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Prognostic factor analysis of patients with small cell lung cancer: Real-world data from 988 patients

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Abstract

Background: Small cell lung cancer (SCLC) is characterized by aggressive spread and poor prognosis, but has limited treatment options. Results of prognostic factors from randomized trials on treatment arrangement are conflicting and large-scale real-world analysis is lacking.

Methods: Patients diagnosed SCLC between 2008 and 2018 in Peking University Cancer Hospital were included in this study. Kaplan–Meier methods were adopted, and univariate analysis and multivariate Cox regression models were constructed to analyze prognostic factors.

Results: Among 1045 patients who presented to our center, 988 eligible patients were identified. Median overall survival (OS) was 16.0 months for the whole group, 24.0 months and 11.0 months for limited stage small cell lung cancer (LS-SCLC) and extensive stage small cell lung cancer (ES-SCLC), separately. Limited-stage, good performance status (PS) (ECOG 0–1), response to primary systemic treatment, and patients who received initiative irradiation and three or more lines of chemotherapy were predicted to have better OS in the whole group. Only response to first-line systemic therapy and prophylactic cranial irradiation (PCI) were independent prognostic factors of survival in LS-SCLC; while good PS (ECOG 0–1), without liver, bone, or subcutaneous metastases, response to first-line therapy, initial local irradiation, and three or more lines of systemic therapy predicted a favorable prognosis in ES-SCLC.

Conclusions: The present study retrieved from large real–world data suggested that response to primary systemic therapy and aggressive radiotherapy are independent prognostic factors for SCLC. PCI and initiative irradiation for original or metastatic sites improved the OS in LS-SCLC and ES-SCLC, respectively.

KEYWORDS
prognostic factor, small cell lung cancer, survival, treatment

INTRODUCTION

Lung cancer is the most common malignant carcinoma and the leading cause of death due to cancer both in China and in the world.[1, 2] Small cell lung cancer (SCLC) accounts for approximately 14% of all lung cancer cases.[3] SCLC is divided into limited disease and extensive disease according to the staging system of Veterans Administration Lung Study Group.[4] Systemic therapy is an essential component of appropriate treatment. Chemoradiotherapy and chemotherapy are standard therapies for limited stage (LS) SCLC and extensive stage (ES) SCLC, respectively.[5, 6] For decades, etoposide plus platinum (cispatin or carboplatin) has been the most commonly used initial combination chemotherapy regimen. Until 2019, following the IMpower133 study,[7] the addition of PD-L1-targeted immune checkpoint inhibitors to chemotherapy were recommended, with an improvement in overall survival by two months reported compared to

chemotherapy as first-line treatment. Taking into consideration a healthy economy, accessibility to this regimen still needs to be greatly improved. In real-world clinical practice, the disease characteristics and treatment arrangement which may favor the outcomes are still something to be explored emergently. As large-scale real-world analyses are currently lacking, in this study we analyzed 1045 cases of SCLC retrospectively to explore the prognostic factors in the real-world clinical practice.

METHODS

Patients and data

A total of 1045 consecutive patients presented to Peking University Cancer Hospital from August 1, 2008 to December 31, 2018 for SCLC therapies were enrolled retrospectively in this study. The inclusion criteria were histologically or cytologically-confirmed small cell lung cancer

TABLE 1 Characteristics of patients in the whole group, LS-SCLC and ES-SCLC subgroups

Characteristic	Whole group (n = 998)	LS-SCLC (n = 481)	ES-SCLC (n = 507)
Total	988	481	507
Age			
Median (SD)	59 (10.4)	58 (10.3)	59 (10.4)
<65 years	707 (71.6%)	360 (74.8%)	347 (68.4%)
≥65 years	281 (28.4%)	121 (25.2%)	160 (31.6%)
Gender (%)			
Male	760 (76.9%)	355 (73.8%)	405 (79.9%)
Female	228 (23.1%)	126 (26.2%)	102 (20.1%)
ECOG			
0–1	887 (89.8%)	448 (93.1%)	439 (86.6%)
2–3	101 (10.2%)	33 (6.9%)	68 (13.4%)
First-line chemotherapy regimen			
EP/EC	815 (82.5%)	412 (85.7%)	403 (79.5%)
Others	173 (17.5%)	69 (14.3%)	104 (20.5%)
Response to first-line regimen			
CR/PR	724 (73.3%)	396 (82.3%)	328 (64.7%)
SD	152 (15.4%)	55 (11.4%)	97 (19.1%)
PD	112 (11.3%)	30 (6.3%)	82 (16.2%)
Local irradiation			
No	361 (36.5%)	104 (21.6%)	257 (50.7%)
Yes	627 (63.5%)	377 (78.4%)	250 (49.3%)
Local irradiation timing			
No or passive	521 (52.7%)	150 (31.2%)	368 (72.6%)
Initiative	467 (47.3%)	331 (68.8%)	139 (27.4%)
Prophylactic cranial irradiation (PCI)			
No	771 (78.0%)	293 (60.9%)	478 (94.3%)
Yes	217 (22.0%)	188 (39.1%)	29 (5.7%)
Lines of systemic treatment			
1–2 lines	771 (78.0%)	369 (76.7%)	402 (79.3%)
3 or more	217 (22.0%)	112 (23.3%)	105 (20.7%)
Site of metastases	-	-	
Liver			141 (27.8%)
Brain			110 (21.7%)
Adrenal gland			77 (15.2%)
Bone			146 (28.8%)
Subcutaneous			15 (3.0%)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; EP/EC, etoposide and cisplatin/carboplatin; ES-SCLC, extensive stage small cell lung cancer; LS-SCLC, limited stage small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

patients, who were newly diagnosed without prior treatment. Patients who received only surgery or radiotherapy were excluded. Among this cohort, 988 patients who received at least one line of systemic chemotherapy and had a record of efficacy for measurable lesions (according to RECIST) were included for further analysis.

Electronic medical records were used to obtain demographic, clinical variables and medications as follows: age, gender, stage (The Veterans Administration Lung Study Group [VALSG]), Eastern Cooperative Oncology Group (ECOG) performance status, sites of metastases, systemic therapy treatments, local therapies, efficacy, most recent follow-up, and death. Mortality data were obtained from the electronic medical records of the Follow-up System of Beijing Cancer Prevention and Research Institute. The construction of the database was conducted by an independent researcher who was not involved in the care of patients.

Treatment

Among all 988 patients, EP/EC (etoposide and cisplatin/carboplatin) was the most often used initial chemotherapy regimen (815 patients). A total of 11 patients received etoposide only according to their physical conditions. In the early period, non EP regimens were administered according to the guidelines or clinician's decision at that time: IP (irinotecan, cisplatin) in 52 patients, CAV (cyclophosphamide, doxorubicin, vincristine) in 39 patients, CODE (cyclophosphamide, doxorubicin, vincristine, etoposide) in 13 patients, paclitaxel plus cisplatin in 27 patients, topotecan in 17 patients, GP (gemcitabine, cisplatin) in five patients, vincristine plus etoposide in four patients, vincristine plus cisplatin in three patients, paclitaxel plus doxorubicin in one patient, and teniposide plus cisplatin in one patient.

TABLE 2 Univariate and multivariate analysis of factors associated with survival in the whole group

	Univariate analysis		Multivariate analysis		
Factor	**mOS (month)**	***p*-value**	**HR**	**95% CI**	***p*-value**
Gender			0.822	0.676–1.001	0.051
Male	15.0	0.017			
Female	19.0				
Age					
<65-year	16.5	0.226			
≥65-year	14.5				
ECOG			0.655	0.518–0.829	0.000
0–1	17.0	0.000			
2–3	11.0				
Stage at diagnosis			0.445	0.374–0.530	0.000
LS	24.0	0.000			
ES	11.0				
First-line chemotherapy regimen			1.038	0.854–1.262	0.707
EP/EC	17.0	0.023			
Others	12.0				
Response to first-line regimen					
CR/PR	20.0	0.000			0.000
SD	11.0		0.325	0.253–0.418	
PD	7.0		0.593	0.446–0.788	
Local irradiation			1.162	0.932–1.448	0.182
No	10.0	0.000			
Yes	20.0				
Local irradiation timing			1.828	1.444–2.315	0.000
No or passive	11.0	0.000			
Initiative	24.0				
Lines of systemic treatment			0.786	0.654–0.945	0.010
1–2 lines	14.0	0.016			
3 or more	20.0				

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; EP/EC, etoposide and cisplatin/carboplatin; ES, extensive stage; LS, limited stage; mOS, median overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 3 Univariate and multivariate analysis of the prognostic factors of LS-SCLC and ES-SCLC, respectively

	Univariate analysis			Multivariate analysis		
Factor	**mOS (month)**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
	LS-SCLC					
Gender			0.333			
Male	23.0	20.2, 25.8				
Female	25.0	17.9, 32.1				
Age			0.747			
<65-years	25.0	21.6, 28.4				
≥65-years	23.0	19.5, 26.5				
ECOG			0.003	0.749	0.499–1.123	0.167
0–1	25.0	22.0, 28.0				
2–3	20.0	15.9, 24.1				
First-line systemic regimen			0.472			
EP/EC	25.0	22.5, 27.5				
Others	21.0	14.9, 27.1				
Response to first-line regimen			0.000			
CR/PR	26.0	22.8, 29.2		0.000		0.000
SD	15.0	13.0, 17.0		0.000	0.201–0.514	0.000
PD	10.0	7.0, 13.0		0.053	0.342–1.007	0.053
Local irradiation			0.005	0.781	0.539–1.313	0.287
Yes	25.0	22.4, 27.6				
No	15.5	12.3, 18.7				
Local irradiation timing			0.000	0.841	0.539–1.313	0.446
Initiative	27.0	23.4, 30.6				
No/passive	15.0	12.4, 17.6				
PCI			0.000	2.684	1.920–3.753	0.000
No	16.0	14.2, 17.8				
Yes	39.0	28.5, 49.5				
Lines of chemotherapy			0.492			
1–2 lines	25.0	20.0, 30.0				
3 or more	23.0	20.9, 25.1				
	ES-SCLC					
Gender			0.053			
Male	11.0	10.2, 11.8				
Female	12.0	9.5, 14.5				
Age			0.237			
<65-years	12.0	11.3, 12.7				
≥65-years	11.0	9.9, 11.7				
ECOG			0.000	0.671	0.498–0.905	0.009
0–1	12.0	11.0, 13.0				
2–3	9.0	6.9, 11.1				
First-line systemic regimen			0.396			
EP/EC	11.0	10.3, 11.7				
Others	10.0	8.5, 11.5				
Response to first-line regimen						
CR/PR	13.5	12.2, 14.8	0.000			0.000
SD	9.0	7.9, 10.1		0.354	0.265–0.473	0.000
PD	6.0	5.1, 6.9		0.603	0.428–0.849	0.004

(Continues)

TABLE 3 (Continued)

	Univariate analysis			Multivariate analysis		
Factor	**mOS (month)**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Local irradiation				1.260	0.966–1.642	0.088
Yes	14.5	13.1, 15.9	0.000			
No	8.0	7.1, 8.9				
Local irradiation timing				1.620	1.166–2.728	0.004
Initiative	19.0	16.3, 21.7	0.000			
No/passive	9.0	8.3, 9.7				
PCI			0.000	1.631	0.975–2.728	0.062
No	11.0	10.3, 11.7				
Yes	23.5	20.1, 26.9				
Lines of chemotherapy				1.627	1.259–2.10	0.000
1–2 lines	10.0	9.1, 10.9	0.000			
3 or more	15.0	12.9, 17.1				
Site of metastases						
Brain			0.811			
No	11.0	10.3, 11.7				
Yes	12.0	9.4, 14.6				
Liver			0.000	0.717	0.547–0.940	0.016
No	12.0	11.1, 12.9				
Yes	9.0	8.1, 9.9				
Adrenal			0.049	0.842	0.611–1.163	0.297
No	11.0	10.1, 11.9				
Yes	10.5	9.3, 11.7				
Bone			0.000	0.744	0.578–0.957	0.022
No	12.0	11.1, 12.9				
Yes	9.0	8.1, 9.9				
Subcutaneous			0.005	0.544	0.315–0.938	0.028
No	11.0	10.2, 11.8				
Yes	8.0	7.1, 8.9				

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; EP/EC, etoposide and cisplatin/carboplatin; ES-SCLC, extensive stage small cell lung cancer; LS-SCLC, limited stage small cell lung cancer; mOS, median overall survival; PCI, prophylactic cranial irradiation; PD, progressive disease; PR, partial response; SD, stable disease.

Radiotherapy was the main local treatment administered to 627 patients. Only 16 patients received other local treatment such as radiofrequency ablation (12 patients), and surgery (four patients) for palliative purposes. Radiotherapy for thoracic lesions was given as 60–66 Gy (1.8 Gy daily) or 45 Gy (1.5 Gy twice daily) for LS-SCLC, while 55–60 Gy (1.8 Gy daily) was given for ES-SCLC. Patients with LS-SCLC were given concurrent thoracic radiotherapy no later than the beginning of the third cycle of chemotherapy, or sequential radiotherapy depending on performance status. After primary treatment, prophylactic cranial irradiation (PCI), 25 Gy in 10 daily fractions, was given to patients with PR/CR for primary systemic therapy when cranial magnetic resonance imaging (MRI) (contrast computed tomography [CT] when MRI could not be tolerated) revealed no brain metastases. Patients with ES-SCLC received thoracic radiotherapy selectively when they had finished first-line chemotherapy and achieved a partial or complete response. Whole brain radiotherapy (WBRT) (30 Gy in 10 daily fractions) and stereotactic radiosurgery (SRS) were used in patients with brain metastases. Irradiation of other metastatic sites was dependent on the location and normal tissue constraints.

Assessment of efficacy

All patients underwent standardized evaluation. CT, MRI, positron emission tomography (PET)/CT and bone scan were employed to evaluate the efficacy and progression. An assessment was given every two cycles of systemic therapy, and every three months during the first three years of follow-up. Efficacy was evaluated as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

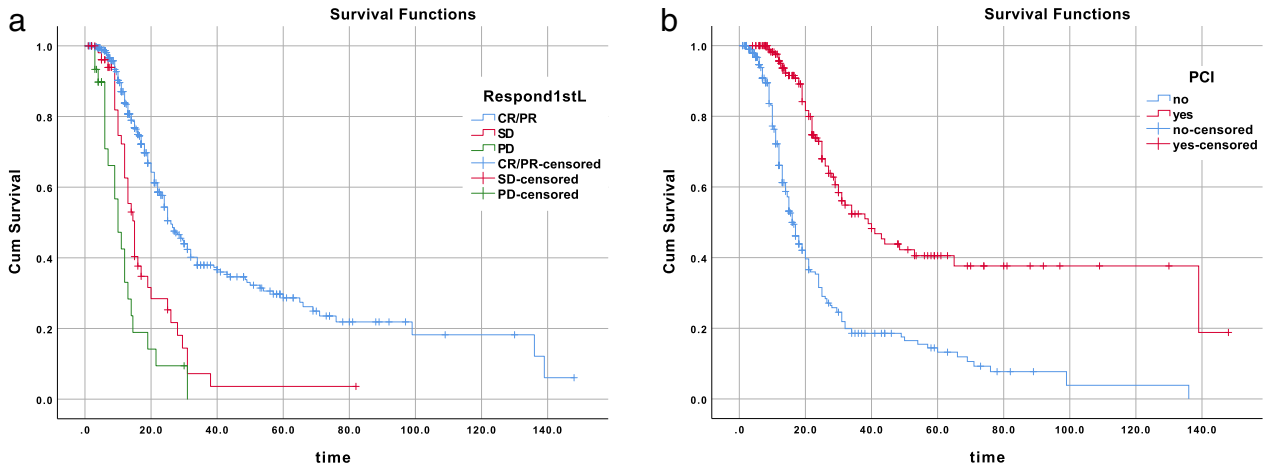

FIGURE 1 Survival curves of patients with limited stage small cell lung cancer (LS-SCLC) (Log-rank test). (a) Response to first-line systemic therapy. CR/PR, complete response/partial response; SD, stable disease; PD, progressive disease ($p < 0.001$). (b) Prophylactic cranial irradiation (PCI) versus no PCI ($p < 0.001$)

Statistical analysis

Descriptive statistics were employed to describe the clinical characteristics of patients. Kaplan–Meier methodology was used to estimate the median overall survival (OS), whereas the differences were estimated by using Log-rank test. Factors associated with risk of death were examined by univariable analysis. The variables with a p-value less than 0.05 by univariate analysis were incorporated into the subsequent multivariable analysis with Cox proportional hazards model. A p-value less than 0.05 was defined as statistically significance. Statistical analyses were performed using SPSS version 22.0.

RESULTS

Patient characteristics and treatment

Between August 1, 2008 and December 31, 2018, a total of 988 patients were legally confirmed to be eligible for analysis in the study. At the time of data cutoff, the median follow-up was 10.0 months (interquartile range 7–19 months). A total of 603 patients (60.3%) had died. Median age was 59.0 years (range: 16–83), and 281 patients (28.4%) were 65 years old or above. A total of 481 (48.7%) patients initially presented with limited stage disease, while 507 (51.3%) patients had extensive stage disease at diagnosis. A total of 89.8% (887) of the patients had good performance status at the beginning of treatment. For the subgroups of LS and ES disease, there were more male, older patients and more patients of ECOG 2–3 in the ES subgroup. A total of 32.9% of patients with ES-SCLC had multiple extra-thoracic organ metastases at diagnosis. The top three common metastatic organs were bone (28.8%), liver (27.8%) and brain (21.7%).

A total of 815 (82.5%) patients received EP as first-line systemic treatment, while 173 (17.5%) patients had other systemic chemotherapy regimens. There were more patients with LS-SCLC (85.7%) who accepted EP/EC as first-line chemotherapy. In total, 73.3% of patients achieved a CR/PR for the first systemic regimen, 15.4% of SD and 11.3% of PD. More patients with LS-SCLC achieved CR/PR (82.3% vs. 64.7%) whereas more patients with ES-SCLC (16.2% vs. 6.3%) had progression on first-line chemotherapy. A total of 771 (78.0%) patients received no more than two lines of systemic therapy, and 217 (22.0%) had three or more lines. A total of 67.1% of the patients had local treatments during the course of disease, and most (625/663) had received irradiation. Initiative irradiation was defined as concurrent thoracic irradiation or sequential irradiation depending on the tolerance of patients with LS-SCLC, or thoracic radiotherapy for patients with ES-SCLC who had responded to primary systemic therapy and selective radiotherapy for stable or slowly progressing, asymptomatic metastases conditions; conversely, limited-term radiotherapy for rapidly progressing, symptomatic lesions was defined as passive irradiation. In total, 467 (47.3%) patients received initiative radiotherapy, while 160 (16.2%) patients had passive radiotherapy and 360 (36.5%) patients had no radiotherapy. There was a higher ratio of patients who received local irradiation (78.4% vs. 49.3%) in LS-SCLC compared with ES-SCLC, and many more patients (331/68.8% vs. 139/27.4%) received initiative radiotherapy in LS-SCLC. In total, 22.0% of patients accepted PCI, and 39.1% of patients with LS-SCLC while 5.7% of ES-SCLC. The demographic characteristics and treatments of the whole group are shown in Table 1.

Survival and prognosis factors

The median overall survival (OS) of the whole group was 16.0 months. Univariate and multivariate analysis revealed that limited-stage, good performance score (PS) Eastern

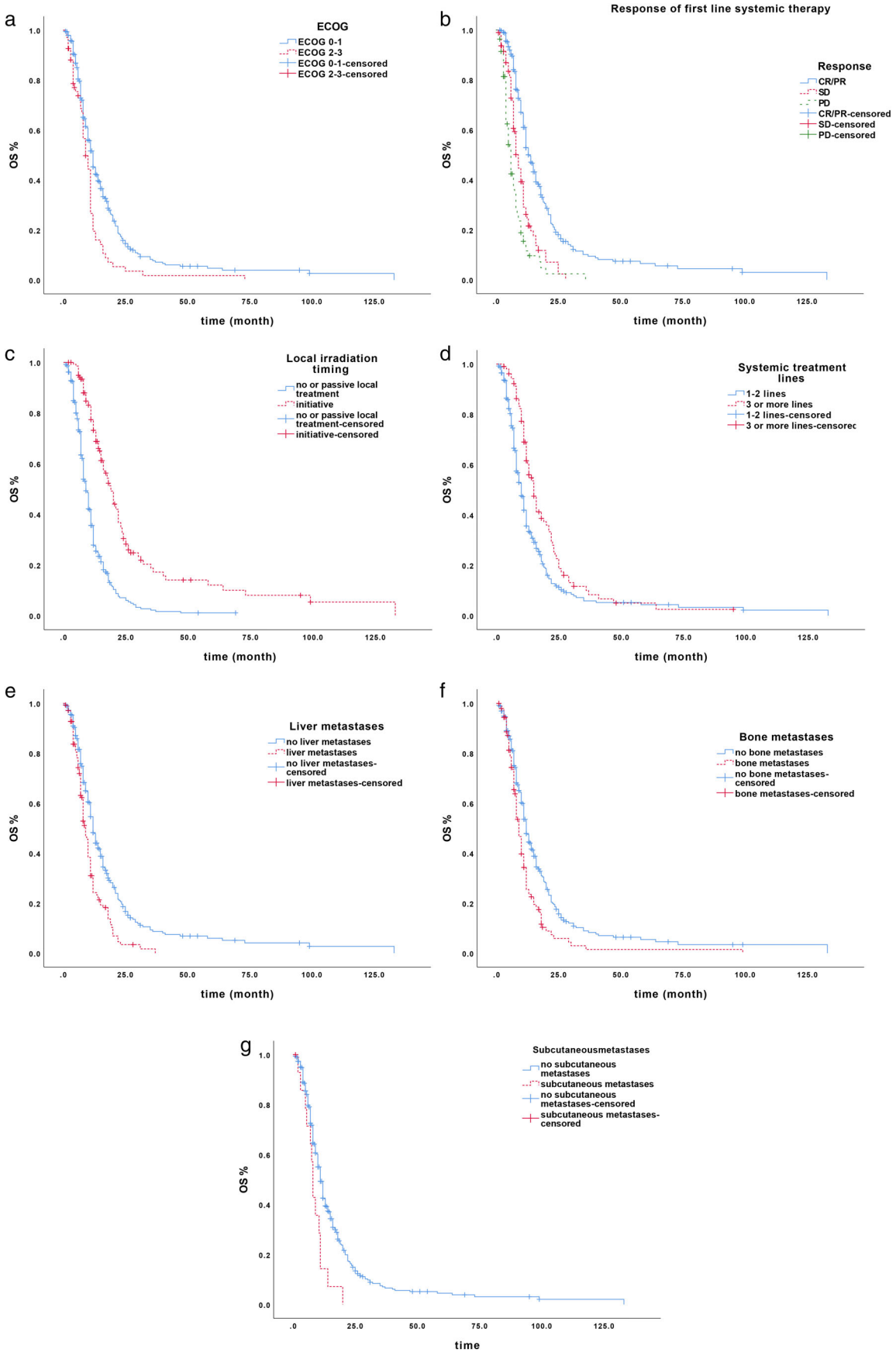

FIGURE 2 Survival curves of patients with extensive stage small cell lung cancer (ES-SCLC) (Log-rank test). (a) Performance status (PS) Eastern Oncology Cooperative Group (ECOG) before treatment 0–1 versus 2–3 ($p = 0.009$). (b) Responses to first-line systemic therapy. CR/PR, complete response/partial response; SD, stable disease; PD, progressive disease ($p < 0.001$). (c) Initiative irradiation versus passive irradiation or no irradiation ($p = 0.004$). (d) Systemic therapy lines: 1–2 lines versus 3 or more ($p < 0.001$). (e) Liver metastases versus no liver metastases ($p = 0.016$). (f) Bone metastases versus no bone metastases ($p = 0.022$). (g) Subcutaneous metastases versus no subcutaneous metastases ($p = 0.028$)

Cooperative Oncology Group (ECOG: 0–1), response to first-line systemic treatment (CR/PR), receiving initiative irradiation and more lines of chemotherapy (three or more lines) were independent prognostic factors for OS (Table 2).

Patients with LS-SCLC had a median OS of 24.0 months, the one-, two-, and five-year overall survival rates were 78.7%, 48.8% and 24.2%, whereas the median OS of patients with ES-SCLC was just 11.0 months, and one-, two-, and five-year overall survival rates were 41.6%, 14.4% and 4.3%. In the LS-SCLC subgroup, only response to first-line systemic therapy and PCI were revealed by multivariate analysis to be related to survival.

For patients with ES disease, multivariate analysis revealed good PS (ECOG 0–1), response to first-line therapy, initiative local irradiation, and three or more lines of systemic therapy were associated with a more favorable prognosis, while liver, bone, or subcutaneous metastases predicted worse survival (Table 3).

In the LS-SCLC subgroup, patients who received a CR/PR to first systemic therapy had a median OS of 26.0 months, whereas it was 15.0 months for SD and only 10 months for PD. The median survival of patients receiving PCI and not receiving PCI were 39.0 months and 16.0 months, respectively (Figure 1).

In the ES-SCLC subgroup, median OS of patients who achieved CR/PR was 13.5 months compared with 9.0 months of SD and 6.0 months with PD. Patients who accepted initiative irradiation therapy had a superior median survival (19.0 vs. 9.0 months). Having three or more lines of systemic therapy was related to better survival (15.0 vs. 10.0 months). Good PS (12.0 vs. 9.0 months), no metastasis of the liver (12.0 vs. 9.0 months), bone (12.0 vs. 9.0 months) or subcutaneous condition (11.0 vs. 8.0 months) at diagnosis provided survival benefits in those patients (Figure 2).

DISCUSSION

SCLC is characterized by rapid progression and widespread metastases. In addition to epidemiological characters such as performance status, stage and metastases, treatment arrangements also have great impacts on overall survival. Systemic therapy is an essential component of appropriate treatment. Thoracic radiotherapy is recommended for patients with LS-SCLC with the goal being to achieve a cure; for selected patients with ES-SCLC, radiotherapy is recommendeded to palliate symptoms. However, some studies have reported that more aggressive radiotherapy improved survival of selected patients with ES-SCLC.[8, 9]

As far as we know, this study may be one of the largest studies of SCLC from a single center. The real-world data from 988 patients confirmed that stage is still one of the most important prognostic factors for survival. The performance status (ECOG) at diagnosis was confirmed to be the characteristic related with survival, especially in the ES group. Different from previous studies,[10] gender or age were not involved with prognosis in this group. Compared to no or single metastases, multiple metastases outside the thoracic region is an unfavorable factor for survival as previously reported.[11] In this study, the presence of liver metastases was shown to predict a worse prognosis in the ES-SCLC group,[12–14] as well as bone metastases at diagnosis. Our data first revealed that subcutaneous metastasis at diagnosis is an independent risk factor for survival in ES-SCLC and may predict the shortest median OS of only eight months compared with other distant metastases. Subcutaneous metastasis is uncommon at diagnosis, and is therefore rarely described in previous studies.

Beyond the characteristics at diagnosis, treatment arrangement played a more crucial role in overall survival. A systematic analysis performed by Taofeek et al.[15] showed the survival for patients with refractory SCLC and sensitive SCLC were definitely different (5.4 months vs. 7.7 months). A retrospective analysis of 207 patients revealed response to chemotherapy was the most important prognostic factor over disease characteristics at diagnosis.[16] Another study included 407 Chinese patients, and showed that the patients who achieved CR/PR to initial therapy had a superior OS of 8.3 months for LS-SCLC and 7.8 months for ES-SCLC than those who achieved SD/PD.[17] In our study, patients who received a response to first-line chemotherapy with CR/PR, SD and PD had a different median OS of 26.0, 15.0 and 10.0 months in the LS-SCLC group ($p < 0.05$), whereas it was 13.5, 9.0 and 6.0 months in the ES-SCLC group ($p < 0.05$). Response to primary systemic therapy is one of the independent prognosis factors for both LS-SCLC and ES-SCLC proven by multivariate analysis.

Initiative radiotherapy in LS-SCLC included concurrent thoracic irradiation or sequential irradiation and depended on tolerance in this study. Patients who accepted initiative radiotherapy had a prolonged OS of almost double those who did not (27.0 months vs. 15.0 months). Perhaps due to consistency of initial treatment and the relatively high ratio (68.8%) of initiative radiotherapy in this group, only PCI was the independent prognosis factor for survival in multivariate analysis, but not initiative radiotherapy. Although PCI was only performed in 39.1% patients, those who received PCI had a much longer survival of 39.0 months (vs. 16.0 months) than reported in this group.[18]

In contrast to its established role in LS-SCLC, the results of radiation therapy as an important part of the treatment regimen for OS are conflicting. The pivotal study of Jeremic et al. showed patients in ES-SCLC with good performance (PS 0), achieved PR/CR at local (intrathoracic) and CR at the distant level (metastases) from three cycles of initial chemotherapy, and achieved survival benefits from thoracic radiation therapy followed by PCI.[19] Data of 260 patients excluded intracanial and pleural metastasis with ES-SCLC from a randomized CREST trial, showed low dose thoracic radiotherapy (30 Gy in 10 fractions) after first-line chemotherapy (six cycles) improved progression-free survival (PFS) but did not meet the primary endpoint of OS.[9, 20] The results were conflicting, but the large gap between the two

studies in patient characteristics and treatment aspects should not be ignored. The Radiation Therapy Oncology Group study 0937 compared radiation therapy to the thorax and metastases following PCI and PCI in ES-SCLC patients. After achieving a response to initial chemotherapy, the study was closed prior to meeting its accrual target as it crossed the futility boundary for OS.[21] ES-SCLC is such a widespread disease and the sites of failure after initial chemotherapy are likely to be the sites of presenting disease, and radiation therapy in these sites may alter the failure patterns. Instead of focusing on thoracic radiation therapy or radiotherapy to sites of metastases, we analyzed the impact of initiative radiotherapy for ES-SCLC in our study. Initiative radiotherapy for ES-SCLC in this study included not only higher dose thoracic radiotherapy after response to primary chemotherapy, but also aggressive radiotherapy for stable or slowly progressing, asymptomatic metastatic sites outside the thoracic region. A total of 139 patients (27.4% of 507 cases) accepted initiative irradiation therapy and achieved much higher OS (19.0 vs. 9.0 months). Consolidation radiotherapy with chemotherapy in this study, other than the benefits of PFS as reported,[22] improved OS in ES-SCLC, and may potentially be involved with changing the pattern of recurrence.

Another independent prognostic factor for survival in addition to a response to primary chemotherapy and initiative irradiation, is patients who receive three or more lines of systemic therapy. More opportunities for systemic therapy provide greater patient survival benefits. A retrospective analysis of 202 SCLC patients showed good PS, and a longer period to treatment failure after second-line chemotherapy were favorable prognostic factors for those patients who had received third-line chemotherapy.[23] Irrespective of this, all the above mentioned data suggests that a more aggressive strategy of systemic therapy, especially combined with initiative radiotherapy, provides survival benefits for patients with ES-SCLC.

Although data from one center means consistency of principles for treatment selection, this is also one of the limitations of the present study. However, this study involved a relatively large number of patients both with LS-SCLC and ES-SCLC. Real-world data showed the proportion of patients receiving PCI was still low in LS-SCLC although that evidence might not influence our conclusions. Recently, whether to give PCI to patients with ES-SCLC has been controversial. Data from the present study is so small that it possibly affects the results.

Real-world data demonstrates in addition to PS and metastatic sites, response to primary systemic treatment and PCI for LS-SCLC, and initiative irradiation of original and metastatic sites for ES-SCLC was found to improve overall patient survival. A more aggressive treatment strategy for SCLC, especially for ES-SCLC, initiative radiotherapy and more lines of systemic therapy provided survival benefits. The results indicate that further studies, especially well-controlled prospective studies, focusing on local treatment combined with systemic therapy in ES-SCLC, are urgently required.

CONFLICT OF INTEREST

No authors report any conflict of interest.

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