A Nomogram From The SEER Database For Predicting The Prognosis of Small Cell Lung Cancer With Different Patterns of Metastases

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Research

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Abstract

Background:

Distant metastases are one of the leading causes of high mortality in small cell lung cancer (SCLC). This research is aimed to investigate the different patterns of metastases in SCLC patients and their impact on prognosis based on the data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods:

The 2010-2015 SEER database of 15637 SCLC patients diagnosed from January to August were used as a training set for development of a nomogram. 7310 SCLC patients diagnosed from September to December were used as the validation set.

Results:

The overall survival (OS) of SCLC patients with no distant metastases, bone metastases, brain metastases, and liver metastases were 16.6, 9.1, 8.8 and 6.0 months, respectively. Patients with solitary liver metastases have the worst prognosis in the cases with single metastatic site. In the patients with multi-site metastases, the clinical outcomes of the cases combined with liver metastases were the worst. Our Cox model indicated that age, gender, American Joint Committee on Cancer (AJCC) stage, metastases, chemotherapy, radiation and surgery were independent predictors for OS in SCLC patients. The c-index value of nomogram was 7.52 in training set and 7.48 in of validation set for predicting OS in SCLC, indicating that the predictive ability of our nomogram model was of great superiority.

Conclusion:

The prognosis of SCLC patients with liver metastases alone or combined with other metastatic sites were worse than other metastatic models. Our nomogram model that integrated significant factors can aid as an individualized clinical predictive tool in SCLC patients.

Introduction

Lung cancer is the most common malignancy and the first leading cause of cancer-related death worldwide [1]. Small cell lung cancer (SCLC) is highly aggressive neuroendocrine carcinomas and is reported in 15% of lung cancer patients [2]. Patients with SCLC have high rate of distance metastases and poor clinical outcomes. The median survival time of SCLS patients was reported to be less than one year. Surgery, chemotherapy and radiation were performed to improve outcomes.

SCLC is an aggressive malignancy with many metastatic sites, of which brain, bone and liver are the most common [3]. Distant metastases in most SCLC patients are one of the leading causes of high mortality in lung cancer [4]. Approximately 70% of new onset SCLC patients have metastases at the time of diagnosis. The 5-year survival rate of extensive-stage SCLC is only 1%-2% [5]. Previous studies have
reported that SCLC patients with liver metastases alone or in combination with other metastatic sites appear to have worse outcomes[6, 7]. However, few studies could demonstrate any site metastases with a significantly different prognosis compared to others. And there are few effective risk-stratified tools to optimize the prognosis predicting roles of metastases in the survivals of SCLC.

Therefore, this research is aimed to investigate the different metastases patterns of SCLC and their impact on prognosis based on the Surveillance, Epidemiology, and End Results (SEER) database. And we developed a nomogram to predict the 1- and 2-year OS for patients with distant metastases using a population-based cohort from SEER.

**Patients And Methods**

**Data sets**

Data was obtained using the Surveillance, Epidemiology, and End Results database (18 registries) from SEER*Stat 8.3.6 software. This was a retrospective, population-based research through the on-line access to SEER database. We identified SCLC patients with age 18 to 99 that was diagnosis from 2010 to 2015. The data of patients diagnosed from January to August were used as the training set for nomogram development. The data of patients diagnosed from September to December were used as the validation set. Patients with the following histologic categories based on the International Classification of Diseases for Oncology Third Edition (ICD-O-3) were included: 8041/3: Small cell carcinoma, NOS; 8042/3: Oat cell carcinoma; 8043/3: Small cell carcinoma, fusiform cell; 8044/3: Small cell carcinoma, intermediate cell; 8045/3: Combined small cell carcinoma. Cases without sufficient information were excluded regarding race, sex, tumor size, nodal status, treatment (surgery, radiotherapy and/or chemotherapy), survival months, vital status and cause of death.

**Nomogram Development**

A nomogram based on the associated risk factors from a Cox model was developed to predict the 1-and 2-year overall survival probabilities. Validation of the nomogram was conducted using the SEER validation set. The accuracy of the nomogram was performed by Concordance index (C-index). Calibration was carried out with 500 bootstrapped samples.

**Statistical Analysis**

Baseline clinical characteristics were compared using chi-squared test or Fisher exact test for categorical parameters, nonparametric test or student t-test for continuous variables. Kaplan-Meier curves were used to demonstrate overall survival (OS) and Case specific mortality. Cox regression model was used to evaluate the effect of potential factors by univariate and multivariate analysis. SPSS 16.0 and R language version 3.5.2 were used for all analyses. Two-sided P-values <0.05 were considered statistically significant.

**Ethics statement**
Our signed Research Data Agreement is on file in SEER. We are allowed to use the SEER*Stat client-server system to access the SEER Research Data. The informed consent from the study was not required because the author had no access to the individual identifying information. This study was approved by the Ethical Committee and Institutional Review Board of Taizhou Central Hospital.

Results

Baseline characteristics of the study cohort

15637 SCLC patients in training set and 7310 SCLC patients in validation set were included in the study. Patients were diagnosed at average age of 66. The clinical characteristics and demographic of all patients are listed in Table 1. No significant difference between training and validation set was found with respect to age, race, gender and 7th American Joint Committee on Cancer (AJCC) stage, tumor metastases, radiation, surgery and chemotherapy (P > 0.05). In the training set, 52.3% of SCLC patients had no metastases. SCLC patient with solitary bone, brain and liver metastases were 1258 (8.0%), 1332 (8.5%) and 2258 (14.4%), respectively. Among patient with two metastatic sites, the frequency of patients with both bone and liver metastases is higher than patients with both liver and brain, or brain and bone metastases (1540 vs. 372 vs. 303, respectively.). The number of SCLS patients with bone, brain and liver metastases were 402 (2.69%). In the validation set, 51.7% of SCLC patients had no metastases. Among these patients with one metastatic site, 8.2% had bone metastases, 9.0% had brain metastases, and 14.3% had liver metastases. Among SCLS patients with multi-metastatic site, 1.9% had bone and brain metastases, 9.8% had bone and liver metastases, 2.5% had liver and brain metastases, and 2.5% had liver, bone and brain metastases.
Table 1
Patient characteristics of the training set and validation set in the SEER database

| Variable | Training set (N = 15637) | Validation set (N = 7310) | P value |
|----------|--------------------------|---------------------------|---------|
|          | Mean (SD)/N (%)          | Mean (SD)/N (%)           |         |
| Age      | 66 (19–99)               | 66 (18–97)                | 0.890   |
| Race     |                          |                           |         |
| White    | 13464 (86.1)             | 6292 (86.1)               | 0.953   |
| Black    | 1502 (9.6)               | 704 (9.6)                 |         |
| Other    | 671 (4.3)                | 314 (4.3)                 |         |
| Gender   |                          |                           | 0.084   |
| Male     | 7745 (49.5)              | 3600 (49.2)               |         |
| Female   | 7892 (50.5)              | 3710 (50.8)               |         |
| Histology|                          |                           |         |
| Small cell carcinoma, NOS | 15051 (96.3)           | 7065 (96.6)               | 0.136   |
| Oat cell carcinoma        | 188 (1.2)               | 79 (1.1)                  |         |
| Small cell carcinoma, fusiform cell | 10 (0.1)            | 5 (0.1)                   |         |
| Small cell carcinoma, intermediate cell | 35 (0.2)          | 10 (0.1)                  |         |
| Combined small cell carcinoma | 353 (2.3)          | 151 (2.1)                 |         |
| T 7th stage |                          |                           |         |
| T0       | 189 (1.2)                | 86 (1.2)                  | 0.465   |
| T1       | 2035 (13.0)              | 947 (13.0)                |         |
| T2       | 4170 (26.7)              | 2019 (27.6)               |         |
| T3       | 3498 (22.4)              | 1596 (21.8)               |         |
| T4       | 5745 (36.7)              | 2662 (36.4)               |         |
| N 7th stage |                          |                           |         |
| N0       | 2691 (17.2)              | 1260 (17.2)               | 0.746   |
| N1       | 1332 (8.5)               | 622 (8.5)                 |         |
| N2       | 8321 (53.2)              | 3863 (52.8)               |         |
| N3       | 3293 (21.1)              | 1565 (21.4)               |         |
| Variable               | Training set (N = 15637) | Validation set (N = 7310) | P value |
|------------------------|----------------------------|----------------------------|---------|
|                        | Mean (SD)/N (%)            | Mean (SD)/N (%)            |         |
| **M 7th stage**        |                            |                            |         |
| M0                     | 5407 (34.5)                | 2521 (34.5)                | 0.983   |
| M1                     | 10257 (65.5)               | 4789 (65.5)                |         |
| **AJCC 7th stage**     |                            |                            |         |
| I—II                   | 1371 (8.8)                 | 629 (8.6)                  | 0.891   |
| III                    | 392 (25.1)                 | 1834 (25.1)                |         |
| IV                     | 10338 (66.1)               | 4847 (8.6)                 |         |
| **Chemotherapy**       |                            |                            |         |
| Yes                    | 11559 (73.9)               | 5305 (72.6)                | 0.124   |
| No                     | 4078 (26.1)                | 2005 (27.4)                |         |
| **Surgery**            |                            |                            | 0.563   |
| Yes                    | 2030 (12.9)                | 672 (8.7)                  |         |
| No                     | 13607 (87.1)               | 6638 (91.3)                |         |
| **Radiation**          |                            |                            | 0.276   |
| Yes                    | 7845 (50.2)                | 3611 (49.4)                |         |
| No                     | 7792 (49.8)                | 3699 (50.6)                |         |
| **Metastasis**         |                            |                            | 0.322   |
| None                   | 8172 (52.3)                | 3779 (51.7)                |         |
| Bone                   | 1258 (8.0)                 | 597 (8.2)                  |         |
| Brain                  | 1332 (8.5)                 | 655 (9.0)                  |         |
| Liver                  | 2258 (14.4)                | 1050 (14.3)                |         |
| Bone and brain         | 303 (1.9)                  | 138 (1.9)                  |         |
| Bone and liver         | 1540 (9.8)                 | 724 (9.9)                  |         |
| Liver and brain        | 372 (2.4)                  | 180 (2.5)                  |         |
| Liver, bone and brain  | 404 (2.7)                  | 187 (2.5)                  |         |

**Metastases Effect on OS**
To further investigate the prognostic value of metastases in SCLC patients, we further analyze the relationship between OS and metastases in training set (Table 2). The median survival of this cohort is 12.2 months. When stratified by different metastatic site, the OS in SCLC patients with no distant metastases, bone metastases, brain metastases, and liver metastases were 16.6, 9.1, 8.8 and 6.0 months, respectively. And 1-year survival rate of them were 42.3%, 24.8%, 23.3% and 14.7%, respectively. OS in SCLC patients with two distant metastases sites were 6.6, 6.3 and 5.0 with bone and brain metastases, bone and liver metastases and liver and brain metastases, respectively. 1-year survival rate of them were 14.1%, 12.1%, 8.9% and 9.5%, respectively. OS of SCLS patients with bone, brain and liver metastases were 5.1 (1-year survival rate, 9.5%).

Table 2
Log-rank test for the overall survival according to metastasis status in training set

| Group | Number | Metastatic site       | 1-year      | 2-year      | OS  | CSS  |
|-------|--------|-----------------------|-------------|-------------|-----|------|
| 1     | 8172   | None                  | 42.3% (N = 3786) | 20.9% (N = 1712) | 16.6 | 11.2 |
| 2     | 1258   | Bone                  | 24.8% (N = 312)  | 5.5% (N = 69)    | 9.1  | 8.3  |
| 3     | 1332   | Brain                 | 23.3% (N = 311)  | 6.1% (N = 81)    | 8.8  | 7.4  |
| 4     | 2258   | Liver                 | 14.7% (N = 332)  | 2.6% (N = 58)    | 6.0  | 5.6  |
| 5     | 303    | Bone; Brain           | 14.1% (N = 43)   | 3.6% (N = 11)    | 6.6  | 6.5  |
| 6     | 1540   | Bone; Liver           | 12.1% (N = 187)  | 1.6% (N = 25)    | 6.3  | 6.1  |
| 7     | 372    | Brain; Liver          | 8.9% (N = 33)    | 0.8% (N = 3)     | 5.0  | 4.9  |
| 8     | 402    | Bone; Brain; Liver    | 9.5% (N = 38)    | 1.2% (N = 5)     | 5.1  | 5.0  |
| Total | 15637  | /                     | 32.3% (N = 5045) | 12.6% (N = 1967) | 12.0 | 8.6  |

Among the cases with single metastatic site, patients with solitary liver metastases have the worst prognosis (P < 0.001; Fig. 1A). There was no statistically significant difference in the survival between the patients with solitary bone and brain metastases (P = 0.104). In the patients with two-site metastases, the clinical outcomes of the cases with brain and liver metastases were the worst (P < 0.001; Fig. 1B). There was no significant difference in the survival between the patients with both bone and brain metastases and the patients with both bone and liver metastases (P = 0.283). The clinical outcomes of the patients with three-site metastases were similar with the patients with brain and liver metastases (P = 0.895). The prognosis of SCLC patients with liver metastases alone or combined with other metastatic sites were worse than other metastases. Similar results were also obtained in the validation set (Table S1 and Figure S1A-B).

Clinical Outcomes
On multivariate analysis, elder age, male gender, higher AJCC stage (7th; III-IV vs. I-II), metastases, no-radiation, no-chemotherapy and no-surgery were associated with worse overall survival (Table 3). The multivariable models demonstrated a statistically significant association between larger size and survival in patients with single-site metastases, with hazard ratios (95% confidence interval) of 1.744(1.668-1.888), 1.878(1.768-1.995), and 2.553(2.430-2.681), for bone, brain, and liver, respectively. In the multi-site metastases model, hazard ratio (95% confidence interval) of Liver, bone and brain metastases was 2.900 (95% CI, 2.619-3.215; P<0.001). To further determine the prognosis values of risk factors, we created the nomogram model that integrated all significant factors in Figure 2A. The predictive ability of nomogram model was quantified by the C-index. Good agreement was revealed in the calibration curve of between the predicted and observed probabilities. The c-index value was 7.52 in training set and 7.48 in of validation set for predicting 1- and 2-year OS (Figure 2B, Figure S1C).

Table 3
Selected prognosticators according to the multivariate Cox analysis
| Variable                  | Multivariate Cox model |
|--------------------------|------------------------|
|                          | Training set           | Validation set        |
|                          | OR (95% CI)            | P value               | OR (95% CI)            | P value               |
| Age                      | 1.015(1.013-1.016)     | <0.001                | 1.013(1.011-1.016)     | <0.001                |
| Race                     |                        |                        |                        |                       |
| White                    | Reference              |                        | Reference              |                        |
| Black                    | 1.036(0.954-1.126)     | 0.398                  | 1.129(0.997-1.279)     | 0.055                  |
| Other                    | 0.970(0.880-1.069)     | 0.537                  | 1.036(0.895-1.198)     | 0.636                  |
| Gender                   | 1.135(1.098-1.174)     | <0.001                 | 1.100(1.046-1.156)     | <0.001                 |
| Histology                |                        |                        |                        |                       |
| Small cell carcinoma, NOS| Reference              |                        | Reference              |                        |
| Oat cell carcinoma       |                        |                        |                        |                       |
| Small cell carcinoma, fusiform cell | 1.196(1.059-1.351) | 0.004                  | 1.242(1.031-1.496)     | 0.129                  |
| Small cell carcinoma, intermediate cell | 1.187(0.980-1.436) | 0.078                  | 1.213(0.901-1.631)     | 0.203                  |
| Combined small cell carcinoma | 1.535(0.759-3.102) | 0.691                  | 1.498(0.552-4.061)     | 0.012                  |
|                          | 0.925(0.631-1.357)     |                        | 2.679(1.402-5.116)     |                        |
| AJCC 7th stage           |                        |                        |                        |                       |
| I—II                     | Reference              |                        | Reference              |                       |
| III                      | 1.526(1.185-1.965)     | 0.001                  | 1.322(1.155-1.514)     | <0.001                 |
| IV                       | 2.318(1.790-3.002)     | <0.001                 | 1.698(1.454-1.984)     | <0.001                 |
| Metastasis               |                        |                        |                        |                       |
| None                     | Reference              |                        | Reference              |                       |
| Bone                     | 1.744(1.668-1.888)     | <0.001                 | 1.577(1.437-1.731)     | <0.001                 |
| Brain                    |                        | <0.001                 |                        | <0.001                 |
| Diagnosis            | HR (95% CI)   | p-value | HR (95% CI)   | p-value |
|----------------------|---------------|---------|---------------|---------|
| Liver                | 1.878(1.768-1.995) | <0.001  | 1.976(1.799-2.151) | <0.001  |
| Bone and brain       | 2.553(2.430-2.681)   | <0.001  | 2.019(1.870-2.180)  | <0.001  |
| Bone and liver       | 2.327(2.071-2.614)   | <0.001  | 2.334(1.961-2.779)  | <0.001  |
| Liver and brain      | 2.924(2.630-3.250)   | <0.001  | 2.702(2.314-3.154)  | <0.001  |
| Liver, bone and brain| 2.900(2.619-3.215)   | <0.001  | 2.855(2.451-2.326)  | <0.001  |
| Chemotherapy         | 0.345(0.331-0.360)   | <0.001  | 0.337(0.317-0.358)  | <0.001  |
| Surgery              | 0.562(0.512-0.617)   | <0.001  | 0.637(0.602-0.675)  | <0.001  |
| Radiation            | 0.634(0.610-0.659)   | <0.001  | 0.481(0.421-0.549)  | <0.001  |

**Discussion**

The National Cancer Institute SEER database is the comprehensive source of population-based information [8]. In this study, we present comprehensive analysis of the effect of tumor metastases on OS of SCLC patients using the SEER database. Tumor metastases provided additional predictive information for overall survival with all other clinical parameters including age, gender, AJCC stage, and therapeutic methods in our COX model. A nomogram based former mentioned factors was built for survival prediction of SCLC patients. Our research focusing on metastatic patterns in small cell lung cancer, the findings may provide sufficient information for clinical decision and cancer research.

Lung cancer is the leading cause of death worldwide. Distant metastases of lung cancer are a frequent clinical problem. Previous study reported that the prognosis of metastatic lung cancers differs according to the different site of metastases[6, 9]. Yijiu Ren et al demonstrated that Liver metastases is the worst prognostic factor for SCLC patients with distant metastases[7]. In Xuan Wang et al' study, they elucidated the point that all single-site metastases were independent prognostic factors and co-metastases were correlated with even worse clinical outcomes [10].
Although tumor metastases have been recognized previously as an important factor for prognosis of patients with SCLC, a comprehensive analysis and the predictive value of its impact within the subgroups of patients with single-site and multi-site metastases has not been performed.

In present study, we reported that liver [Cases, 2258(14.4%)] was the most common metastases site, followed by brain [Cases, 1332(8.5%)], and bone [Cases, 1258(8.0%)] in SCLC patients with isolated metastases. In the survival analysis, we found patients with liver metastases had the worst survival outcome (OS, 6.0 months), followed by brain metastases (OS, 8.8 months) and bone metastases (OS, 9.1 months). The survival of SCLC patients with brain or bone metastases were better than the patient with liver metastases, which may be partly attributed to the early diagnoses of metastatic lesions and treatment strategies. Central nervous system failure rates are approximate 50–60% at 2 years following diagnosis in SCLC patients [11]. Prophylactic cranial irradiation (PCI) represents a meaningful benefit for people with extensive stage SCLC, particularly as the person with symptomatic brain metastases[12, 13]. Sharma et al had shown that the median survival patients with extend stage SCLC was 13.9 months with PCI and 11.1 months with no PCI (P < 0.001). 1-year survival rate for PCI compared to no PCI was 61% versus 44% (P < 0.001)[14]. Current therapies for brain metastases include surgery, whole brain radiotherapy, and stereotactic radiosurgery [15, 16] Bone metastases represent an independent predictor of a worse prognosis among patients with SCLC, which was consistent with previously studies [17, 18]. Our results showed that the prognosis of SCLC patients with liver metastases alone or combined with other metastatic sites were worse than other metastases, and the prognosis of patients with single metastatic site was better than those with multiple sites. The current standard treatments for liver metastases conclude chemotherapy and radiation therapy [19]. However, some SCLC patients with liver metastases may not tolerance to chemotherapy due to liver dysfunction, which account for the reason why patients diagnosed with liver metastases had the worse survival [20].

Nomogram has been used in clinical oncology assessment in various cancers [21–23]. Several prognostic nomograms for SCLC patients also have been established previously [24–27]. However, few studies focused exclusively on patients presenting with different distant metastases. Our data also corroborate the prediction function of nomogram that can evaluate multiple variables not encompassed by the current staging system. In our cox model, we further subgroup the metastatic mode of SCLC patients to single-site and multi-site metastases. The C-index for the nomogram to predict OS were 0.752 and 0.748 respectively in the training cohort and the validation cohort in this study, indicating that this Nomogram have the high predictive accuracy and a superior discriminating ability for predicting survival in SCLC patients.

**Conclusion**

Our large population-based study suggests that in SCLC patients with liver metastases have the worst survival. Risk models and nomograms incorporating multiple factors, such as age, gender, AJCC stage, metastatic mode, chemotherapy, radiation and surgery are more accurate in predicting OS in SCLC
patients. Our findings would be beneficial for future research design, treatment strategies and clinical practice.

**Abbreviations**

SEER
Surveillance, Epidemiology, and End Results; SCLC:Small cell lung cancer; OS:Overall survival; ICD-O-3:International Classification of Diseases for Oncology Third Edition; C-index:Concordance index; PCI:Prophylactic cranial irradiation; AJCC:American Joint Committee on Cancer

**Declarations**

**Ethics approval and consent to participate**

Not applicable. SEER is a publically available anonymous data source, so this study was not reviewed by a Human Subjects Committee.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data that support the findings of this study are available on request from the corresponding author.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

PPL designed the study. HLR arranged the data and wrote the manuscript. YML, HLS, YD and SPY arranged the data.

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**Figures**

![Figure 1](image-url)

**Figure 1**

The effect of tumor size on OS according to single-site metastases (A) and multi-site metastases (B).
Figure 2

Nomogram for predicting OS (A). Instructions: for each parameter (age, gender, AJCC stage, chemotherapy, radiation, surgery, and metastases), read the points assigned on a 0 to 10 scale and add these points. Read the results on the ‘Total Points’ scale and then read the corresponding predictions below it. Example: a 50-year-old male SCLC patient, IV AJCC stage involving brain metastases, with chemotherapy and radiation, would score a total of 161 points: 4.5 (age) + 1.25 (male) + 5.5 (IV AJCC stage) + 2.75 (brain metastases) + 6.75 (no surgery). His total point is 20.75 and the predicted 1-year and 2-year survival rate would be approximately 42% and approximately 18%, respectively. Calibration plot for the nomogram (B). The dots are calculated from our data and represent the performance of the nomogram based on Cox model. The solid line is close to the dashed line, indicating that the accuracy of the model predicts OS.
Supplementary Files

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