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Tumor size and lymph node metastasis are prognostic markers of small cell lung cancer in a Chinese population

Liang Wang, MD[a], Xuejun Dou, BM[b], Tao Liu, BM[c], Weiqiang Lu, BM[b], Yunlei Ma, MD[b], Yue Yang, MD[a,*]

Abstract

Small cell lung cancer (SCLC) is a high-grade neuroendocrine tumor characterized by rapid growth, early metastatic spread, and poor prognosis. This study aimed to explore the prognosis factors of survival in Chinese SCLC patients.

A total of 78 patients with stage IIIA SCLC (mean age: 53.9 years, 65 males and 13 females) were enrolled in this retrospective study. At least of 5 years follow-up was performed.

The survival time of these patients ranged from 1 month to 66 months with a median survival time of 11 months. Kaplan–Meier method with log-rank test was performed and showed that survival time in patients with tumor size ≤4 cm (median: 16 months) was significantly longer ($P < .001$) than that in patients with tumor size > 4 cm (median: 8 months); the median survival time of the patients with single lymph node metastasis was significantly longer than that in patients with multiple lymph node metastasis ($P = .043$). Combined multiple lymph node metastasis and tumor size >4 cm presented the worst survival outcome than others. Multivariate analysis by Cox Hazard model shows that the lymph node metastasis and tumors size were prognostic factors independent of age, sex, smoke, surgery, and treatment regimen ($P < .05$).

Results showed that larger tumor size and multiple lymph node metastasis were associated with the poor survival in SCLC.

Abbreviations: ES = extensive stage, NSCLC = nonsmall cell lung cancer, SCLC = small cell lung cancer, TNM = tumor, node, metastasis, UICC = Union for International Cancer Control, VEGF = vascular endothelial growth factor.

Keywords: lymph node metastasis, prognosis, small cell lung cancer, survival, tumor size

1. Introduction

Small cell lung cancer (SCLC), which accounts for about 15% lung cancer, is a high-grade neuroendocrine tumor characterized by rapid growth and early metastatic spread.[1,2] Although the incidence of SCLC is declining recently, the prognosis of SCLC patients is still poor and the 5-year survival rate is only about 6%.[3] Extensive-stage (ES)-SCLC, which accounts for approximately 70% of SCLC, only showed a median overall survival, which ranged from 8 to 12 months.[4,5] Surgery along with chemotherapy is still the common treatment of lung cancer.[6,7] However, it is still unknown which one is the optimum strategy to improve the outcome and prognosis of SCLC patients.

Recently, more and more studies were performed to explore the prognosis-associated risk factors to improve survival of SCLC patients. According to the previous publications, prognosis of patients with SCLC can be influenced by several clinical factors, such as patient's age, gender, performance status, and clinical stage.[8–10] Moreover, tumor size has been found to be a prognostic factor of many cancers, such as non-SCLC (NSCLC),[11] colon cancer,[12] and breast cancer.[13] In addition, lymph node metastasis is also a risk factor associated with the survival of NSCLC.[14–16] Therefore, these findings indicated that the tumor size and lymph node metastasis may be also the prognostic factors of SCLC. However, the relevant study on Chinese population is still rare. Considering the ethnic difference, it is also necessary and important to further investigate the SCLC prognosis-associated risk factors in a Chinese population.

Thus, this study was performed to explore the prognostic factors of survival in Chinese SCLC patients who underwent surgery combined chemotherapy. Moreover, concerning the existing knowledge, the tumor size and lymph node metastasis were specially considered. According to these investigations, we hope to provide some new insights in treating advanced SCLC in clinic.

2. Materials and methods

2.1. Study design and patients

This study was a single-center, observational, retrospective study to investigate the survival of SCLC patients. The protocol of this

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[a] Key Laboratory of Carcinogensis and Translational Research (Ministry of Education), Department of Thoracic Surgery II, Peking University Cancer Hospital and Institute, [b] Department of Thoracic Surgery, Aerospace Center Hospital, [c] Department of Thoracic Surgery, Beijing Chest Hospital, Beijing, China.

[*] Correspondence: Yue Yang, Key Laboratory of Carcinogensis and translational Research (Ministry of Education), Department of Thoracic Surgery II, Peking University Cancer Hospital and Institute, No. 52 Fucheng Road, Haidian District, Beijing 100142, People's Republic of China (e-mail: yangyueyy66@163.com).

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study was approved by the Institutional Review Board of Peking University Cancer Hospital and Institute.

Generally, surgery combined with chemotherapy was often applied for the advanced SCLC treatment. Therefore, 78 SCLC patients, including 65 males and 13 females, at IIIA stage were enrolled from our hospital from January 2010 to December 2012. Pathological diagnosis was performed according to the tumor, node, and metastasis (TNM) classification recommended by the Union for International Cancer Control (UICC).

These patients aged from 27 to 75 years with a mean age of 53.9 years. About 46% of patients (n = 36) were smokers. All patients underwent pneumonectomy (n = 48, 61.5%) or pulmonary lobectomy (n = 30, 38.5%). Approximately 60% of patients received chemotherapy before and after surgery and the rest of the patients only received chemotherapy after surgery. Most of the chemotherapy regimens were VP-16 and Cis-platinum, and the chemotherapy period was ranged from 4 to 6 cycles. Postoperative chemotherapy was performed 1 month after surgery. For individual patients, postoperative chemotherapy could be put off for 5 to 6 weeks after surgery. Surgery was performed when patients had reduced mass shadow and mediastinal lymph nodes and normal levels of white blood cells, platelets, liver, and kidney function whether before or after chemotherapy. Tumor sizes were measured before the first chemotherapy (chemotherapy + surgery +chemotherapy) or surgery (surgery + chemotherapy) and 38 of enrolled patients (48.7%) had this size more than 4 cm. Single lymph node metastasis was found in 64.1% of patients (n = 50) and multiple lymph node metastasis was found in the rest patients (n = 28, 35.9%). The baseline characteristics of these enrolled patients are summarized in Table 1. At least of 5 years of follow-up was performed for each individual.

2.2. Statistical analysis

The overall survival curve was drawn according to the life table method. The effect of the characteristics of patients on survival was investigated by Kaplan–Meier method with log-rank test. The Cox Hazard model was used for the multivariate analysis. For all these analyses, P values $< .05$ were considered significant.

Table 1

Characteristics of participants.

Characteristics	N (%)
Age, y	
< 60	41 (52.6%)
≥ 60	37 (47.4%)
Sex	
Male	65 (83.3%)
Female	13 (16.7%)
Smoke	
Yes	36 (46.2%)
No	42 (53.8%)
Tumor size, cm	
≤ 4	40 (51.3%)
> 4	38 (48.7%)
Surgery	
Pneumonectomy (right)	42 (53.8%)
Pneumonectomy (left)	6 (7.7%)
Pulmonary lobectomy	30 (38.5%)
Treatment regimens	
Chemotherapy + surgery + chemotherapy	47 (60.3%)
Surgery + chemotherapy	31 (39.7%)
Metastases	
Single lymph node metastasis	50 (64.1%)
Multiple lymph node metastasis	28 (35.9%)

3. Results

3.1. Survival results

Patients included in the current study were all dead during follow-up. The survival time of these patients ranged from 1 month to 66 months with a median survival time of 11 months. The 1-year, 3-year, and 5-year survival rates were 41.0%, 2.6%, and 2.6%, respectively. Overall survival curve is shown in Fig. 1A.

3.2. The prognostic factors

As shown in Fig. 1, no significant differences were identified in the survivals of SCLC patients grouped by age ($P = .704$), sex ($P = .356$), smoke ($P = .393$), surgery ($P = .516$), and treatment regimen ($P = .362$). However, the survival time in patients with tumor size ≤4 cm (median: 16 months) was significantly longer ($P < .001$) than that in patients with tumor size >4 cm (median: 8 months). Moreover, the median survival time of patients with single lymph node metastasis was significantly longer than that in patients with multiple lymph node metastasis (median survival time: 12 vs 10 months, $P = .043$).

According to the aforementioned findings, lymph node metastasis and tumors size were 2 prognostic factors associating with the survival of SCLC patients. Therefore, the multivariate analysis by Cox Hazard model was performed to explore the independent prognostic factors. As summarized in the Table 2, lymph node metastasis and tumors size were prognostic factors independent of age, sex, smoke, surgery, and treatment regimen. Moreover, we also estimated the combined effect of tumor size and lymph node in influencing the survival of patients using Kaplan–Meier method and a significant difference was identified among single metastasis+ tumor size ≤4 cm, single metastasis+ tumor size >4 cm, multiple metastasis + tumor size ≤4 cm, and multiple metastasis + tumor size >4 cm ($P < .001$, Fig. 2). Specifically, multiple metastasis + tumor size >4 cm presented the worst survival rate and single metastasis+ tumor size ≤4 cm presented the best survival rate compared with other groups.

4. Discussion

In the present study, we found that the tumor size and lymph node metastasis were the independent prognostic factors of survival in patients with SCLC. Patients suffering from multiple metastasis + tumor size >4 cm presented the worst survival outcome, while patients with single metastasis+ tumor size ≤4 cm presented the best survival rate compared with single metastasis+ tumor size >4 cm and multiple metastasis + tumor size ≤4 cm.

Tumor size is widely found to be associated with the survival of cancers and can be used as a prognostic factor in many cancers.[17,18] As expected, tumor size can also be used for predicting the survival of SCLC patients. Previous studies showed that tumor size was positively correlated with the deficiency of immune ability of patients,[19,20] which may be associated with the poor prognosis of patients after cancer surgery. Moreover, the preoperative immune-enhancing diet is benefit to the outcomes

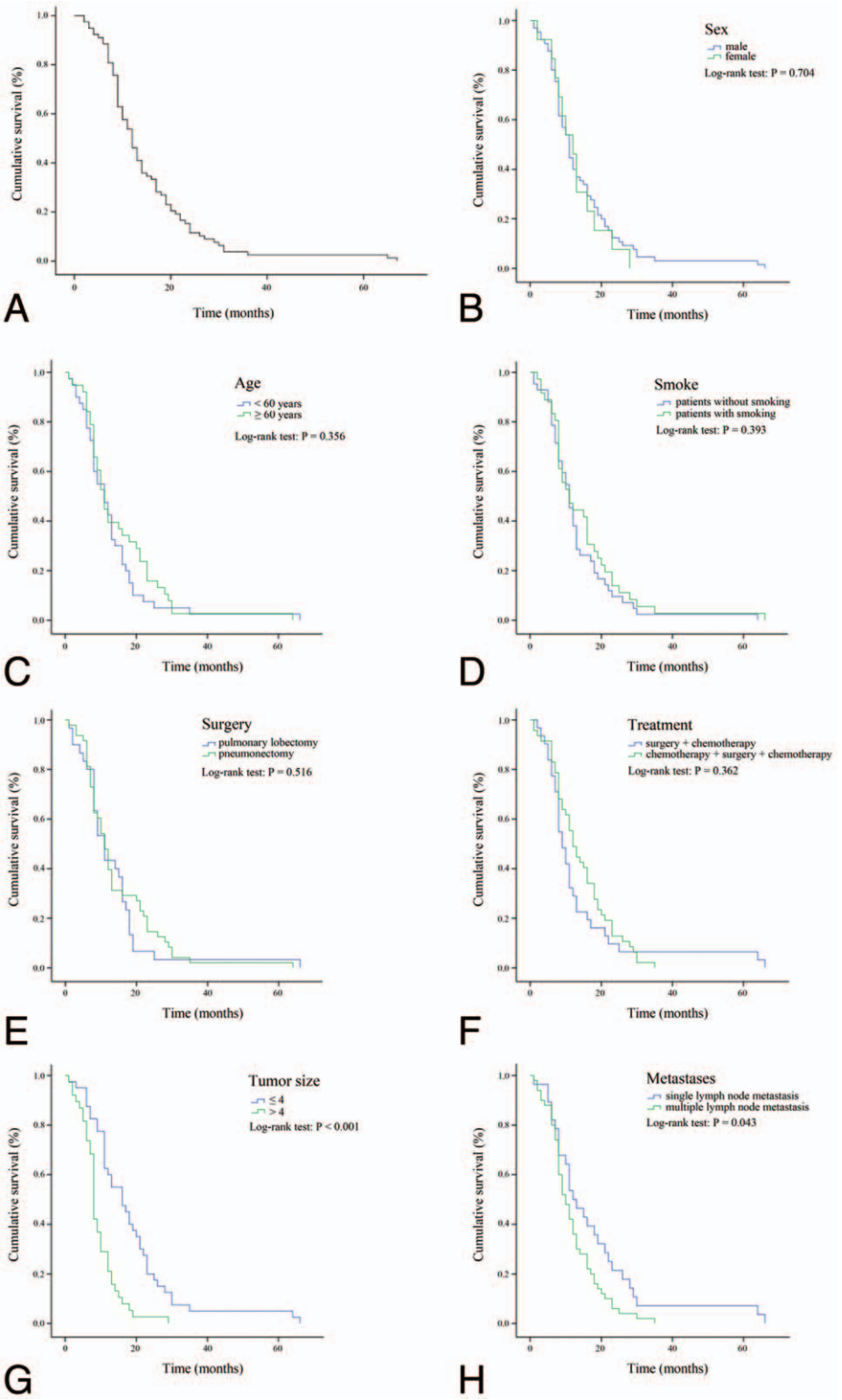

Figure 1. Survival curves. (A) The overall survival curves; (B–H) The survival curves drawn by Kaplan–Meier method using factors such as sex (B), age (C), smoke (D), surgery (E), treatment (F), tumor size (G), and metastases (H). The effect of these factors on survival of SCLC patients was evaluated by log-rank test.

after surgery in colorectal cancer [21] and improves the postoperative immune function in gastric cancer. [22] Tada et al [23] reported that pretreatment immune status was significantly correlated with progression-free survival of metastatic colorectal cancer patients treated with chemotherapy. These evidences indicated that immune system is associated with the cancer survival,[24–26] and tumor size is markedly correlated with the immune deficiency of cancer patients. Therefore, we inferred that the positive correlation between tumor size and immunity deficiency might be the reason for tumor size was a

Table 2

The multivariate analysis results by Cox Hazard model.

Characteristics	HR (95% CI)	P
Age, y		
<60	1	.618
≥60	1.148 (0.667–1.974)	
Sex		
Female	1	.624
Male	1.183 (0.604–2.317)	
Smoke		
No	1	.487
Yes	0.833 (0.497–1.395)	
Tumor size, cm		
≤4	1	< .001
>4	3.545 (2.049–6.133)	
Surgery		
Pulmonary lobectomy	1	.740
Pneumonectomy	0.913 (0.535–1.560)	
Treatment		
Surgery + chemotherapy	1	.113
Chemotherapy + surgery + chemotherapy	0.654 (0.386–1.106)	
Metastases		
Single lymph node metastasis	1	.001
Multiple lymph node metastasis	2.496 (1.430–4.359)	

95% CI = 95% confidence interval, HR = hazard ratio.

prognostic factor in many cancers, including the SCLC in the present study.

In lung cancer, it was found that the vascular endothelial growth factor (VEGF) is a marker of lymph node metastasis in lung cancer.[27,28] Many studies showed that VEGF over-expression was associated with the poor prognosis of patients with NSCLC and SCLC.[29–31] Thus, the survival of SCLC patients may be affected by lymph node metastasis via VEGF-associated mechanism. However, Dowell et al[32] found that the expression of VEGF is an independent risk factor for the survival of SCLC patients. Thus, further studies should be performed to explore the mechanism of correlation between lymph node metastasis and survival outcome of SCLC patients.

In addition, we also investigated that the impacts of age, sex, smoke, surgery, and treatment regimen on the survival of SCLC patients. However, no significant effect was found in this study. A previous study based on 1623 patients found that age and gender are significantly associated with the overall survival of SCLC patients.[8] As it is widely accepted, the combined chemotherapy and surgery can obviously increase the survival of SCLC patients.[33] However, no significant difference was identified between the chemotherapy + surgery + chemotherapy and surgery + chemotherapy. The inconsistency between the results of the present study and the previous studies may be caused by the ethnic difference or study design. In addition, patients normally received the optimal strategy according to their disease status and preoperative chemotherapy could alleviate the stage, tumor size, and metastasis of patients to get a better physical status for surgery. However, this point should also be confirmed in the future based on a large sample size. The small sample size was a limitation of this study. The perspective study with a larger sample size should be performed to verify the results of this study.

In conclusion, tumor size and lymph node metastasis can used as prognostic markers for survival of SCLC patients.

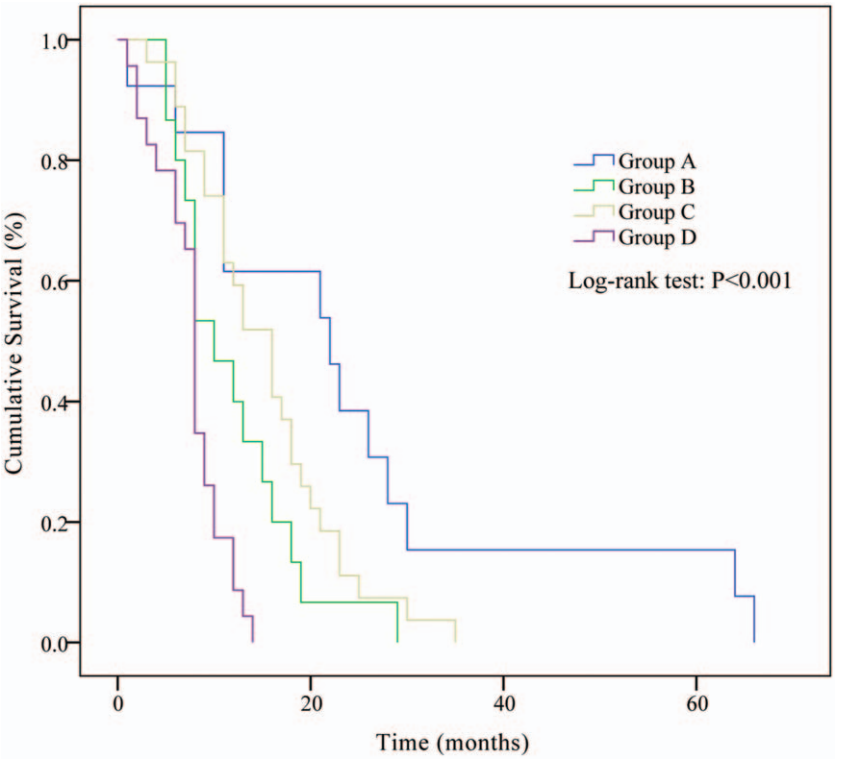

Figure 2. Kaplan–Meier method estimates the combined effect of lymphonode metastasis and tumor size in affecting survival outcome. (A) Single metastasis+ tumor size ≤4 cm; (B) Single metastasis+ tumor size >4 cm; (C) Multiple metastasis + tumor size ≤4 cm; (D) Multiple metastasis + tumor size >4 cm.

Author contributions

Conceptualization: Liang Wang.
Data curation: Xuejun Dou, Tao Liu, Weiqiang Lu, Yunlei Ma.
Formal analysis: Tao Liu, Weiqiang Lu, Yunlei Ma.
Writing – original draft: Liang Wang, Xuejun Dou.
Writing – review & editing: Yue Yang.
Author name: orcid number.

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