Prognostic Factors for Survival in Extensive Stage Small Cell Lung Cancer (ED-SCLC)

The Importance of Smoking History, Socioeconomic and Marital Statuses, and Ethnicity

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Background: We investigated whether independent prognostic factors for overall survival (OS) in non-small cell lung cancer such as ethnicity, smoking history, socioeconomic, and marital statuses are also applicable to extensive stage small cell lung cancer (ED-SCLC).

Methods: SCLC patients diagnosed from 1991 to 2005 from 3 Southern California counties were identified. Prognostic factors for ED-SCLC patients were evaluated by univariate and multivariate analysis.

Results: Of the 4782 SCLC patients analyzed, only 2.5% of the patients were never-smokers and 71.7% of patients presented with ED-SCLC. By multivariate analysis, a positive smoking status was a statistically significant poor prognostic factor for OS in ED-SCLC patients (versus never-smoker; hazard ratio [HR] = 1.310; $p = 0.0125$), in addition low socioeconomic status (SES) (from the lowest to the highest SES score; $p_{trend} = 0.0128$) and being unmarried (versus married; HR = 1.179; $p < 0.0001$). Asian ethnicity was a favorable prognostic factor in ED-SCLC (versus Caucasian; HR = 0.785; $p = 0.0076$). Female gender was another independent favorable prognostic factor (versus male; HR = 0.823; $p < 0.0001$).

Conclusions: A positive history of smoking, low SES, and being unmarried are independent unfavorable prognostic factors for OS in ED-SCLC while Asian ethnicity and female gender are independent favorable prognostic factors for OS in ED-SCLC by multivariate analysis.

Key Words: Extensive stage small cell lung cancer (ED-SCLC), Asian ethnicity, Smoking status, Female gender, Socioeconomic status, Marital status, California Cancer Registry, Prognostic factors.

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Lung cancer is the number one cancer cause of mortality worldwide.[1] Small cell lung cancer (SCLC) used to account for 20 to 25% of all lung cancer but the incidence of SCLC has been decreasing in the United States.[2] SCLC has been highly associated with smoking among the four major lung cancer histologies.[3] It is now recognized that patients with non-small cell lung cancer (NSCLC) who are life-long nonsmokers constitute a distinct clinical entity.[4,5] These patients tend to be found in women from East Asia and they tend to have better survival.[5,6] We previously performed a retrospective population-based study of NSCLC patients in three Southern California counties and found that never-smoking status is a favorable prognostic factor in NSCLC. In addition, Asian ethnicity is another favorable prognostic factor in NSCLC patients independent of smoking status.[7] Other independent favorable prognostic factors identified are high socioeconomic status (SES) and being married.[7] In this report we investigated the proportion of never-smokers with SCLC and whether smoking status is an independent prognostic factor in SCLC similar to NSCLC. We further investigated whether Asian ethnicity, SES, and marital status are independent prognostic factors similar to our findings in NSCLC patients.

PATIENTS AND METHODS

Population

This is a retrospective study involving analysis of data from the Cancer Surveillance Programs of Orange, San Diego and Imperial counties in southern California covering an area

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with estimated population of 6.2 million. SCLC patients diagnosed between 1991 to 2005 who had complete follow-up data were included in the study. Tumor site was abstracted as previously described.[8] The ICD-O-3 histology codes 8041 to 8045 were designated as SCLC.[9] Limited disease (LD-SCLC) is defined as local and regional disease stage and extensive disease (ED-SCLC) is defined as distant disease stage according to Surveillance, Epidemiology, and End Results (SEER) summary staging. Patients with unknown or missing staging information were excluded in the analysis. Patient demographic data were abstracted using SEER codes. The measurement of SES used in this analysis was a composite measure using California Cancer Registry (CCR) and census data as previously described.[10] Radiation therapy and surgical techniques were abstracted using SEER codes. Chemotherapy given during the first course of therapy was ascertained using CCR codes.

Smoking status was abstracted by examining text files of individual patient database as previously described.[8] Patients with any documented history of smoking were classified as smokers. Patients with documentation of no smoking history were classified as never-smokers. Patients lacking documented information on smoking history were listed as unknown.

Statistical Analyses

Comparisons of demographic, clinical, and pathologic variables were made for SCLC patients, using Pearson χ^2 statistic or Fisher's exact test for nominal variables and Student t test for continuous variables. Univariate survival rate analyses were estimated using the Kaplan and Meier method, with comparisons made between groups by the log-rank test. Cox proportional hazards modeling using time since diagnosis were performed. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was assumed for a two-tailed p value less than 0.05.

Ethical Considerations

This research study was approved by the University of California Irvine Institutional Review Board (#2004-3971 and #2007-6078).

RESULTS

Characteristic of SCLC Patients

Between 1991 and 2005 a total of 4782 SCLC patients whose staging status were available were analyzed of which 71.7% of these patients presented with ED-SCLC. Only 2.5% of the patients ($n = 120$) were never-smokers. The median time of follow-up for LD-SCLC patients was 12 months (95% confidence interval: 1–77 months) and 5 months for ED-SCLC patients (95% CI: 0–25 months). We only performed analysis of prognostic factors in ED-SCLC patients because of the limited numbers of LD-SCLC patients. The clinical, pathologic, and demographic characteristics of ED-SCLC patients are shown in Table 1.

TABLE 1. Clinicopathologic Characteristics of the Extensive Stage Small-Cell Lung Cancer Patients (ED-SCLC)

	Extensive Disease (ED-SCLC) (%)
n	3428
Median age	68
Smoking status	
Yes	2539 (74.1)
No	93 (2.7)
Unknown	796 (23.2)
Ethnicity	
Caucasian	2958 (86.3)
Hispanic	234 (6.8)
Asian	144 (4.2)
African American	85 (2.5)
Other	7 (0.2)
Gender	
Male	1830 (53.4)
Female	1598 (46.6)
Age	
0–39	19 (0.6)
40–49	134 (3.9)
50–59	587 (17.1)
60–69	1149 (33.5)
70–79	1158 (33.8)
80+	381 (11.1)
Socioeconomic status (SES)	
SES1	353 (10.3)
SES2	614 (17.9)
SES3	828 (24.2)
SES4	894 (26.1)
SES5	739 (21.6)
Marital status	
Married	1854 (54.1)
Unmarried	1503 (43.8)
Unknown	71 (2.1)
Chemotherapy	
Yes	2359 (68.8)
No	1061 (31.0)
Unknown	8 (0.2)
Radiation	
Yes	1204 (35.1)
No	2224 (64.9)
Surgery	
Lobectomy	5 (0.1)
Other surgeries	31 (0.9)
No	3390 (98.9)
Unknown	2 (0.1)

ED-SCLC, extensive stage small-cell lung cancer patients; SES, socioeconomic status; *n*, number.

Age at Diagnosis

The median age of diagnosis of smokers with ED-SCLC was 68 years compared with 73 years for never-smokers with ED-SCLC ($p < 0.0001$).

TABLE 2. Distribution of SES Quintiles Among ED-SCLC Patients

	SES1 (%)	SES2 (%)	SES3 (%)	SES4 (%)	SES5 (%)	*p*
n	353	614	828	894	739	
Smoking status						
Yes	257 (72.8)	449 (73.1)	616 (74.4)	660 (73.8)	557 (75.4)	0.6678
No	6 (1.7)	13 (2.1)	25 (3.0)	29 (3.2)	20 (2.7)	
Unknown	90 (25.5)	152 (24.8)	187 (23.5)	205 (22.9)	162 (21.9)	
Gender						
Male	206 (58.4)	315 (51.3)	450 (54.3)	474 (53.0)	385 (52.1)	0.2464
Female	147 (41.6)	299 (48.7)	378 (45.7)	420 (47.0)	254 (47.9)	
Ethnicity						
African American	34 (9.6)	21 (3.4)	21 (2.5)	6 (0.7)	3 (0.4)	<0.0001
Asian	20 (5.7)	29 (4.7)	48 (5.8)	25 (2.8)	22 (3.0)	
Caucasian	219 (62.0)	507 (82.6)	717 (86.6)	825 (92.3)	690 (93.4)	
Hispanic	78 (22.1)	54 (8.8)	40 (4.8)	38 (4.3)	24 (3.3)	
Other/unknown	2 (0.6)	3 (0.5)	2 (0.2)	0 (0.0)	0 (0.0)	
Age of diagnosis						
0–39	0 (0.0)	3 (0.5)	7 (0.8)	6 (0.7)	3 (0.4)	0.1265
40–49	15 (4.2)	29 (4.7)	23 (2.8)	38 (4.3)	29 (3.9)	
50–59	62 (17.6)	105 (17.1)	133 (16.1)	163 (18.2)	124 (16.8)	
60–69	121 (34.3)	207 (33.7)	302 (36.5)	275 (30.8)	244 (33.0)	
70–79	123 (34.8)	201 (32.7)	278 (33.6)	306 (34.2)	250 (33.8)	
80+	49 (9.1)	69 (11.2)	85 (10.3)	106 (11.9)	89 (12.0)	
Marital status						
Married	150 (42.5)	310 (50.5)	415 (50.1)	529 (59.2)	450 (60.9)	<0.0001
Unmarried	195 (55.2)	289 (47.1)	393 (47.5)	349 (39.0)	277 (37.5)	
Unknown	8 (2.3)	15 (2.4)	20 (2.4)	16 (1.8)	12 (1.6)	
Chemistry						
Yes	231 (65.4)	417 (67.9)	556 (67.2)	634 (70.9)	521 (70.5)	0.1698
No	121 (34.3)	196 (31.9)	272 (32.9)	258 (28.9)	214 (29.0)	
Unknown	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)	4 (0.5)	
Radiation						
Yes	115 (32.6)	200 (32.6)	281 (33.9)	320 (35.8)	288 (39.0)	0.0830
No	238 (67.4)	414 (67.4)	547 (66.1)	574 (64.2)	451 (61.0)	
Surgery						
Yes	2 (0.6)	9 (1.5)	8 (1.0)	12 (1.3)	5 (0.7)	0.3191
No	351 (99.4)	605 (98.5)	820 (99.0)	880 (98.4)	734 (99.3)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	

ED-SCLC, extensive stage small-cell lung cancer patients; SES, socioeconomic status; *n*, number.

Socioeconomic Status (SES)

The distribution of clinicopathologic characteristics of ED-SCLC patients among the five SES quintiles is shown in Table 2. There were significantly more Hispanic, African American, and unmarried patients in the lower SES quintiles.

Marital Status

The distribution of clinicopathologic characteristics of ED-SCLC according to marital status is shown in Table 3. There were significantly more females, more African Americans, more patients >80 years old, less treatment received (chemotherapy, radiation, surgery), and with lower SES in ED-SCLC patients who are unmarried.

Univariate Survival Analysis

Stage

The 1-year, 2-year, and median overall survival (OS) for LD-SCLC patients were 51.9%, 23.9%, and 13 months which was significantly better than the corresponding values for ED-SCLC patients (20.3%, 5.7%, and 5 months; $p < 0.0001$).

Smoking Status

There was no statistical significant difference in the 1-year, 2-year, and median OS of never-smokers with ED-SCLC (21.9%, 6.9%, and 6 months respectively) when compared with the 1-year, 2-year, and median OS of smokers with ED-SCLC (20.9%, 5.5%, and 6 months respectively; $p = 0.7455$).

TABLE 3. Distribution of Marital Status Among ED-SCLC Patients

	Married (%)	Unmarried (%)	Unknown (%)	*p*
n	1854	1503	71	
Smoking status				
Yes	1367 (73.7)	1122 (74.7)	50 (70.4)	0.3480
No	56 (3.0)	37 (2.5)	0 (0.0)	
Unknown	431 (23.2)	344 (22.9)	21 (29.6)	
Gender				
Male	1204 (64.9)	597 (39.7)	29 (40.8)	<0.0001
Female	650 (35.1)	906 (60.3)	42 (59.2)	
Ethnicity				
African American	34 (1.8)	50 (3.3)	1 (1.4)	0.0042
Asian	99 (5.3)	42 (2.8)	3 (4.2)	
Caucasian	1591 (85.8)	1308 (87.0)	59 (83.1)	
Hispanic	126 (6.8)	102 (6.8)	6 (8.5)	
Other/unknown	4 (0.2)	1 (0.1)	2 (2.8)	
Age of diagnosis				
0–39	9 (0.5)	10 (0.7)	0 (0.0)	<0.0001
40–49	70 (3.8)	60 (4.0)	4 (5.6)	
50–59	327 (17.6)	245 (16.3)	15 (21.1)	
60–69	697 (37.6)	435 (28.9)	17 (23.9)	
70–79	616 (33.2)	519 (34.5)	23 (32.4)	
80+	135 (7.3)	234 (15.6)	12 (16.9)	
Socioeconomic status (SES)				
SES1	150 (8.1)	195 (13.0)	8 (11.3)	<0.0001
SES2	310 (16.7)	289 (19.2)	15 (21.1)	
SES3	415 (22.4)	393 (26.2)	20 (28.2)	
SES4	529 (28.5)	349 (23.2)	16 (22.5)	
SES5	450 (24.3)	277 (18.4)	12 (16.9)	
Chemistry				
Yes	1365 (73.6)	956 (63.6)	38 (53.5)	<0.0001
No	485 (26.2)	543 (36.1)	33 (46.5)	
Unknown	4 (0.2)	4 (0.3)	0 (0.0)	
Radiation				
Yes	717 (38.7)	467 (31.1)	20 (28.2)	<0.0001
No	1137 (61.3)	1036 (68.9)	51 (71.8)	
Surgery				
Yes	21 (1.1)	12 (0.8)	3 (4.2)	0.0331
No	1833 (98.9)	1489 (99.1)	68 (95.8)	
Unknown	0 (0.0)	2 (0.1)	0 (0.0)	

ED-SCLC, extensive stage small-cell lung cancer patients; SES, socioeconomic status; *n*, number.

Gender

The 1-year, 2-year, and median OS for female ED-SCLC patients were 22.7%, 6.8%, and 6 months respectively were statistically significant better than the corresponding numbers for male ED-SCLC patients (18.2%, 4.8%, and 5 months respectively; $p = 0.0042$).

Ethnicity

The OS of Asian ED-SCLC patients was statistically significant better than African American, Caucasian, and Hispanic ED-SCLC patients ($p = 0.0438$) (Figure 1).

Surgery

The survival of ED-SCLC patients who received surgical interventions did not differ significantly from ED-SCLC patients who did not receive surgical interventions ($p = 0.4924$) as only 31 ED-SCLC patients received surgeries (0.9%) and only 5 of 3428 ED-SCLC patients received lobectomy (0.1%).

Chemotherapy

The 1-year, 2-year, and median OS of ED-SCLC patients who received chemotherapy were 27.4%, 7.7%, and 8 months and were significantly better than ED-SCLC patients who did not receive chemotherapy (4.3%, 1.1%, and 1 month respectively; $p < 0.0001$).

Radiation

The 1-year, 2-year, and median OS of ED-SCLC patients who received radiation were 27.8%, 9.3%, and 8 months and were significantly better than ED-SCLC patients who did not receive radiation (16.2%, 3.8%, and 4 months respectively; $p < 0.0001$).

Socioeconomic Status (SES)

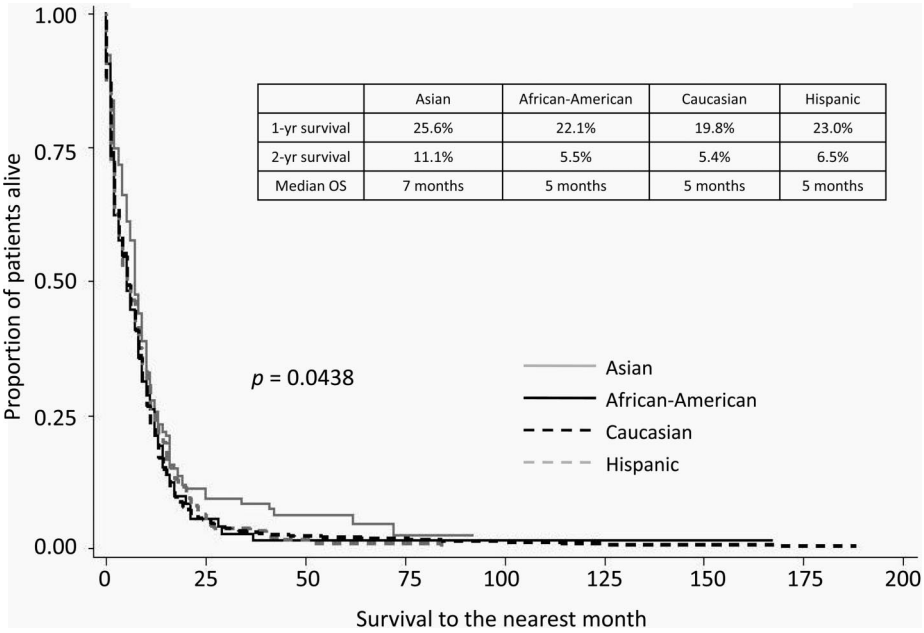
The 1-year, 2-year, and median OS for ED-SCLC patients in the highest SES quintile (SES5) were 28.0%, 6.2%, and 7 months. For ED-SCLC patients in the SES4 quintile, the corresponding values were 17.7%, 5.1%, and 6 months respectively. For ED-SCLC patients in the SES3 quintile, the values were 17.8%, 5.8%, and 5 months respectively. For ED-SCLC patients in the SES2 quintile, the values were 18.7%, 5.0%, and 5 months respectively. For ED-SCLC patients in the lowest SES quintile (SES1), the values were 19.2%, 7.0%, and 4 months respectively. The difference in survival of ED-SCLC patients among the 5 SES quintiles is statistically significant ($p = 0.0011$).

Marital Status

The 1-year, 2-year, and median OS for ED-SCLC patients who were married were 23.1%, 6.7%, and 7 months respectively were statistically significant improved than ED-SCLC patients who were not married (16.8%, 4.4%, and 4 months respectively; $p < 0.0001$).

Multivariate Survival Analysis

A positive history of smoking (versus never-smoker, hazard ratio [HR] = 1.310; $p = 0.0125$) was a significant independent unfavorable prognostic factor for OS in ED-SCLC. Being unmarried (versus married, HR = 1.179; $p < 0.0001$) was another independent unfavorable prognostic factor. Low SES was another significant unfavorable prognostic factor (from lowest to highest SES score; HR = 0.965; $p_{trend} = 0.0128$). However, Asian ethnicity was an independent favorable prognostic factor (versus Caucasian; HR = 0.785; $p = 0.0076$). Other favorable prognostic factors were female gender, younger age of diagnosis, and treatment (radiation, chemotherapy) (Table 4).



	Asian	African-American	Caucasian	Hispanic
1-yr survival	25.6%	22.1%	19.8%	23.0%
2-yr survival	11.1%	5.5%	5.4%	6.5%
Median OS	7 months	5 months	5 months	5 months

FIGURE 1. Overall survival curves of 4 major ethnicities with extensive stage small cell lung cancer (ED-SCLC).

TABLE 4. Cox Multivariate Analysis of ED-SCLC Patients

Variable	HR	95% CI	*p*
Smoking			
No	1.00		
Yes	1.310	(1.060–1.618)	0.0125
Unknown	1.234	(0.991–1.537)	0.0625
Ethnicity			
Caucasian	1.00		
African American	0.973	(0.776–1.221)	0.8154
Asian	0.785	(0.657–0.938)	0.0076
Hispanic	0.917	(0.796–1.055)	0.2253
Other	2.934	(1.216–7.082)	0.0166
Gender			
Male	1.00		
Female	0.823	(0.766–0.884)	<0.0001
Age	1.012	(1.008–1.016)	<0.0001
Socioeconomic status (SES)[a]	0.965	(0.939–0.993)	0.0128
Marital status[b]			
Married	1.00		<0.0001
Unmarried[c]	1.179	(1.095–1.269)	
Chemotherapy[b]			
No	1.00		<0.0001
Yes	0.335	(0.309–0.364)	
Radiation			
No	1.00		<0.0001
Yes	0.721	(0.670–0.776)	
Surgery[b]			
No	1.00		0.1700
Yes	0.791	(0.565–1.106)	

[a] Analyzed as a continuous variable from the lowest to the highest SES score.
[b] Unknown included in Cox proportional hazards model but not shown.
[c] Unmarried (single, separated, divorced, widowed).
HR, hazard ratio; CI, confidence interval; SES, socioeconomic status; ED-SCLC, extensive stage small-cell lung cancer patients.

DISCUSSION

In this report, we confirmed that SCLC is highly associated with tobacco smoking as only 2.5% of the patients in the study were never-smokers. We found that never-smokers with SCLC were statistically significant older than smokers with SCLC. Additionally, a positive smoking history is an independent poor prognostic factor for OS in ED-SCLC patients by multivariate analysis despite a 5-year increase in the median age of diagnosis for never-smokers. Wolf et al.[11] have also shown that never-smokers had higher median survival (13.6 months versus 9.9 months) and 2-year survival rate (17% versus 7%) than smokers with SCLC, and that positive history is an independent unfavorable prognostic factor for both male and female SCLC patients by Cox regression analysis. The study included a substantial number of never-smokers ($n = 63$; 8.3%),[11] in contrast the lack of a prognostic effect of smoking history in SCLC reported by others are likely due to the small numbers of never-smokers: 7 (9.2%),[12] 10 (9.1%),[13] and 5 (6.6%) respectively.[14] Lassen et al.[15] reported that only 1 of 1714 SCLC patients was a never-smoker and of the 60 long-term survivors (>5 years) none were never-smokers. Smoking causes many more genetic disruptions in smokers[16] and likely result in more comorbidities in patients. Given the very low percentage of never-smokers with SCLC further studies are required to distinguish whether SCLC in never-smokers is a distinct clinical entity as in the case of NSCLC[4,5] or as a result of passive exposure to tobacco.

Second, we showed that Asian ethnicity is a favorable prognostic factor in ED-SCLC by both univariate and multivariate analyses. There is paucity in the literature about the significance of ethnicity in the survival outcome in SCLC. Albain et al.[17] using Southwest Oncology Group (SWOG) database reported that Caucasian is an independent favorable prognostic factor in survival in LD-SCLC but the significance

disappears if only more recent clinical trials were included. Blackstock et al.[18] have previously showed that African American patients had similar survival as non-African American patients in ED-SCLC. There were only 12 Hispanic and 8 Asian patients in that study thus the contribution of Asian or Hispanic ethnicity cannot be adequately determined. Our conclusion is strengthened by the inclusion of SES and marital status in the Cox multivariate analysis. We have previously shown in stage one NSCLC lung cancer that African American and Hispanic patients had poorer survival as compared with Caucasians but this survival disadvantage disappeared after SES and marital status were factored in the Cox proportional hazards model.[19] Studies of SCLC patients from Asian countries indicated Asian SCLC patient had similar clinicopathologic characteristics and survival outcome as Western SCLC patients, however, there were no direct comparison.[12,20] A potential explanation is the ethnic variability in the genetic polymorphism of drug metabolizing genes. Irinotecan in combination with platinum had been shown to confer superior OS in the treatment of first line ED-SCLC from randomized trials performed in Japan[21] but not in the United States.[22,23] The active metabolite of irinotecan, SN-38, is inactivated by glucuronidation by the enzyme UGT1A1. There is well known racial variability in the UGT1A1 promoter from single nucleotide polymorphism leading to varying level of expression of the enzyme and resultant toxicities and potential efficacies from irinotecan.[24,25] Our results should be considered as preliminary and hypothesis-generating and will require validation from other population-based epidemiologic and molecular studies and/or clinical trials.

Third, this is the first report to show SES is an independent prognostic factor in ED-SCLC. There were significantly more Hispanic and African American patients in the lower SES quintiles, and significantly more unmarried patients in the lower SES with 55.2% of patients in the lowest SES quintile (SES1) being unmarried compared with only 37.5% of the patients in the highest SES quintile (SES5) (Table 2). Our report also showed that marital status is an independent prognostic factor in ED-SCLC. Comparing to married patients, unmarried patients consisted of significantly more females, more African Americans, more patients who were >80 years old, and more patients in the lower SES. Also fewer unmarried patients received chemotherapy or radiation for the treatment of their ED-SCLC and this observation may partially account for the poorer survival for patients who were unmarried as SCLC are very responsive to chemotherapy and/or radiation. All these prognostic factors were included in the Cox multivariate model but SES and marital status remained as independent prognostic factors. This observation is similar to our report on stage one NSCLC where SES and marital status remained as independent prognostic factors after inclusion in multivariate analysis.[11] Further studies will be needed to investigate and understand the role of these two social factors in determining the survival outcome in ED-SCLC.

Finally, we identified female gender, younger age at diagnosis, radiation, and chemotherapy treatment as favorable prognostic factors in ED-SCLC. It has been well-established that female SCLC patients survived longer than male SCLC patients[18,26–33] and it has been shown that female SCLC patients had higher complete and overall response rates to chemotherapy[12,26,30–33] though females also developed more treatment-related toxicities.[32]

Limitations of this study include there was no central pathologic review and about 40% patients had incomplete TNM staging data. The time period included in this study is over 15 years but there is essentially no major change in the treatment of ED-SCLC. There was also no information in CCR on the tumor marker lactate dehydrogenase[16,18,31,33–35] or performance status[16,26–35] which has been shown to be an independent important prognostic factor in many studies. Moreover, the site and number of metastasis in ED-SCLC is not coded thus we are not able to include the number of metastatic sites into the Cox model as both brain metastasis and the number of metastatic sites have been shown to be prognostic.[18,26,27,31,35] Thus, the independence of Asian ethnicity, SES, and marital status as prognostic factors are significant but hypothesis-generating and should be validated in future studies where lactate dehydrogenase, performance status, and number of metastatic sites are also incorporated in the multivariate analysis. Lastly, we were unable to determine whether patients had received any prophylactic cranial irradiation which has been shown to increase OS in LD-SCLC[36] and ED-SCLC.[37] In summary, we have shown that a positive history of smoking is an unfavorable prognostic factor for OS in ED-SCLC. Other independent prognostic factors identified in this study such as Asian ethnicity, SES, and marital status will require future validation and investigations.

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