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Research paper

Clinical predictors of survival in young patients with small cell lung cancer: Results from the California Cancer Registry☆

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ABSTRACT

Background: Small cell lung cancer (SCLC) is an often lethal disease that commonly occurs in older individuals with a history of heavy tobacco use. Limited epidemiologic and outcomes data are available on young SCLC patients aged less than 50 years of age. We assessed clinical variables related to cause specific survival (CSS) of young patients with SCLC.

Methods: SCLC patients in the California Cancer Registry diagnosed between 1998 and 2012 were included. Primary outcome measure was CSS. Hazard ratios (HR) for CSS were calculated using Cox Proportional Hazards (pH) models for all ages & for patients < 50 years, adjusted for baseline variables: age, gender, stage, race, year of diagnosis, initial treatment, socioeconomic status (SES), and location (urban vs. rural).

Results: We identified 22,863 SCLC patients, of which 975 were less than 50 years of age (4.2%). Most patients < 50 years of age were male (51%), white race (71%), and had stage IV disease (60%). A lower proportion of patients aged 50 years or younger was diagnosed in later years: from 40% in 1998–2002 to 24% in 2008–2012. For all SCLC patients, age less than 50 years was an independent predictor of improved CSS (HR = 0.82, p < 0.0001). Multivariate Cox pH models showed that in younger patients, female sex (HR = 0.81, p = 0.0045), Asian race (HR = 0.57, p = 0.0075), and rural residence (HR = 0.75, p = 0.042) were associated with better CSS, among other variables.

Conclusions: In patients with SCLC, age less than 50 years was an independent predictor of improved CSS. Baseline clinical variables associated with better CSS were identified. These results have potential clinical applications.

1. Background

Small cell lung cancer (SCLC) represents approximately 10–15% of all lung cancer diagnoses in the United States. It is a uniformly lethal disease that commonly occurs in older individuals with a history of heavy tobacco use. Unfortunately, long-term survival and treatment options for extensive stage SCLC have remained unchanged since the 1970s. Currently, platinum and etoposide remains the preferred first line chemotherapy regimen for the treatment of extensive stage SCLC. Although high response rates occur following platinum-based chemotherapy, tumor recurrence is universal and virtually all patients succumb to the disease [1]. Efforts to optimize treatment for these patients include the identification of baseline prognostic variables that may help inform therapeutic decision-making at the time of initial diagnosis [2].

Age at the time of diagnosis has been described as prognostic for survival in patients with non-small cell lung cancer (NSCLC), the more common subset of lung cancer, which includes adenocarcinoma and squamous cell cancer histologic subtypes. Specifically, younger patients (less than 50 years of age) with NSCLC have been reported to have better survival outcomes when compared to older patients [3,4]. In contrast, very little data have been reported with regard to young patients with SCLC. Identifying the clinical characteristics young patients with SCLC and establishing their subsequent survival outcomes would help develop a foundational database for future research. We therefore analyzed a state-based cancer registry to explore the clinical variables related to cause specific survival (CSS) of young patients with SCLC.

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Table 1
Small Cell Lung Cancer Patient Characteristics, California, 1998–2012.

Variable	All		Age < 50		Age ≥ 50		P-Value
	N	%	N	%	N	%	
Total	22,863	100.0%	975	4.3%	2188	95.7%	
Age							
Age < 30	7	0.0%	7	0.7%	.	.	
30–39	88	0.4%	88	9.0%	.	.	
40–49	880	3.8%	880	90.3%	.	.	
50–59	3979	17.4%	.	.	3979	18.2%	
60–69	7327	32.0%	.	.	7327	33.5%	
70–79	7592	33.2%	.	.	7592	34.7%	
80+	2990	13.1%	.	.	2990	13.7%	
Gender							
Females	11,140	48.7%	477	48.9%	10,663	48.7%	0.8994
Males	11,723	51.3%	498	51.1%	11,225	51.3%	
Race/Ethnicity							
Non-Hispanic White	17,652	77.2%	689	70.7%	16,963	77.5%	< 0.0001
Non-Hispanic African American	1495	6.5%	120	12.3%	1375	6.3%	
Hispanic	2152	9.4%	118	12.1%	2034	9.3%	
Asian/PI	1381	6.0%	43	4.4%	1338	6.1%	
Other/unknown	183	0.8%	5	0.5%	178	0.8%	
Year of Diagnosis							
1998–2002	8555	37.4%	387	39.7%	8168	37.3%	0.0008
2003–2007	7648	33.5%	356	36.5%	7292	33.3%	
2008–2012	6660	29.1%	232	23.8%	6428	29.4%	
Stage							
Stage I	1001	4.4%	36	3.7%	965	4.4%	0.5237
Stage II	345	1.5%	11	1.1%	334	1.5%	
Stage III	6069	26.5%	274	28.1%	5795	26.5%	
Stage IV	13,845	60.6%	583	59.8%	13,262	60.6%	
unknown	1603	7.0%	71	7.3%	1532	7.0%	
Treatment-Surgery							
Yes	488	2.1%	22	2.3%	466	2.1%	0.6182
No	22,355	97.8%	953	97.7%	21,402	97.8%	
unknown	20	0.1%	.	.	20	0.1%	
Treatment-Chemotherapy							
Yes	14,672	64.2%	769	78.9%	13,903	63.5%	< 0.0001
No	7754	33.9%	186	19.1%	7568	34.6%	
unknown	437	1.9%	20	2.1%	417	1.9%	
Treatment-Radiation							
Yes	9050	39.6%	552	56.6%	8498	38.8%	< 0.0001
No	13,802	60.4%	423	43.4%	13,379	61.1%	
unknown	11	0.0%	.	.	11	0.1%	
Location							
Urban	21,072	92.2%	894	91.7%	20,178	92.2%	0.5734
Rural	1791	7.8%	81	8.3%	1710	7.8%	
Neighborhood Socioeconomic Status (SES)-imputed							
Lowest SES-1	4028	17.6%	218	22.4%	3810	17.4%	< 0.0001
2	5194	22.7%	262	26.9%	4932	22.5%	
3	5351	23.4%	207	21.2%	5144	23.5%	
4	4600	20.1%	166	17.0%	4434	20.3%	
Highest SES-5	3360	14.7%	105	10.8%	3255	14.9%	
Unknown	330	1.4%	17	1.7%	313	1.4%	

2. Methods

Data on lung cancer patients from the California Cancer Registry (CCR), a statewide population-based cancer surveillance system composed of 3 regional registries collecting cancer incidence and mortality information since 1988, were evaluated. Cases are reported to the Cancer Surveillance Section of the California Department of Public Health from hospitals and any other facilities providing care or therapy to cancer patients residing in California.

The CCR database that was used in this study was housed under the Cancer Registry/Epidemiology Shared Resource of the UC Davis Comprehensive Cancer Center. There were no links to patient identifiers in this dataset.

Cases included in these analyses were any stage SCLC diagnosed between January 1, 1998 and December 31, 2012 and reported to the Cancer Surveillance Program as of October 2013. Patient demographic data included age, race/ethnicity, gender, location of residence at diagnosis, and neighborhood SES. Neighborhood socioeconomic status in the CCR is a multicomponent index of U.S. Census characteristics (education, occupation, unemployment, household income, poverty, rent and house values) based on residential census-block group at diagnosis. Stage and initial treatment (surgery, chemotherapy, and radiation) were also included.

Descriptive statistics were used to describe the demographic and tumor characteristics of the cohort. The primary outcome variable was cause-specific survival (CSS). The Kaplan-Meier method was used to determine survival. Hazard ratios (HR) for CSS were calculated using multi-variable Cox Proportional Hazards (pH) models for all ages and for patients < 50 years, adjusted for baseline variables: age, gender, stage, race, year of diagnosis, treatment, socioeconomic status (SES), and location (urban vs. rural). All the analyses were performed using SAS 9.3 (SAS, Cary, NC) and all p-values were two-sided.

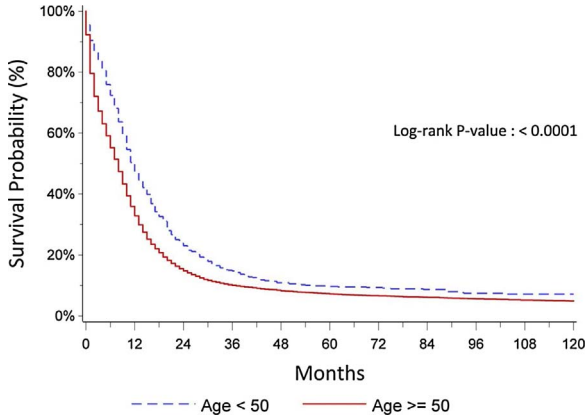

Fig. 1. Cause specific survival of SCLC patients by age group (< 50 vs. ≥50 years of age).

3. Results

Of 22,863 SCLC patients in the CCR, 975 were less than 50 years of age (4.3%). Clinical characteristics for all patients and for those < 50 years of age are shown in Table 1. Young patients with SCLC were likely male (51%), predominantly Non-Hispanic White race (71%), had stage IV disease (60%), and lived in an urban location (92%). Only 11% were among the high SES (4–5) group. Fewer patients were diagnosed in later years: from 40% in 1998–2002 to 24% in 2008–2012. Additionally, the proportions of Hispanic and non-Hispanic African Americans appear to be higher in young patients when compared to older patients and the entire population. Specifically, non-Hispanic African Americans accounted for 12.3% of the younger cohort, 6.3% of the older cohort, and 6.5% of the total cohort. Similarly, Hispanics accounted for 12.1% of the younger cohort, 9.3% of the older cohort, and 9.4% of the total cohort.

Fig. 1 shows Kaplan Meier curves for CSS for all patients by age group. In this unadjusted analysis, patients younger than 50 years of age had significantly better CSS than patients ≥50 years of age (Log-rank p < 0.0001).

Multivariable analyses of all patients and patients < 50 years of age are summarized in Table 2. For all patients, age < 50 years of age was significantly associated with an improved CSS (HR = 0.82; 95% CI 0.76–0.88; p < 0.0001). Females (HR = 0.91; p < 0.0001) and Asian/Pacific Islanders (HR = 0.84; p < 0.0001) experienced improved CSS compared to males and Non-Hispanic Whites, respectively. Increasing stage at diagnosis and low SES (HR = 1.05; p = 0.0011) were associated with worse CSS compared to Stage I.

Among patients < 50 years old, females (HR = 0.81; p < 0.0001) and Asian/Pacific Islander race (HR = 0.57; p < 0.0001) were significantly associated with improved CSS, as well as treatment received. Conversely, only advanced stage at diagnosis was associated with worse CSS (Stage III HR = 1.81; p = 0.0282, Stage IV HR = 3.81; p < 0.0001).

4. Discussion

Small cell lung cancer is a disease of older individuals. In clinical trials of new agents in extensive stage SCLC, the typical median age at study entry is in the low sixties [2]. SCLC patients younger than 50 years of age are considered uncommon. In the Cancer and Leukemia Group B (CALGB) database, less than 40% of all patients with extensive stage SCLC were less than 60 years of age [5]. Nevertheless, there are anecdotal reports of young patients with SCLC – some of whom are never smokers – that have arisen in recent years [6–8]. In addition, a recent retrospective analysis of Turkish patients, the risk of developing SCLC was reported to be 1.6 times higher among men younger than 45 years of age compared to older men, with an odds ratio of 1.6 [9].

It is unclear whether younger SCLC patients in more modern series have differential outcomes when compared to older patients. Published data generally have conflicting results. In one of the earliest large-scale analyses of SCLC outcomes from the Southwest Oncology Group (SWOG), 2580 SCLC patients treated on SWOG trials between 1976 and 1988 were included [10]. In this study, age less than 70 years was found to be associated with more favorable outcome but only in patients with limited stage disease. In a 1996 retrospective analysis of National Cancer Institute of Canada (NCIC) trials in limited stage SCLC (n = 608) who were treated in a fairly uniform manner, 520 patients were found to be less than 70 years of age [11]. Tumor response, 5-year

Table 2
Multivariable Cox Proportional Hazards Analysis, Cause Specific Survival, California Small Cell Lung Cancer (SCLC) patients 1998–2012.

Variables	All SCLC patients			SCLC patients < 50 years old		
	HR	95% CI	P-Value	HR	95% CI	P-Value
Age at Diagnosis (vs. Age > = 50						
Age < 50	0.82	(0.76, 0.88)	< 0.0001	NA	NA	NA
Gender (vs. Male)						
Female	0.91	(0.88, 0.94)	< 0.0001	0.81	(0.70, 0.94)	0.0045
Race/Ethnicity (vs Non-Hispanic White)						
Non-Hispanic African American	0.95	(0.90, 1.01)	0.1207	0.89	(0.71, 1.13)	0.3374
Hispanic	0.95	(0.90, 1.00)	0.0709	0.99	(0.78, 1.26)	0.9635
Asian	0.84	(0.79, 0.90)	< 0.0001	0.57	(0.38, 0.86)	0.0075
Year of Diagnosis (vs. 1988–2002)						
2003–2007	0.96	(0.92, 0.99)	0.0096	0.95	(0.81, 1.12)	0.5562
2008-2011	0.94	(0.90, 0.98)	0.0017	0.89	(0.72, 1.10)	0.2796
Stage at Diagnosis (vs. Stage I)						
Stage II	1.22	(1.05, 1.43)	0.0111	1.20	(0.43, 3.31)	0.7255
Stage III	1.80	(1.65, 1.97)	< 0.0001	1.81	(1.07, 3.08)	0.0282
Stage IV	2.93	(2.70, 3.20)	< 0.0001	3.81	(2.26, 6.43)	< 0.0001
Stage Unknown	1.31	(1.18, 1.44)	< 0.0001	2.16	(1.21, 3.86)	0.0089
Treatment						
Surgery (vs. No)	0.43	(0.38, 0.49)	< 0.0001	0.37	(0.18, 0.73)	0.0040
Chemotherapy (vs. No)	0.44	(0.43, 0.46)	< 0.0001	0.49	(0.40, 0.60)	< 0.0001
Radiation (vs. No)	0.66	(0.64, 0.69)	< 0.0001	0.71	(0.60, 0.83)	< 0.0001
Location (vs Urban)						
Rural	0.97	(0.92, 1.03)	0.3042	0.75	(0.57, 0.99)	0.0419
Neighborhood Socioeconomic Status (SES) vs. High SES 4 & 5						
Low SES (1, 2, 3)	1.05	(1.02, 1.09)	0.0011	1.04	(0.89, 1.21)	0.6306

survival, and toxicity rates were similar between the age groups. The investigators ultimately concluded that “age is not a significant adverse prognostic variable in SCLC patients with limited disease.” A comprehensive review on elderly patients with SCLC stated that age alone is an “uncertain prognostic criteria for outcome” [12]. In a 2002 retrospective study of 516 Greek patients with SCLC treated on Hellenic Oncology Group trials, age ≥60 years was found to be associated with poor response to therapy [13]. A more recent (2011) single institution retrospective analysis of 397 patients with SCLC from Germany likewise reported that age was not a significant prognostic variable [14].

In our current study, we identified clinically relevant baseline prognostic features in patients with SCLC younger than 50 years of age. We found that age less than 50 years was indeed an independent predictor of improved CSS (HR = 0.82, $p < 0.0001$). Furthermore, female sex (HR = 0.81, $p = 0.0045$), Asian race (HR = 0.57, $p = 0.0075$), and rural residence (HR = 0.75, $p = 0.042$) were also associated with better CSS, among other variables. Survival outcomes of future clinical trials of SCLC patients should consider these variables as potentially confounding. Additionally, it is likely that the higher proportions of minority groups in the younger patients is attributable to the existing demographics of the state of California, which has seen growth in its migrant population in recent times. Finally, this work represents one of the largest registry studies of younger patients with SCLC ever reported and serves as a more contemporary foundational reference for future research in this field.

Conflict of interest statement

None declared.

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