Incidence and Prognosis Nomogram of Small Solitary Lung Cancer (≤2 cm) With Extra-Thoracic Metastasis at Initial Diagnosis: A Population-Based Study

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Abstract

Background: Small solitary lung cancer (≤2 cm) with extra-thoracic metastasis and no nodal metastasis or intra-thoracic metastasis is a rare situation in clinic.

Methods: Lung cancer patients with stage T1aN0M0 and T1aN0M1b from 2010 to 2015 were identified from the Surveillance, Epidemiology, and End Results database. The identified significant parameters were utilized to develop 2 nomogram to predict the extra-thoracic metastasis rates and the overall survival for the group of patients with stage T1aN0M1b.

Results: Small solitary lung cancers which occur in the males, younger patients, or locate in the main bronchus or left lung, or with histologic type as small cell lung cancer, or with undifferentiated type, tend to have extra-thoracic metastasis. Application of the nomogram in the intra-group still gave good discrimination and good calibration. Univariable and multivariable analysis identified several clinical data as the prognostic factors for lung cancer patients with stage T1aN0M1b, all the factors above were incorporated into the nomogram. ROC curve analysis showed that the nomogram had good discrimination, with AUC of .779, .786 and .77 for 1-, 3- and 5-year survival in the development group and validation group, respectively. Moreover, decision curve analysis has been implemented to evaluate and compare prediction and prognostic nomogram.

Conclusions: Younger male patients whose lung cancer locates in main bronchus or left lung, or with undifferentiated type, or with histologic type as small cell lung cancer are more likely to have extra-thoracic metastasis. The proposed nomogram reliably predicted OS for lung cancer patients with stage T1aN0M1b, though further validation is needed, it may be a useful tool in clinical practice. These models can be wildly used for easy facilitate the lung cancer individualized prediction of extra-thoracic metastasis and OS.

Keywords
small solitary lung cancer, extra-thoracic metastasis, nomogram, prognosis, SEER

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Introduction

With the widespread use of thoracic CT screening, more and more small pulmonary nodules are detected. A pulmonary nodule is defined as a single, well-circumscribed, spherical, diameter ≤ 3 cm nodule surrounded by lung tissue, which is not associated with hilar lymph node enlargement, atelectasis, or pleural effusion. In NELSON trial, lung cancer probability was .4%, 1.3%, and 15.2% for pulmonary nodules with maximum diameter smaller than 5 mm, 5-9 mm, and ≥ 10 mm, respectively. Surgery is recommended for a malignant pulmonary nodule (T1aN0M0, Stage IA). However, some patients already have distant metastasis even though it appears as a small solitary pulmonary nodule on thoracic CT scan (T1aN0M1b, Stage IV, in other words, small cancer with distant metastasis), surgery is not suitable in this situation. The 5-year survival rate of Stage IA non-small cell lung cancer, which can be fully resected by surgery, can exceed 90%. But the rate for Stage IV non-small cell lung cancer is less than 10%. So differentiating T1aN0M0 (Stage IA) from T1aN0M1b (Stage IV) is critical. However, the study of small cancer with distant metastasis is scarce.

Therefore, in the present study, we conducted the population-based study with SEER to investigate the incidence of this situation and the characteristics, risk factors and prognosis of the group of patients, that is, small solitary lung cancer (≤2 cm) with distant metastasis, without nodal metastasis and intrathoracic metastasis. Two simple-to-use nomogram that incorporated the clinicopathologic risk factors are also constructed to predict the possibility of distant metastasis and 1-, 3- and 5-year OS of these patients.

Materials and Methods

Patients and Study Design

SEER database is a national public database that comprises approximately 30% of the total US population, collecting population-level data from 18 cancer registries covering information on cancer incidence, patient demographics, tumor morphology, primary tumor site, stage at diagnosis, first course of treatment, and follow-up for survival time and vital status.

SEER*Stat version 8.3.8 software (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc. Calverton, MD, USA), SEER 18 registries Research Data (1975-2016, Nov 2018 Sub) were adopted to identify lung cancer patients diagnosed with T1aN0 (AJCC seventh) between 2010 and 2015. Inclusion criteria for patients were as follows: Age at diagnosis >18 years old; Solitary primary lung cancer with T1aN0M0 and T1aN0M1b (AJCC seventh edition). Lung cancer was pathological confirmed by histology. Consistent with the 2015 WHO classification of lung tumors, we categorized patients by histology into adenocarcinoma (SEER codes 8050, 8140, 8200, 8244, 8250-8255, 8260, 8323, 8333, 8430, 8441, 8480-8481, 8507, 8576), squamous cell carcinoma (SEER codes 8052, 8070-8074, 8083-8084), other non-small cell lung cancer (NSCLC) (SEER codes 8012, 8022, 8030, 8032, 8046, 8550, 8560, 8570, 8574-8575), small cell lung cancer (SEER codes 8013, 8041, 8042, 8044-8046), and unknown type (SEER codes 8000, 8010, 8020, 8033, 8082, 8123, 8201, 8230, 8249, 8310, 8490). Patients who were diagnosed via autopsy or death certificate, diagnosed with multi-primary lung cancer or with lymph node metastasis or intra-thoracic metastasis, whose detailed information was incomplete or who had a history of prior malignancy were excluded. The flow chart for the population selection was shown in Figure 1. A total of 10 968 patients in the SEER cohort meeting the criteria were selected for further analysis.

Analysis of data from SEER program was exempt from ethics review, and informed consent was not required.

Variables

The patients’ variables were evaluated to design the nomograms, the extra-thoracic metastasis prediction nomogram includes the following: age, sex, histological type, primary site, grade, and laterality. The prognostic nomogram includes the following: age, sex, histological type, radiation, chemotherapy, cancer-directed surgery, metastasis to the bone, the brain, and the liver (without involving other organs). Age was categorized subjectively as 2 groups: ≤ 60 and >60 years old. To evaluate the rate of extra-thoracic metastasis: extra-thoracic metastasis is defined as metastasis to extra-thoracic organs, bone or peritoneum confirmed with imaging or histology. To evaluate overall survival (OS): 1-, 3- and 5-year OS rate. OS is defined as time from randomization to death from any cause.

Statistical Analysis

Quantitative variables were compared by analysis of variance (ANOVA) and qualitative variables using Pearson’s chi-squared test. Quantitative variables were dichotomized. All the categorical variables were described as frequencies and percentages in forest plots. The Kaplan-Meier method was used to generate survival plots. The log-rank test was then used to compare groups. Univariate and multivariate logistic regression analyses were used to identify independent prognostic factors predicting OS in patients with T1aN0M1b (Stage IV) and develop the nomogram in the developing cohort. We selected significant variables by using the backward stepwise method and the nomogram was constructed based on the results of multivariable Cox regression. The maximum score for each factor was defined as 100. The model’s performance was evaluated by C-index, the area under the receiver operating characteristics curve (AUC) and calibration curves. P < .05 was considered statistically significant.

All significance levels were two-sided with a probability threshold of P < .05. All of the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA).
Results

Study Population Characteristics

Figure 1 summarizes the patient selection process. The demographics and clinic-pathological characteristics of the eligible patients are presented in Table 1. A total of 10,968 patients were identified (median age is 69 years old, 41.94% were men, 84.24% were white), of these, 1,749 patients (15.95%) had tumors ≤1 cm in diameter, 9,219 (84.05%) had tumors between 1 cm and 2 cm in diameter. Concerning the race, most patients were white (84.2%), black patients and patients of other races accounted for 15.8% of the study population. In terms of the histological type, adenocarcinoma is the major type in total (61.15% for total) and in the 2 subgroups (61.16% for group T1aN0M0, 60.98% for group T1aN0M1b). Majority of the patients are insured (97.36% for total, 97.47% for group T1aN0M0, 95.66% for group T1aN0M1b), the common primary site is upper lobe (62.45% for total, 62.14% for group T1aN0M0, 67.20% for group T1aN0M1b). Majority of the patients in group T1aN0M0 received cancer directed surgery (74.36%), while most patients in group T1aN0M1b received chemotherapy and radiotherapy (50.72% and 57.37%, respectively). Overall, 692 (6.31%) patients had extra-thoracic metastasis at the time of diagnosis with a prevalence of .98% in lesions ≤10 mm and 5.33% in lesions 11 to 20 mm in diameter. Gender, histologic type, primary site, laterality, grade, age at diagnosis were associated with extra-thoracic metastasis. The median overall survival for group T1aN0M0 and group T1aN0M1b is 32 months (Min-Max, 18-51) and 9 months (Min-Max, 3-19.25), respectively.

Risk Factors for Extra-thoracic Metastasis

In Figure 2, the forest plot presents univariate and multivariable analysis of the primary patients identified the risk factors for extra-thoracic metastasis in patients with stage T1aN0 as age (P < .0001), gender (P < .0001), histologic type (P < .0001), primary site (P < .05), grade (P < .001), and laterality (P = .0202). In detail, small solitary lung cancers which occur in the males, younger patients, or locate in the main bronchus or left lung, or with histologic type as small cell lung cancer, or with undifferentiated type, tend to have extra-thoracic metastasis.

Development of an Individualized Prediction Model

In Figure 3A, logistic regression analysis identified the age, sex, histologic, site, grade, and laterality as independent predictors. The model that incorporated the above
| Group                          | Total | T1aN0M0 | T1aN0M1b | P-Value  |
|-------------------------------|-------|---------|----------|---------|
| Survival months(Median (Q1-Q3)) | 10968 | 10276 (93.69%) | 692 (6.31%) | <.001   |
| Gender (n, %)                 |       |         |          |         |
| Male                          | 4600  | 4249 (41.35%) | 351 (50.72%) | <.001   |
| Female                        | 6368  | 6027 (58.65%) | 341 (49.28%) |         |
| Race                          |       |         |          | .171    |
| White                         | 9239  | 8654 (84.22%) | 585 (84.54%) |         |
| Black                         | 947   | 879 (8.55%)  | 68 (8.93%)  |         |
| Others                        | 782   | 743 (7.23%)  | 39 (5.64%)  |         |
| Marital status at diagnosis   |       |         |          | .096    |
| Married + partner             | 5707  | 5334 (51.91%) | 373 (53.90%) |         |
| Single + divorced + separated + windowed | 4731 | 4434 (43.15%) | 297 (42.92%) |         |
| Unknown                       | 530   | 508 (4.94%)  | 22 (3.18%)  |         |
| Histology type                |       |         |          | <.001   |
| Adenocarcinoma                | 6707  | 6285 (61.16%) | 422 (60.98%) |         |
| Squamous carcinoma            | 2293  | 2240 (21.80%) | 53 (7.66%)  |         |
| Other non-small cell lung cancer | 1091 | 1022 (9.95%)  | 69 (9.97%)  |         |
| Small cell lung cancer        | 643   | 530 (5.16%)  | 113 (16.33%)|         |
| Unknown                       | 234   | 199 (1.94%)  | 35 (5.06%)  |         |
| Insurance                     |       |         |          | <.001   |
| Uninsured                     | 150   | 126 (1.23%)  | 24 (3.47%)  |         |
| Insured                       | 10678 | 10016 (97.47%) | 662 (95.66%) |         |
| Unknown                       | 140   | 134 (1.30%)  | 6 (0.87%)   |         |
| Primary site                  |       |         |          | <.001   |
| Main bronchus (the vicinity of main bronchus) | 27 | 18 (1.8%) | 9 (1.30%) |         |
| Upper lobe                    | 6850  | 6385 (62.14%) | 465 (67.20%) |         |
| Middle lobe                   | 644   | 602 (5.86%)  | 42 (6.07%)  |         |
| Lower lobe                    | 3447  | 3271 (31.83%) | 176 (25.43%)|         |
| Grade                         |       |         |          | <.001   |
| Well differentiated            | 2368  | 2349 (22.86%) | 19 (2.75%)  |         |
| Moderately differentiated      | 3831  | 3775 (36.74%) | 56 (8.09%)  |         |
| Poorly differentiated          | 2224  | 2103 (20.47%) | 121 (17.49%)|         |
| Undifferentiated              | 142   | 128 (1.25%)  | 14 (2.02%)  |         |
| Unknown                       | 2403  | 1921 (18.69%) | 482 (69.65%)|         |
| Laterality                    |       |         |          | .008    |
| Left                          | 4438  | 4125 (40.14%) | 313 (45.23%)|         |
| Right                         | 6530  | 6151 (59.86%) | 379 (54.77%)|         |
| Cancer directed surgery       |       |         |          | <.001   |
| No/unknown                    | 3264  | 2635 (25.64%) | 629 (90.90%)|         |
| Yes                           | 7704  | 7641 (74.36%) | 63 (9.10%)  |         |
| Radiation                     |       |         |          | <.001   |
| No/unknown                    | 8495  | 8200 (79.80%) | 295 (42.63%)|         |
| Yes                           | 2473  | 2076 (20.20%) | 397 (57.37%)|         |
| Chemotherapy                  |       |         |          | <.001   |
| No/unknown                    | 10239 | 9898 (96.32%) | 341 (49.28%)|         |
| Yes                           | 729   | 378 (3.68%)  | 351 (50.72%)|         |
| Metastasis to bone            |       |         |          | <.001   |
| No                            | 10650 | 10276 (100.00%) | 374 (54.05%)|         |
| Yes                           | 318   | 0 (0.00%)  | 318 (45.95%)|         |
| Metastasis to brain           |       |         |          | <.001   |
| No                            | 10692 | 10276 (100.00%) | 416 (60.12%)|         |
| Yes                           | 276   | 0 (0.00%)  | 276 (39.88%)|         |

(continued)
independent predictors was developed and presented as the nomogram. The calibration plots of the nomogram showed a good agreement between the actual and nomogram-predicted occur rates by nomogram (Figure 3B). The ROC curves for the nomogram indicated that the AUC values for extra-thoracic metastasis rates was .824 (Figure 3C). The decision curve analysis and clinical impact curve for the nomogram and that for the extra-thoracic metastasis with different clinical factor integrated is presented in Figure 3D and 3E. It showed that if the risk threshold of a patient is between 2% and 62%, there will be more net benefit than either treating all patients or treating none by using the nomogram to decide whether or not to conduct treatment. The decision curve analysis (DCA) demonstrated that the nomogram had a favorable clinical utility. The cutoff value (6.9%) obtained from the ROC curve of the cohort was within the threshold probability range of the above DCA curves, indicating that the nomogram prediction model has good clinical usefulness. A further analysis of the DCA curves of the nomogram prediction model showed that the net clinical benefit of the cohort was 56%, respectively, when 6.9% was set as the threshold probability value for diagnosing diabetic foot and taking intervention. In other words, 56 of every 100 patients with T1aN0 who were diagnosed with extra-thoracic metastasis using the nomogram prediction model in the cohort would has clinical benefits. The clinical impact curve of the model to identify at-risk individuals for extra-thoracic metastasis testing was observed at thresholds ≥10%. The greatest effect on 50%. A threshold ≥10% to guide screening was better than screening of all individuals. Within a broad range, net benefit was comparable, on the basis of the extra-thoracic metastases model with clinical variables.

**Univariate Association of Distant Metastasis and Clinic-Pathological Characteristics With Overall-Free Survival**

In group T1aN0M1b, bone and brain are the most common single metastatic organs (33.67% and 31.65%, respectively). Race, primary site, marital status, laterality, insurance, grade, tumor size have no correlation with overall survival (\(P > .05\)), while age (\(P < .05\)), gender (\(P < .001\)), metastasis pattern (\(P < .05\)), histologic type (\(P < .05\)), chemotherapy (\(P < .0001\)), cancer directed surgery (\(P < .0001\)), radiotherapy (\(P < .005\)), and metastasis to liver (\(P < .0001\)) are related to overall survival (Figure 4).

Kaplan–Meier survival curves showed that M0 (\(P < .0001\)), age ≤60 years (\(P < .0001\)), female (\(P < .0001\)), well differentiated (\(P < .0001\)), adenocarcinoma (\(P < .0001\)), tumor size ≤1 cm (\(P < .0001\)), patients with surgery (\(P < .0001\)), patients with radiation (\(P < .0001\)), and patients with chemotherapy (\(P < .0001\)) had significantly longer survival times than M1, age >60 years, male patients, undifferentiated grade, small cell lung cancer, tumor size >1 cm, patients without surgery, patients without radiation, and patients without chemotherapy, respectively (Figure 5).

**Table 1.** (continued)

| Group                        | Total | T1aN0M0 | T1aN0M1b | \(P\)-Value |
|------------------------------|-------|---------|----------|-------------|
| Metastasis to liver          |       |         |          |             |
| No                           | 10816 (98.61%) | 10276 (100.00%) | 540 (78.03%) | <.001       |
| Yes                          | 152 (1.39%)  | 0 (0.00%) | 152 (21.97%) |             |
| Metastasis pattern           |       |         |          |             |
| No brain, liver and bone metastasis | 58 (53%)    | 58 (8.38%)   |             |             |
| Only bone metastasis         | 233 (2.1%)  | 233 (33.67%) |             |             |
| Only brain metastasis        | 219 (1.99%) | 219 (31.65%) |             |             |
| Only liver metastasis        | 83 (76%)   | 83 (11.99%)  |             |             |
| Brain and bone metastasis    | 30 (76%)   | 30 (4.34%)   |             |             |
| Bone and liver metastasis    | 42 (38%)   | 42 (6.07%)   |             |             |
| Brain and liver metastasis   | 14 (13%)   | 14 (2.02%)   |             |             |
| Bone, brain and liver metastasis | 13 (12%) | 13 (1.88%) |             |             |
| Age at diagnosis (years, median (min-max)) | 69.00 (22.00-96.00) | 69.00 (22.00-96.00) | 67.00 (34.00-93.00) | .001       |
| ≤60 (N,%, median (min-max))  |       |         |          |             |
| 2410 (21.97%)                | 2224 (21.64%) |             | 186 (26.88%) |             |
| 56.00 (22.00-60.00)          | 56.00 (22.00-60.00) | 55.00 (34.00-60.00) |             |             |
| >60 (N, Median (Min-Max))    | 8558 (78.03%) | 8052 (78.36%) | 506 (73.12%) |             |
| 71.00 (61.00-96.00)          | 71.00 (61.00-96.00) | 71.00 (61.00-93.00) |             |             |
| Tumor size (mm)              | 13 (1.88%) | 15.00 (1.00-20.00) | 16.00 (1.00-20.00) | .719       |
| ≤10 (N, Median (Min-Max))    |       |         |          |             |
| 1749 (15.95%)                | 1642 (15.98%) | 107 (15.46%) |             |             |
| 9.00 (1.00-10.00)            | 9.00 (1.00-10.00) | 8.00 (1.00-10.00) |             |             |
| >10 (N, Median (Min-Max))    | 9219 (84.05%) | 8634 (84.02%) | 585 (84.54%) |             |
| 16.00 (11.00-20.00)          | 16.00 (11.00-20.00) | 17.00 (11.00-20.00) |             |             |
Survival Analysis

A nomogram is a useful predictive tool that could provide a specific outcome’s overall probability. Significant independent factors, including age, sex, histologic type, cancer directed surgery, radiation, chemotherapy, metastasis to bone, metastasis to brain, metastasis to liver were incorporated to establish the nomogram (Figure 6). The nomogram to predict the individual small solitary lung cancer patients of 1-, 3-, and 5-year overall survival (OS) rates of individual small solitary lung cancer patients (Figure 7A). The calibration plots of the nomogram showed good agreement between the actual and nomogram-predicted 1-, 3- and 5-year survival rates. ROC curve analysis showed that the nomogram had good discrimination, with an area under the curve (AUC) of .779, .786 and .77 for 1-, 3- and 5-year survival in development group and validation group, respectively (Figure 7B).

Clinical Use

The decision curve analysis for the small solitary lung cancer survival nomogram is presented in Figure 7C. The decision curve showed the prognostic signature have the great net benefit. The nomogram based on the risk score added more net benefit than the 1 without the risk score. The small solitary lung cancer survival nomogram to predict 1-, 3- and 5- survival year adds more benefit than either the treat-all-patients scheme or the treat-none scheme.

Discussion

In this study, we used the national population-based SEER database to identify a unique cohort of patients with small solitary lung cancer (≤2 cm) on thoracic CT scan but with extra-thoracic metastasis at initial diagnosis. We found that the incidence of extra-thoracic metastasis (M1b) in all small solitary lung cancer (≤2 cm) is 6.31% (692/10 968), and the incidence is elevated rapidly with the increase of the tumor size, from .98% in lesions ≤10 mm to 5.33% in lesions 11 to 20 mm in diameter. The extra-thoracic metastasis in patients with T1aN0M1b may occur through occult vascular vessel invasion or lymphatic vessel invasion, or both. It was reported that the rate of intra-tumoral vessel invasion in Stage I NSCLC is as high as 48%. There is another study found that microscopic vascular invasion was observed in 34%

![Table](image-url)
pT1-T2N0 NSCLC patients, and microscopic vascular invasion was a more robust prognostic indicator than tumor size.\(^7\) In a study conducted in China, the researchers found about 6.6% of patients with lymph node metastasis in clinical stage T1aN0M0 after surgery.\(^8\) Another study conducted in the USA reported 9.6% nodal metastasis in clinical stage T1aN0M0 after surgery.\(^9\) Two previous studies showed extra-thoracic metastasis was identified in 12%-13% of patients with T1 NSCLC at the time of diagnosis.\(^10,11\)

However, the studies included the patients with tumor size 20-30 mm and nodal metastasis or intra-thoracic metastasis. The present study is the first to report the ratio of the extra-thoracic metastasis in a large national cohort of T1aN0 lung cancer. Compared with the above-mentioned studies, our data has validity. Based on the results above, we should pay enough attention to the special group of small solitary lung cancer with clinical stage T1aN0 on thoracic CT scan, because there are 6.3% of these patients have distant metastasis.

**Figure 3.** A nomogram prediction model for extra-thoracic metastasis was constructed based on the multiple clinicopathologic risk factors. (A) Risk factors nomogram system for the extra-thoracic metastasis prediction. (B) Calibration plots for predicting for extra-thoracic metastasis. The blue dotted line indicates the ideal nomogram, blue X indicates the bootstrap-corrected estimates, vertical bars indicate the 95% CIs. (C) ROC curves of the extra-thoracic metastasis prediction nomogram of T1N0 lung cancer patients. The red bars represent a new nomogram predicted OS, whereas the black bars represent the TNM stage predicted OS. (D) Decision curve analysis for the extra-thoracic metastasis prediction nomogram. (E) Clinical impact curve for the biomarker-based risk model. Of 1000 patients, the heavy red solid line shows the total number who would be deemed high risk for each risk threshold. The blue dashed line shows how many of those would be true positives (cases).
As to the metastasis pattern, lung cancers prefer to metastasize to the bone and brain, which account for 2.9% and 2.52% of the total study population. A previous study reported that approximately 2% of NSCLC patients eligible for radical surgical treatment had synchronous brain metastases, and the rate of brain metastases in stage IA is about .7%. The brain metastasis rate in our study is 2.52%, which is higher than .7%. Several reasons contribute to the result: firstly, the previous study only used a CT scan to detect brain metastasis. As we all know, contrast-enhanced head MRI is much more...
Figure 5. Survival analysis depicted by Kaplan-Meier curve.
sensitive to detect metastatic brain tumor than CT. Secondly, only NSCLC is included in previous studies, whereas we include all types of lung cancer in our study, especially small cell lung cancer, which is more likely to have distant metastasis. Thirdly, the total sample number in the previous study (1074) is much smaller than ours (10968). In addition, brain metastasis has been reported to occur in early-stage lung cancer, for example, a study reported that in 181 NSCLC patients with brain metastasis, 60 (33.1%) had N0 disease, 51 (28.2%) had T1 disease. Japanese Lung Cancer Society guideline recommended screening for brain metastasis in all patients with NSCLC, and the European Society for Medical Oncology (ESMO) also noted the importance of brain MRI before curative therapy. Furthermore, lung cancer with EGFR sensitive mutation is more likely to develop brain metastasis, therefore, brain MRI is essential in the East Asia, where patients have a higher frequency of EGFR sensitive mutation, even the tumor appears in early stage.

The laterality of the lung cancer has no impact on overall survival, which is consistent with previous studies. However, in Figure 2, we noticed that left small solitary lung cancer is more likely to have extra-thoracic metastasis, more researches are needed to confirm the finding. In the present study, we also noted that the lung cancer in females had a better prognosis, which is consistent with previous studies. In addition, we found the patients with the main bronchus as the primary tumor site and liver metastasis had a worse prognosis, which is also consistent with previous studies. Moreover, SCLC has been widely recognized with high malignancy and early extensive brain metastases in lung cancer, and reduced responsiveness to therapy. The lung cancer patients with left tumor with a propensity for distant metastasis and appeared to have a worse OS.

Our study is the first study that reported the incidence of small solitary lung cancer (<2 cm) with extra-thoracic metastasis at initial diagnosis based on a national scale population and analyzed the metastasis pattern; What’s more, we constructed an easy-to-use nomogram to predict the overall survival of this group of patients. It has clinical significance in that it urges doctors to take attention of this specific group of patients: small solitary tumors with distant metastasis, and to proceed with caution when making a final curative decision before further metastatic screening.

We argue that the most important role of the nomogram is to interpret individual need more therapeutic targets and treatment options. However, the risk-prediction model, discrimination and calibration, could not play an important role in clinical decision-making. Therefore, in order to verify the clinical value, we tested whether the nomogram-associated decisions curve analysis would improve individual overall prognosis. Our approach provides a new insight into clinical decision-making based on threshold probability, and the net benefit could be derived. The decision curve analysis showed that using the prediction and prognostic nomogram in our research to predict metastases and survival year adds more benefit than either the treat-all-patients scheme or the treat-none scheme.

Figure 6. Nomogram for predicting 1-, 3- and 5-year OS in lung cancer patients with stage T1aN0M1b.
This study has several limitations. To begin with, the study was conducted retrospectively, selection bias may be inevitable that we did not calculate the sample size in advance. Second, Staging according to AJCC version 8 would have been preferred, but not possible as patients were staged before 2017. Third, the SEER database merely recorded the presence/absence of brain metastases based on the initial diagnosis. Diagnosis methods for brain metastases were not reported, such as MRI or PET-CT. Fourth, some information was not collected in SEER database, such as performance status, smoking status, drive gene mutation, immune microenvironment, the radiotherapy plan, the regimen of chemotherapy, detailed clinicopathological data, and other metastatic organs, such as adrenal glands, which may affect the precision of the predictive nomogram. Lastly, we didn’t perform external validation of the nomogram, more studies are needed in the future.

Figure 7. Calibration curves, ROC, and DCA of the prognostic nomogram. (A) Calibration plots for predicting for T1aN0M1b lung cancer patients OS at 1-, 3-, and 5-year. The blue dotted line indicates the ideal nomogram, blue X indicates the bootstrap-corrected estimates, vertical bars indicate the 95% CIs. (B) ROC curves of the 1-, 3-, and 5-year nomograms of T1aN0M1b lung cancer patients. The red bars represent a new nomogram predicted OS, whereas the black bars represent the TNM stage predicted OS. (C) Decision curve analysis for the 1-, 3-, and 5-year nomograms of T1aN0M1b lung cancer patients.
Conclusions

The incidence of small solitary lung cancer (≤2 cm) with extra-thoracic metastasis and without nodal or intra-thoracic metastasis at initial diagnosis is relatively high. Doctors should pay more attention to such a group of patients and make enough metastasis screening. Younger male patients whose lung cancer locates in main bronchus or left lung, or with undifferentiated type, or with histologic type as small cell lung cancer are more likely to have extra-thoracic metastasis. These model can be wildly used for easy facilitate the lung cancer individualized prediction of extra-thoracic metastasis and OS. In particular, the second nomogram showed reliable prognostic prediction for lung cancer patients with stage T1aN0M1b, it could improve individualized evaluations of survival and therapeutic decisions for these patients.

Appendix

Abbreviation

AUC Area under the curve
CT Computed Tomographic
DCA Decision Curve Analysis
EGFR Epidermal growth factor receptor
NSCLC Non-small cell lung cancer
OS Overall survival
ROC Receiver operating characteristics curve
SEER The Surveillance, Epidemiology, and End Results

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Author contributions

CD and CL conceived and designed this study. CL, ZC and AH extracted the information from the databases. CL, AH and ZC performed experiments and prepared the manuscript. YG and XL analyzed the data. All authors read and approved the study.

Declaration of Conflicting Interests

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Ethical Statement

Analysis of data from SEER program was exempt from ethics review, and informed consent was not required.

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