[16] The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system-7th and 8th editions were used for clinical tumor staging of the patients between 2015-2017 and 2017-2019.[17]

All NSCLC patients with the stages of IIIB (with metastatic supraclavicular lymph nodes), IIIC, IVA, and IVB, who were not amenable to surgery and treated via chemotherapy, were included. The exclusion criteria were the age of <18, duration of medical treatment less than one month, absence of appropriate hepatic and renal functions and hematopoietic reserves, and history of other malignant tumors. For patients with locally advanced and metastatic disease, chemotherapy with or without radiotherapy was performed in all patients.

We classified the patients according to the age at the time of diagnosis into the non-geriatric (<70 years) and the geriatric patient (≥70 years) groups (18-20).

Variables

The data considering demographic characteristics (age, sex) and clinical features (loss of weight, smoking history, number and type of comorbidities, the TNM stages, and details of the chemotherapy regimens) were extracted from the patients' medical records using the hospital information system. The loss of more than 5% of the total body weight for the last three months was regarded as the positivity criterion. The patients were evaluated using their medical history and physical examination findings, laboratory tests, imaging techniques, and fiberoptic bronchoscopy.

Statistical Analysis

The primary outcome was the overall survival (OS) time calculated based on the follow-up data. It was defined as the time from pathological diagnosis to the date of death or the most recent follow-up in December 2019. The groups were compared considering gender, smoking history, comorbidities, tumor features, and overall survival. Descriptive statistics were given as mean±standard deviation and median with minimum-maximum values for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The normal distribution of the numerical variables was analyzed by the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. In comparing two independent groups, the Mann-Whitney U test was applied for variables without normal distribution. Pearson Chi-Square and Fisher's Exact tests were used to comparing the differences between categorical variables in 2x2 tables. The Fisher Freeman Halton test was used in RxC tables. Kaplan-Meier survival analysis was performed to determine the temporal relationship between the length of overall survival and the groups based on 70 years of age. Multivariate Cox regression models were used to determine the independent demographic and clinical risk factors for the overall survival.

For statistical analysis, "Jamovi project (2020), Jamovi (Version 2.2.2) [Computer Software] (Retrieved from https://www.jamovi.org), and JASP (Version 0.15) (Retrieved from https://jasp-stats.org) were used. The significance level (p-value) was set at 0.05 in all statistical analyses.

Results

The study was performed with a total of 244 patients with a mean age of 67.63±10.0 years. The male to female ratio was 4.8 among all patients.

The grouping based on a cut-off value of 70 years yielded 136 non-geriatric (55.7%) and 108 geriatric patients (44.3%) who were <70 and ≥70 years, respectively. The demographic and clinical characteristics are given in Table 1. We detected significant differences in smoking history, the presence and the type of comorbidities between the groups. There were significantly more active smokers in the non-geriatric group (p<0.001). The rate of the comorbidities increased with age (61.1% vs. 36.0%) (p<0.001). The percentage of the geriatric patients with ≥2 comorbidities was significantly higher than the non-geriatric patients (p<0.001). The groups were similar in gender distribution and other clinical characteristics (Table 1).

Adenocarcinoma was more frequently detected in patients younger than <70 years compared to patients ≥70 years (97.8% vs. 70.4%) (p<0.001). No significant differences between the patient groups were detected in either the stages (p=0.390) or the extension of the disease (p=0.753). The incidence of metastasis to the opposite lung was significantly higher in patients who were 70 years or more compared to patients younger than 70 (28.7% vs. 16.9%) (p=0.040) (Table 2).

Details of the treatment protocols and the chemotherapy cycles are given in Table 3. There were 10 (8.1%) and 13 patients (12.9%) who were followed by the best supportive care in the non-geriatric and geriatric groups, respectively (p=0.336). The rate of the second-line chemotherapy was 26.7% considering the patients with the first-line chemotherapy (60 patients among 225 patients). Its rate was significantly higher in patients aged less than 70 years (33.9% vs. 17.8%, p=0.007). There were also more non-geriatric patients with the second-line and fourth-line chemotherapy than the geriatric geriatric patients (p=0.016 and p=0.0447). The mortality rates were 72.1% and 82.4% in patients aged <70 years and ≥70 years, respectively. The difference in the mortality rates between the groups was insignificant (p=0.081).

The rates of weight loss and ≥2 comorbidities were significantly higher in the non-survivors (p=0.001 and p=0.040). The TNM stage of 4B was more frequently seen in patients who were non-survivors (p=0.012). We also detected significant differences in the frequencies of chemotherapy lines between the groups (Table 4).

Table 1. Demographic and clinical characteristics of the patients

	Patients		p
	<70 year (n=136)	≥70 year (n=108)	
Sex[a]			
Male	113 (83.1)	89 (82.4)	0.999
Female	23 (16.9)	19 (17.6)	
Weight loss[a]	116 (88.5)	93 (90.3)	0.830
Smoking[a]			
Non-smoker	9 (6.6)	19 (17.6)	
Smoker	103 (75.7)	48 (44.4)	<0.001
Ex-smoker	24 (17.6)	41 (38.0)	
Cigarette use (pack/year)[b]	40.0 [35.0, 60.0]	50.0 [35.0, 75.0]	0.046
Familial lung cancer[a]	66 (48.5)	44 (41.1)	0.307
Comorbidities, any type[a]	49 (36.0)	66 (61.1)	<0.001
Diabetes mellitus	11 (22.4)	25 (37.9)	0.118
Hypertension	20 (40.8)	45 (68.2)	0.006
Coronary artery disease	20 (40.8)	25 (37.9)	0.900
Chronic obstructive pulmonary disease	17 (34.7)	22 (33.3)	0.999
≥2 comorbidities[a]	13 (9.6)	36 (33.3)	<0.001

[a]: n (%); [b]:median [min-max].

Table 2. Tumoral features of the patients

	Patients		p
	<70 year (n=136)	≥70 year (n=108)	
Pathological diagnosis[a]			
Adenocarcinoma	133 (97.8)	76 (70.4)	<0.001
Squamous cell carcinoma	3 (2.2)	32 (29.6)	
TNM stage[a]			
3B	17 (12.5)	8 (7.4)	0.390
3C	5 (3.7)	7 (6.5)	
4A	74 (54.4)	56 (51.9)	
4B	40 (29.4)	37 (34.3)	
Extension of the disease[a]			
Locally advanced	22 (16.2)	15 (13.9)	0.753
Metastatic	114 (83.8)	93 (86.1)	
Oligometastasis[a]	6 (4.4)	5 (4.6)	0.999
Metastasis location[a]			
Brain	29 (21.3)	20 (18.5)	0.702
Liver	9 (6.6)	15 (13.9)	0.093
Bone	55 (40.4)	49 (45.4)	0.520
Adrenal glands	18 (13.2)	14 (13.0)	0.999
Opposite lung	23 (16.9)	31 (28.7)	0.040
Lymph node	30 (22.1)	22 (20.4)	0.871
Pleura	18 (13.2)	17 (15.7)	0.711
Others	19 (14.0)	12 (11.1)	0.636

[a]: n (%).

The overall survival in patients aged 70 years or older was 264.5 days [min-max: 220-1741]. Although it was shorter than that of the patients younger than 70 years (307 days [min-max: 18-1433]), the difference was insignificant (p=0.137) (Fig. 1). There were no significant differences in the overall survival of the patients with adenocarcinoma and squamous cell carcinoma (294.0 days [min-max: 18- 1741] and 255 days [min-max: 22-1127], respectively; p=0.503).

The Cox proportional analysis revealed that the overall survival was significantly associated with weight loss (HR=2.22, 95 % CI: 1.23-4.01), ≥2 comorbidities (HR=1.86, 95 % CI: 1.27-2.71), and TNM stage 4 (HR=2.03, 95 % CI: 1.27-3.24) (Table 5).

Discussion

Our study showed no significant differences in the overall survival between the elderly and younger patients with NSCLC when the cut-off point for defining the old age group was accepted as 70 years. However, the median survival was shorter in geriatric patients. Weight loss, increased number of comorbidities, and TNM stage IV were the significantly poor prognostic factors for reduced overall survival in patients with NSCLC.

The overall survival of NSCLC patients was previously shown to be affected by several factors, including age, stage of the disease, nutritional status, and treatment modalities.[15,18,19,21] Janssen-Heijnen et al. showed a significant decrease in the relative three-year survival of the patients aged 80 years or more (13%) compared with those of the patients younger than 60 years (62%) in their study that included all NSCLC patients with various age ranges. [15] Cardia et al. reported an increased survival associated with the use of chemotherapy in the elderly lung cancer patients who underwent thoracic radiotherapy with or without chemotherapy.[18] Another population-based study in lung cancer patients 80 years or older showed inferior outcomes due to lower treatment rates.[10,11] Tas et al. reported poor outcomes of the elderly patients (≥60 years).[5] Our findings revealed a tendency for shorter overall survival in geriatric patients. Also, the transition from first-line to second-line chemotherapy was significantly lower in the geriatric patient group. So, our findings did not support the negative impact of older age on survival. The discrepancy between our results and others might be

Table 3. Details of the treatment protocols and the chemotherapy cycles

	Patients		p
	<70 year (n=136)	≥70 year (n=108)	
Neoadjuvant chemoradiotherapy[a]	20 (14.7)	15 (13.9)	0.999
Induction chemotherapy[a]	20 (14.7)	15 (13.9)	0.999
Radiotherapy[a]	19 (14.0)	14 (13.0)	0.968
First-line chemotherapy[a]	124 (91.2)	101 (93.5)	0.662
Single agent, classical	1 (0.8)	0 (0.0)	0.999
Cisplatin-based double-agent	113 (91.1)	87 (86.1)	0.331
Targeted tyrosine kinase inhibitor	0 (0.0)	1 (1.0)	0.449
Best supportive care	10 (8.1)	13 (12.9)	0.336
Second-line chemotherapy[a]	42 (30.9)	18 (16.7)	0.016
Single-agent, classical	19 (45.2)	11 (61.1)	0.398
Cisplatin-based double-agent	19 (45.2)	4 (22.2)	0.164
Targeted tyrosine kinase inhibitor	3 (7.1)	3 (16.7)	0.352
Immunotherapy	1 (2.4)	0 (0.0)	0.999
Third-line chemotherapy[a]	15 (11.0)	4 (3.7)	0.060
Single agent, classical	12 (80.0)	3 (75.0)	0.999
Cisplatin-based double-agent	1 (6.7)	0 (0.0)	0.999
Targeted tyrosine kinase inhibitor	2 (13.3)	1 (25.0)	0.530
Fourth-line chemotherapy[a]	8 (5.9)	1 (0.9)	0.047
Single agent, classical	6 (75.0)	0 (0.0)	0.333
Immunotherapy	2 (25.0)	1 (100.0)	0.333
Fifth-line chemotherapy[a]	2 (1.5)	0 (0.0)	0.505
Immunotherapy	2 (1.5)	0 (0.0)	0.505
Prognosis [a]			
Survive	38 (27.9)	19 (17.6)	0.081
Non-survive	98 (72.1)	89 (82.4)	

[a]: n (%).

related to the differences in patient and treatment characteristics. The reciprocal relationships between the clinical and tumoral characteristics may be essential and lead to such controversial outcomes.

It is generally accepted that there is a positive correlation between the number of comorbidities and the age of the patients.[15] The prevalence of comorbidities increases with age.[19] Yet, the influence of coexisting diseases on survival has been only speculated by several authors, possibly due to the perception about their decreased importance in lethal oncological situations.[15] Cardia et al. showed no impact of comorbidity on the survival of patients treated primarily with thoracic radiotherapy.[18] No effect of comorbidity on the survival of untreated elderly lung cancer patients was also reported.[19] In this study, we found that the number of comorbidities was negatively associated with overall survival. Based on the controversies around age and comorbidities, we recommend that the patients with lung cancer should be overviewed for their general condition, age, and comorbidities in order to plan surgical and medical treatment options accordingly. In most cases, a single of those factors does not suffice to explain how the physicians decide the treatment plan.[15] Besides the age of the patients, the number of comorbidities, especially if their numbers are high, should be considered.

The use of different lines of chemotherapy shows some variations between the studies. In a real-world setting, the authors found that 23 % of patients with the first-line chemotherapy received the second-line treatment.[7] Our rate was 26.7% for all patients. Besides, younger patients were more likely to receive second-line chemotherapy. There might be several explanations for this lower transition rate from the first-line to the second-line chemotherapy in geriatric patients. Older age, a higher number of comorbidities or aggressive behavior of lung cancer might be the rea-

Table 4. Comparison of the demographic and clinical characteristics of the patients who survived and non-survived

	Prognosis		p
	Non-survived (n=187)	Survived (n=57)	
Age[a]			
<70 year	98 (52.4)	38 (66.7)	0.081
≥70 year	89 (47.6)	19 (33.3)	
Sex[a]			
Male	158 (84.5)	44 (77.2)	0.281
Female	29 (15.5)	13 (22.8)	
Weight loss[a]	167 (93.3)	42 (76.4)	0.001
Smoking[a]	49 (86.0)	167 (89.3)	0.489
Coexisting disease[a]	90 (48.1)	25 (43.9)	0.679
≥2 comorbidities[a]	43 (23.0)	6 (10.5)	0.040
Pathological diagnosis[a]			
Adenocarcinoma	52 (91.2)	157 (84.0)	0.248
Squamous cell carcinoma	5 (8.8)	30 (16.0)	
TNM stage[a]			
3B	13 (7.0)	12 (21.1)	0.012
3C	8 (4.3)	4 (7.0)	
4A	101 (54.0)	29 (50.9)	
4B	65 (34.8)	12 (21.1)	
Chemotherapy[a]			
First-line	177 (94.7)	48 (84.2)	0.020
Second-line	40 (21.4)	20 (35.1)	0.054
Third-line	8 (4.3)	11 (19.3)	0.001
Fourth-line	2 (1.1)	7 (12.3)	0.001
Fifth-line	0 (0.0)	2 (3.5)	0.054

[a] : n (%).

sons. We have difficulty clarifying the impact of these factors on the relatively shorter survival of geriatric patients. Thus, prospective studies are needed to evaluate such controversies.

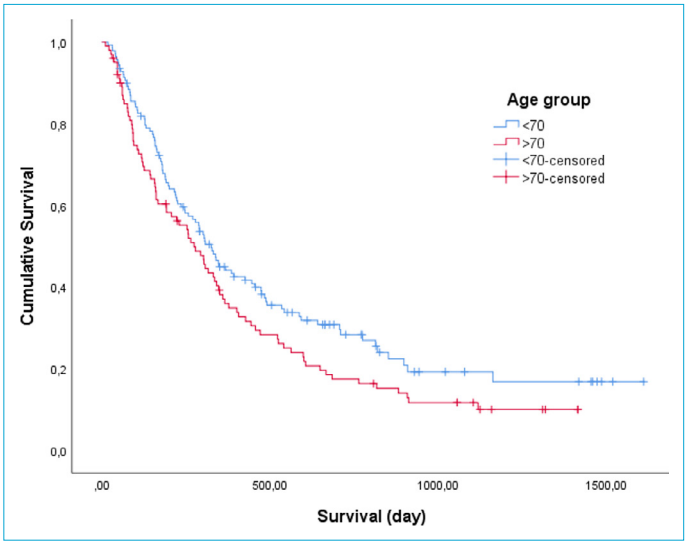

Figure 1. Survival curves of individuals over and under 70 years old.

The retrospective design was the major limitation of this study. Some clinical information, including the Eastern Cooperative Oncology Group scores and the Karnofsky performance status, the assessment of the nutritional status and data on the adherence to the treatment was not available to collect and analyze. The current study classified the comorbidities according to their numbers and did not use any comorbidity scoring system such as Charlson Comorbidity Index. This may be regarded as another limitation leading to insufficient evaluation of the burden of multiple diseases on the prognosis of lung cancer. Although the median overall survival was shorter in patients ≥70 years than <70 years, we found no statistically significant difference. The sample size of both groups might be inadequate to detect a significance.

Conclusion

The age of the patients with NSCLC has no significant impact on overall survival. Decreased survival is associated with weight loss, increased comorbidities, and TNM stage IV in patients with NSCLC.

Table 5. Univariate and multivariate Cox proportional hazard models of the overall survival

	Univariate		Multivariate	
	HR [95%CI]	p	HR [95%CI]	p
Age: *≥70-year vs <70 year*	1.25 [0.93-1.68]	0.134	1.09 [0.79-1.52]	0.597
Weight loss: *Present vs absent*	2.39 [1.33-4.29]	0.004	2.22 [1.23-4.01]	0.008
≥2 comorbidities: *Present vs absent*	1.66 [1.16-2.36]	0.005	1.86 [1.27-2.71]	0.001
Pathological diagnosis: *Squamous cell vs adenocarcinoma*	1.24 [0.84-1.84]	0.282	1.09 [0.70-1.69]	0.704
TNM stage: *Stage 4 vs stage 3*	1.92 [1.22-3.04]	0.005	2.03 [1.27-3.24]	0.003

HR: Hazard ratio; CI: Confidence interval.

Disclosures

Ethics Committee Approval: The local ethical committee approved the study (116.2017.124).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept: A.O., O.O.; Design: A.O.; Supervision: C.A.B.; Materials: A.O., O.O.; Data Collection and/or Processing: A.O., O.O., M.H.I., M.K.; Analysis and/or Interpretation: A.O.; Literature Search: A.O., O.O., O.B.T; Writing: A.O., O.O.; Critical Review: C.A.B., M.G.

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