

Original Article

The prognostic factors in the elderly patients with small cell lung cancer: a retrospective analysis from a single cancer institute

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Received June 30, 2015; Accepted August 20, 2015; Epub September 1, 2015; Published September 15, 2015

Abstract: Objectives: We conducted a retrospective study to evaluate the prognostic factors of elderly patients with small cell lung cancer (SCLC). Patients and methods: The records of elderly patients (≥ 65 years) with histologically-proven SCLC were reviewed. The patients' information including demographic, clinical and laboratory parameters, staging status on the Veterans Administration Lung Study Group staging system, and treatment modalities were registered. Univariate and multivariate survival analysis was performed by the Kaplan-Meier method and Cox proportional hazards model, respectively. Results: Between January 2004 and December 2012, 247 elderly patients with SCLC were analyzed, 129 patients initially presented with limited stage (LS) and 118 with extensive disease (ES). The median age of the patients was 70.7 years (range, 65-83 years). The median follow-up period for all patients was 22.0 months (range, 1.0-84.0 months) and 39.9 months for the surviving patients (range, 4.7-84.0 months). The median survival time (MST) was 17.3 months, and the 2-year and 3-year OS rates were 36.3% and 22.7%, respectively. The MST, 2-year and 3-year OS rates were 22 months, 45.0% and 30.5% in patients with limited stage, versus 13.4 months, 26.5% and 13.7% in patients having extensive diseases, respectively. Multivariate analysis revealed that disease extent (HR = 3.034; $P < 0.001$) and the number of chemotherapy cycles (HR = 0.486; $P = 0.003$) were independent prognostic factors for the OS. Additionally, a normal serum NSE level (HR = 0.447, $P = 0.017$) at the time of diagnosis was independent positive prognostic factors for patients with LS-SCLC, but not for ES-SCLC. Conclusion: Disease extent and the number of chemotherapy cycles were independent prognostic factors of elderly patients with SCLC. The fit cohort might benefit from positive treatment.

Keywords: Elderly, small cell lung cancer, survival, prognosis factor, overall survival

Introduction

Lung cancer is the most common malignant carcinoma and the leading cause of death due to cancer in the world, and now it is regarded as a senile disease because the median age of patients diagnosed with lung carcinoma is 70 years [1, 2]. Small cell lung cancer (SCLC) represents approximately 15% to 20% of all new cases of lung carcinomas [3, 4]. The data of Surveillance Epidemiology and End Results (SEER) showed that 68% of patients with SCLC were older than 65 years, and more than 30% were older than 70 years [2]. On the basis of these observations, SCLC represents a signifi-

cantly serious health problem in the elderly patients.

SCLC is usually classified into two stages: limited disease (LS) and extensive stage (ES) according to the staging system of Veterans Administration Lung Study Group [5]. It is characterized by a high incidence of metastatic disease at presentation, rapid doubling time, and poor survival. A platinum-based chemotherapy (ChT) regimen combined with thoracic radiotherapy (TRT) concurrently or sequentially is the standard treatment for limited-disease, and the median survival time is about 12-16 months and the overall survival is 20% at 5-year approx-

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Table 1. Clinical features of elderly patients with SCLC

Characteristic	Total	%	LS-SCLC		ES-SCLC	
			Total	%	Total	%
Gender						
Male	201	81.4	103	79.8	98	83.1
Female	46	18.6	26	20.2	20	16.9
Age (years)						
Range	65-83		65-82		65-83	
Median	70		70		71	
65-70	106	42.9	60	46.5	46	39.0
≥ 70	141	57.1	69	53.5	72	61.0
KPS score						
≥ 80	173	70.0	87	67.4	86	72.9
< 80	74	30.0	42	32.6	32	27.1
Wight loss						
< 5%	213	86.2	115	89.1	98	83.1
≥ 5%	34	13.8	14	10.9	20	16.8
Smoking status						
Yes	166	67.2	86	66.7	80	67.8
No	81	32.8	43	33.3	38	32.2
Cycle of ChT						
< 4	61	25.4	32	25.8	29	25.0
≥ 4	179	74.6	92	74.2	87	75.0
Pleural effusion						
Yes	48	19.4	4	3.1	44	37.3
No	199	80.6	125	96.9	74	62.7
Obstructive Pneuontise						
Yes	113	46.3	40	31.3	73	62.9
No	131	53.7	88	36.1	43	37.1
Treatment 1						
TRT+ChT	69	48.6	36	66.7	33	28.0
ChT alone	73	51.4	18	33.3	55	72.0
Treatment 2						
S+ChT±TRT	43	23.2	39	41.9	4	4.3
ChT±TRT	142	76.8	54	58.1	88	95.7
NSE (ng/mL)						
< 17	138	73.4	60	62.5	79	85.9
≥ 17	50	26.6	36	37.5	13	14.1
CEA (ng/mL)						
< 3.4	95	52.5	51	52.6	44	52.4
≥ 3.4	86	47.5	46	47.4	40	47.6

LS-SCLC, limited-stage small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; KPS, Karnofsky performance status; ChT, chemotherapy; TRT, thoracic radiation therapy; S, surgery; NSE, neuron-specific enolase; CEA, carcinoembryonic antigen.

imately [6, 7]. For ES diseases, combination ChT remains the standard treatment. TRT is

most commonly used as palliative approach, even though consolidative TRT improved the 5-year survival rate and local control in patients who responded to initial ChT [8, 9].

Among patients with SCLC, the elderly cohort usually accompanied with poor physiologic status and comorbidities, there was still no high-grade evidence of optimal treatment guide for this special subgroup [10]. Few retrospective studies attempted to evaluate the treatment modalities and identify prognostic factors for elderly patients with SCLC, however, the results could not be satisfied because of highly individual heterogeneity in the study population [11-13]. The current study is aiming to investigate the prognostic factors of elderly patients (≥ 65 years) with SCLC and attempt to afford evidence of treatment selection.

Patients and methods

Patients

Elderly patients (≥ 65 years) diagnosed as SCLC on the basis of cytological or histological proof at Shandong Cancer Hospital between January 2004 and December 2012 were retrospectively reviewed. The clinical data were drawn from their inpatient records. All patients had undergone standardized evaluation, including thoracic and abdominal computed tomography scanning or abdominal ultrasonography, brain magnetic resonance imaging, and bone radionuclide imaging, and the disease stage was reached according to the system of the Veterans' Administration Lung Study Group [10]. Detailed data including gender, age, weight loss, smoking status, KPS score, the serum levels of biological markers including neuron-specific enolase (NSE) and carcinoembryonic antigen (CEA), and treatment modalities of enrolled patients were recorded.

The study was approved by the institutional review board/ethics committee at Shandong Cancer Hospital.

Treatment

Surgical procedures included wedge resection, lobectomy or pneumonectomy with ipsilateral

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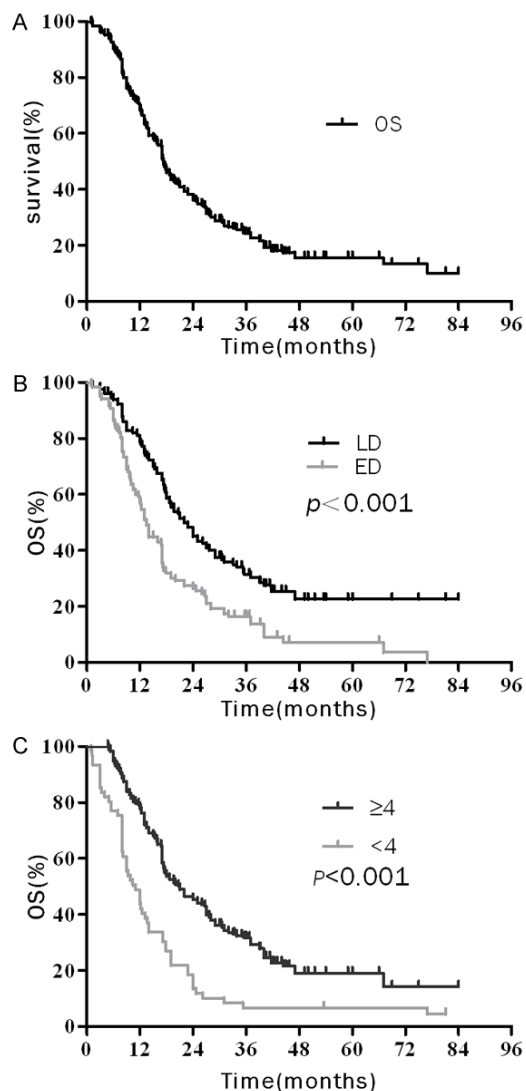


Figure 1. Over survival (OS) curves of elderly patients with SCLC: A. OS curves of all elderly patients; B. OS curves of patients according to disease extent (C) OS curves of patients according to number cycles of chemotherapy (D) OS curves of patients according to serum NSE level.

hilar and mediastinal lymphadenectomy. Chemotherapy regimens were consisted of either cisplatin and etoposide (PE: cisplatin, 30 mg/m² on days 1-3 and etoposide, 100 mg/m² on days 1-5 or 100 mg/m² on days 1-3), or carboplatin/etoposide (CE: carboplatin AUC 5 or 300 mg/m² on day 1 and etoposide, 100 mg/m² on days 1-5 or 100 mg/m² on days 1-3). TRT was administered by three-dimensional conformal radiotherapy technique (3D-CRT), the gross target volume (GTV) included the primary tumour and positive lymph nodes; the clinical target

volume (CTV) included the GTV with a 0.8-cm margin and the draining area of positive lymph nodes, and the CTV of patients undergoing complete resection only included bronchial stump, ipsilateral hilum, and adjacent mediastinal lymph nodes; and the planning target volume (PTV) included the CTV with a 1-cm margin. Radiation was delivered with megavoltage linear accelerators. A total dose of 40-60 Gy was administered with 1.8-2 Gy per fraction for 5 days a week. During this period, prophylactic cranial irradiation (PCI) was not institutional policy, and only 22 patients achieving a complete remission (CR) after primary therapy received PCI in all of the groups. PCI dose fractionation was 25 Gy in 10 fractions over 2 weeks.

The follow-up

Patients were followed up every 3 months for the first year, then every 6 months for the following 2 years, and annually thereafter. The follow-up evaluations consisted of history, physical examination, and radiologic examination. Radiologic examination included a chest X-ray, chest CT, abdominal ultrasound or CT. Other necessary examinations were conducted as clinically indicated.

Statistical analysis

The overall survival (OS), calculated from the date of diagnosis to the date of death from any cause or the last known date when the patient was alive, was evaluated using Kaplan Meier method and a comparison between survival curves was done with log-rank test. Multivariate Cox regression analysis with a backward-forward stepwise method assessed the prognostic factors for OS. In the multivariate Cox regression model, all variables with p values < 0.05 in the univariate analysis were included. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Between January 2004 and December 2012, 247 patients (≥ 65 years) with SCLC were included in this trial, 129 patients initially presented with LS-SCLC, while 118 patients had extensive stage. The median age of the all

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Table 2. Univariate analysis and multivariate analysis of the prognostic factors on OS in patients with total SCLC

Factors	Univariate analysis				Multivariate analysis		
	MST (m)	2-y OS (%)	3-y OS (%)	P	HR	95% CI	P
Gender							
Male	17	33.5	19.1				
Female	22	46.2	38.8	0.077			
Age (years)							
65-70	19.7	43.0	25.9	0.296			
≥ 70	17.0	31.4	22.3				
KPS							
≥ 80	17.2	40.1	25.2				
< 80	17.3	34.6	20.0	0.092			
Weight loss							
< 5%	17.7	37.1	22.7				
≥ 5%	13.0	28.1	19.0	0.166			
Smoking							
Yes	17.0	37.5	22.9				
No	17.9	33.7	20.5	0.888			
Cycle of ChT							
< 4	11.0	13.5	4.5			0.301-	
≥ 4	20.7	45.1	29.2	< 0.001	0.486	0.786	0.003
Pleural effusion							
Yes	14.0	30.0	12.3				
No	17.9	37.7	23.8	0.251			
Disease extent							
LS	22.0	45.0	30.5			2.022-	
ES	13.4	26.5	13.7	< 0.001	3.034	4.552	< 0.001
Obstructive Pneuontise							
Yes	14.0	32.2	20.1				
No	19.0	39.6	24.6	0.082			
NSE (ng/mL)							
≥ 17	17.0	32.1	18.9			0.642-	
< 17	26.0	50.4	34.4	0.003	1.111	1.924	0.706
CEA (ng/mL)							
≥ 3.4	17.0	33.5	22.4				
< 3.4	17.4	42.8	23.9	0.552			

OS, overall survival; SCLC, small cell lung cancer; KPS, Karnofsky performance status; ChT, chemotherapy; LS, limited-stage; ES, extensive-stage; NSE, neuron-specific enolase; CEA, carcinoembryonic antigen.

patients was 70.7 (range 65-83). The median follow-up period for all patients was 22.0 months (range, 1.0-84.0 months) and 39.9 months for surviving patients (range, 4.7-84.0 months). The characteristics of 247 elderly patients were summarized in **Table 1**.

Survival

At the end of follow-up, 52 patients were still alive. The median survival time (MST) was 17.3 months, and the 2-year and 3-year OS rates were 36.3% and 22.7%, respectively, for the entire cohort of patients (**Figure 1A**). The MST, the OS rates at 2-year and 3-year were 22 months, 45.0% and 30.5% in patients with limited stage, versus 13.4 months, 26.5% and 13.7% in patients with extensive stage, respectively ($P < 0.001$). The MST, 2-year and 3-year OS rates in the patients who accepted ≥ 4 cycles of ChT were 20.7 months, 45.1% and 29.2%, and those of patients who accepted < 4 cycles of ChT were 11.0 months, 13.5% and 4.5%, respectively ($P < 0.001$). Additionally, the analysis showed that the survival of patients with elevated NSE level (≥ 17 ng/mL) or elevated LDH level (≥ 245 u/l) was worse than that of patients with normal NSE level (< 17 ng/mL) or normal LDH level (< 245 u/l), p value were 0.003 and 0.027, respectively (**Figure 1**). The survival data of the whole group were detailed in **Table 2**.

In the subgroup patients with limited stage, those who accomplished ≥ 4 cycles of chemotherapy, accepted surgery-included treatment or with normal serum NSE had higher overall survival rates than patients who accepted < 4 cycles of chemotherapy, non-surgical treatment modalities or with elevated serum NSE (**Figure 2**), the data were detailed in **Table 3**. In the subgroup of ES-SCLC, the overall survival of the patients with weight loss $< 5\%$, ≥ 4 cycles of chemotherapy or TRT were significantly higher than that for patients with weight loss

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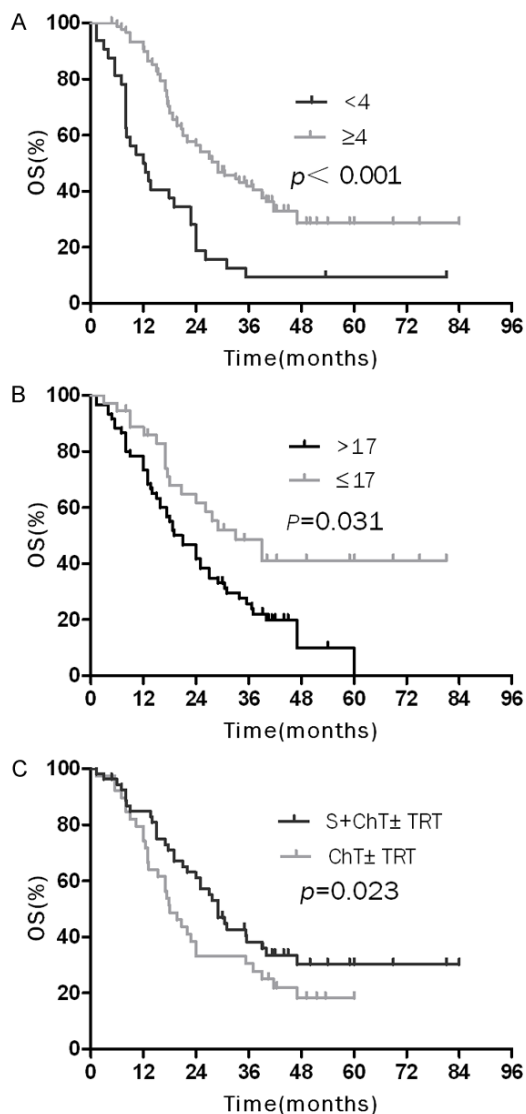


Figure 2. Over survival (OS) curves of elderly patients with LD-SCLC: A. OS curves of patients according to number cycles of chemotherapy; B. OS curves of patients according to serum NSE level; C. OS curves of patients who underwent surgery followed by chemotherapy \pm thoracic radiation therapy and chemotherapy \pm thoracic radiation therapy.

$\geq 5\%$, < 4 cycles of chemotherapy or non-TRT (Figure 3; Table 3).

Factors predictive of the OS

The clinical factors were assessed to determine their prognostic value. With regard to OS, multivariate analysis revealed that extensive-stage disease [hazard ratio (HR) = 3.034, $P < 0.001$], and < 4 cycles of chemotherapy (HR = 0.486, $P = 0.003$) were independent negative

prognostic factors of OS (Table 2); In the subgroup of patients with LS-SCLC, a normal serum NSE level (HR = 0.447, $P = 0.017$) at the time of diagnosis was independent positive prognostic factors of OS, and < 4 cycles of chemotherapy (HR = 0.348, $P = 0.001$) was independent negative prognostic factors of OS (Table 3); In the subgroup of extensive stage, ≥ 4 cycles of chemotherapy (HR = 0.529, $P = 0.016$) was the only independent prognostic factors of OS (Table 3).

Discussion

Generally, elderly patients with SCLC have significantly more comorbidities, smaller bone marrow reserve, poor performance status that affect worse tolerability to chemotherapy, therefore, the optimal treatment for elderly SCLC patients is still controversial and prognostic indicators are heterogeneous [10-14]. According to analyze the 247 elderly patients with SCLC, the retrospective study revealed that extensive-stage disease and < 4 cycles of chemotherapy were independent negative prognostic factors for the elderly patients with SCLC. Additionally, a normal serum NSE level (HR = 0.53, $P = 0.021$) at the time of diagnosis was independent positive prognostic factors for the elderly patients with limited stage SCLC.

The prognostic role of age in elderly patients with SCLC could not reach a consensus. One retrospective study conducted by Safont revealed that age was likely to affect the OS of elderly patients with LD-SCLC, the MST was 60.3 weeks in the subgroup of patients with 65-70 years, while it was 49.4 weeks in patients with ≥ 70 years, $P = 0.005$ [12]. However, several previous studies did not show a significant relationship between age and survival status [14-17]. In the current analysis, 106 patients (42.9%) were 65-70 years old and 141 patients (57.1%) were aged ≥ 70 years, the 2y-OS was 43.0 % in the group aged with 65-70 years and that was 31.4 % in the group aged with ≥ 70 years. The prognostic role of age for the survival in elderly patients was not established ($P = 0.296$). Therefore, in the routine clinical practice the treatment should be based on biological rather than chronological age.

It is well accepted that the extent of disease has traditionally been included in prognostic

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Table 3. Univariate analysis and multivariate analysis of the prognostic factors on OS in patients with LS-SCLC and ES-SCLC

Factors	LS-SCLC								ES-SCLC							
	Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
	MST (m)	2-y OS (%)	3-y OS (%)	P	HR	95% CI	P	MST (m)	2-y OS (%)	3-y OS (%)	P	HR	95% CI	P		
Gender																
Male	21.0	42.1	26.3					13.0	24.3	11.2						
Female	33.9	52.6	43.1	0.467				17.0	31.8	0.0	0.068					
Age (years)																
65-70	27.6	54.0	32.8					12.0	26.0	13.2						
≥ 70	19.0	37.7	26.6	0.268				14.0	25.3	10.9	0.941					
KPS																
≥ 80	20.7	42.5	23.7					13.0	23.7	10.2						
< 80	24.0	50.0	30.6	0.816				14.0	26.3	15.4	0.361					
Wight loss																
< 5%	29.0	50.0	28.8					14.0	29.4	15.1		0.319-				
≥ 5%	22.0	43.5	23.8	0.680				12.0	6.2	0.0	0.043	0.576	1.038	0.067		
Smoking																
Yes	21.0	38.3	22.3					12.0	25.7	11.6						
No	22.8	45.9	33.1	0.593				13.4	25.5	19.8	0.888					
Cycle of ChT																
< 4	12.0	18.8	9.4			0.184-		9.8	3.7	0.0			0.315-			
≥ 4	27.6	55.8	40.0	< 0.001	0.348	0.658	0.001	16.0	33.6	17.3	0.003	0.529	0.889	0.016		
Pleural effuion																
Yes	20.7	33.3	0.0					11.7	29.6	8.6						
No	22.0	45.3	30.3	0.718				14.0	24.6	12.7	0.286					
Obstructive Pneuontise																
Yes	17.7	43.7	29.7					13.0	24.1	11.0						
No	22.8	44.4	30.4	0.896				16.0	27.8	9.7	0.399					
Treatment 1																
TRT+ChT	24.0	43.4	25.7					17.0	24.4	10.5		0.840-				
ChT alone	17.3	48.4	26.3	0.577				9.8	11.9	5.9	0.035	1.380	2.268	0.204		
Treatment 2																
S+ChT±TRT	27.0	53.7	42.3			0.627-										
ChT±TRT	19.0	40.9	28.0	0.023	0.512	2.724	0.474									
NSE (ng/mL)																
≥ 17	21.0	43.3	24.7			0.231-		12.3	22.8	11.9						
< 17	29.0	59.2	39.4	0.031	0.447	0.865	0.017	13.4	23.1	7.7	0.838					
CEA (ng/mL)																
≥ 3.4	22.0	39.2	26.9					14.0	26.5	12.6						
< 3.4	29.0	57.6	20.4	0.211				13.0	23.0	5.7	0.397					

OS, overall survival; LS-SCLC, limited-stage small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; KPS, Karnofsky performance status; ChT, chemotherapy; TRT, thoracic radiation therapy; S, surgery; NSE, neuron-specific enolase; CEA, carcinoembryonic antigen.

evaluation for SCLC [18-21]. A retrospective study included 284 patients with LS-SCLC and 328 patients with ES-SCLC between 1974 and 1986 showed that median survival time of patients with limited-stage disease (53 weeks) was significantly better than that those with extensive disease (35 weeks, $P < 0.00005$)

[21]. The current study manifested that the extreme differences in survival between patients with LS and ES-SCLC (2-year and 3-year OS rate of 45.0 and 30.5% versus 26.5 and 13.7%, $P < 0.001$). So the discovery of the disease in the shortest possible time is vital for SCLC patients.

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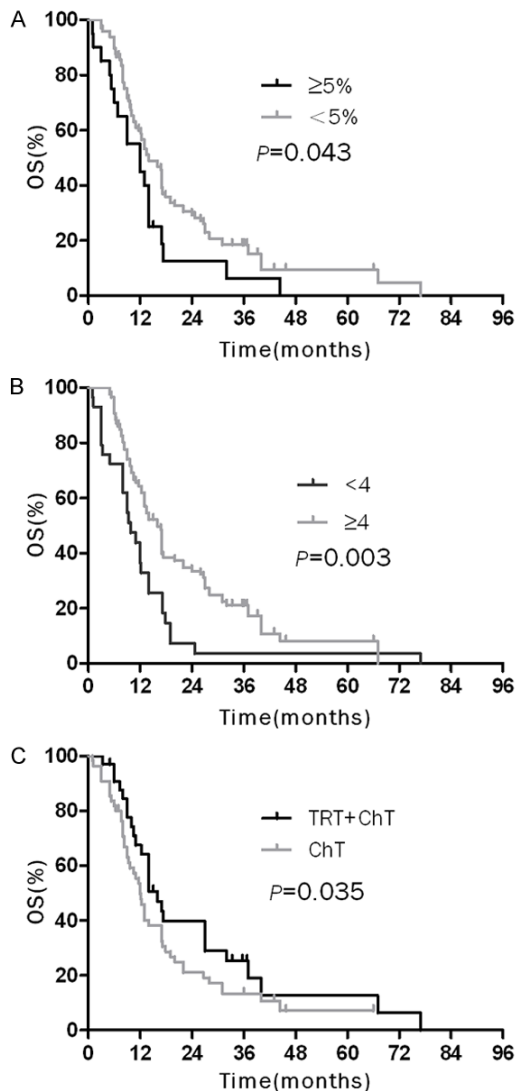


Figure 3. Over survival (OS) curves of elderly patients with ED-SCLC: A. OS curves of patients according to weight loss; B. OS curves of patients according to number cycles of chemotherapy; C. OS curves of patients who underwent chemotherapy combined with thoracic radiation therapy and only chemotherapy.

As SCLC is a systemic disease, chemotherapy plays a key role in the treatment. Four to six cycles of a platinum-based chemotherapy doublet is recommended usually, and many studies have demonstrated that less than four cycles of chemotherapy could incur a poor prognosis. The result of Intergroup Trial 0096 showed that elderly patients (age > 70 years) had non-inferior response and survival figures compared with younger patients if the elderly subgroup could get through four cycles of chemotherapy [11]. A randomized trial by Maryska concluded that

the survival of elderly patients who could complete at least 4 cycles of chemotherapy was better than that less than 4 cycles of chemotherapy, the MST was 11.5 months versus 3.6 months, $P < 0.0001$ [13]. This conclusion was similar to our current study.

Chemotherapy combined with TRT was assumed as the standard treatment for the management of LS-SCLC [10], surgery has been known to be a valuable local treatment approach for LS-SCLC since the last three decades. Nevertheless, the role of surgery as a part of multimodality treatment remains uncertain in elderly patients. A matched-pair analysis comparing 67 patients who underwent surgery followed by adjuvant ChT and 67 patients who received conventional non-surgical management revealed a 5-year OS rate of 27% for the surgical group and 4% for the matched non-surgical cohort [22]. Other several trials have demonstrated that surgery followed by adjuvant ChT results in a favorable survival rate for early stage disease [23-25]. In this retrospective study, the MST and 3-year OS rates for the surgical subgroup were 27.0 months and 42.3% respectively, and those for patients who received non-surgical therapy were 19.0 months and 28.0% respectively ($P = 0.023$). Interestingly, surgery was not revealed as the independent prognostic indicator for the OS in multivariate analysis. The reason for this discrepancy might be a relatively higher percentage of elderly patients with stage III SCLC at the diagnosis and relatively small sample size in our study.

For ES-SCLC patients, the role of radiotherapy was controversial. A retrospective study in 1999 first demonstrated that TRT could improve the 5-year OS rate for a favorable patient subgroup of complete responders compared with ChT alone (9.1% vs 3.7%), and it decreased the local recurrence rate [8]. A phase III randomized controlled trial at 42 hospitals manifested that thoracic radiotherapy after chemotherapy improved 2-year survival for patients with ES-SCLC ($P = 0.004$) [26]. Our retrospective study also confirmed the positive role of TRT in ES-SCLC [9]. However, for the elderly, the role of TRT as palliative or curative intent is inconclusive. Our current study demonstrated that comparing with ChT alone, ChT combined with TRT almost doubled the median

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survival from 9.8 months to 17.0 months, 3-year OS rates were increased from 5.9% and 10.5%, respectively ($P = 0.0035$), but it was not an independent positive factor of prognosis for elderly patients. So much caution should be exercised when thoracic radiotherapy is planned for elderly patients with ES-SCLC.

NSE, an enolase isoenzyme, has been regarded as a sensitive tumor marker in SCLC. Serum NSE levels are elevated in 61-83% of SCLC patients [27]. Studies have indicated that the NSE level is associated with disease stage, response to therapy, and survival. It can also be used to monitor disease progression [19, 27, 28]. In our study, the subgroup of patients with elevated NSE levels had poor survival status. And multivariate analysis confirmed that the serum NSE level was an independent prognostic marker of elderly patients with LS-SCLC.

Our study has several limitations. First, the study is retrospective and biases were inevitable, even though the multivariate analysis can aid in decreasing these biases to a certain degree. Second, the number of patients was moderate, and the elderly patients of our study who all have accepted treatment are not completely on behalf of the general elderly patients. Third, other important prognostic indicators such as co-morbidities, toxicity, socioeconomic, emotional and cognitive conditions, functional and nutritional status which may be benefit of improving treatment suitability were not included in the study. The last but not least, a certain proportion of patients did not receive prophylactic cranial irradiation. This might cause some inconsistency with other similar investigations which precluded the generalization of the results in our study.

Conclusion

Our study manifested disease extent and chemotherapy cycle were strongly associated with survival rate of the elderly patient with SCLC. We hope these prognostic factors will be useful for the better evaluation of treatment outcome in future clinical trials and the guidance of an individual treatment.

Acknowledgements

This study was supported by Grant NO. ZR20011HM089 from the Natural Science Foundation of Shandong Province to Li Kong.

Disclosure of conflict of interest

None.

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