Original Article

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TANAFFOS

Trends in Epidemiology and Outcome of Small Cell Lung Cancer over 10 Years at Tertiary Cancer Care Center in Iran

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Background: Lung cancer is the leading cause of cancer death. Among different lung cancer histopathologies, small cell lung cancer (SCLC) has been known to be the most aggressive and lethal nature. This study analyzed the epidemiological characteristics, outcomes, and trends of SCLC at a tertiary cancer care center in Iran.

Materials and Methods: Retrospectively collected demographic characteristics and survival outcome data on histologically proven SCLC patients during 2009-2019 at the National Research Institute of Tuberculosis and Lung Disease (NRITLD) were reviewed.

Results: In a study of 334 SCLC patients, there were more male patients than female, with a ratio of 2.5 to 1, and the mean age at diagnosis was 58.36 years. While gender distribution and smoking status among women remained consistent over the study period, there was a significant increase in male smokers ($P<0.001$). Female patients were diagnosed at younger age and had a significantly lower proportion of smokers compared to males ($P<0.016$). The mean and median overall survival were 10.9 and 8.2 months, with one-, two-, and three-year survival rates of 21%, 10%, and 3% respectively. Younger patients and females had significantly higher survival rates. In both uni/multivariate analyses, only age < 58 years and female gender were significantly associated with longer survival.

Conclusion: The relatively unchanged trend of SCLC in our series suggests that further research on prevention strategies especially smoking cessation, early detection, and new treatment options is urgently required.

Keywords: Epidemiology; Small Cell Lung Carcinoma; Survival

INTRODUCTION

Lung cancer- top of the league table of cancer death (1) is divided into two main histopathological types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Even though the lung cancer epidemic has significantly declined in developed countries, it has a growing trend (2). In Iran, the Incidence of lung cancer is not very high but in terms of mortality, it is in the second and third position in men and women, respectively (3).

SCLC originates in neuroendocrine cells accounting for 13-15% of all lung cancers (4). In past decades, its incidence has decreased but its mortality is still high (5). Systemic platinum-based chemotherapy with or without radiotherapy is the main treatment recommended by

guidelines. Surgery is limited to only a small proportion of limited-stage patients (6). SCLC has a very aggressive course and most patients are diagnosed in metastatic/extensive stages (7). Less than 7% of SCLC patients will survive after 5 years of initial disease diagnosis (8). Moreover, unlike NSCLC, not much progress has been made in the treatment and survival of SCLC. Thus, it is essential to emphasize clinical awareness for screening and early detection of SCLC. This aim is achieved through preventive and control programs, including regular monitoring of cancer surveillance (9).

To our knowledge, there have been some studies at an international level to assess the trend in some aspects of SCLC, but few studies have previously analyzed the epidemiological characteristics of SCLC in Iran. This study analyzed the epidemiological characteristics of SCLC to provide a reference for SCLC epidemiologic trend in our country.

MATERIALS AND METHODS

This cross-sectional retrospective and hospital-based study included all SCLC cases that were classified according to the International Classification of Diseases for Oncology, Version 3, code as follows: SCLC (8041 and 8043-8045) from 20 March 2009 to 19 March 2019 at the National Research Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital. Informed written consent was obtained according to Shahid Beheshti Medical University's ethics and scientific committees (Number: IR.SBMU.MSP.REC.1399.077). Disease staging was done according to The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification (10). In summary, extensive-stage disease describes tumors that extend beyond the ipsilateral hemithorax.

Statistical analysis

The mean ± standard deviation (SD) was calculated for the continuous variables. For categorical values, numbers and percentages were obtained and the chi-square test (or Fisher's exact test when appropriate) and Student's t-test were used, respectively. For comparing differences of 1, 2, and 3 years survival in life table with risk factors (including age, gender, and disease stage), the Wilcoxon (Gehan) test was used.

All confidence intervals (CIs) for parameters to be estimated were constructed with a significance level of alpha=0.05 (a 95% confidence level). The Cox proportional hazards model was utilized for both uni/multivariate analyses assessing the impact of independent variables (including age, gender, disease stage, and smoking status) in relation to overall survival (OS).

Kaplan Meier's survival curves were obtained for OS. OS was calculated from the date of registration in the study to the date of death. Patients who were alive or lost to follow-up at the time of data analysis were censored for OS analysis. The log-rank test was used to assess the differences between OS rates. The history of smoking status was recorded by self-report. Non-smoker is defined as a person who has smoked less than 100 cigarettes in his/her lifetime (11). Patients who had smoked in their life but did not smoke at the time of the examination were regarded as ex-smokers.

A P-value of less than 0.05 was considered statistically significant. IBM SPSS statistical software version 19 for Windows (IBM, Armond, NY, USA) was used for the data analysis.

RESULTS

The analysis was performed on 334 patients who were diagnosed with SCLC. The range of follow-up time was between 1 and 99.8 months. The study cohort included 97% of Iranian patients and 3% of other nationalities. Among the patients, 239 (87.7%) cases were male, and the rest of them were female (n=41, 12. 3%). The mean age was 58.36 years (median: 59 years, SD: 10.8, and range: 21-89 years). Over the study period, the mean age at diagnosis did not change significantly overall (p-value=0.699). This lack of change was also observed in both male and female

groups (p-values=0.11 and 0.425 for males and females, respectively). The majority of cases were aged between 50 and 65 years old (n=191, 57.2%). Most cases were diagnosed as an extensive stage compared to the limited stage (n=196, 56.71% vs. n=138, 41.3%, respectively). The proportion of non-smokers was 20.9%. Table 1 shows the demographic and clinical characteristics of the patient's study. According to this table, the proportion of smoker cases among females was lower than male cases (P- value = 0.016).

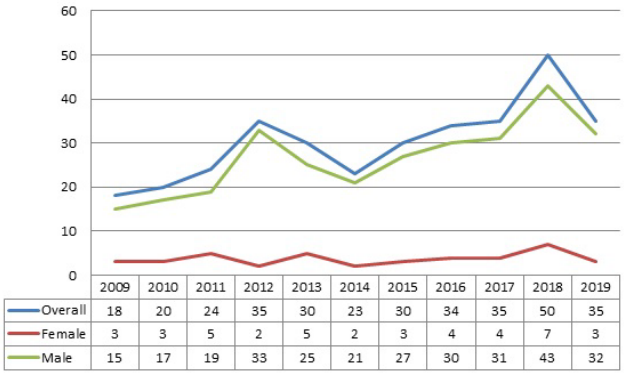
Table1. Demographic and clinical parameters in the study population

	Gender		P-value
	Female	Male	
Mean± SD of age [a]	56.5±13.3	58.6±10.4	0.346
Disease stage [b]			
Limited	22(15.9%)	116(84.1%)	0.087
Extensive	19(9.6%)	177(90.4%)	
Smoking Status [c]			
Non-smoker	28(40%)	42(60%)	
Smoker	11(5%)	213(95%)	0.016*
Ex-smoker	2(5%)	38(95%)	

a: SD: standard deviation; b: disease staging was done according to The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification, c: Non-smoker defined as a person who has smoked less than 100 cigarettes in his/her lifetime. Patients who had never smoked in their life but did not smoke at the time of the examination were regarded as ex-smokers.

* Significant P-value, student's t-test test (for comparing mean of age), and Chi-Square test (for comparing disease stage and smoking status) were used.

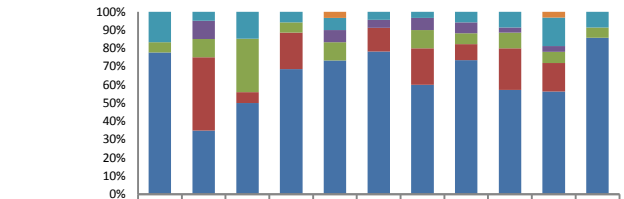
Figure 1 shows the SCLC incidence by gender during the study period. The Chi-Square test showed no statistically significant difference between the incidence of disease in the two groups (P-value =0.887).



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Overall	18	20	24	35	30	23	30	34	35	50	35
Female	3	3	5	2	5	2	3	4	4	7	3
Male	15	17	19	33	25	21	27	30	31	43	32

Figure 1. SCLC trends (overall and by gender) from 2009 to 2019 in the study population. The Chi-Square test showed no statistically significant difference between males and females (P-value =0.887)

The trend of smoking status by gender during the study period is shown in Figure 2. Smoking status has statistically significant trend changes in the Chi-Square test only in males (P-value<0.001) but has not changed in females (P-value=0.593) during 2009-2019.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Ex-smoker females	0	0	0	0	1	0	0	0	0	1	0
Non-smoker females	3	1	5	2	2	1	1	2	3	5	3
Smoker females	0	2	0	0	2	1	2	2	1	1	0
Ex-smoker males	1	2	10	2	3	0	3	2	3	2	2
Non-smoker males	0	8	2	7	0	3	6	3	8	5	0
Smoker males	14	7	17	24	22	18	18	25	20	18	30

Figure 2. The trend of smoking status by gender during the study period. Smoking status has statistically significant trend changes in the Chi-Square test only in males (P-value<0.001) but has not changed in females (P-value=0.593)

Survival analysis

At the time of data analysis, 276 (82.6%) patients (including 246 male and 30 female) had been expired but information about the exact date of death was available only in 201 cases. Means and medians of OS were 10.9±0.8 months (range 4.5-16 months) and 8.2±0.59 (range 4.2-11.2 months), respectively. Figure 3 shows the OS of the patients.

The statistically significant difference in the Log-rank test between means and medians of OS during the study period is shown in Figure 4 (P- value= 0.007).

Mean OS±SD in limited and extensive stages were 12.2±1.3 and 10.4±1.06 months, respectively. However, it wasn't statistically significant (P-value=0.229). One, two, and three-year survival rates of the study population are demonstrated in Table 2 concerning sex, age, and disease stage. Significant differences were observed by the Wilcoxon test only in younger patients and females (P-values= 0.005 and 0.014, respectively).

The relationship between demographic characteristics (such as age, disease stage, and smoking status) and overall survival (OS) was assessed through both uni and

multivariate analysis (Table 3). In Cox regression analysis --both uni and multivariate analysis-- female and younger (<58 years) patients had significantly longer OS.

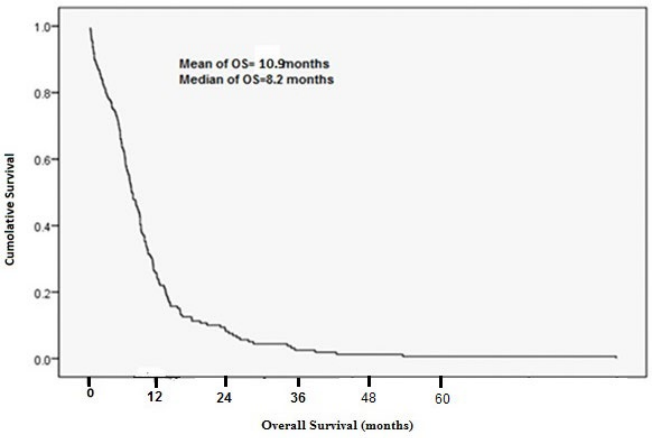


Figure 3. The Kaplan-Meier survival curve from overall survival (OS) in the study population

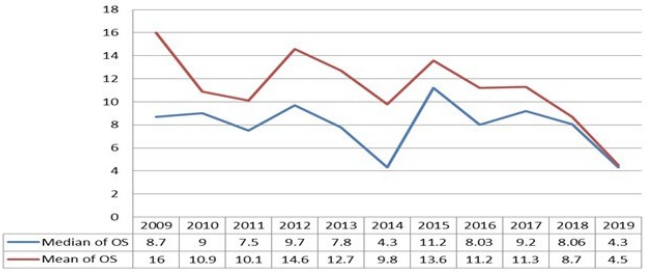


Figure 4. The means and medians of overall survival (OS) from 2009 to 2019. The Log-rank test showed a statistically significant difference between means and medians of OS during the study period (P- value= 0.007)

Table 2. One, two, and three-year survival rates of study population

	One year survival	Two years survival	Three years survival	P-value
Overall	21%	10.3%	3%	-
Gender				
Female	37%	27%	16%	0.005*
Male	27%	17%	14%	
Age [a]				
<58 years	15.3%	14%	5.3%	0.014*
>58 years	14.3%	3.6%	3.4%	
Stage [b]				
Limited	25%	14.3%	9.1%	0.355
Extensive	18.1%	16.6%	2.5%	

a: the median of age has been used for age cutoff; b: disease staging was done according to The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification.

* Significant P-value

Table 3. Association between demographic characteristics and OS in uni/multivariate COX regression analysis

	Univariate analysis			P-value	Multivariate analysis		P-value
	n(%)	OR[a]	CI[b](95%)		OR	CI(95%)	
Gender							
Male vs. Female	182(90.5) 19(9.5)	1 1.677	1.018-2.764	0.042*	1 1.685	1.003-2.830	0.049*
Age							
<58 vs. >58 years	115(57.2) 86(42.8)	1 1.628	1.211-2.188	0.001*	1 1.574	1.159-2.139	0.004*
Stage							
Limited vs. Extensive	77(38.3) 124(61.7)	1 0.836	0.624-1.120	0.230	1 0.971	0.715-1.320	0.971
Smoking status							
Non-smoker vs. Smoker[c]	71(35.3) 130(64.7)	1 0.963	0.717-1.293	0.802	1 0.901	0.662-1.225	0.504

a: Odds ratio, b: CI: confidence interval, c: the median of age has been used for age cutoff; d: disease staging was done according to The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification. e: smoker including active smokers and ex-smokers

* Significant P-value

DISCUSSION

To the best of our knowledge, our study is the first 10-year single institute analysis to evaluate the clinical trend of SCLC in Iran. The present report confirmed that SCLC is highly associated with smoking as most of the study patients were smokers. Our results demonstrated that age, gender distribution, and smoking status in women were unchanged over the study period. Increased male smoker proportion and changes in the mean and median of OS were statistically significant during the study period. Survival in our study population was poor but younger age at diagnosis and female gender were associated with better survival.

Different surveys have revealed that the female gender is a prognostic factor that predicts better survival (12-15). One possible explanation may be described by more benefits from chemotherapy in females than males as Spiegelman et al. (16) showed. Another possible cause for longer survival in females may be a lower tobacco smoking

rate in women than in men. Previous studies have confirmed that smoker patients have shorter survival than non-smokers (17). Also, genetic, hormonal, and metabolic differences between men and women are other probable factors affecting survival rates.

The average of age in our study is similar to other studies (18,19). Age at disease diagnosis was unchanged over the study period which was similar to Singh et al. (20) and another study from Iran (21). Age has been a topic of debate as a prognostic factor for survival in several studies of small cell lung cancer (SCLC). Most studies agreed that younger patients have better outcomes than older cases (22-26). Our result was in accordance with the currently mentioned studies. Christodolou et al. (27) showed that older patients have poorer responses to treatment. The worse outcome may be related to the presence of comorbidities in the elderly (20,28). In addition, drug-related toxicities have been reported more in older patients and can limit appropriate treatment.

The majority of SCLC patients are diagnosed in the advanced stage of the disease (27) because tumoral cells in SCLC have a short doubling time and high growth fraction (29). In addition, the unavailability of early screening methods is another reason for more patients with advanced stages than limited stages at the time of disease diagnosis. Similar to the mentioned studies, most of our patient population was diagnosed at advanced stages of the disease. Also, in the present study, a greater percentage of men than women were diagnosed with advanced disease. Rodríguez-Martínez et al. (30) showed that smokers may have an increased risk of presenting with advanced stage at diagnosis. A higher proportion of male smokers and ex-smokers than female smokers and ex-smokers in our series may result in the diagnosis of most patients at advanced stages.

Among other major lung cancer histologies, SCLC has been highly associated with smoking (7). More than 90% smoking rate was reported in most studies (30). It is believed that discontinuation of smoking, even at diagnosis, may have beneficial effects on survival. Our results showed the marginal effect of smoking history on survival as in some other studies (31,32). Even though, smoking status had no significant effect on OS in Lee et al (33) study. The lack of a prognostic effect of tobacco smoking history on survival in our cohort may be likely due to the small numbers of non-smokers as has been reported in other studies (33,34).

Although smoking history remains the most important risk factor for SCLC pathogenesis, lung cancer is still diagnosed in non-smokers. The smoking rate is estimated at 12% in Iran which is relatively lower than other countries (35). The proportion of non-smokers with SCLC in East Asian patients seems to be higher than that in Caucasian patients (36,37). Secondhand smoking can be attributed to developing SCLC in non-smokers. Another recognized etiological factor of SCLC in non-smokers is radon exposure (38). Also, some investigators have observed differences in gene landscapes of smoker and non-smoker SCLC patients such as epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) (39).

During the study period, we did not observe a significant decrease in the number of SCLC patients as Breitling et al. observed, too (40). Many studies have shown that the rates and trends of SCLC reflected the trend of tobacco consumption (29,41). An increasing pattern in the number of cases from 2009 to 2019 highlights the need for further educational and preventive programs such as smoking cessation in the Iranian population.

In most studies, patients with SCLC have a very poor prognosis with a median survival time of 8 to 12 months (25). The mean and median survival for the present study was similar to other studies (15,25,26). The sudden decrease in the mean and median of survival in 2019 is due to the COVID-19 pandemic and probably fewer patient referrals. Also, the overall one- and two-year survival of our series is similar to other studies (23, 24,27,42).

The single-center and retrospective nature of our study was the most important limitation of the present study. So, our findings need to be validated in large-scale prospective studies.

CONCLUSION

In conclusion, this study presents a detailed clinical characterization of a unique, large real-life cohort of SCLC patients. Our study highlights the need to implement smoking cessation programs aiming to decrease SCLC incidence.

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