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ORIGINAL RESEARCH

Clinicopathological Difference and Survival Impact of Patients with c-SCLC and SCLC

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Background: Combined small cell lung cancer (c-SCLC) distinguishes itself from small cell lung cancer (SCLC) due to its inclusion of both SCLC and non-small cell lung cancer (NSCLC) components. Few studies have compared clinicopathological characteristics, prognosis and factors affecting survival. We therefore addressed the issues in this study.

Patients and Methods: A total of 400 c-SCLC and 20,841 SCLC patients were enrolled using SEER database. Difference in clinicopathological characteristics of SCLC and c-SCLC patients was analyzed using chi-square. Kaplan–Meier was applied to compare their survival before and after propensity score matching (PSM). Cox regression model was adopted to assess the impact of different clinical variables on survival. Logistic regression was applied to identify risk factors for c-SCLC and SCLC patients.

Results: Differences in race, sex, T stage, N stage, surgery, bone, brain and liver metastasis were detected between c-SCLC and SCLC patients. c-SCLC patients had better overall survival (OS) than SCLC patients before PSM. Age, race, sex, T stage, N stage, surgery, bone, brain, liver and lung metastasis were prognostic factors affecting OS for c-SCLC and SCLC ($P < 0.05$). However, a significant OS benefit was not observed in c-SCLC after adjusting for clinicopathological variables (HR, 0.950; 95% CI, 0.842–1.073; P=0.411). No significant OS difference was found between c-SCLC and SCLC patients after PSM ($P = 0.789$). c-SCLC patients had lower risk of lymph node (OR: 0.555; 95% CI: 0.439–0.703; $P < 0.001$) and liver metastasis (OR: 0.591; 95% CI: 0.448–0.779; $P < 0.001$), whereas had no significant differences in bone and brain metastasis risks ($P > 0.05$) compared with SCLC patients.

Conclusion: The prognosis of c-SCLC did not significantly differ from that of SCLC if clinicopathological characteristics are controlled. Better prognosis for c-SCLC patients over SCLC patients may be ascribed to fewer liver and lymph node metastases upon diagnosis.

Keywords: prognosis, overall survival, clinicopathological features, c-SCLC, SCLC

Background

Small cell lung cancer (SCLC) accounts for 15–20% in all types of lung cancer.[1–3] And the World Health Organization (WHO)/International Association for the Study of Lung Cancer (IASLC) classification has divided SCLC into two subtypes: pure SCLC and c-SCLC.[4] c-SCLC was defined as SCLC combined with any of non-small cell lung cancer (NSCLC) histological types. And NSCLC can be squamous cell carcinoma, adenocarcinoma, large cell neuroendocrine carcinoma and so forth. The components of c-SCLC could be the combination of SCLC with several histological types of NSCLC, with the SCLC combined with squamous cell carcinoma as the most common type. The incidence of c-SCLC was much lower than that of pure SCLC, which could be attributed to insufficient diagnostic information. One important factor is that samples acquired from small biopsy and cytological

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analyses are rather limited. Previous studies have shown that c-SCLC may have distinct biological behavior compared with pure SCLC.[5,6] However, most of these studies either refer to SCLC as pure SCLC, or confuse SCLC with c-SCLC.[7,8]

Considering the shortfalls of previous studies, we screened 400 patients diagnosed with c-SCLC and 20,841 patients diagnosed with SCLC from 2010 to 2015 using SEER database. We aimed to compare the clinicopathological difference and survival impact of patients with c-SCLC and SCLC.

Patients and Methods

Data Source

We used the SEER*Stat software to identify the appropriate patients.[9] In the present study, c-SCLC was defined as SCLC combined with any of NSCLC histological types, such as squamous cell carcinoma, adenocarcinoma, large cell neuroendocrine carcinoma and so forth. In c-SCLC, the combined components may contain one or more of NSCLC histological types. According to the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) seventh edition TNM stage, we screened 400 patients diagnosed with c-SCLC and 20,841 patients diagnosed with SCLC from 2010 to 2015. The included patients should meet the following criteria: the c-SCLC and SCLC diagnosis was pathologically confirmed, with active follow-up, with only one primary tumor and with or without surgical treatment. Patients with benign or borderline tumors, unknown TNM stage and the ambiguous information of clinicopathological features and survival were all excluded. Our study was mainly based on the SEER database. Institutional approval and patient consents were not needed due to open access to the public database, according to the stipulations by Shandong Cancer Hospital and Institute, Fudan University Shanghai Cancer Center.

Statistical Analysis

For all patients with c-SCLC and SCLC, the following variables were analyzed including Age, Race, Sex, T stage, N stage, Surgery, Bone metastasis, Brain metastasis, Liver metastasis and Lung metastasis. In this study, OS was regarded as the primary endpoint. The chi-square test was used to analyze the differences in baseline characteristics among the included patients.

In addition, propensity score matching (PSM) was used to eliminate any bias between patients with c-SCLC and SCLC. Using the chi-square test, the data on Age, Race, Sex, T stage, N stage, Bone metastasis, Brain metastasis, Liver metastasis and Lung metastasis were included in the propensity model to generate a matching ratio of 1:1.

The Kaplan–Meier and Log rank tests were used to analyze the survival curves. The univariate and multivariate Cox proportional hazards regression models were used to evaluate different variables affecting OS. Risk factor analysis of metastasis pattern for patients with c-SCLC compared with SCLC was conducted using multivariate logistic regression. A $P < 0.05$ was considered statistically significant. The statistical software SPSS 22.0 (SPSS, IL, Chicago) was used for data analysis.

Results

Clinicopathological Characteristics of Patients with SCLC and c-SCLC

We first analyzed the difference in clinicopathological characteristics between c-SCLC and SCLC patients. A total of 20,841 SCLC patients and 400 c-SCLC patients from the SEER database from 2010 to 2015 were included for analysis. Of all these patients, the proportion of was 1.9% for c-SCLC and 98.1% for SCLC. Compared with SCLC patients, there were more patients with T1 disease (21.5% vs 12.1%) and fewer with T4 stage (27.3% vs 38.6%) among c-SCLC patients. Similarly, the proportion of patients with N0-N1 stage (42.5%) was higher in c-SCLC patients than that in SCLC patients (21.8%). However, in contrast, the proportion of N2-N3 stages patients was lower in c-SCLC (57.5%) than that in SCLC (78.1%). In addition, for c-SCLC patients, there were fewer bone metastasis (15.5% vs 23.3%), brain metastasis (11.8% vs 16.7%) and liver metastasis (16.0% vs 30.2%) compared with SCLC patients. And patients with c-SCLC (26.5%) were more likely to undergo surgery than patients with SCLC (2.4%). Our result showed that there was no significant difference in age ($P = 0.158$) and lung metastasis ($P = 0.291$) between SCLC and c-SCLC patients. However, there were significant differences in race ($P = 0.030$), sex ($P = 0.018$), T stage ($P < 0.001$), N stage ($P < 0.001$), surgery ($P < 0.001$), bone metastasis ($P < 0.001$), brain metastasis ($P = 0.008$) and liver metastasis ($P < 0.001$) between them. The baseline characteristics of these patients are shown in Table 1.

Survival Analysis for Patients with c-SCLC and SCLC Before PSM

Next, the survival was compared between patients with c-SCLC and SCLC. Kaplan–Meier analysis and Log rank test were used to compare survival differences between c-SCLC and SCLC patients. Then, the respective survival curves of these patients were depicted before PSM. The result revealed that c-SCLC patients' survival was significantly longer than that of SCLC patients (P < 0.001) (Figure 1). Multivariate Cox regression analyses were further applied to determine prognostic factors for OS in patients with c-SCLC and SCLC. Results have shown that age, race, sex, T stage, N stage, surgery, bone metastasis, brain metastasis, liver metastasis and lung metastasis are important factors that would affect OS for patients with SCLC and c-SCLC (P < 0.05). However, cancer type was not an independent prognostic factor for OS for patients with SCLC and c-SCLC (hazard ratio (HR), 0.950; 95% confidence interval (CI), 0.842–1.073; P=0.411). These results indicated that patients with c-SCLC did not gain an obvious survival advantage compared with SCLC after adjusting for clinicopathological variables including age, race, sex, T stage, N stage, surgery, bone metastasis, brain metastasis, liver metastasis and lung metastasis (Table 2).

Survival Analysis for Patients with c-SCLC and SCLC After PSM

Before PSM, there were 400 c-SCLC patients and 20,841 SCLC patients included in the present study. In order to better analyze the influence of clinical variables on OS, we conducted PSM to eliminate bias between patients with c-SCLC and SCLC. After 1:1 matching, a cohort of 400 patients were enrolled in each group. In addition to surgery, the ratio of patients with other clinical characteristics was divided on average between c-SCLC and SCLC patients, as demonstrated in Table 3.

Then, we further depicted the survival curves for c-SCLC and SCLC patients after PSM. Results showed that there was no significant difference in OS between c-SCLC patients and SCLC patients (P = 0.789) (Figure 2A). Similarly, the survival curves for patients with c-SCLC and SCLC undergoing surgical treatments were depicted. It was also shown that there was no significant difference in OS between patients with c-SCLC and SCLC after surgery (P = 0.162) (Figure 2B).

Table 1 Combined Small Cell Lung Cancer and Small Cell Lung Cancer Patient Characteristics from SEER Database

Variables	SCLC (%)	C-SCLC (%)	*P*
Total	20,841 (100)	400 (100)	
Age			0.158
< 65	8599 (41.3)	151 (37.8)	
≥ 65	12,242 (58.7)	249 (62.3)	
Race			0.030
White	17,990 (86.3)	328 (82.0)	
Black	1975 (9.5)	53 (13.3)	
Others	876 (4.2)	19 (4.8)	
Sex			0.018
Female	10,469 (50.2)	177 (44.3)	
Male	10,372 (49.8)	223 (55.8)	
T stage			< 0.001
T0	266 (1.3)	1 (0.3)	
T1	2529 (12.1)	86 (21.5)	
T2	5451 (26.2)	115 (28.8)	
T3	4542 (21.8)	89 (22.3)	
T4	8053 (38.6)	109 (27.3)	
N stage			< 0.001
N0	3049 (14.6)	136 (34.0)	
N1	1510 (7.2)	34 (8.5)	
N2	11,614 (55.7)	160 (40.0)	
N3	4668 (22.4)	70 (17.5)	
Surgery			< 0.001
Yes	495 (2.4)	106 (26.5)	
No	20,346 (97.6)	294 (73.5)	
Bone metastasis			< 0.001
Yes	4853 (23.3)	62 (15.5)	
No	15,988 (76.7)	338 (84.5)	
Brain metastasis			0.008
Yes	3479 (16.7)	47 (11.8)	
No	17,362 (83.3)	353 (88.3)	
Liver metastasis			< 0.001
Yes	6291 (30.2)	64 (16.0)	
No	14,550 (69.8)	336 (84.0)	
Lung metastasis			0.291
Yes	2994 (14.4)	50 (12.5)	
No	17,847 (85.6)	350 (87.5)	

Risk Factor Analysis of Metastasis Pattern for Patients with c-SCLC Compared with SCLC

In the present study, we mainly focused on the risk of metastasis pattern for patients with c-SCLC compared

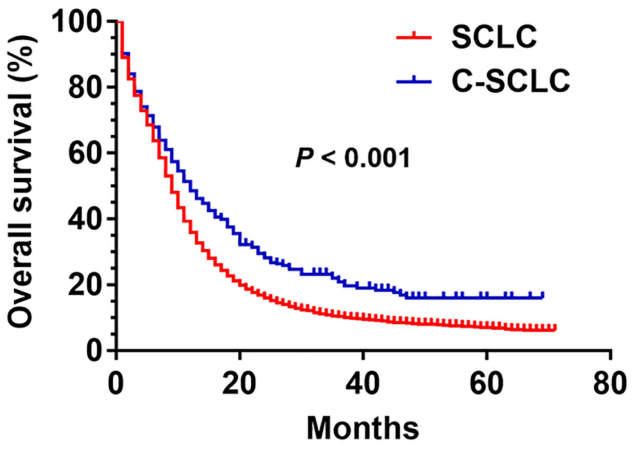

Figure 1 Survival curves for patients with c-SCLC and SCLC before PSM (P < 0.001).

with SCLC. Multivariate logistic regression analysis was used to analyze the influence variables including lymph node metastasis, bone metastasis, brain metastasis, liver metastasis and lung metastasis in c-SCLC and SCLC. Compared with SCLC patients, the risk of lymph node metastasis (OR: 0.555; 95% CI: 0.439–0.703; P < 0.001) and liver metastasis (OR: 0.591; 95% CI: 0.448–0.779; P < 0.001) was lower among patients with c-SCLC. However, there was no significant difference in the other risk factors including bone metastasis, brain metastasis and lung metastasis (all, P > 0.05). The specific details are shown in Supplementary Table 1.

Discussion

Previous studies indicated that c-SCLC accounted for 2–24% among all SCLC patients.[5,10,11] SCLC patients had worse survival than NSCLC patients; however, there were few studies on prognosis of patients with c-SCLC. Various studies reported that the clinical outcomes of patients diagnosed with c-SCLC differ significantly, and the median OS ranged from 9.4 to 27 months for c-SCLC patients with I–IV stage.[12–15] Baker et al showed that patients with c-SCLC had a fairly favorable prognosis.[16] However, Radice et al showed that patients with SCLC had better survival than those with c-SCLC.[6] Similarly, Zhang et al also indicated that the mixed NSCLC components within c-SCLC had a significant influence on the survival.[14] In contrast, several researches reported that no difference in survival was found between c-SCLC and pure SCLC.[13,17] The survival difference between c-SCLC and SCLC has been controversial. Therefore, in the present study, we analyzed the clinicopathological characteristic and survival difference between c-SCLC and SCLC. Notably, we also analyzed factors, particularly on metastasis sites, that may possibly contribute to their survival difference.

In the present study, to address this issue, we have screened a total of 20,841 SCLC and 400 c-SCLC using

Table 2 Propensity Score Matching Was Conducted Among Small Cell Lung Cancer and Combined Small Cell Lung Cancer Patients

Variables	SCLC (%)	C-SCLC (%)	P
Total	400 (100)	400 (100)	
Age			0.714
< 65	146 (36.5)	151 (37.8)	
≥ 65	254 (63.5)	249 (62.3)	
Race			0.865
White	332 (83.0)	328 (82.0)	
Black	52 (13.0)	53 (13.3)	
Others	16 (4.0)	19 (4.8)	
Sex			0.943
Female	176 (44.0)	177 (44.3)	
Male	224 (56.0)	223 (55.8)	
T stage			0.999
T0	1 (0.3)	1 (0.3)	
T1	83 (20.8)	86 (21.5)	
T2	117 (29.3)	115 (28.8)	
T3	88 (22.0)	89 (22.3)	
T4	111 (27.8)	109 (27.3)	
N stage			0.998
N0	136 (34.0)	136 (34.0)	
N1	33 (8.3)	34 (8.5)	
N2	162 (40.5)	160 (40.0)	
N3	69 (17.3)	70 (17.5)	
Surgery			< 0.001
Yes	24 (6.0)	106 (26.5)	
No	376 (94.0)	294 (73.5)	
Bone metastasis			
Yes	62 (15.5)	62 (15.5)	1.000
No	338 (84.5)	338 (84.5)	
Brain metastasis			
Yes	43 (10.8)	47 (11.8)	0.654
No	357 (89.3)	353 (88.3)	
Liver metastasis			
Yes	64 (16.0)	64 (16.0)	1.000
No	336 (84.0)	336 (84.0)	
Lung metastasis			0.663
Yes	46 (11.5)	50 (12.5)	
No	354 (88.5)	350 (87.5)	

Table 3 Cox Regression Analyses of Prognostic Factors for Overall Survival for Patients with Small Cell Lung Cancer and Combined Small Cell Lung Cancer

Variables	Univariate Analysis		Multivariate Analysis	
	Wald χ^2	*P*	HR (95% CI)	*P*
Age	368.60	< 0.0001		< 0.0001
< 65			Reference	
≥ 65			1.424 (1.380–1.469)	< 0.0001
Race	14.53	0.001		0.011
White				
Black			0.941 (0.893–0.991)	0.022
Others			0.922 (0.856–0.995)	0.035
Sex	110.88	< 0.0001		< 0.0001
Female				
Male			1.123 (1.090–1.158)	< 0.0001
Cancer type	35.35	< 0.0001		0.411
SCLC				
c-SCLC			0.950 (0.842–1.073)	0.411
T stage	312.94	< 0.0001		< 0.0001
T0			Reference	
T1			0.926 (0.800–1.073)	0.308
T2			1.169 (1.014–1.348)	0.032
T3			1.217 (1.055–1.405)	0.007
T4			1.243 (1.079–1.433)	0.003
N stage	259.52	< 0.0001		< 0.0001
N0			Reference	
N1			0.974 (0.907–1.045)	0.456
N2			1.169 (1.116–1.225)	< 0.0001
N3			1.174 (1.113–1.239)	< 0.0001
Surgery	295.21	< 0.0001		< 0.0001
Yes			Reference	
No			1.927 (1.717–2.163)	< 0.0001
Bone metastasis	607.88	< 0.0001		< 0.0001
No			Reference	
Yes			1.136 (1.093–1.180)	< 0.0001
Brain metastasis	396.61	< 0.0001		< 0.0001
No			Reference	
Yes			1.415 (1.360–1.472)	< 0.0001
Liver metastasis	1829.23	< 0.0001		< 0.0001
No			Reference	
Yes			1.789 (1.727–1.854)	< 0.0001
Lung metastasis	459.14	< 0.0001		< 0.0001
No			Reference	
Yes			1.232 (1.180–1.286)	< 0.0001

the SEER database. We firstly demonstrated that patients diagnosed with c-SCLC had better survival than those diagnosed with pure SCLC. However, multivariate Cox regression analyses found that cancer type was not an independent prognostic factor in OS after adjusting for clinicopathological variables. Further, using the

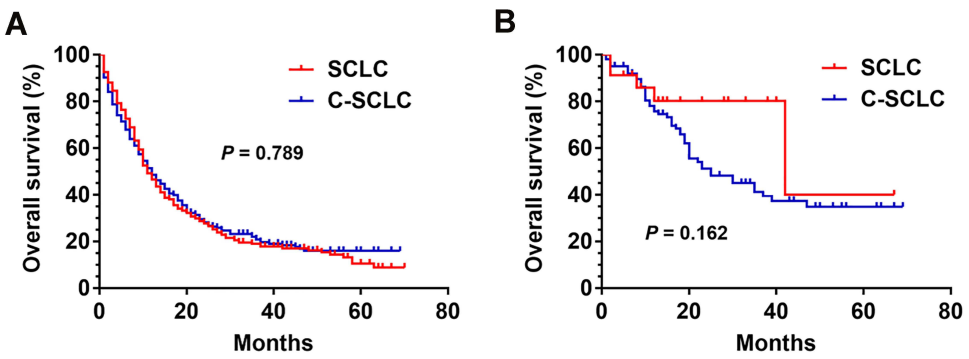

Figure 2 (**A**) Survival curves for patients with c-SCLC and SCLC after PSM (P = 0.789). (**B**) Survival curves for c-SCLC and SCLC patients after surgery (P = 0.162).

multivariate Cox regression analysis, we analyzed the factors influencing the survival of 400 c-SCLC patients. We found that liver and lung metastasis were not prognostic factors for c-SCLC patients. However, patients with liver metastasis in SCLC had the worst prognosis, as reported in our previous study.[18] This may be an important reason that c-SCLC patients had better survival compared with SCLC patients.

In order to better observe the influence of clinical variables on the prognosis, PSM method was used for 1:1 matching analysis. PSM-matched age, race, sex, T stage, N stage, bone metastasis, brain metastasis, liver metastasis and lung metastasis. And surgery was not included in the matching variable. However, our results demonstrated that there was no significant difference in survival between patients with c-SCLC and pure SCLC after PSM, suggesting that the survival benefits of c-SCLC patients may be associated with clinical variables upon diagnosis and metastasis mode, whereas they may not be associated with follow-up treatment. Since c-SCLC patients' survival had little association with treatment, we took the variable of surgery as an example and found that there was no significant difference in survival between patients undergoing surgery and those without. Therefore, we concluded that the survival may not be linked with follow-up treatment among c-SCLC patients. In the present study, we mainly focused on the odds ratio (OR) of metastasis sites in c-SCLC compared with SCLC. In multivariate logistic regression analysis, we found that the risk of lymph node and liver metastasis of c-SCLC patients was lower compared with SCLC patients, whereas there was no statistical significance in bone, brain and lung metastasis. This suggested that c-SCLC patients' survival benefit may be attributed to fewer liver and N metastases. This may serve as a feasible explanation for the prolonged survival of c-SCLC patients over SCLC patients. Nevertheless, it has not to be neglected that there might be other factors, such as race, sex, T stage, surgery contributing to the survival difference between SCLC and c-SCLC.

However, this study has some limitations that should be noted. First, this was a retrospective study. Secondly, some other variables, including type of surgery, other treatments affecting the prognosis and smoking history were not included in the analysis. Thus, the response to the different regimens was difficult to accurately evaluate between SCLC and c-SCLC. Thirdly, not all the SCLC and c-SCLC patients have undergone surgical resection in the present study. Since pathological confirmation by biopsies may not be as convincing as diagnosis by surgical resection, therefore some c-SCLC cases would have been mistakenly categorized as SCLC. Furthermore, since detailed information on the subtype of c-SCLC is not available from SEER database, the analysis of the subtype of c-SCLC associated with prognosis could not be conducted. These aspects would be improved in our future studies. Additionally, due to the small samples of c-SCLC, these results may be biased. Therefore, further large-scale prospective clinical studies are required to confirm these recommendations.

Conclusions

We showed that c-SCLC differed from SCLC in many clinicopathological features. We also demonstrated the prognosis of c-SCLC did not significantly differ from that of SCLC if clinicopathological characteristics are controlled. Better prognosis for c-SCLC patients over SCLC patients may be ascribed to fewer liver and lymph node metastases upon diagnosis. From a clinical standpoint, we should take liver and lymph node metastases into account in the comparison of prognosis of c-SCLC and SCLC patients. The status of liver and lymph node metastases should be monitored in the follow-up of SCLC and c-SCLC patients to better

evaluate prognosis. Due to distinct clinicopathological features and risk factors, future clinical trials for SCLC and c-SCLC may be conducted differentially.

Data Sharing Statement

The datasets used and/or analyzed during the present study are available from the corresponding authors on reasonable requests.

Ethics Approval and Consent to Participate

Our study was mainly based on the SEER database. Institutional approval and patient consents were not needed due to open access to the public database, according to the stipulations by Shandong Cancer Hospital and Institute, Fudan University Shanghai Cancer Center.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Chenyue Zhang and Xiaoling Shang are the co-first authors for this study; Chenyue Zhang and Haiyong Wang are the corresponding authors for this study.

Disclosure

The authors declare no conflicts of interest in this work.

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