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Prognostic factors for limited-stage small cell lung cancer: A study of 284 patients

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Abstract

Combined modality therapy is the standard care for limited stage-small cell lung cancer (LS-SCLC) and has led to a significant improvement in patients' survival. This study sought to investigate and define the importance of prognostic effects of known and controversial factors especially the impact of smoking status and treatment strategies. A total of 284 patients with LS-SCLC diagnosed and prospectively followed from 1997 to 2008 at Mayo Clinic; their characteristics and survival outcome were assessed on the basis of age, gender, smoking history, performance status (PS), tumor recurrence or progression, and treatment using Cox proportional hazards models. Our main results are as follows: (1) Although neither smoking status (former or current smokers) nor intensity (pack-years smoked) at the time of SCLC diagnosis were significant survival predictors, compared to continued smokers (who never quit smoking), patients who quit at or after diagnosis cut the risk of death by 45% (HR=0.55, 95% CI 0.38–0.79); patients who quit before lung cancer diagnosis also experienced survival benefit (HR=0.72, 95% CI 0.52–1.00). (2) Thoracic radiotherapy and platinum-based chemotherapy could significantly improve survival but the timing (within or after one month of diagnosis) of starting chemotherapy or radiation therapy did not. (3) After adjusting for other known factors, a lower PS did not predict poorer survival, suggesting PS should not be the only factor for

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Conflict of Interest

None of the authors have any conflicts of interest.

making treatment decisions. In conclusion, this study demonstrated the negative impact of continued cigarette smoking on survival; therefore, clinicians and all care providers should strongly encourage smoking cessation at diagnosis of LS-SCLC.

Keywords

Limited stage-small cell lung cancer; prognosis; cigarette smoking; chemotherapy; radiotherapy; performance status

Introduction

Approximately 30 to 40 percent of small cell lung cancer (SCLC) is limited-stage SCLC (LS-SCLC) at first clinical presentation. The median ranges of survival for LS-SCLC are 15 to 20 months. In the last a few decades, a modest yet significant improvement of the survival rate of LS-SCLC has been shown in North America and other countries (1–4). Some prognostic factors such as age, gender, smoking status, or different strategies of combined chemo-radiotherapy have been studied in LS-SCLC, but the role of some of these factors in predicting patients' survival remains controversial. Although a personal history of cigarette smoking has been associated with decreased overall survival among patients receiving treatment for non-small cell lung cancer (5,6), only a few studies have reported the impact of smoking status after diagnosis and/or during treatment on survival in patients with SCLC. Videtic et al (7) showed that LS-SCLC patients who continued to smoke during treatment had poorer survival rates than those who quit smoking; however, the authors failed to provide quantitative information on smoking history and to demonstrate any dose-response effect of smoking, such as quantification of cigarette use at the onset of therapy and the duration of smoking cessation in the patients who were not smoking at the time of diagnosis. Two earlier studies on SCLC used mixed limited- and extensive-stage SCLC (ES-SCLC) populations and provided conflicting conclusions. Johnston-Early (8) et al showed worse survival with continuation of smoking while Bergman and Sorenson (9) reported no difference in survival. Thus, a firm conclusion could not be drawn on whether and at what magnitude smoking status carries a prognostic effect among LS-SCLC patients.

Another issue the current study sought to clarify is the timing of combined modality therapy. Although unequivocal data support the benefit from combined modality therapy for LS-SCLC patients' survival, the optimal timing to start chemoradiotherapy is still controversial. An early trial by the CALGB compared chemotherapy alone versus TRT (50 Gy) with either cycle 1 or 4. The arms containing TRT were superior to the chemotherapy alone arm. The difference was statistically significant for delayed (cycle 4) TRT but not for early TRT ($p=0.082$) (10). In contrast, the National Cancer Institute of Canada (NCIC) reported TRT (40 Gy) initiated with either the second or sixth cycle of chemotherapy and showed a survival advantage for early versus late TRT (5-year survival rate of 20% vs 11%, respectively; $p=0.008$) (11). In an attempt to replicate the NCIC trial using the identical inclusion and exclusion criteria, Spiro et al (12) failed to show a benefit for early versus late TRT. In addition, several meta-analyses addressing the timing of TRT suggested a modest benefit of early versus delayed TRT (13). It also seems that the benefit of early concurrent chemoradiotherapy may be maximized by more intensified TRT delivered with uncompromised doses of chemotherapy.

In this study, we performed a retrospective cohort study of LS-SCLC patients at Mayo Clinic, Rochester, Minnesota. We analyzed the association of LS-SCLC with multiple factors including age, sex, smoking status at time of diagnosis, smoking cessation, performance status (PS), and treatment regimens, to determine which of these factors has an independent impact on survival and to determine the magnitude of the impact.

Methods

Study cohort and data collection

From January 1997 to December 2007, a total of 1,124 patients with a pathologically confirmed diagnosis of SCLC at Mayo Clinic were enrolled and actively followed. Only patients who provided informed consent as approved by the Mayo Clinic Institutional Review Board were included in this study. Two hundred eighty-four LS-SCLC cases were identified in this cohort. Detailed procedures of patient enrollment, diagnosis, data collection, and follow-up have been described in a previous publication (14). Full medical record abstraction was conducted to obtain demographics (age and sex), history of tobacco use, lung cancer pathology, PS, anatomic site, and types and timing of treatment. Clinical staging and recurrence or progression was determined by results from available chest radiography, computerized tomography, bone scans, position emission tomography (PET) scans, and magnetic resonance imaging. All patients were actively followed up beginning six months after diagnosis, with subsequent annual follow-up by mailed questionnaires. Annual verification of patients' vital status was accomplished through the Mayo Clinic's electronic medical notes and registration database, next-of-kin reports, death certificates, and obituary documents filed in the patients' medical records, as well as through the Mayo Clinic Tumor Registry and Social Security Death Index website.

Determination of smoking status

Information on tobacco history was self-reported. Never smokers were patients who had smoked less than 100 cigarettes in their lifetime and were not current smokers. Former smokers were patients who indicated they had previously smoked greater than 100 cigarettes and were not currently smoking. Current smokers were patients who reported they were smoking at the time of their cancer diagnosis. In addition, we also subcategorized patients according to their duration of smoking abstinence at the time of diagnosis and during follow-up. Four groups were defined as follows: (1) quit greater than or equal to 5 years prior to diagnosis or never smokers, (2) quit for 1–4 years, (3) quit at or after diagnosis, and (4) never quit. There were seven never smokers in this study and all reported heavy exposure to second-hand cigarette smoke.(15) The cigarette "dose" or "intensity" categories were defined as self-reported packs per day (PPDs) as well as the total number of pack-years of smoking history. The total number of pack-years was calculated by multiplying the self-reported number of PPDs by the number of years of regular cigarette smoking.

Determination of timing and types of treatment

Early chemotherapy was defined as initiating chemotherapy within 30 days after diagnosis; early chest irradiation was defined as beginning therapy within 30 days after starting chemotherapy. Types of treatment included surgery, chemotherapy or radiation only, and combined chemotherapy and radiation. For chemotherapy, comparison between platinum-based chemotherapy and non-platinum-based chemotherapy was analyzed. Prophylactic cranial irradiation (PCI) was also evaluated.

Statistical analysis

The primary outcome in this study was survival after a LS-SCLC diagnosis. Survival was defined as the years from lung cancer diagnosis to death or the last known date alive. Patients known to be alive at last contact were censored. Sex difference of each variable was assessed by a chi-square test for categorical variables and an analysis of variance for continuous variables. Univariate survival association of age at diagnosis, sex, smoking history, PS (<2 vs. ≥2), tumor recurrent or progression, and treatment with survival was evaluated by the Kaplan-Meier method. To evaluate the independent role of each variable on survival, a multivariate Cox proportional hazards model was applied to include all above-mentioned variables and

adjusted hazard ratios (HR) were estimated. Three model building processes were performed in order to define a robust set of survival predictors: forward selection, backward elimination, and predictors based on prior knowledge. In the forward selection, one variable was added at a time; a p-value of 0.1 by chi-square statistics was used as the entry level cut-off; and the first variable chosen to be added was the one that had the smallest p-value. Once a variable was entered in the model, it remained in the model; the process was repeated until none of the remaining variables met the 0.1 level for entry. In the backward elimination, all potential variables were examined together first. The least significant variable that did not meet the predefined level (p-value of 0.1) was removed. Once a variable was removed from the model, it remained excluded. The process was repeated until no other variables in the model met the level for removal. For variables with multiple levels, if one level met the entry criterion, other levels were also included in the final model.

We also used tumor recurrence/progression as an additional end point to model the effect of smoking cessation on the event. Adjusted survival curves were created for quit smoking and recurrence/ progression status. All analyses were performed with SAS software, version 8.2 (SAS Institute, Cary, NC).

Results

Basic Characteristics and Univariate Analysis

The demographics and clinical information of 284 LS-SCLC patients were summarized in Table I. Sex difference of each variable was compared and none was statistically different. In univariate survival analysis of all factors in Table I, age, smoking cessation, recurrence or progression, early radiation, chemotherapy started after one month of diagnosis, concurrent chemoradiotherapy, PCI, platinum-based chemotherapy, and combined chemotherapy were all significantly associated with post diagnosis survival (Table II). For smoking cessation, the median survival as well as 1, 2, and 5 year survival rates of continued smokers, i.e., patients who never quit smoking significantly differed from others who never smoked or quit smoking before or after diagnosis (Table III).

Multivariate Analysis

In order to answer our key questions regarding continued smoking after diagnosis and timing of starting chemo- or radiation therapy, we developed multivariate models using both forward and backward variable selection procedures and reached the same final model (Table IV). Virtually all patients had exposure history to cigarette smoking; neither smoking status at the time of SCLC diagnosis (former or current smokers) nor intensity (pack-years smoked) had significant impact on LS-SCLC survival. However, compared to smokers (who never quit smoking), patients who quit at or post diagnosis cut the risk of death by 45% (HR=0.55, 95% CI 0.38–0.79), after adjusting for other variables (Figure 1A). Treatment modality significantly influenced the risk of death but the timing of starting chemo- or radiation therapy did not.

Recurrence/progression was an independent indicator for poor prognosis. Patients who developed recurrence/progression during treatment had a three-fold (HR=2.72, 95% CI 2.01–3.68) higher risk of death (Figure 1B). Patients who quit at or after diagnosis reduced the risk of tumor recurrence or progression by 41% (HR=0.59, 95% CI 0.34–0.98; Figure 1C, disease-free survival). Other factors that were found to significantly influence the risk of death included age at diagnosis, sex, and PS.

Discussion

In our analysis of 284 LS-SCLC patients, multiple factors were associated with the survival of LS-SCLC. Younger age, female, smoking cessation at or after diagnosis, and combined modality treatment had favorable impact on survival, while recurrence/progression during treatment universally indicated very poor prognosis. Most of these were consistent with previous reports and provided additional evidence to support the benefit of current combined modality therapy. However, we also found the timing of starting chemo- or radiation therapy did not significantly change the risk of death of LS-SCLC patients.

Compared to smokers (who never quit smoking), patients who quit at or after diagnosis cut the risk of death by 45%, by both forward and backward modeling approaches after adjusting for other variables (Table 4, Figure 1A). In addition, our data also showed that former smokers may experience a longer survival (by 28%), consistent with a previous report by Ebbert and colleagues (5). The mechanisms of negative impact of continued cigarette smoking on survival during treatment remain unclear. Nicotine has been shown to protect cancer cells from apoptosis induced by diverse stimuli, such as tumor necrosis factor, UV light, and chemotherapeutic drugs (16–18). Moreover, several studies have reported nicotine exerts proangiogenic activities in tumor xenografts and chick chorioallantoic membrane models of angiogenesis (19,20). Smoking can increase blood carboxy-hemoglobin, producing relative hypoxia, and hypoxia induced factor-1 α has been shown to contribute, at least in part, to nicotine-promoted cell migration, invasion, and tumor angiogenesis by lung cancer cells (21). These studies suggest nicotine possesses both tumor-promoting and angiogenic activities conducive to a more aggressive tumor phenotype. Tobacco smoke also contains polyphenolic agents that generate oxidants that may increase tumor invasion and metastasis (22). Lastly, smoking induces changes in natural-killer cell activity and cell-mediated immunity, both of which are linked to accelerated tumor progression (23). Given the above evidence, clinicians should ask their patients' smoking status before starting treatment, advise them to quit smoking, and provide the necessary support to do so.

Although SCLC has always been considered a chemo-radiotherapy-sensitive disease, SCLC usually relapses and becomes refractory to treatment within one or two years. A significant improvement has been achieved in the last two decades, mainly due to the use of combined modality therapy (3). In our study LS-SCLC patients with early TRT (start <1 month after chemotherapy) showed a better prognosis in univariate analysis; however, the benefit diminished in the adjusted multivariate model, suggesting that, as long as LS-SCLC patients receive combined concurrent chemo-radiotherapy, to start TRT within one month of diagnosis may not be very critical to patients' outcome. In addition, we also found that after adjusting for other known factors, lower PS did not predict poorer survival, suggesting PS should not be the only factor for making treatment decisions.

Brain metastasis is one of the most important causes of treatment failure in patients with SCLC. Among the patients who survived more than two years, about 50 percent of patients had brain metastasis (24). With longer survival, brain metastases are being observed more often. PCI is effective in reducing the incidence of brain metastasis of SCLC. PCI in near or complete responders to induction chemoradiotherapy has been shown to improve long-term survival. Auperin et al (25) reported a meta-analysis combining the individual patient data from seven clinical trials in SCLC. There was a significant survival benefit to PCI; 3-year survival rates increased from 15.3% to 20.7% ($p < 0.01$) for an absolute benefit of 5.4%. PCI has been shown to reduce the incidence of brain metastases and to prolong survival not only in ES-SCLC (26) but also in LS-SCLC (27). It has been generally accepted that PCI should be offered to patients with LS-SCLC who have a complete or near-complete response after induction chemoradiotherapy (25). Our univariate analysis showed a significant positive impact of PCI

on LS-SCLC patients; although, the effect did reach the level of significance in either of the two multivariate models (HR of 0.73–0.74, 95% confidence intervals of 0.49–1.09), there was a trend of protective effect, mainly reflecting a relatively low statistical power. As expected, recurrence/progression does have a significant negative impact of survival on LS-SCLC. Although brain metastasis is one of the most important causes of treatment failure, recurrence and metastasis to other sites also play very important roles in the prognosis of LS-SCLC patients.

The prognostic significance of age in SCLC was debatable in several studies. In a retrospective review of 1,521 patients, the Cancer and Leukemia Group B (CALGB) identified female sex and performance status as important predictors of survival in both LS- and ES-SCLC. LS-SCLC patients older than 60 years had a higher mortality rate than younger patients, but age was not predictive of survival duration among patients with ES-SCLC (28). Similarly, the Southwest Oncology Group (SWOG) reported being less than 70 years of age was considered a favorable variable only in LS-SCLC (29). Rawson et al concluded stage and performance status were most predictive of both short- and long-term survival in SCLC; whereas, age played a minor role in survival only in the initial six months (30). Siu et al studied 608 LS-SCLC patients and found age was not a significant adverse prognostic variable in LS-SCLC patients (31). Ludbrook et al (32) reported increasing age was associated with decreased performance status and increased comorbidity. However, other reports showed survival outcomes for elderly patients were identical to their younger counterparts despite the elderly having more weight loss and poorer performance status (33,34). The optimal therapeutic approach in older patients remains challenging. Most studies showed elderly patients were less likely to be treated with combined chemoradiotherapy, more intensive chemotherapy, and PCI. Elderly patients were also less likely to respond to therapy and had poorer survival outcomes. Whether this was a result of age and its associated comorbidities or suboptimal treatment delivery remains unknown. These data suggested age alone should not exclude patients with LS-SCLC from more aggressive chemoradiotherapy, but careful selection and close monitoring must be carried out to avoid treatment-related morbidity and mortality. Our next step in further improving patient care of SCLC is to assess the health- and treatment-related quality of life among survivors, which will provide more information and justification that the best patient care should aim at improving both quantity and quality of life.

Conclusion

This study provides strong evidence for multiple prognostic factors including epidemiology, clinical features, and treatment in LS-SCLC; whereas, the majority of the literature focused on one or a few aspects only. Although neither smoking status (former or current smokers) nor intensity (pack-years smoked) at the time of SCLC diagnosis were significant survival predictors, compared to continued smokers (who never quit smoking), patients who quit at or after diagnosis cut the risk of death by 45% (HR=0.55, 95% CI 0.38–0.79); patients who quit before lung cancer diagnosis also experience survival benefit (HR=0.72, 95% CI 0.52–1.00). In addition, younger age, concurrent chemoradiotherapy, and combined platinum-based chemotherapy (regardless if the treatment was started within one month post diagnosis) have important prognostic value for LS-SCLC as determined in a cohort of patients with extensive follow-up data, while recurrence/progression during treatment universally indicates very poor prognosis. Our findings provide useful information for better patient management, in particular, the negative impact of continuing cigarette smoking on survival during treatment for LS-SCLC patients.

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Figure 1.

A, survival curves by smoking cessation for patients who quit smoking at or after cancer diagnosis versus those who never quit after adjustment for age, gender, performance status, recurrence/progression, and treatment. **B**, survival curves by recurrence/progression for all patients after adjustment for age, gender, performance status, smoking cessation, and treatment. **C**, adjusted curves for time to recurrence or progression by quit smoking status for patients who quit smoking at or after cancer diagnosis versus those who never quit after adjustment for age, gender, performance status, recurrence/progression, and treatment.

Table I

Demographic and clinical characteristics of 284 LS- SCLC patients

Age at Diagnosis		Treatment modality	
Mean (standard deviation)	65.1 (10.5)	No surgery or radiation or chemotherapy	3 (1.1%)
Cigarette smoking status		Surgery with/without chemo/radiation therapy	36 (12.7%)
Never	7 (2.5%)	Chemo or radiation only	49 (17.3%)
Former	106 (37.3%)	Chemo and radiation	196 (69.0%)
Current	151 (53.2%)	Chemotherapy	
Ever (former/current unknown)	20 (7.0%)	No chemotherapy	12 (4.2%)
Pack-years		Within one month	232 (81.7%)
Missing	18	After one month	40 (14.1%)
Never smokers	7 (2.6%)	Platinum agent	
≤40	76 (28.6%)	No	32 (11.3%)
41–60	86 (32.3%)	Yes	252 (88.7%)
≥61	97 (36.5%)	Chemo-agent combination*	
Quit smoking years		Agent 1 & 3 or 2 & 3	246 (86.6%)
Quit ≥1 years (included 7 never smokers)	121 (42.6%)	Other agents	15 (5.3%)
Quit at or after diagnosis	87 (30.6%)	Agents unknown	11 (3.9%)
Never quit	76 (26.8%)	No chemotherapy	12 (4.2%)
Performance status		Radiation therapy	
<2	256(90.1%)	No radiation	61 (21.5%)
≥2	28(9.1%)	Within one month	107 (37.7%)
Recurrence or progression		After one month	116 (40.8%)
No	182 (64.1%)	PCI**	
Yes	102 (35.9%)	No	233 (82.0%)
		Yes	51 (18.0%)

* 1=Carboplatin; 2=Cisplatin; 3=Etoposide

** PCI: Prophylactic cranial irradiation.

Table II

Factors associated with survival of 284 LS-SCLC patients by univariate analysis

Patients characteristics	Hazard ratio	95% CI	p value
Age at diagnosis	1.03	1.01, 1.04	<0.01
Quit years (vs. Never quit)			<0.01
Quit •1years and never smoker	0.73	0.53, 1.01	
Quit at or after diagnosis	0.54	0.37, 0.77	
Performance status (vs. <2)			0.68
•2	1.11	0.68, 1.80	
Recurrent or progression (vs. None)			<0.01
Yes	1.93	1.42, 2.47	
Treatment (vs. Chemo and radiation therapy)			<0.01
Surgery with/without chemo/radiation	0.72	0.47, 1.16	
Chemo or radiation therapy only	2.61	1.87, 3.67	
No surgery or chemo or radiation	3.35	1.20, 9.15	
Chemotherapy (vs. Within one month)			<0.01
After one month	0.61	0.42, 0.97	
No chemotherapy	2.07	1.12, 3.84	
Platinum agent (vs. No)			0.02
Yes	0.63	0.42, 0.91	
Agent combination of 1&3 or 2&3* (vs. not in specified combination)			<0.01
Yes	0.91	0.57, 1.69	
Unknown	1.92	0.89, 3.89	
Radiation (vs. Within one month)			<0.01
After one month	1.12	0.83, 1.56	
No radiation	2.07	1.46, 2.99	
Prophylactic cranial irradiation (vs. No)			<0.01
Yes	0.56	0.40, 0.86	

*
1=Carboplatin; 2=Cisplatin; 3=Etoposide

Table III

The effect of smoking cessation on survival of 284 LS-SCLC patients

Survival outcome measures	Former smoker (Quit>=1 years) or never smokers (n=121, 42.6%)	Smoker who quit at or after diagnosis (n=87, 30.6%)	Continued smoker (Never quit) (n=76, 26.8%)	p-value*
Median survival (years) Post-diagnosis survival (95% CI)	1.78	2.36	1.36	0.003
1 year	0.73 (0.66, 0.82)	0.84(0.77, 0.92)	0.65(0.55, 0.77)	
2 years	0.47(0.39, 0.57)	0.57(0.48, 0.69)	0.35(0.25, 0.48)	
5 years	0.21(0.14, 0.31)	0.33(0.24, 0.46)	0.10(0.05, 0.24)	

Table IV

Factors associated with survival of 284 LS-SCLC patients by multivariable analyses

Patients characteristics	Hazard Ratio (95% CI) (p value)
Age at diagnosis	1.03 (1.02, 1.05) (<0.01)
Quit years (vs. Never quit)	
Quit 1 years (included never smoker)	0.72 (0.52, 1.00)
Quit at or after diagnosis	0.55 (0.38, 0.79) (0.01)
Recurrence or progression (vs. None)	
Yes	2.72 (2.01, 3.68) (<0.01)
Treatment (vs. Chemo & radiation therapy)	
Surgery with/without chemo/radiation therapy	0.60 (0.38, 0.94)
Chemo or radiation only	2.55 (1.79, 3.63)
No surgery/chemo/radiation	3.24 (1.15, 9.14) (<0.01)