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# The prognostic risk stratification model for metastatic small-cell lung cancer

## An analysis of the SEER database

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**Abstract**

Distant metastases of small-cell lung cancer (DM-SCLC) is an important factor in the selection of treatment strategies. In this study, we established a nomogram to predict DM-SCLC and determine the benefit of radiotherapy (RT) for DM-SCLC. We analyzed DM-SCLC prognosis based on surveillance, epidemiology, and end result database (SEER) data. A comprehensive and practical nomogram that predicts the overall survival (OS) of DM-SCLC was constructed and the results were compared with the 7th edition of the American Joint Committee on Cancer (AJCC) TNM stage system. A concordance index (C-index) and receiver operating characteristic plot were generated to evaluate the nomogram discrimination. The calibration was evaluated with a calibration plot, and its effectiveness was evaluated by a decision curve analysis (DCA). A score was assigned to each variable, and a total score was established for the risk stratification model. A total of 13,403 DM-SCLC patients were included. Eight characteristic variables were identified as independent prognostic variables. The C-index of the validation and training cohorts was 0.716 and 0.734, respectively. The area under the receiver operating characteristic curve (AUC) values of the nomogram used to predict 1-, 2-, and 3-year OS were 0.751, 0.744, and 0.786 in the validation cohorts (0.761, 0.777, 0.787 in the training cohorts), respectively. The calibration curve of 1-, 2-, 3-year survival rates showed that the prediction of the nomogram was in good agreement with the actual observation. The nomogram exhibited higher clinical utility after evaluation with the 1-, 2-, 3-year DCA compared with the AJCC stage system. A predictive nomogram and risk stratification model have been constructed to evaluate the prognosis of DM-SCLC effectively and accurately. This nomogram may provide a reference for prognosis stratification and treatment decisions.

**Abbreviations:** AJCC = American joint committee on cancer, AUC = area under the receiver operating characteristic curve, C-index = concordance index, CI = confidence interval, DCA = decision curve analysis, DM-SCLC = distant metastases of small-cell lung cancer, HR = hazard ratio, KM = Kaplan–Meier, MOM = multiple organ metastases, OS = overall survival, PCI = prophylactic cranial irradiation, RT = radiotherapy, SCLC = small-cell lung cancer, SEER = surveillance, epidemiology, and end results, TRT = thoracic radiotherapy.

**Keywords:** distant metastases, nomogram, overall survival, prognosis, small-cell lung cancer

## 1. Introduction

Lung cancer is one of the most common malignant tumors in the world and has the highest incidence among cancers.[1] Overall, approximately 15% of lung cancers are small-cell lung cancer (SCLC), and distant metastases of small-cell lung cancer (DM-SCLC) accounts for approximately 70% of all SCLC when diagnosed. SCLC is characterized by its aggressiveness, high recurrence rate, and rapid growth, which is a challenge to the treatment of SCLC in clinical practice. Little progress has been made in the treatment of DM-SCLC. Currently, first-line treatment for DM-SCLC includes chemotherapy combined with platinum drugs and etoposide or irinotecan as possible alternatives. The median survival with standard care is still only 9 to 10 months.[2] The IMPOWER133 study, published in 2018, demonstrated that the addition of atezolizumab significantly extended overall survival (OS) and progression-free survival as first-line chemotherapy for DM-SCLC.[3] AJCC system is based on TNM and is used to characterize the amount and spread of disease and thereby used to guide treatment. Therefore, more practical and convenient tools are needed to improve the predictive ability of DM-SCLC.

Multiple organ metastases (MOM) is the most common metastases model for SCLC, accounting for 32.8% (3396/10347) of the cases. The second is liver metastases (19.0%, 1971/10347). Brain metastases accounts for 12.1%

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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(1251/10347), whereas bone metastases accounts for 10.0% (1033/10347). The specific mortality rate of SCLC is 77.2% (797/1033) with bone metastases, 74.1% (927/1251) with brain metastases, 82.4% (1 625/1 971) with liver metastases, 73.4% (504/687) with lung metastases, and 81.6% (2770/3396) for MOM. Cox regression analysis revealed that the MOM group and the liver metastases group exhibited the highest hazard ratio (HR) (95% confidence interval [CI]: 1.80 (1.66–1.96) and 1.69 [1.54-1.85], respectively), followed by the bone metastases group and the brain metastases group at 1.24 (1.12–1.39) and 1.28 (1.16–1.42), respectively ($P < .001$). The lung metastases group had the lowest HR for death (1.07) (95% CI: 0.95–1.21, $P = .27$). In SCLC, multi-organ and liver metastases had the worst prognosis and highest specific mortality, followed by bone and brain metastases, whereas intrapulmonary metastases exhibited the best prognosis. Therefore, for patients with SCLC complicated with distant metastases, different intensities of treatment should be administered according to the different metastatic organs, and intensive treatment should be performed for patients with liver metastases and MOM.[4–6]

The stage criteria for SCLC are very important for the formulation of a treatment plan and the prediction of OS. Currently, the most commonly used stage criteria for SCLC is the AJCC TNM stage criteria recommended by the International Union against Cancer. The TNM staging system primarily relies on surgery to confirm its accuracy; however, most patients with SCLC have lost the chance for surgery at diagnosis and instead are treated with radiotherapy (RT) and chemotherapy. AJCC cannot accurately assess the prognosis of SCLC, especially for those with distant metastases. For DM-SCLC, the prognosis is determined by the site and number of metastases. In addition, the prognosis of DM-SCLC is influenced by clinical factors including sex, age, T and N stage, and the status of the distant metastases. Therefore, it is necessary to establish an accurate and comprehensive prognostic model to evaluate the prognosis of DM-SCLC, which can help clinicians make accurate treatment decisions.

A nomogram is a method to combine multiple factors to simplify a complex regression equation into an intuitive graph, making the result practical and readable. It has been widely accepted in the medical research field in recent years.[7,8] There have been several nomograms constructed to predict the survival of individuals with SCLC[9–12]; however, no nomogram has been available to predict survival in DM-SCLC. In this study, we used the surveillance, epidemiology, and end results (SEER) database to establish and validate a nomogram survival assessment for DM-SCLC.

## 2. Methods

All analyses were based on the SEER published database, thus no ethical approval and patient consent are required.

### *2.1. Data retrieved from SEER*

All data in this study were extracted from the SEER database. The SEER database covers approximately 28% of the U.S. population and is comprised of cancer registries in 18 geographic regions. The database has been de-identified of patient information in compliance with the Institutional Review Board. The council and the ethics committee requested that the information be made publicly available.

### *2.2. Patient screening*

Patients with primary SCLC from 2010 to 2015 were identified using SEER*Stat software (version 8.3.5). SCLC was diagnosed based on the International Classification of Diseases for Oncology (ICD-O-3) (ICD-O-3 code: 8041/3, 8002/3, 8042/3, 8043/3, 8044/3, 8045/3). Inclusion criteria were as follows: age over 18 years; histologically diagnosed as small-cell carcinoma; patients diagnosed between 2010 and 2015; and (VI) all enrolled patients had complete information on race, sex, age, T

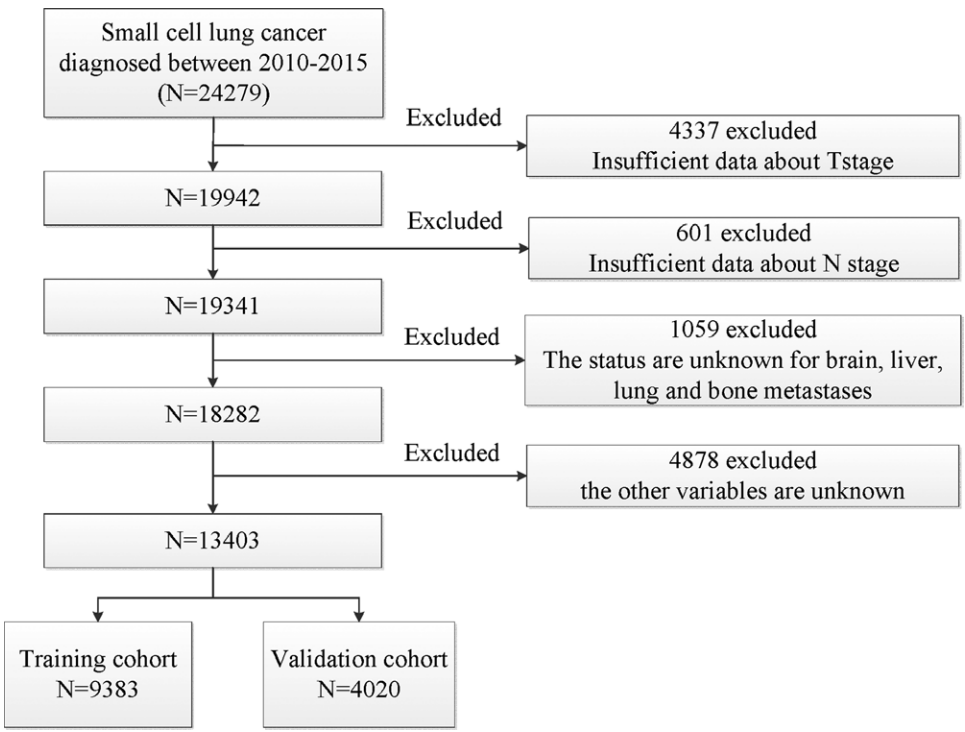


**Figure 1.** The flow chart for the selection of the study population.

stage, N stage, RT, chemotherapy, the status of brain metastases, bone metastases, liver metastases, bone metastases, and complete survival data. Patients with incomplete information and confirmed from clinical manifestations, imaging, and/or death certificates or autopsy reports were excluded. A total of 13403 patients were identified as eligible for inclusion, and the filtering process is shown in Figure 1. All DM-SCLC patients included in this study were divided into training cohorts and validation cohorts at a 7:3 ratio (Training cohort, N = 9383; Validation cohort, N = 4020). This study was carried out according to the Declaration of Helsinki (revised in 2013).[13]

### 2.3. Prognostic variables

Definition of variables in this study: race/ethnicity (black, white, or others), laterality (right/left/other), age at diagnosis (<66, 66–79, and > 79 years), T stage (T1, T2, T3, and T4), N stage (N0, N1, N2, and N3), tumor size (<26 mm, 27–44 mm, and > 44 mm) radiation recode (Yes/None/Unknown), chemotherapy recode (Yes/None/Unknown), brain metastases (Yes/No), bone metastases (Yes/No), lung metastases (Yes/No), and liver metastases (Yes/No).

### 2.4. Statistical analysis

In this study, the 13,403 enrolled patients were randomly divided into training cohorts and validation cohorts at a 7:3 ratio by the "caret" package of R software.

The optimal cutoff value for continuous variables (age) was obtained using X-tile software (version3.6.1). Cox proportional risk regression was used to determine independent predictors of OS in DM-SCLC in univariate and multivariate analyses. OS curve was generated by the Kaplan–Meier (KM) method. SPSS 21.0 software was used for the statistical analysis.

Based on cox proportional risk regression results, the "rms" package in R software (version4.1.1) was used to construct a nomogram for all independent prognostic variables combined with 1-, 2-, and 3-year OS.

To test the performance of the nomogram prediction model in the validation cohorts, resampling of the data from the training cohorts and the validation cohorts to obtain calibration plots were done to evaluate the consistency between the predicted 1-, 2-, and 3-year OS and the actual OS of the model. A concordance index (C-index), AUC, and decision curve analysis (DCA) were established to evaluate and compare the prediction performance of the nomogram and TNM stage systems.

C-index was calculated by the "survival" package in R software. To evaluate the relationship between the accuracy of the predicted probabilities and the observations, calibration plots were generated using 1000 self-sampling repetitions of the training cohorts and validation cohorts. DCA was obtained by the "ggDCA" package in R software.

By calculating the nomogram predicted total score for each patient in the training cohorts after matching, the risk group was stratified according to the cutoff value of the total score, which was divided into 3 groups: low-risk, medium-risk, and high-risk groups. In the training and validation cohorts, KM curves were used to plot survival curves for the 3 risk groups, and the log-rank test was used to test the differences between the 3 groups to evaluate the accuracy of risk stratification based on nomogram prediction model scores.

## 3. Results

### 3.1. DM-SCLC clinical characteristics and demographics

A total of 13,403 DM-SCLC patients were enrolled in this study. Of all DM-SCLC patients, 9383 were assigned to the training cohorts and 4020 to the validation cohorts. Clinical characteristics and demographics of DM-SCLC patients are shown in Table 1, and the filtering process is shown in Figure 1. In general, the majority of patients were male (6931; 51.7%), aged < 66 years (6135; 45.8%), and white (11,676; 87.1%). In addition, most patients received chemotherapy (9301; 69.4%), and 5516 (41.2%) of the patients received RT. Overall, 34.3% (4597), 25% (3348), 44.6% (5973), and 20.2% of 2709 DM-SCLC had bone, brain, liver, and lung metastases, respectively. In addition, 10.3% (1377), 25.8% (3457), 25.9% (3465), and 38.1% (5104) patients of DM-SCLC had stage T1, T2, T3, and T4, respectively, whereas 12.9% (1728), 7.1% (952), 63.8% (8557) and 16.2% (2166) of the patients had stage N0, N1, N2, and N3 tumors, respectively.

### 3.2. The results of univariate and multivariate analysis in the training cohorts

In Table 2 and Figure 2, significant differences were observed for 8 variables: age (66–79 years: HR 1.159, 95% CI 1.107–1.214; >79 years: HR 1.424, 95% CI 1.328–1.526; <66 years as a reference), N stage (N1: HR 1.122, 95% CI 0.964–1.306;

**Table 1**

**Patients' demographics and clinicopathological characteristics.**

| Characteristics | | Whole patients (n = 13403) | Training cohort (n = 9383) | Validation cohort (n = 4020) |
|---|---|---|---|---|
| **Race (%)** | Black | 1216 (9.1) | 849 (9.0) | 367 (9.1) |
| | Other | 511 (3.8) | 357 (3.8) | 154 (3.8) |
| | White | 11676 (87.1) | 8177 (87.1) | 3499 (87.0) |
| **Sex (%)** | Female | 6472 (48.3) | 4570 (48.7) | 1902 (47.3) |
| | Male | 6931 (51.7) | 4813 (51.3) | 2118 (52.7) |
| **Laterality (%)** | Left | 5549 (41.4) | 3935 (41.9) | 1614 (40.1) |
| | other | 511 (3.8) | 365 (3.9) | 146 (3.6) |
| | Right | 7343 (54.8) | 5083 (54.2) | 2260 (56.2) |
| **T stage (%)** | T1 | 1377 (10.3) | 967 (10.3) | 410 (10.2) |
| | T2 | 3457 (25.8) | 2431 (25.9) | 1026 (25.5) |
| | T3 | 3465 (25.9) | 2419 (25.8) | 1046 (26.0) |
| | T4 | 5104 (38.1) | 3566 (38.0) | 1538 (38.3) |
| **N stage (%)** | N0 | 1728 (12.9) | 1213 (12.9) | 515 (12.8) |
| | N1 | 952 (7.1) | 660 (7.0) | 292 (7.3) |
| | N2 | 8557 (63.8) | 6008 (64.0) | 2549 (63.4) |
| | N3 | 2166 (16.2) | 1502 (16.0) | 664 (16.5) |
| **Radiotherapy (%)** | None/Unknown | 7887 (58.8) | 5488 (58.5) | 2399 (59.7) |
| | Yes | 5516 (41.2) | 3895 (41.5) | 1621 (40.3) |
| **Chemotherapy (%)** | None/Unknown | 4102 (30.6) | 2846 (30.3) | 1256 (31.2) |
| | Yes | 9301 (69.4) | 6537 (69.7) | 2764 (68.8) |
| **Bone metastases (%)** | No | 8806 (65.7) | 6189 (66.0) | 2617 (65.1) |
| | Yes | 4597 (34.3) | 3194 (34.0) | 1403 (34.9) |
| **Brain metastases (%)** | No | 10055 (75.0) | 6991 (74.5) | 3064 (76.2) |
| | Yes | 3348 (25.0) | 2392 (25.5) | 956 (23.8) |
| **Liver metastases (%)** | No | 7430 (55.4) | 5204 (55.5) | 2226 (55.4) |
| | Yes | 5973 (44.6) | 4179 (44.5) | 1794 (44.6) |
| **Lung metastases (%)** | No | 10694 (79.8) | 7497 (79.9) | 3197 (79.5) |
| | Yes | 2709 (20.2) | 1886 (20.1) | 823 (20.5) |
| **Tumor size (%)** | <26 mm | 2695 (20.1) | 1846 (19.7) | 849 (21.1) |
| | 27-44 mm | 3219 (24.0) | 2307 (24.6) | 912 (22.7) |
| | >45 mm | 7489 (55.9) | 5230 (55.7) | 2259 (56.2) |
| **Age (%)** | <66 yrs | 6135 (45.8) | 4310 (45.9) | 1825 (45.4) |
| | 66-79 yrs | 5548 (41.4) | 3885 (41.4) | 1663 (41.4) |
| | >79 yrs | 1720 (12.8) | 1188 (12.7) | 532 (13.2) |

**Table 2**

**Univariate analyses for OS in patients with DM-SCLC.**

| Characteristics | | HR | 95%CI | *P* value |
|---|---|---|---|---|
| **T stage** | T1 (reference) | | | 0 |
| | T2 | 1.08 | 1 - 1.17 | .046 |
| | T3 | 1.24 | 1.15 - 1.34 | 0 |
| | T4 | 1.19 | 1.1 - 1.28 | 0 |
| **N stage** | N0 (reference) | | | 0 |
| | N1 | 1.02 | 0.92 - 1.12 | .748 |
| | N2 | 1.15 | 1.08 - 1.23 | 0 |
| | N3 | 1.06 | 0.98 - 1.15 | .143 |
| **Radiotherapy** | No (reference) | | | 0 |
| | Yes | 0.57 | 0.54 - 0.59 | |
| **Chemotherapy** | No (reference) | | | 0 |
| | Yes | 0.25 | 0.24 - 0.26 | |
| **Bone metastases** | No (reference) | | | 0 |
| | Yes | 1.12 | 1.07 - 1.17 | |
| **Brain metastases** | No (reference) | | | .001 |
| | Yes | 1.08 | 1.03 - 1.14 | |
| **Liver metastases** | No (reference) | | | 0 |
| | Yes | 1.55 | 1.48 - 1.61 | |
| **Lung metastases** | No (reference) | | | .002 |
| | Yes | 1.08 | 1.03 - 1.14 | |
| **Tumor size** | <26 mm (reference) | | | .001 |
| | 27-44 mm | 1.09 | 1.02 - 1.16 | .008 |
| | >44 mm | 1.12 | 1.06 - 1.18 | 0 |
| **Age** | <66 yrs (reference) | | | 0 |
| | 66-79 yrs | 1.28 | 1.22 - 1.34 | 0 |
| | >79 yrs | 2.02 | 1.89 - 2.15 | 0 |
| **Race** | Black (reference) | | | .681 |
| | Other | 1.046 | 0.922-1.187 | .485 |
| | White | 0.997 | 0.927-1.072 | .929 |
| **Sex** | Female (reference) | | | .948 |
| | Male | 0.999 | 0.958-1.041 | |
| **Laterality** | Left (reference) | | | .939 |
| | Other | 1.002 | 0.898-1.118 | .974 |
| | Right | 0.993 | 0.951-1.036 | .735 |

CI = confidence interval, DM-SCLC = small-cell lung cancer, HR = hazard ratio, OS = overall survival.

N2: HR 1.317, 95% CI 1.142–1.520; N3: HR 1.321, 95% CI 1.124–1.552; N0 as a reference), tumor size (27-44 mm: HR 1.076, 95% CI 1.01–1.146; >44 mm: HR 1.191, 95% CI 1.125–1.261; <26 mm as a reference), RT (Yes: HR 0.705, 95% CI 0.672–0.74; no as a reference), chemotherapy (Yes: HR 0.303, 95% CI 0.287–0.318; no as a reference), bone metastases (Yes: HR 1.126, 95% CI 1.077–1.178; no as a reference), brain metastases (Yes: HR 1.422, 95% CI 1.349–1.498; no as a reference), liver metastases (Yes: HR 1.463, 95% CI 1.4–1.53; no as a reference), and lung metastases (Yes: HR 1.029, 95% CI 0.976–1.085; no as a reference).

### *3.3. Nomogram construction and validation*

According to the results of univariate and multivariate analysis, we used 8 independent factors in the training cohorts in the nomogram to predict 1, 2, and 3-year OS (Fig. 3).

The discrimination of this nomogram was evaluated using a C-index and receiver operating characteristic curve to compare the AJCC stage system. The C-indices of this nomogram in the training cohorts and the validation cohorts were 0.731 (95% CI: 0.728–0.740) and 0.737 (95% CI: 0.733–0.741), whereas the AJCC stage system yielded C-indices of 0.538 (95% CI: 0.535–0.541) and 0.522 (95% CI: 0.516–0.527) in the training cohorts and the validation cohorts, respectively (Table 3).

In addition, the AUC was used to evaluate the discrimination of this nomogram compared with the AJCC stage system. In the training cohorts, the 1-, 2-, and 3-year OS of AUC of this nomogram was superior to that of the AJCC stage system (1-year OS AUC: 0.771 vs 0.585, 2-year OS AUC: 0.783 vs 0.649, 3-year OS AUC: 0.8 vs 0.664, respectively, Fig. 4A–C), whereas the AUC of this nomogram and the AJCC stage system is shown in Figure 4D–F for the validation cohorts (1-year OS AUC: 0.784 vs 0.664, 2-year OS AUC: 0.797 vs 0.664, 3-year OS AUC: 0.822 vs 0.664).

The calibration curve shows that there was a high degree of agreement between the nomogram prediction and the actual 1-, 2-, and 3-year OS in the training cohorts (Fig. 5A–C) and the validation cohorts (Fig. 5D–F).

### *3.4. Differences in the nomogram and the 7th AJCC TNM stage system*

The clinical application value for our nomogram compared with the AJCC TNM stage system was evaluated by DCA. We found that the nomogram in this study had a higher net benefit in predicting 1-, 2-, and 3-year OS in DCA compared with the AJCC TNM stage system because of the wide threshold probability range in the training cohorts (Fig. 6A–C) and the validation cohorts (Fig. 6D–F).

### *3.5. Risk stratification model and survival analysis.*

The total nomogram predicted score for each patient in the training cohorts was calculated to stratify risk into 3 levels: low-, intermediate-, and high-risk groups (Fig. 7). After the cut-off value was determined, the OS risk was divided into a low-risk (0-112), intermediate-risk (113–189), and high-risk (>189)

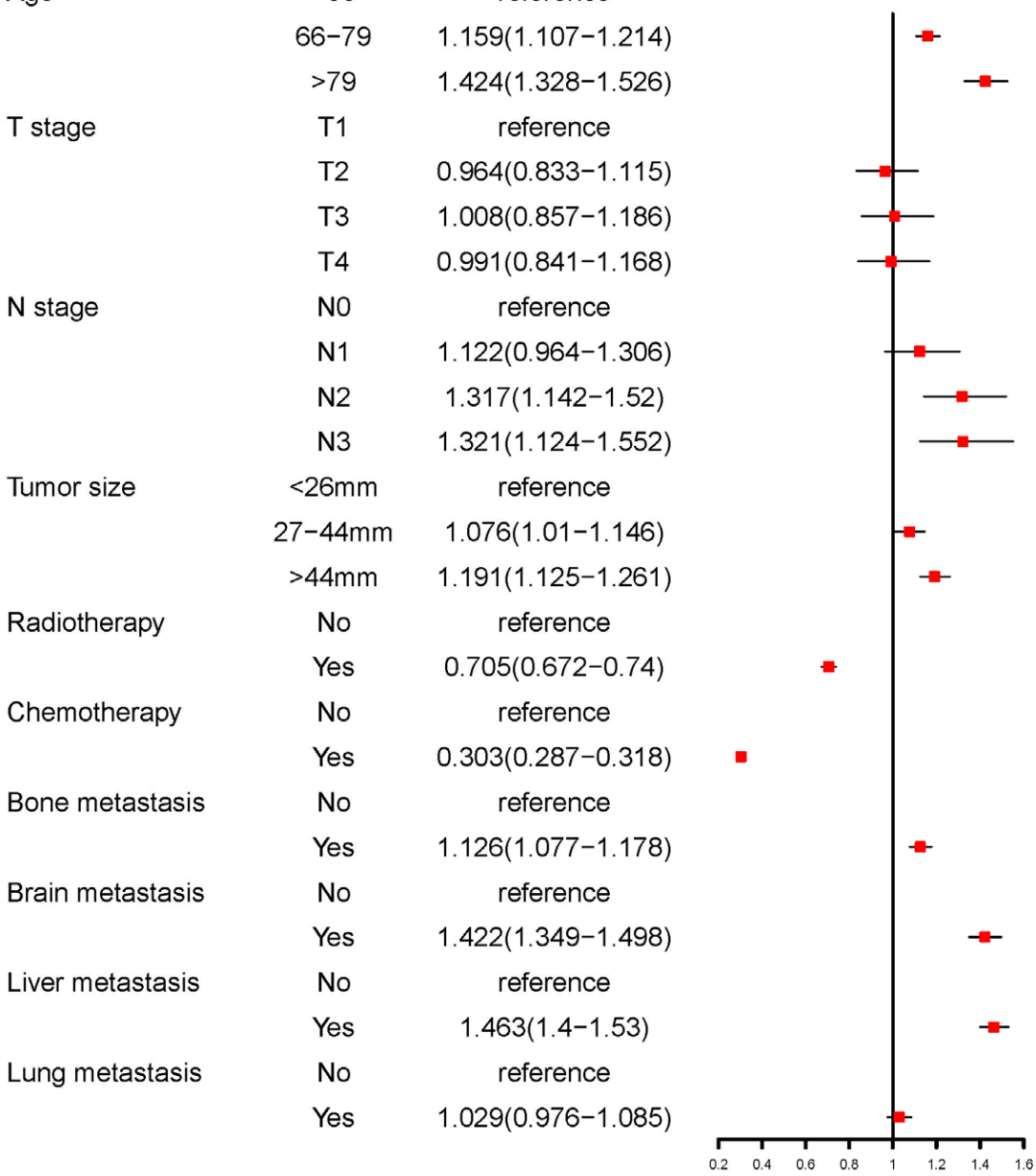


**Figure 2.** Forest plot of multivariate analyses for OS in patients with DM-SCLC. DM-SCLC = small-cell lung cancer, OS = overall survival.

group. KM survival plots (Fig. 8) were used to show the OS of each risk group, and the differences were tested by log-rank between the groups, showing the accuracy of risk stratification based on the nomogram prediction model score.

## 4. Discussion

Small-cell lung cancer accounts for 13% to 20% of all lung cancers, of which 2/3 of patients have extensive stage lesions at the time of diagnosis. Extensive stage patients are often accompanied by MOM, with a short natural course and poor prognosis. However, the prognosis of small cell lung cancer is different according to different metastatic organs, which is a large group of heterogeneous people. In various guidelines, the treatment of metastatic small-cell lung cancer is dominated by platinum-based chemotherapy, with no clear independent prognostic factors and no risk stratification for this group of patients.

Two retrospective studies of DM-SCLC based on the SEER database have been published. The study from Hongxiang Gao[14] reported 10025 patients with DM-SCLC from January 2010 to December 2016 who were included in the SEER database. The variables included in the predictive model in that study were age, sex, race, T stage, N stage, distant metastatic site, and chemotherapy. Another study, published in 2019, enrolled a total of 16,554 patients with DM-SCLC from 2004 to 2014.[15] Sex, race, age, TNM stage, and treatment (surgery, CT, and RT) were identified as independent prognostic factors for DM-SCLC. The present study included 13,404 DM-SCLC patients enrolled in the SEER database from 2010 to 2015. Our results showed that the independent prognostic factors affecting DM-SCLC patients were age, tumor size, N stage, RT, chemotherapy, bone metastases, brain metastases, and liver metastases, which was in agreement with previously reported studies. Compared with the previous 2 related studies, the

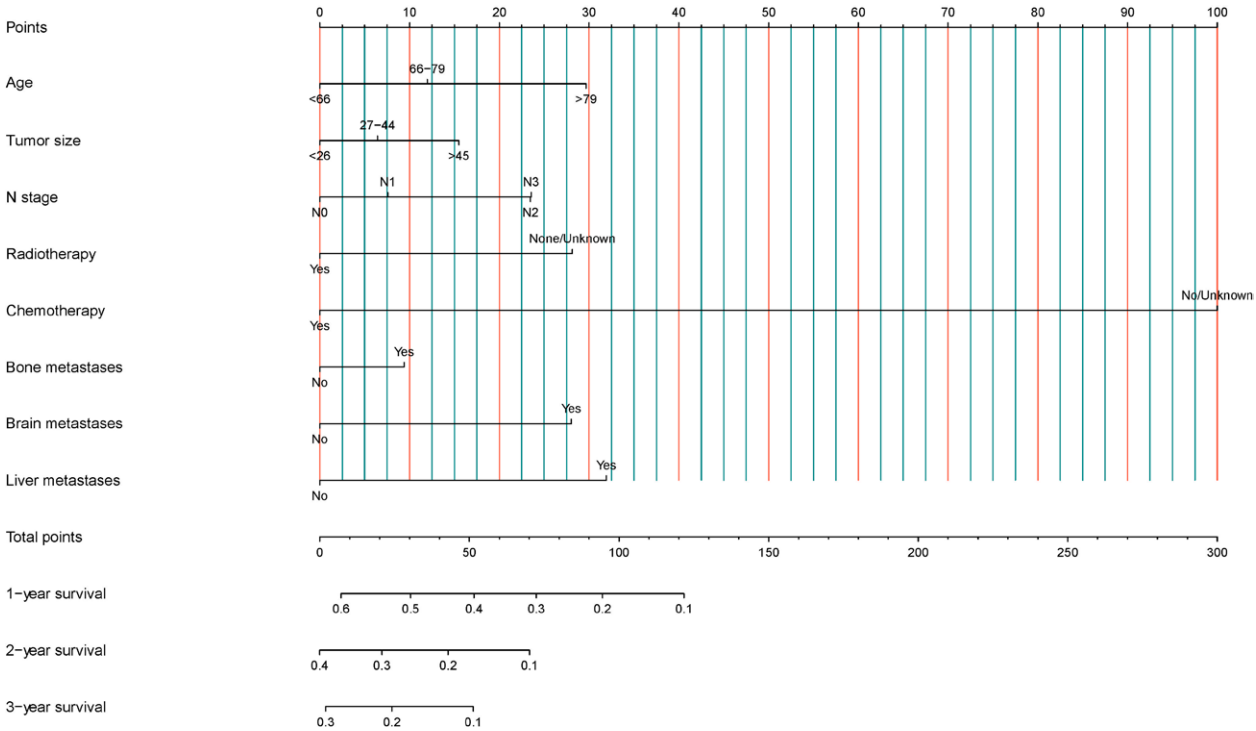


**Figure 3.** Nomogram predicted 1-, 2-, and 3-year OS for DM-SCLC with 8 available factors. DM-SCLC = small-cell lung cancer, OS = overall survival.

**Table 3**

**The C-indexes of the nomogram compared to the AJCC stage system.**

| | Training cohorts | | Validation cohorts | |
|---|---|---|---|---|
| **Survival types** | **C-indexes** | **95% CI** | **C-indexes** | **95% CI** |
| **Nomogram** | 0.731 | 0.728-0.740 | 0.737 | 0.733-0.741 |
| **AJCC stage** | 0.538 | 0.535-0.541 | 0.522 | 0.516-0.527 |

AJCC = American Joint Committee on Cancer, CI = confidence interval.

C-index of our prediction model is significantly higher than those of the 2 published studies. AJCC TNM staging system is a widely used survival prediction tool for patients with small-cell lung cancer. In this study, the area under the receiver operating characteristic curve and C-index was used to evaluate the differentiation of the prediction nomogram. After the model is built, the model needs to be evaluated and verified, that is, the gap between the survival rate predicted by the model and the actual situation. In this study, the calibration curve is used to evaluate 1-, 2-, and 3- year OS in the training cohorts and the validation cohorts. The clinical utility was evaluated using DCA between the nomogram and the AJCC stage. DCA is a method that evaluates the benefit degree of patients and introduces a "threshold probability" to trigger medical intervention under the same threshold probability. Compared with the AJCC stage, the nomogram constructed in this study may yield a greater net benefit to patients, and its clinical practicality will be better. Moreover, we further stratified the risk of DM-SCLC based on the variables of the prediction model and further conducted KM survival analysis for each risk stratification. These in-depth studies are helpful for clinicians to make correct decisions in the treatment of DM-SCLC.

The results from this study are consistent with that of previously published findings in which SCLC with brain or liver metastases has a worse prognosis compared with those with metastases to other sites.[16,17] It has been reported that liver metastases have a worse prognosis than brain metastases.[18–20] The 1-year OS for patients with liver metastases was only 19% compared with 41% for patients with brain metastases.[19] The reason for this is that brain metastases can be improved by RT to the brain. Brain metastases have a high response rate to RT and can significantly improve OS. The liver, as an immunosuppressive organ, hinders the immune monitoring of the body, and liver metastases are growing. SCLC with liver metastases has a poor response to chemotherapy and a low response rate, which can also be found in liver cancer.[21] Therefore, liver metastases are considered to have the worst prognosis.

In our study, age was also considered an independent risk factor in predicting the prognosis of DM-SCLC. A Dutch study of 43,111 cancer patients found that cancer patients over the age of 65 were 1.4 times as likely as those under the age of 64 to have serious comorbidities at diagnosis, the most common being cardiovascular disease.[22] Due to the high number of comorbidities in the elderly, physiological changes in organ function, drug metabolism, and overall functional status also occur, making treatment more challenging. We speculate that the reasons for the poor prognosis of elderly patients are as follows: first, the patients' organ and physiological function compensation is reduced, the tolerance is poor, and the rate of adverse reactions caused by drugs is increased; Second, the combination of age-related chronic diseases, resulting in inadequate drug dosage, reduced course of treatment, and limited means of treatment. This study also found that larger tumor size and higher N stage also affected survival, which is consistent with previously published findings. A retrospective study[23] based on the SEER database indicated that tumor size larger than 7cm were more likely to develop brain and liver metastases, compared with tumors smaller than 3cm. Therefore, we hypothesized that this might be the reason for the poor prognosis of patients with large tumor sizes. Similarly, tumor size may be associated with a higher probability of lymph node metastases and local disease spread. Further, another study[24] found that a higher N stage was associated with a higher incidence of liver and bone metastases, so

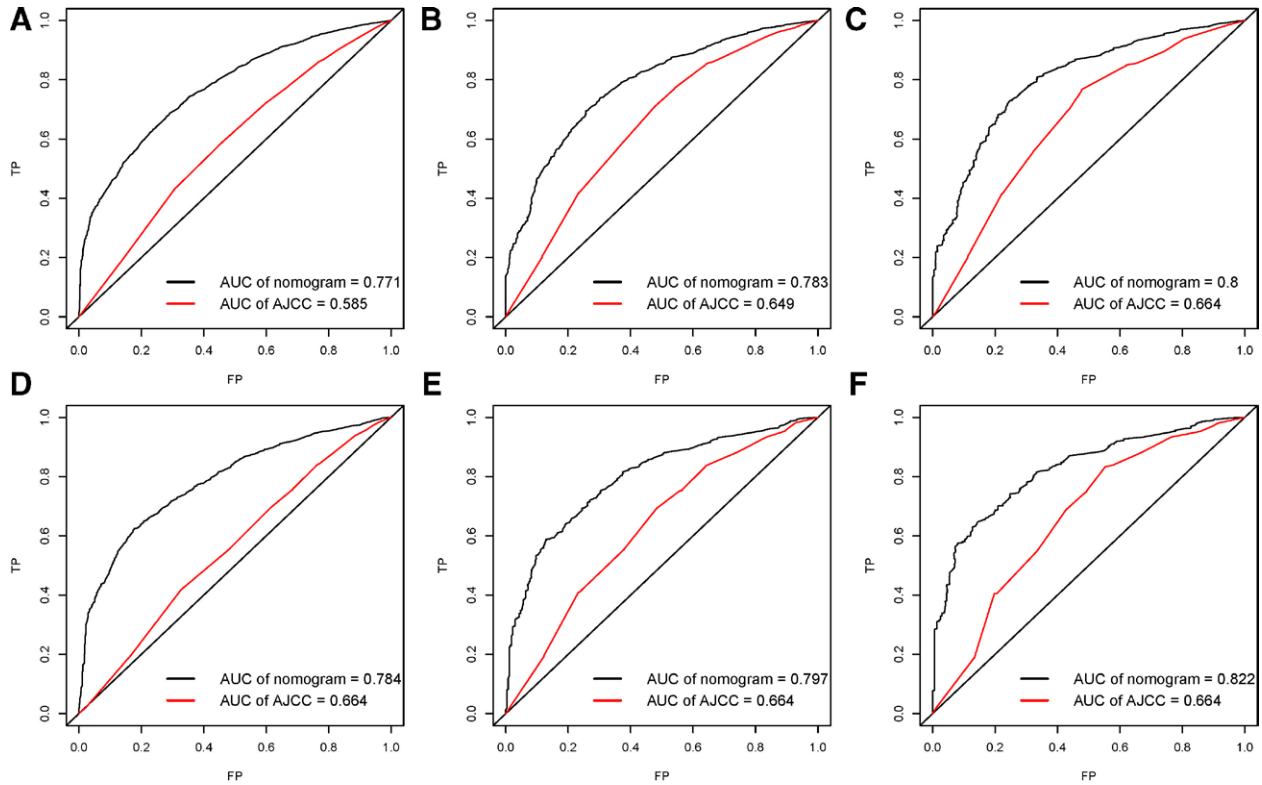


**Figure 4.** AUC value of ROC predicting: (A) 1-year OS of the nomogram in the training cohorts; (B) 2-year OS of the nomogram in the training cohorts; (C) 3-year OS of the nomogram in the training cohorts; (D) 1-year OS of the nomogram in the validation cohorts; (E) 2-year OS of the nomogram in the validation cohorts; (F) 3-year OS of the nomogram in the validation cohorts. AUC = area under the ROC curve, OS = overall survival, ROC = receiver operating characteristic.

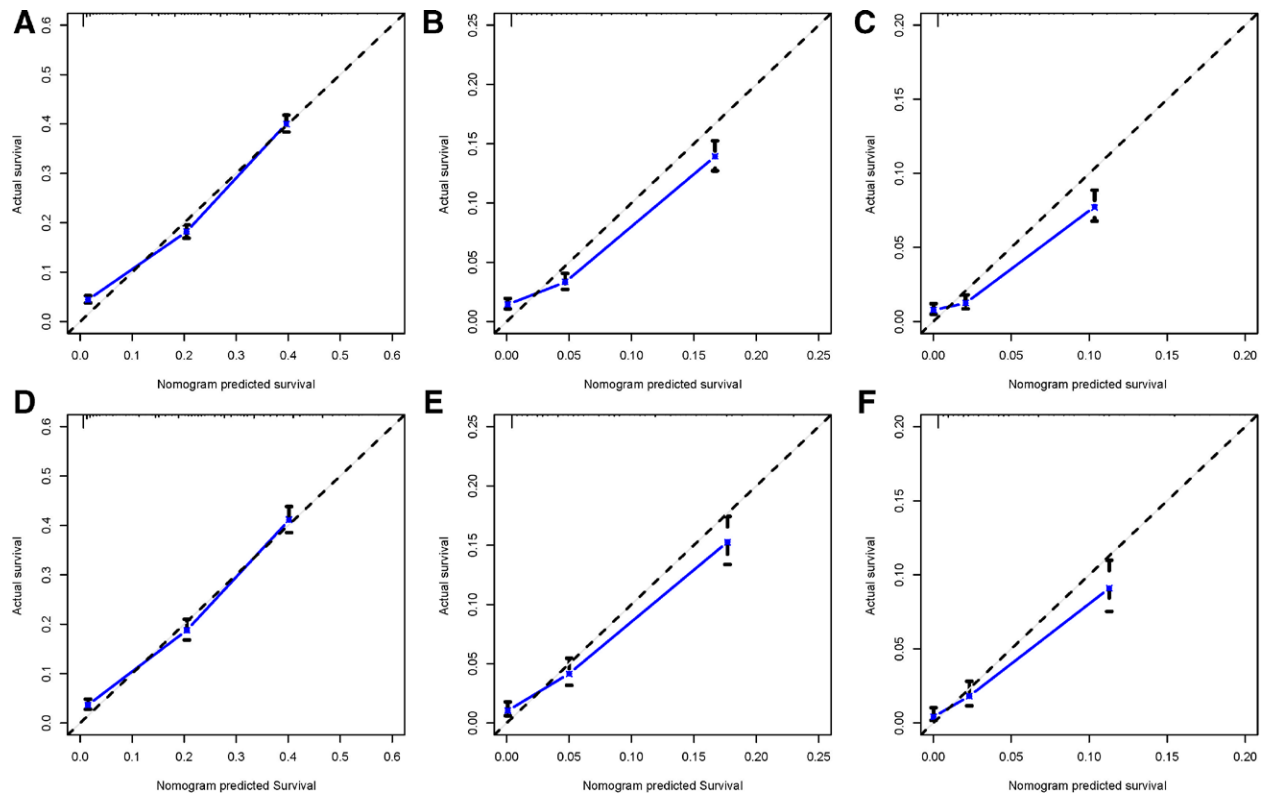


**Figure 5.** The calibration curve for predicting patient survival: (A) 1 year in the training cohorts; (B) 2 years in the training cohorts; (C) 3 years in the training cohorts; (D) 1 year in the validation cohorts; (E) 2 years in the validation cohorts; (F) 3 years in the validation cohorts.

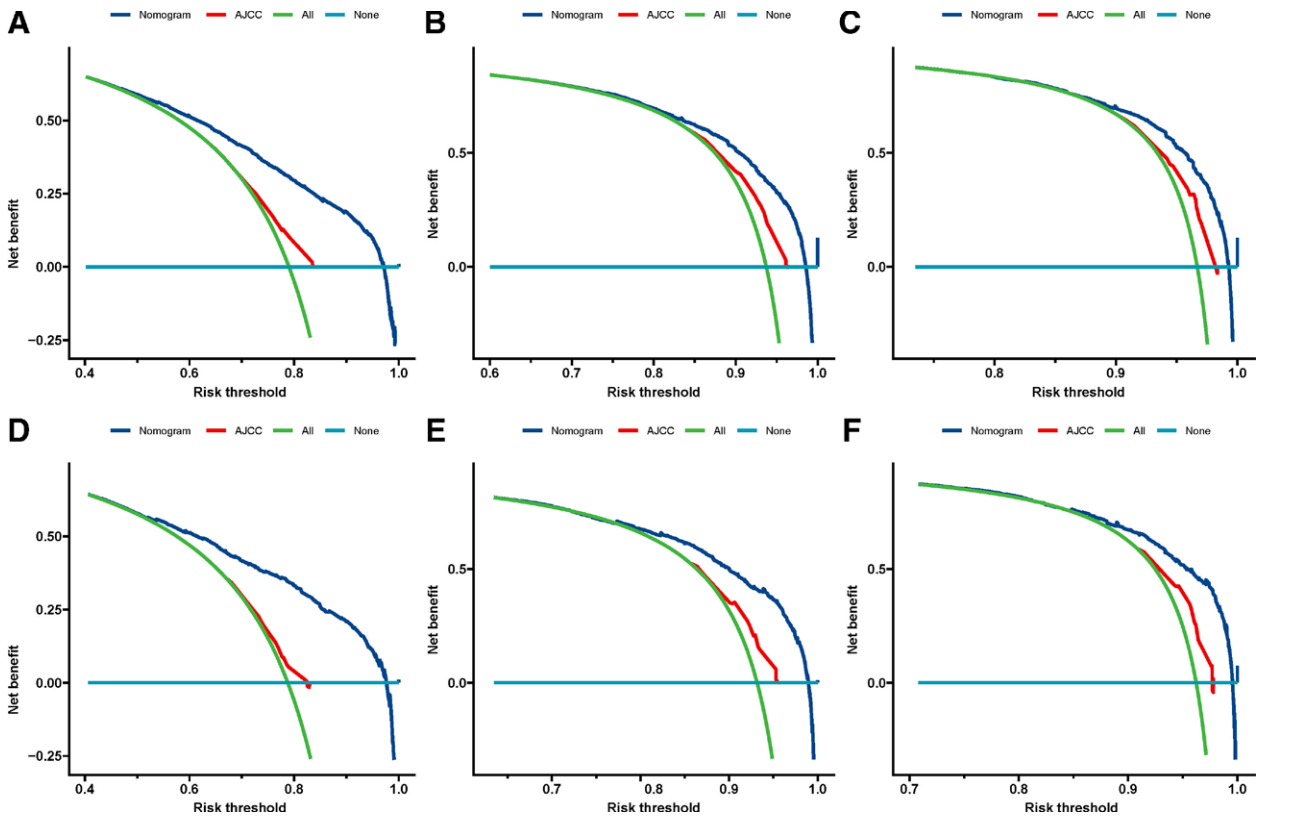


**Figure 6.** Decision curve analysis for DM-SCLC using nomogram and TNM stage system in terms of the (A) 1-, (B) 2-, and (C) 3-year OS in the training cohorts, and the (D) 1-, (E) 2-, and (F) 3-year OS in the validation cohorts. The *x*-axis represents the threshold probability. The *y*-axis measures the net benefit. The threshold probability is where the expected benefit of treatment balances the expected benefit of avoiding treatment. DM-SCLC = small-cell lung cancer, OS = overall survival.

a higher N stage was associated with poorer survival, which is roughly in line with our findings.

RT for DM-SCLC includes 3 dimensions: thoracic radiotherapy (TRT), metastatic site of RT, and prophylactic cranial irradiation (PCI). The standard treatment for DM-SCLC is still chemotherapy, and the combination of chemotherapy produces objective responses in 60% to 70% of patients. Good response to chemotherapy patients who are eligible and in good health should be considered for TRT or PCI, which may improve patient survival. In the 1999 Yugoslavia Randomized controlled Phase III clinical study,[25] patients who achieved a partial or complete response to chest lesions after chemotherapy were randomly divided into hyperinflated RT (50.4 Gy/36 f, twice a day, for a total of 18 days) with concurrent chemotherapy and chemotherapy alone. The results showed that there was a statistically significant difference in the 5-year survival rate between the 2 groups, and the median survival time increased from 11 months without TRT to 17 months, though there was no difference in distant metastasis-free survival between groups 1 and 2. TRT was recommended for DM-SCLC. TRT was recommended for DM-SCLC. The results of the prospective Phase III NTR1527 trial[26] in 2015 showed that TRT reduced the intrathoracic recurrence rate by nearly 50% compared with the control group. Although the application of TRT did not improve the OS for 1 year, the survival of the TRT group was significantly better than that of the control group at 2 years of follow-up. Reconfirming the role of TRT in DM-SCLC, the authors suggest that TRT should be routine in patients with DM-SCLC after effective chemotherapy. The European CREST study[27] showed no significant difference in survival between patients with 0 to 2 metastases and significantly better survival than patients with 3 or more metastases.

There was no difference in survival and the worst prognosis among patients with liver metastases who received TRT. Patients with bone metastases received TRT with no significant survival benefit but prolonged progression-free survival. Studies have found that there is no significant difference in survival between single-organ involvement and multi-organ involvement in patients with DM-SCLC once metastases involves the liver. The prognosis was worst when the liver was involved in single-organ metastases and worst when the liver and bone were involved in multi-organ metastases. The presence of brain metastases had little effect on prognosis. Compared with chemotherapy alone, the 2-year survival rate of patients with DM-SCLC oligo metastases was significantly improved by RT and chemotherapy, and similar conclusions were obtained for multiple metastases. Compared with chemotherapy alone, the 2-year survival rate of patients with DM-SCLC oligo metastases was significantly improved by RT and chemotherapy, and similar conclusions were obtained for multiple metastases.

In Phase III randomized controlled EORTC trial,[28] PCI resulted in a 1-year brain metastases rate in patients with ES-SCLC who were effective after first-line treatment from 40% to 15%, and survival time significantly increased from 5.4 months to 6.7 months. In Phase III randomized controlled study[29] in Japan in 2014, a total of 224 patients were enrolled, all of whom were confirmed to have no brain metastases by brain MRI examination before enrollment. The results showed that PCI (25 Gy/10 F) could reduce the incidence of brain metastases in DM-SCLC, but did not improve 1 year-OS. However, that study was a multi-center study, and the results were biased due to the different enrollment speeds and patient situations in each center. The lack of neurocognitive function assessment in follow-up could not well explain the reason why PCI reduced the

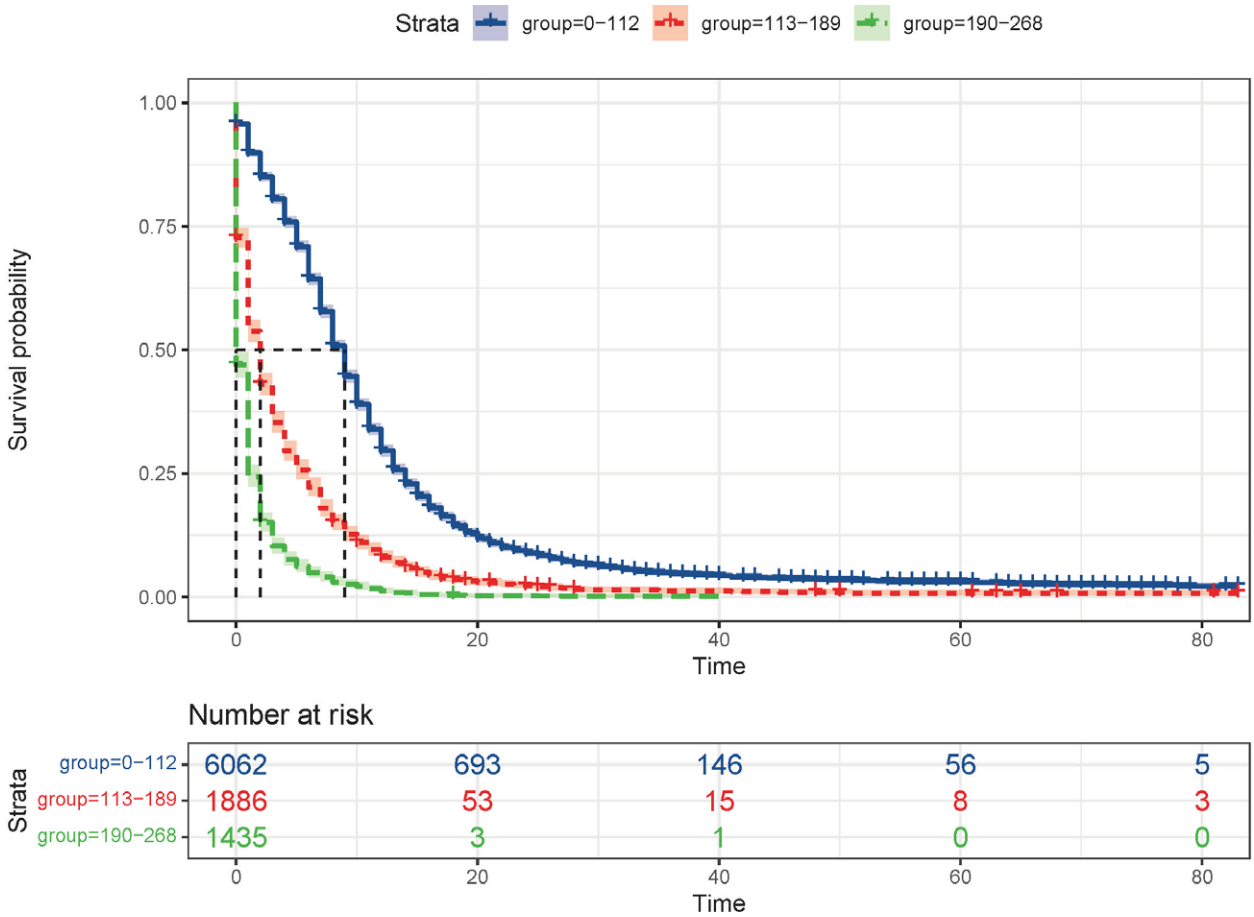


**Figure 7.** Kaplan–Meier curves of the low-, intermediate- and high-risk groups in training cohorts.

rate of brain metastases but did not gain survival benefit. The study was conducted only in Japan, and it is uncertain whether racial differences affect the results; Fifty-eight percent of patients in the observation group subsequently received delayed RT. Our results were consistent with those studies, however, due to the limitations of the SEER database specific information on the site of RT was not collected.

This study had several limitations. First, there may be selection bias because we excluded patients with incomplete information. Second, SEER data lacked variables related to treatment, such as chemotherapeutic regimen, RT site, and dose. Third, because of a lack of sufficient external data, we only randomly divided the patients with original data into 2 groups (training cohorts and validation cohorts), so the universality of this study should be verified. Finally, our study was a retrospective analysis and provided a relatively low level of clinical evidence, which requires further verification in prospective clinical trials.

## 5. Conclusion

This is the first nomogram prediction model for DM-SCLC using a large population-based cohort. The results indicated that age, tumor size, N stage, chemotherapy, metastasis of bone, brain, and liver are independent variables for OS and prognosis of DM-SCLC. Secondly, we developed a new survival prediction model with high accuracy, and its prediction performance was significantly better compared with that of the AJCC stage system. It can more accurately and individually predict the OS of patients and assist clinicians in formulating better individual treatment strategies.

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## Author contributions

**Methodology:** Fang Wang, Fangyu Liu.
**Resources:** Xi Zhang.
**Software:** Hongyun Shi, Yanhong Li, Xiaoyue Sun.
**Writing – original draft:** Shuai Qie.

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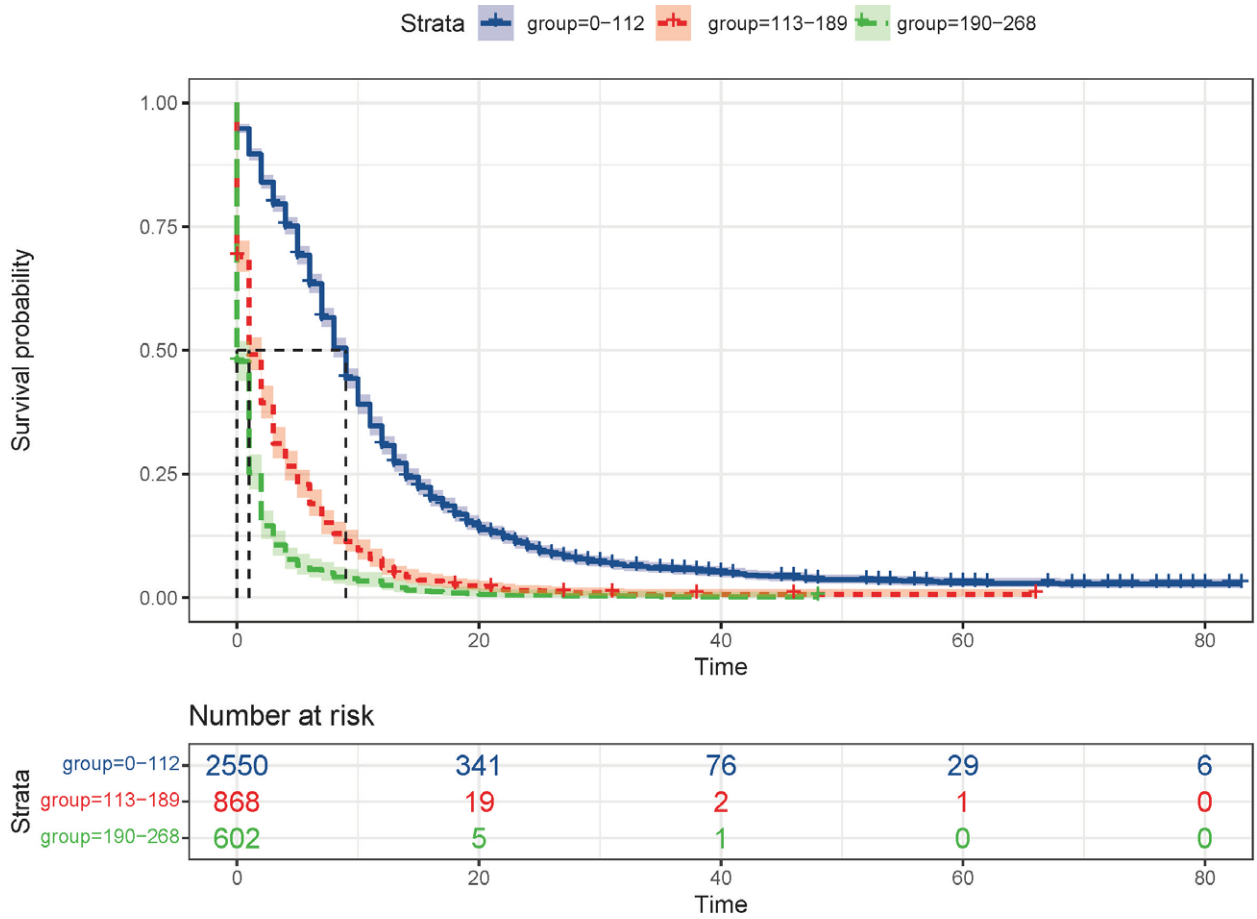


**Figure 8.** Survival benefit of RT in the low-risk, intermediate-risk, and high-risk groups. RT = radiotherapy.


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