

Research Article

Survival Trends for Patients with Small Cell Lung Cancer (SCLC) in the United States: Analysis of the SEER Database

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Keywords

• Small cell lung cancer; Survival

Abstract

Background: Small cell lung cancer (SCLC) generally has poor outcomes. The last thirty years have seen some improvement in management options for these patients, but their impact on the general population is unclear.

Objective: The present study analyzed trends in the diagnosis and survival of SCLC patients between 1988 and 2015.

Method: The Surveillance, Epidemiology, and End Result (SEER) registry was used to identify SCLC cases from 1988 to 2015. Patients were classified as having either limited stage (LS) or extensive stage (ES) disease. Cox regressions were used to compare overall survival (OS).

Results: We analyzed 98,281 SCLC patients. More males were diagnosed with ES-SCLC and had worse OS compared to females (HR: 1.14 [CI 1.11-1.16]). Although younger patients had higher proportion of ES-SCLC diagnosis, the older patients had worse OS for both stages (LS-SCLC: HR 1.36 [CI 1.32-1.40]; ES-SCLC: HR: 1.34 [CI 1.31-1.36]). Among LS-SCLC, Blacks had worse OS compared to Whites (LS-SCLC: HR 1.06 [CI 1.02-1.10]) and no differences in OS in ES-SCLC among races. Compared to the reference period 1988-1992, patients diagnosed with ES-SCLC during the later periods had improved OS: 1998-2002 (HR: 0.97 [CI, 0.94-1.00]), 2003- 2007 (HR: 0.92 [CI 0.90-0.95]), 2008-2012 (HR: 0.91 [CI 0.88- 0.94]), and 2013-2015 (HR: 0.91 [CI 0.88-0.94]).

Conclusion: Females, Whites, and younger patients with SCLC had better OS compared to males, Blacks, and older patients. The results show increase in OS of SCLC patients over time, particularly for those with LS-SCLC.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the United States (U.S.) [1]. According to the American Cancer Society estimate for 2019, there will be 228,150 new cases of lung cancer and 142,670 associated deaths [2]. Approximately 80% to 85% of lung cancer cases are non-small cell lung cancer (NSCLC); small cell lung cancer (SCLC) accounts for 13% of cases [2,3]. Although, the incidence of SCLC has decreased in the past two decades, mortality remains high [3-5]. SCLC follows an aggressive course and tends to metastasize early; hence, about 70% of patients are diagnosed with an extensive stage (ES) [4,6]. The last thirty years have seen limited improvements in options available for these patients, namely the use of platinum-etoposide as the primary chemotherapy option, use of thoracic radiation for patients with limited-stage (LS)- SCLC, addition of prophylactic cranial irradiation following initial therapy, and approval of topotecan as a salvage regimen [7-12]. However, the impact of these advances on outcomes in the general population is unclear. The purpose of this analysis was to examine the survival trend of SCLC patients.

METHODS

Data source

Data from the Surveillance, Epidemiology, and End Result (SEER) 18 Registry Research Database (1975-2015) was used to determine patient characteristics and survival for SCLC. SEER 18 collects data from 18 population-based cancer registries of the U.S., which represents about 28% population of the country.

Staging

The ES-LS system is used to determine management decisions and was used in the present analysis. In addition, this system has not changed despite the changes in the more conventional American Joint Committee on Cancer (AJCC) system. Limited stage (LS) is typically defined as disease that can be encompassed in a single radiation field, whereas extensive stage (ES) is that not encompassed within a single radiation field [13,14]. Thus, LS-SCLC generally corresponds to AJCC stages I to III, whereas ES-SCLC corresponds to AJCC stage IV [15]. Patients with unknown stage or occult stage were excluded.

Study cohort and variables

Site codes C34.0-C34.9 were used to extract information for lung and bronchial cancer for years 1988 to 2015. Histology codes 8041 to 8045 designated for SCLC in the SEER database were used. The 3rd and 6th edition of the AJCC staging was used to encompass all the years analyzed. Patients who were <20 years of age, had missing information, unknown survival time or a zero in survival month were excluded. Patients with zero survival months were excluded because we could not determine if it was due to loss to follow up or if the patient died on or near the day of diagnosis. The SEER variable vital status was used as the censoring variable. The variables analyzed for both stages, LS-SCLC and ES-SCLC, included age at diagnosis, gender, race, and year of diagnosis.

Statistical analysis

To examine changes in survival pattern, year of diagnosis (YOD) was grouped into six intervals: 1988-1992, 1993-1997, 1998-2002, 2003-2007, 2008-2012, and 2013-2015. Age at diagnosis was grouped into two categories: age ≤ 70 and >70 . The race was grouped into White, Black and Other. ES-SCLC and LS-SCLC were created by merging the variables from the 3rd and 6th editions of the AJCC into one variable, and then recoded as dichotomous: 1-3 were made into LS-SCLC and 4 is ES-SCLC.

Descriptive statistics used frequency distributions to determine the feature that predicted survival of SCLC patients. Overall survival (OS) for different variables was compared using Kaplan-Meier curves with log-rank statistics. We used Cox proportional-hazard regressions to examine the association of age at diagnosis, gender, race, and YOD with hazard ratios of death for patients with LS-SCLC or ES-SCLC. A p-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software version 25 (Armonk, NY: IBM Corp.).

RESULTS

The analysis was performed on 98,281 patients who were diagnosed with SCLC between 1988 and 2015, after excluding patients with occult stage or unknown stage, and those who had missing or incomplete information on survival month. Most cases were diagnosed as ES compared to LS (61% vs. 39%). The median survival for the SCLC varied by stages (LS 12 vs. ES 7 months), when no other predictors were included in the models.

Females were more likely to be diagnosed with LS disease than males (52.7% vs 47.3%). Both SCLC stages had a higher proportion of younger (≤ 70) compared to older patients (>70) (LS-SCLC: 57.5% vs 42.5%, $p<.0001$; ES-SCLC: 60.2% vs 39.8%, $p<.0001$).

Further analysis adjusted for predictor variables, such as sex, age, race, and year of diagnosis. Kaplan-Meier survival estimates showed that median OS for younger patients was higher compared to older patients for LS-SCLC (15 vs. 10 months, $p<.0001$) and for ES-SCLC (8 months vs. 5 months; $p<.0001$) (Table 1). Older patients with LS-SCLC had a 1.36-fold increased risk of death (95% CI: 1.32-1.40, $p<.0001$) when compared to younger patients; for ES disease the risk was 1.34 times higher (95% CI: 1.31-1.36, $p<.0001$).

Table 1: Descriptive statistics of study population for SCLC, 1988-2015.

Variables		SCLC Stages	
		LS N=38,182 n (%)	ES N=60,099 n (%)
Gender	Female	20,123 (52.7)	28,157 (46.9)
	Male	18,059 (47.3)	31,942 (53.1)
Age at diagnosis	≤ 70	21,949 (57.5)	36,172 (60.2)
	>70	16,233 (42.5)	23,927 (39.8)
Race	White	32,933 (86.3)	52,755 (87.8)
	Black	3543 (9.3)	5032 (8.4)
	Others	1683 (4.4)	2276 (3.8)
Year of diagnosis	1988-1992	2844 (7.4)	5141 (8.6)
	1993-1997	3,912 (10.2)	5868 (9.8)
	1998-2002	7074 (18.5)	10,487 (17.4)
	2003-2007	9654 (25.3)	14,255 (23.7)
	2008-2012	9251 (24.2)	15,136 (25.2)
	2013-2015	5447 (14.3)	9212 (15.3)

Abbreviations: SCLC: Small Cell Lung Cancer; LS: Limited Stage; ES: Extensive stage. The differences between the two stages for all variables were significant ($p=.0001$).

Median OS for whites with LS was 13 months compared to 12 months for blacks and other races; however, this was not significant (Table 3). The median survival for all races with ES-SCLC was 7 months ($p<.01$) (Table 3). The hazard of death due to LS-SCLC was not different for White and Other race categories (Table 2), but Black patients with LS had 6% increased risk of death compared to Whites (95% CI: 1.02-1.10, $p<.001$). However, for ES-SCLC, there was a significant difference between White and Other (HR: .99, 95% CI: .87-.95, $p<.0001$), but no significant differences between White and Black.

The OS rates for LS and ES-SCLC patients varied by gender. Females with LS-SCLC disease had a better median survival compared to males (13 vs 12 months, p -value $<.0001$) (Table 3). Median survival for females and males with ES-SCLC was 7 months ($p<.0001$) (Table 3). Males had a higher risk of death compared to females in the LS group (HR: 1.14, 95% CI: 1.11- 1.16, $p<.0001$) and the ES group (HR: 1.15, 95% CI: 1.13-1.17, $p<.0001$) (Table 2).

Multivariate analysis showed that the survival improved over time for both LS and ES-SCLC during the study period. Using the years 1988-1992 as the reference, LS-SCLC in years 1993- 1997 HR: 0.96 (CI: 0.91-1.00, $p<.05$) reduced to HR: 0.80 (CI: 0.72- 0.80, $p<.0001$) in years 2013- 2015; ES-SCLC in years 1993-1997 HR: 0.97 (CI: 0.93-1.01, $p<.137$) reduced to HR: 0.91 (CI: 0.88-0.94, $p<.0001$) in years 2013-2015 (Table 2).

DISCUSSION

About 61% of the study population was diagnosed with ES. The findings are consistent with other reports and national estimates [1,16]. The results show little improvement in early detection of SCLC. Challenges from the natural history of the disease, lack of early detection methods, and limited molecular profiling are factors related to the high proportion of SCLC patients diagnosed

Table 2: Multivariate analysis of factors affecting survival in SCLC by stages.

Variable		LS	p-value	ES	p-value
		HR (95% CI)		HR (95% CI)	
Gender	Female	ref		ref	
	Male	1.14 (1.11, 1.6)	<0.0001	1.15 (1.13,1.17)	<.0001
Age	≤70	ref		ref	
	>70	1.36 (1.32, 1.40)	<0.0001	1.13 (1.31, 1.36)	<.0001
Race	White	ref		ref	
	Black	1.06 (1.02, 1.10)	0.004	1.02 (0.99,1.05)	0.242
	Others	0.97 (0.93, 1.03)	0.318	0.99 (0.87, 0.95)	<.0001
Year of diagnosis	1988-1992	ref		ref	
	1993-1997	0.96 (0.91, 1.00)	0.062	0.97 (0.93, 1.01)	0.137
	1998-2002	0.98 (0.89, 0.97)	0.001	0.97 (0.94, 1.00)	0.05
	2003-2007	0.86 (0.83, 0.90)	<0.0001	0.92 (0.90, 0.95)	<.0001
	2008-2012	0.81 (0.78, 0.85)	<0.0001	0.91 (0.88, 0.94)	<.0001
	2013-2015	0.80 (0.72, 0.80)	<0.0001	0.91 (0.88,0.94)	<.0001

Abbreviations: SCLC: Small Cell Lung Cancer; LS: Limited Stage; ES: Extensive Stage. P-value was set at 0.05

Table 3: Kaplan Meier median survival estimates by SCLC stages.

Variables		LS	p-value	ES	p-value
		Median Survival (Months)		Median Survival (Months)	
Gender	Female	13	<0.0001	7	<.0001
	Male	12	<0.0001	7	<.0001
Age	≤70	15	<0.0001	8	<.0001
	>70	10	<0.0001	5	<.0001
Race	White	13	>.05	7	<.001
	Black	12	>.05	7	<.001
	Others	12	>.05	7	<.001

Abbreviations: LS: Limited Stage; ES: Extensive Stage. P-value was set at 0.05.

as ES [6,17,18]. The rapid growth and high malignancy of SCLC have caused difficulties in cancer detection [13,17]. To date, there has been no effective approach for early detection of SCLC as compared to NSCLC [6,18]. For NSCLC, the development of early detection methods have resulted in improved disease outcomes [6]. Unfortunately, early detection using CT screening has not resulted in an improvement in survival from SCLC [19]. These factors have contributed to the relatively unchanged therapeutic options over the past decades [17].

Despite the poor prognosis associated with SCLC, there has been little improvement in treatment over the past two decades. Chemotherapy with a platinum compound and etoposide is the main treatment for this disease [20]. Patients with LS-SCLC are generally treated with a combination of chemotherapy and radiation. A meta-analysis of 2,013 patients showed that, for LS-SCLC, the combination of radiation with chemotherapy translated into an absolute survival benefit of 5.4% at 3 years with a relative risk of death of 0.86 (95% CI, 0.78-0.94) [9]. Another meta-analysis of 1,524 patients showed that early initiation of radiation improved the 2-year survival rate with an OS relative risk of 1.17 (95% CI, 1.02-1.35) [21]. Both LS and ES-SCLC patients are

at increased risk of brain metastasis relative to other types of lung cancer [14,22]. SCLC patients (including ES-SCLC patients in some analyses) who were treated with prophylactic cranial irradiation (PCI) have better survival outcomes and reduced risk of brain metastasis compared to SCLC patients not treated with PCI [23,24].

Results from the present analysis reflect the minimal improvement in treatment outcomes over the decades for either of the stages of SCLC, which is consistent with two previous studies that used SEER database, showing improved or moderately improved survival [3,25]. Govindan et al., estimated survival using a short follow-up time [3], the present study had a longer follow-up period, which could result in a different mortality risk. In addition, our study used data that are more recent from the SEER registry, which has higher population coverage.

In general, the present results, obtained with a large population-based database, demonstrated some improvement in survival over time. ES patients showed steady improvements throughout, while those with LS experienced an increased risk in those diagnosed between 1993 and 1998,

but later improved through 2015. Moreover, more than 40% of patients in our cohort did not have any information about treatment. It is unclear as to how many of these patients were not recommended for treatment, refused treatment, or received suboptimal therapy. Since data regarding receipt of chemotherapy and detailed information about radiation (e.g., PCI, timing of radiotherapy) are unavailable in the SEER dataset, it is unclear if the minimal improvement in outcomes is due to non-receipt of recommended therapy or due to a lack of appreciable benefit. Nonetheless, the trend is promising and as more advancements in treatments and technology enter the field, SCLC outcomes may see further gains. However, since population-based data describing the trend of treatment utilization in the U.S. are limited, it is difficult to associate treatment patterns and outcomes in a real-world setting. A large hospital-based study in the U.S. reported increased use of chemo-radiation for LS-SCLC patients, but the 5-year survival rate for these patients did not increase appreciably [26]. Another study using SEER-Medicare data showed a modest survival benefit over time among SCLC patients who received chemotherapy, but the finding was not statistically significant [27]. A hospital-based study in the United Kingdom suggested that, although there is an upward trend in the receipt of chemo-radiation, the small increase does not substantially affect the OS [28].

In the last three decades, there has been an increase in the proportion of females with SCLC [3,5]. Our analysis also found a higher number of females with a diagnosis of LS-SCLC compared to males. Smoking is the leading cause for SCLC, being responsible for more than 90% of cases. Secondhand smoke increases the risk of developing any kind of lung cancer by 30% [2,3]. The higher numbers of females with SCLC can be attributed to increased prevalence of smoking in this population.

The present results are in agreement with those of other studies indicating that female SCLC patients have better survival outcomes compared to males [3,29,30]. Females have a better prognosis for LS-SCLC as well [30,31]. The reason for this difference is unclear [30]. A study at the National Cancer Institute shows a median survival of 13 months for females compared to 10 months for males for LS-SCLC; other studies conducted by the Cancer and Leukemia Study Group B (CALGB) and Southwest Oncology Group (SWOG) have similar findings [32,33].

With increasing age, survival for SCLC is decreased [34,35]. In accordance with previous studies, we found that overall survival outcomes were worse for older (≥ 70 years) SCLC patients. The reason for worse survival of older patients may be because of more comorbidities, reduced organ function, or organ failure [36,37]. The combination of reduced performance status, comorbidities, and elevated risk for toxicities causes older patients to receive less aggressive treatment and to be withdrawn from treatment [34]. However, elderly patients who can tolerate toxicity from chemotherapy show similar survival relative to younger patients [38]. Thus, it is necessary to identify which elderly patients can tolerate intensive treatment. Our findings show that, compared to Whites, African Americans have a higher risk of dying from SCLC. Previous studies show that this disparity in outcomes is partly because African American patients are diagnosed at an advanced stage [39,40]. The lower socio-

economic status and limited access to health care could be factors that prevent African Americans from receiving timely treatment [39,40]. A study of NSCLC using the SEER Medicare database shows that, compared to whites, African Americans often do not receive proper staging, and, even if they are staged properly, are less likely to receive appropriate treatment [41]. Another study using Veterans Affairs Central Cancer Registry data on NSCLC shows that, compared to Whites, the proportion of African Americans not receiving appropriate staging is higher [42]. However, these studies and others show that if African Americans get proper staging and treatment, after adjusting for socio-economic factors, survival is not different and may be slightly better compared to whites [41-43].

Limitations of the present study include lack of information on the provision of chemotherapy and reasons for not administering radiotherapy. In the study cohort, a large proportion of patients did not receive radiation, but we could not determine if these patients were treated with chemotherapy alone. This limitation made us unable to analyze the impact of treatment on survival. However, the information represents the care received by patients in a real-world setting. Hence, we feel that the findings serve to underline the differences in the efficacy of management approaches.

In conclusion, there has been some improvement in outcomes for SCLC patients in this population-based database, which is in line with advances in SCLC outcomes in clinical trials. We should consider whether there is racial bias in providing and receiving treatment and an effort should be made to provide standard care to all patients irrespective of their race, ethnicity, and gender.

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