Original Article

Characteristics and survival difference of clinical tumor size 0 extensive-stage small cell lung cancer with different metastasis pattern

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Background: Few studies were focused on the characteristics and survival prognosis of clinical tumor size 0 (cT0) extensive-stage small cell lung cancer (ES-SCLC) patients with distant metastasis.

Methods: The proper patients were screened based on the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2013. Chi-square test was used to analyze the characteristics of cT0 stage. The risk factors on cT0 stage were analyzed by Logistic regression model. The survival difference was compared by the Log rank test. The prognostic factors on survival were analyzed by univariate and multivariate Cox regression model.

Results: Only 1.2% of patients were diagnosed at cT0 stage. Clinical nodal status 0 (cN0) stage, no bone metastasis and no lung metastasis were all risk factors on cT0 stage. The patients at cT0 stage had better cancer specific survival (CSS) benefit (P=0.011). The cT0 stage was also an independent prognostic factor on CSS (P=0.018).

Conclusions: The patients at cT0 stage was a different subgroup compared with the patients at cT1–4 stage for ES-SCLC patients with distant metastasis.

Keywords: Extensive-stage small cell lung cancer (ES-SCLC); metastasis; survival; clinical tumor size 0 (cT0)

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Introduction

Small cell lung cancer (SCLC) is a highly aggressive malignancy frequently presenting with metastases at time of diagnosis (1-3). The standard treatment for extensive stage disease SCLC (ES-SCLC) is chemotherapy alone (4-6). Although 70% response rates to chemotherapy is found in ES-SCLC, the 5-year survival rates are still poor and only about 2% (7). Despite changes in demographics and treatment, the median and 5-year survival rates for patients with SCLC have not significantly improved over the past 15 years (8,9). To explore and understand the individualized characteristics of ES-SCLC may have some guiding significance for future treatment. Interestingly, small number of ES-SCLC patients who have no primary lesions [diagnosed as clinical tumor size 0 (cT0) according to American Joint Committee on Cancer (AJCC)] but have distant metastasis are found in clinical practice. What are the clinical characteristics and survival prognosis for these patients? However, few studies have been focused on the interesting clinical issue. In our study, we give a clear answer based on a large population screened from Surveillance, Epidemiology, and End Results (SEER) registered database.

Methods

Patient selection

SEER is supported by the Surveillance Research Program, which provides national leadership in the science of cancer surveillance as well as analytical tools and methodological expertise in collecting, analyzing, interpreting, and disseminating reliable population-based statistics (10). Included patients should be microscopically-confirmed and have only one primary tumor; diagnosed as the cT0 stage according to 7# AJCC staging extracted from the SEER database, and the cT0 was defined as having no primary tumor (11); diagnosed as ES-SCLC with distant metastasis. Importantly, all included patients should have definite cancer specific survival (CSS) and over survival (OS) information. CSS is a net survival measure representing survival of a specified cause of death in the absence of other causes of death. In addition, the variables including age, race, sex, N stage, metastasis sites should have clear information. For the radiation information, we can only know if the patients have received radiotherapy. However, the we cannot know the specific radiotherapy site due to the limitations of SEER database itself.

Ethical evaluation

As previous described (12), this study was conducted in compliance with the Helsinki Declaration. The ethics of this study has been approved by Shandong Cancer Hospital. The patient's informed consent is not required due to the SEER database does not involve personal identifying information.

Statistical analysis

The suitable patients are screened by the SEER*Stat 8.3.4 software from 2010 to 2013. The patient's baseline characteristics were compared by chi-square test. The CSS and OS were regarded as the main study endpoint. The survival curve was depicted by the Kaplan-Meier method and the statistic difference was compared by the Log rank test. The related risk factors on cT0 stage were compared by the Univariate and multivariate Logistic regression analysis. The influence of T stage on CSS and OS was analyzed by the univariate and multivariate Cox regression model.

The SPSS version 22.0 (SPSS, IL, Chicago, USA) was applied to compare the statistical difference. P values were 2-sided and the P<0.05 was considered statistically significant.

Results

Patient demographics

In total of 9,046 patients were included in our study, and only 110 patients (1.2%) were diagnosed at cT0 stage according to the AJCC staging (*Figure 1A*). Among them, 90% of patients were Caucasian. The statistic differences were not found in subgroup variables including age, sex and radiation between the patients with cT0 stage and cT1–4 stage (all, P>0.05). Interestingly, 30.9% of patients at cT0 stage were diagnosed at the clinical nodal status 0 (cN0) stage, however, only 12.0% of patients at cT1–4 stage was diagnosed at cN0 stage (*Figure 1B*). In addition, our results showed that the patients with cT0 stage have fewer bone metastasis and lung metastasis (bone metastasis: 20% for cT0 stage, 34.2% for cT1–4 stage, P=0.002; lung metastasis: 6.4% for cT0 stage, 21.6% for cT1–4 stage, P<0.001) (*Figure 1C*). Statistic differences between the two groups were not found in patients with brain and liver metastasis (P=0.906 for brain metastasis; P=0.540 for liver metastasis) (*Figure 1C*). The detailed statistical information was presented in *Table 1*.

Factors associated with cT0 stage

Our results demonstrated that the variables including age, race, sex and radiation were not risk factors on cT0 stage. Interestingly, the cN0 stage was showed to be an independent risk factor on cT0 stage [N1 *vs.* N0: odds ratio (OR): 0.291; 95% confidence interval (CI): 0.113–0.749, P=0.010; N2 *vs.* N0: OR:0.290; 95% CI: 0.184–0.457, P<0.001; N3 *vs.* N0: OR:0.456; 95% CI: 0.273–0.762, P=0.003] (*Table 2*). Importantly, the patients with bone and lung metastasis were less likely to belong to cT0 stage (bone metastasis: OR:0.521; 95% CI: 0.325–0.835, P=0.007; lung metastasis: OR:0.257; 95% CI: 0.119–0.553, P=0.001) (*Table 2*). However, the brain and liver metastasis were proven not to be risk factors on cT0 stage (P=0.993 for brain metastasis; P=0.827 for liver metastasis) (*Table 2*). Interestingly, the radiation information was also proven not to be a risk factor on cT0 stage (P=0.205) (*Table 2*).

Survival difference for patients with cT0 stage

The results demonstrated that the patients with cT0 stage had better CSS compared with the cT1–4 stage (P=0.011) (*Figure 2A*). However, OS difference was not found between the patients with cT0 stage and the cT1–4 stage (P=0.052)

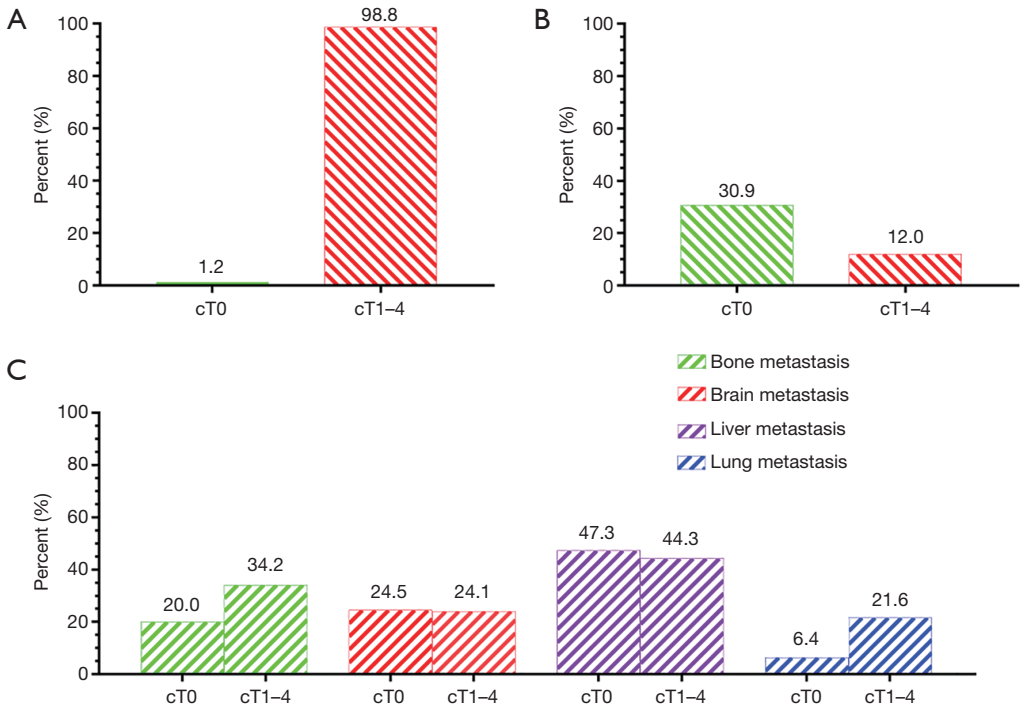

Figure 1 The percent of the baseline variables characteristics. (A) The percent of patients at cT0 stage and cT1–4 stage (1.2% *vs.* 98.8%); (B) the percent of the patients with cN0 stage for patients at cT0 stage and cT1–4 stage (30.9% *vs.* 12.0%); (C) the percent of the patients with different metastasis sites for patients at cT0 stage and cT1–4 stage. cT0, clinical tumor size 0; cN0, clinical nodal status 0.

(*Figure 2B*). Next, we divided T stage into cT0, cT1, cT2, cT3, cT4, and CSS and OS benefit could be found in patients with cT0 stage (P=0.011 for CSS; P=0.017 for OS) (*Figure 2C,D*).

Next, we adjusted for age, race, sex, stage N, stage T, bone metastasis, brain metastasis, liver metastasis, lung metastasis and radiation, and multivariate Cox regression model was used to analyze the prognostic factors for OS and CSS. The results showed that the cT0 stage was an independent prognostic factor for CSS [hazard ratio (HR): 1.318; 95% CI: 1.049–1.656; P=0.018] (*Table 3*). However, the cT0 stage was not an independent prognostic factor for OS (HR: 1.220; 95% CI: 0.985–1.511; P=0.068) (*Table 3*).

Discussion

In our present study, we mainly focused on the characteristics and survival prognostic of ES-SCLC patients with cT0 stage. Several interesting clinical issues were clarified for the first time. Firstly, we found the patients at cT0 stage only accounts for 1.2% of these included patients. Secondly, we found the patients at cT0 stage are less likely to develop lymph nodes metastasis. Thirdly, the patients at cT0 stage had fewer bone and lung metastasis. Last but not the least, the patients at cT0 stage had better CSS benefit, however, an OS benefit was not found in our present study.

We demonstrated that the patients at cT0 stage was a different subgroup compared with the patients at cT1–4 stage for ES-SCLC patients with distant metastasis. Only 1.2% ES-SCLC patients with distant metastasis were diagnosed at cT0 stage in our study. In fact, tumor size is an important factor affecting metastasis of SCLC (13). However, for these patients who lack primary tumor, what is their metastasis pattern? Our results showed that these patients had fewer lung and bone metastasis. However, such a difference was not found in patients with liver and brain metastasis between the patients at cT0 stage and cT1–4 stage. In fact, brain, bone, liver and lung were the most common metastatic site for SCLC (14). Our previous study had demonstrated that the liver was the most common metastatic site, and lung was the least common metastatic site for these patients (15). Interestingly, we also found that 47.3% of patients developed liver metastasis and only 6.4% of study subjects have lung metastasis at cT0 stage in SEER database.

Table 1 Characteristics of ES-SCLC between cT0 and cT1–4 stage extracted from SEER Database

Variables	cT0 (%)	cT1–4 (%)	P
Total	110 (1.2)	8,936 (98.8)	
Age			0.846
<65	45 (40.9)	3,738 (41.8)	
≥65	65 (59.1)	5,198 (58.2)	
Race			0.061
White	99 (90.0)	7,736 (86.6)	
Black	4 (3.6)	844 (9.4)	
Others	7 (6.4)	356 (4.0)	
Sex			0.164
Female	45 (40.9)	4,251 (47.6)	
Male	65 (59.1)	4,685 (52.4)	
N stage			<0.001
N0	34 (30.9)	1,072 (12.0)	
N1	5 (4.5)	583 (6.5)	
N2	44 (40.0)	5,134 (57.5)	
N3	27 (24.5)	2,147 (24.0)	
Bone metastasis			0.002
Yes	22 (20.0)	3,058 (34.2)	
No	88 (80.0)	5,878 (65.8)	
Brain metastasis			0.906
Yes	27 (24.5)	2,150 (24.1)	
No	83 (75.6)	6,786 (75.9)	
Liver metastasis			0.540
Yes	52 (47.3)	3,963 (44.3)	
No	58 (52.7)	4,973 (55.7)	
Lung metastasis			<0.001
Yes	7 (6.4)	1,934 (21.6)	
No	103 (93.6)	7,002 (78.4)	
Radiation			0.073
Yes	36 (32.7)	3,680 (41.2)	
No	74 (67.3)	5,256 (58.8)	

ES-SCLC, extensive-stage small cell lung cancer; cT0, clinical tumor size 0; SEER, Surveillance, Epidemiology, and End Results.

Our results also demonstrated that improved CSS could be found in patients at cT0 stage. Several reasons should be clarified: Firstly, the patients at cT0 stage had less bone and lung metastasis. It has been demonstrated that multiple metastatic sites at diagnosis significantly predicted poor survival in ES-SCLC patients (2). Secondly, studies had showed that large tumor size at diagnosis tended to result in poor survival for these patients (2,16). Therefore, it is easy to understand that the patients at cT0 stage have better survival prognosis without primary lesions. Thirdly, the patients at cT0 stage were more likely to be at cN0 stage. Some studies had showed that the presence of thoracic lymph node involvement significantly affected the long-term survival (17,18). Interestingly, we found OS difference was not found between the patients with cT0 stage and the cT1–4 stage. Complications or treatment-related deaths from SCLC itself may be the cause of no difference. In our study, the results showed that the cT0 stage was an independent prognostic factor for CSS. In fact, a previous study has demonstrated that age less than 50 years, female sex, Asian race, and rural residence were associated with better CSS for SCLC (19). However, the patients in this study included localized SCLC and extensive SCLC. In our study, only the ES-SCLC patients with different metastasis were included.

Several study limitations need to be mentioned. Firstly, our study is a retrospective analysis of a large community-based data set and the selection bias cannot avoid despite of a relatively large sample size. Secondly, some important variables may predict for survival in these particular patients, including younger age, good performance status, nonsmoking history and the oligometastatic disease; however, they were not entered in this exploratory analysis (20,21). Thirdly, due to the limitations of the SEER database itself, we only analyzed the generic use of radiation excluding other treatments such as first line platinum-based chemotherapy, thoracic chemoradiotherapy, and recently involved second line immunotherapy. All these variables can influence outcomes and affect prognosis (7,22,23). In addition, the information which organ received radiation therapy was also lacked in our study duo to limitations of SEER database itself.

Conclusion, our results showed for the first time that ES-SCLC patients at cT0 stage had fewer bone and lung metastases and were more likely to be at cN0 stage. The CSS benefit could be found in patients with cT0 stage compared with cT1–4 stage. Our findings may provide some individualized insights and therapeutic perspectives for ES-SCLC patients with distant metastasis.

Table 2 The effect of subgroup variables on cT0 stage analyzed by Logistic regression analysis

Variables	Univariate analysis		Multivariate analysis	
	Wald χ_2	P	OR (95% CI)	P
Age	0.038	0.981		NI
<65				
≥65				
Race	5.143	0.162		NI
White				
Black				
Others				
Sex	1.923	0.382		NI
Female				
Male				
N stage	34.043	< 0.001		<0.001
N0			Reference	
N1			0.291 (0.113–0.749)	0.010
N2			0.290 (0.184–0.457)	<0.001
N3			0.456 (0.273–0.762)	0.003
Bone metastasis	9.370	0.009		0.007
No			Reference	
Yes			0.521 (0.325–0.835)	0.007
Brain metastasis	0.015	0.993		NI
No				
Yes				
Liver metastasis	0.379	0.827		NI
No				
Yes				
Lung metastasis	12.844	0.002		0.001
No			Reference	
Yes			0.257 (0.119–0.553)	0.001
Radiation	3.165	0.205		NI
No				
Yes				

cT0, clinical tumor size 0; OR, odds ratio; CI, confidence interval; NI, not included.

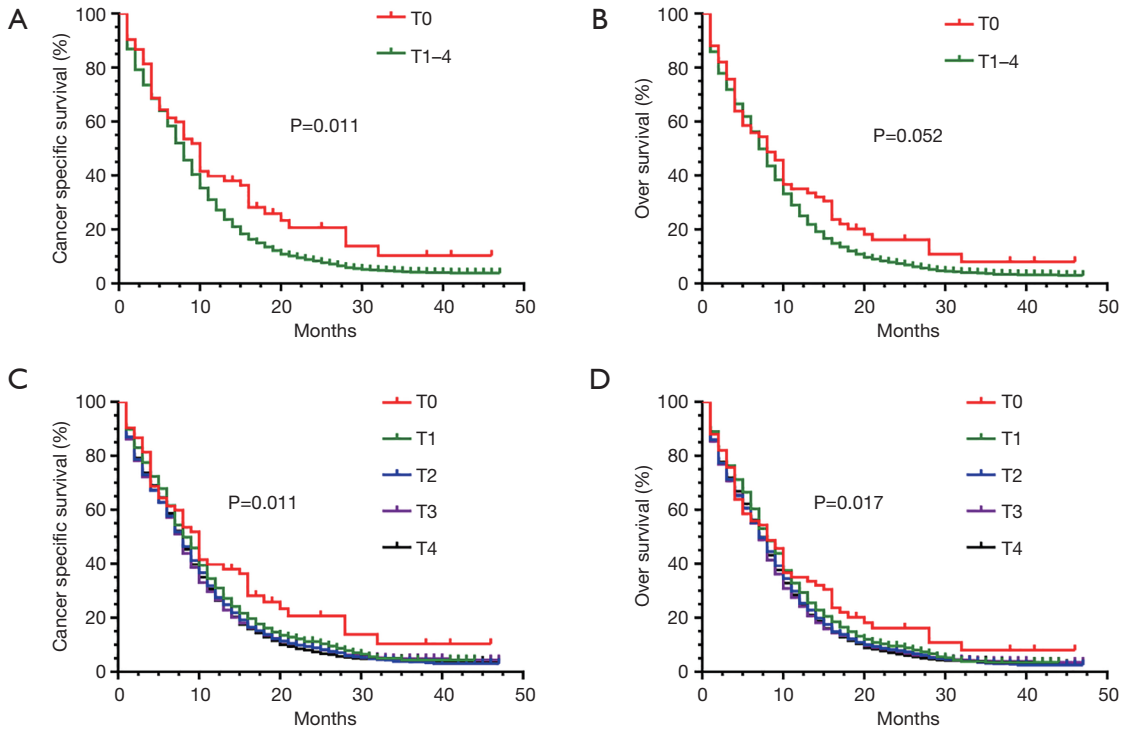

Figure 2 The survival difference among the different groups. (A) The CSS difference between the patients at cT0 stage and cT1–4 stage (P=0.011); (B) the OS difference between the patients at cT0 stage and cT1–4 stage (P=0.052); (C) the CSS difference among the patients at cT0–4 stage (P=0.011); (D) the OS difference among the patients at cT0–4 stage (P=0.017). CSS, cancer specific survival; cT0, clinical tumor size 0; OS, over survival.

Table 3 The effect of T stage on CSS and OS analyzed by Cox regression analysis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
T stage on CSS		0.051		0.018
T0	Reference		Reference	
T1–4	1.254 (0.999–1.575)	0.051	1.318 (1.049–1.656)	0.018
T stage on OS		0.171		0.068
T0	Reference		Reference	
T1–4	1.160 (0.938–1.435)	0.171	1.220 (0.985–1.511)	0.068

CSS, cancer specific survival; OS, over survival; HR, hazard ratio; CI, confidence interval.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The ethics of this study has been approved by Shandong Cancer Hospital. The patient's informed consent is not required due to the SEER database does not involve personal identifying information.

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