Original Article

A nomogram predicting the risk of extrathoracic metastasis at initial diagnosis of $T_{\leq 3cm}N_0$ lung cancer

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Background: The risk and risk factors of extrathoracic metastasis at initial diagnosis in $T_{\leq 3cm}N_0$ lung cancer patients are not fully understood. We aimed to develop a model to predict the risk of extrathoracic metastasis in those patients.

Methods: Clinicopathological data of patients were collected from Surveillance, Epidemiology, and End Results (SEER) database. Univariable and multivariable analyses using logistic regression were conducted to identify risk factors. A predictive model and corresponding nomogram were developed based on the risk factors. The model was assessed using the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow test, and decision curve.

Results: A total of 20,057 $T_{\leq 3cm}N_0$ patients were enrolled, of whom 251 (1.25%) were diagnosed with extrathoracic metastasis at the initial diagnosis. Aged ≤50 [odds ratio (OR): 2.05, 95% confidence interval (CI): 1.19–3.53, P=0.01] and aged ≥81 [1.65 (1.05–2.58), P=0.03], Hispanic [1.81 (1.20–2.71), P=0.004], location of bronchus [3.18 (1.08–9.35), P=0.04], larger tumor size, pleural invasion, and a history of colorectal cancer [2.01 (1.01–4.00), P=0.046] were independent risk factors. In the training cohort and validation cohort, the AUCs of the developed model were 0.727, 0.728 respectively, and the results of Hosmer-Lemeshow test were P=0.47, P=0.61 respectively. The decision curve showed good clinical meaning of the model.

Conclusions: Extrathoracic metastasis at initial diagnosis in $T_{\leq 3cm}N_0$ lung cancer patients was not rare. The model based on the risk factors showed good performance in predicting the risk of extrathoracic metastasis.

Keywords: Lung cancer; metastasis; pleural invasion; pretreatment evaluation

Submitted Apr 16, 2024. Accepted for publication Jul 17, 2024. Published online Aug 08, 2024.
doi: 10.21037/tlcr-24-338
View this article at: https://dx.doi.org/10.21037/tlcr-24-338

Introduction

Lung cancer is a malignant tumor with the highest mortality and the second highest morbidity (1). According to the American Joint Committee on Cancer (AJCC) stage system (8th edition), the stage of lung cancer (TNM system) depends on tumor size and regional invasiveness (T classification), lymph node metastasis (N classification), and distant metastasis (M classification), which defines the treatment strategy for each patient. For patients of early stage, surgery is the only radical treatment; for patients with advanced stage with metastasis, surgery could be palliative treatment but systemic treatment and radiotherapy play more important roles. Due to the different prognosis and treatment strategy, it is important to differentiate patients of advanced stage, especially patients with distant metastasis, from patients of early stage.

To date, the guidelines of lung cancer do not reach consensus on whether it is necessary to screen for distant

metastasis for all patients (2). The National Comprehensive Cancer Network (NCCN) guidelines recommend contrast-enhanced computed tomography of upper abdomen and positron emission tomography/computed tomography (PET/CT) for all lung cancer patients (3), but excessive medical examination could bring a huge burden for government pension insurance. Magnetic resonance imaging (MRI) to screen for brain metastasis is recommended for patients of stage IB (optional) and higher stage, but not for stage IA patients (3). Nowadays, lung cancer of small size (diameter ≤3 cm) is becoming more common due to increased health awareness and the popularity of lung cancer CT screening. But it is controversial whether distant metastasis screening should be routinely performed at initial diagnosis in patients with tumor size ≤3 cm and without evidence of lymph node metastasis ($T_{\leq 3cm}N_0$). Studies have reported that 0.7% stage IA non-small cell lung cancer (NSCLC) patients have brain metastasis (4) and 1% stage IA NSCLC patients have extrathoracic metastasis at initial diagnosis actually (5). Given that physicians might neglect the screening for extrathoracic metastasis in $T_{\leq 3cm}N_0$ patients, we would like to include baseline demographic information and pleural invasion information, which could be assessed from image at pretreatment evaluation in clinical practice, from Surveillance, Epidemiology, and End Results (SEER) database [2016–2020] to identify the risk factors of extrathoracic metastasis and build a model to help physicians to differentiate $T_{\leq 3cm}N_0$ patients at different risks of extrathoracic metastasis. We present this article in accordance with the TRIPOD reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-338/rc).

Highlight box

Key findings

- A nomogram based on the independent risk factors was developed to differentiate $T_{\leq 3cm}N_0$ lung cancer patients at different risks of extrathoracic metastasis (EM) at initial diagnosis.

What is known and what is new?

- It is controversial whether $T_{\leq 3cm}N_0$ lung cancer patients should routinely undergo screening for EM at initial diagnosis.
- We collected data of 20,057 patients from Surveillance, Epidemiology, and End Results database, among whom 251 (1.25%) were diagnosed with EM at the initial diagnosis. The nomogram based on the independent risk factors showed good performance in differentiating patients at different risks of EM.

What is the implication, and what should change now?

- EM is a main factor influencing the prognosis of lung cancer patients, and also influences the treatment strategy. Our nomogram might help with screening out $T_{\leq 3cm}N_0$ lung cancer patients who are at high risk of EM at the diagnosis and promoting the precisive individualized treatment to improve the prognosis of those patients.

Methods

Data source

The SEER database is a national cancer database based on the U.S. population. It records the clinicopathological information of patients at the initial diagnosis and in the follow-up. The data of our interest were downloaded using the software SEER*Stat 8.4.2 (6). The requirements for informed consent and ethical approval were waived because there was no individually identifiable information in the database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients

Patients diagnosed with lung cancer between 2016 to 2020 were retrospectively enrolled. The site recode ICD-O-3/WHO 2008 was set as "Lung and Bronchus". The inclusion criteria were: (I) aged 18 or older; (II) solitary pulmonary nodule with diameter ≤3 cm; (III) histologically diagnosed; (IV) no lymph node metastasis (N_0); (V) primary lung cancer. The exclusion criteria were: (I) not clear primary site or laterality of the tumor; (II) with contralateral lung metastasis; (III) the reporting source was "Autopsy only" or "Death certificate only"; (IV) incomplete clinical information of interest.

Variables and outcomes

The collected clinical information of patients at the initial diagnosis included age, sex, race, hispanic or not, primary tumor site, laterality, tumor size, pleural invasion status, malignancy history, marital status, and income. Pleural invasion statuses were defined as: PL0, no pleural invasion or invading superficially into the pleura but within the elastic layer of the visceral pleura; PL1/2, visceral pleural invasion beyond the elastic layer; PL3, parietal pleural invasion; PL-NOS, pleural invasion but no other specific information about PL1/2 or PL3. The outcome was extrathoracic metastasis at initial diagnosis of lung cancer,

including metastasis to brain, to bone, to liver, to distant lymph node, to other site(s), and to multiple sites. When analysing metastasis to multiple sites, metastasis to other site(s) was considered as one site.

Statistical analysis

The continuous variables were converted into categorical variables based on the clinical meaning. The categorical variables were described as absolute number and percentage and were tested using Pearson Chi-squared test. Univariable and multivariable analyses using the logistic regression model were conducted to identify the independent risk factors of extrathoracic metastasis. Variables whose P value <0.1 in the univariable analysis were included into the multivariable analysis. The odds ratio (OR) and the corresponding 95% confidential interval (CI) of each variable were calculated. The independent risk variables were used to develop the model predicting extrathoracic metastasis. To build the model, two of thirds patients were randomly chosen as training cohort, and the remained one third as validation cohort. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to assess the discrimination ability of the model. Calibration curve and Hosmer-Lemeshow test were used to assess the calibration of the model. Decision curve analysis was used to test the clinical meaning of the model. Software R (R-4.0.3) was used in the study. A P value less than 0.05 was considered significant and all P value were two tailed.

Results

Clinicopathological characteristics of patients

A total of 20,057 lung cancer patients were enrolled, of whom 251 (1.25%) patients were diagnosed with extrathoracic metastasis at the initial diagnosis. The clinicopathological characteristics of the enrolled patients are shown in *Table 1*. Compared to patients without extrathoracic metastasis, more patients with extrathoracic metastasis were ≤50 years old (3.9% *vs.* 7.2%) or ≥81 years old (7.0% *vs.* 10.8%) (P=0.007), male (42.0% *vs.* 49.0%, P=0.03), Hispanic (6.5% *vs.* 11.2%, P=0.004), with tumor in upper lobe (58.9% *vs.* 64.1%) or bronchus (0.4% *vs.* 1.6%) (P=0.005), with tumor size of 2–3 cm (41.6% *vs.* 61.4%, P<0.001), with pleural invasion (16.9% *vs.* 43.4%, P<0.001), and with a history of colorectal cancer (1.7% *vs.* 3.6%, P=0.01). Interestingly, patients with extrathoracic metastasis were less likely to have a history of breast cancer (3.3% *vs.* 0.8%), lung cancer (1.9% *vs.* 0.8%), or multiple cancers (3.9% *vs.* 2.0%) as compared to patients without extrathoracic metastasis. With regard to race, tumor laterality, marital status, or income, no difference was found between groups.

Among the 251 patients with extrathoracic metastasis, 60 (23.9%) were metastasis of brain, 42 (16.7%) to bone, 18 (7.2%) to liver, 6 (2.4%) to distant lymph node, 90 (35.9%) to other sites, and 35 (13.9%) to multiple sites. Table S1 shows the frequencies of metastasis to different sites in patients of different clinicopathological characteristics.

Risk factors of extrathoracic metastasis

The results of the univariable and multivariable analyses demonstrated that aged ≤50 or ≥81 years, Hispanic, location of bronchus, larger tumor size, pleural invasion, history of colorectal cancer were independent risk factors of extrathoracic metastasis (*Table 2*).

Compared to aged 61–70 years, aged ≤50 years (OR: 2.05, 95% CI: 1.19–3.53, P=0.01), and aged ≥81 years (OR: 1.65, 95% CI: 1.05–2.58, P=0.03) were risk factors. Hispanic people have a higher risk for extrathoracic metastasis (OR: 1.81, 95% CI: 1.20–2.71, P=0.004). Compared to location of upper lobe, location of bronchus was a risk factor (OR: 3.18, 95% CI: 1.08–9.35, P=0.04). Compared to tumor size ≤1 cm, 1–2 cm (OR: 4.14, 95% CI: 1.02–16.83, P=0.047) and 2–3 cm (OR: 7.70, 95% CI: 1.90–31.16, P=0.004) were risk factors. Compared to no pleural invasion, PL1/2 (OR: 2.30, 95% CI: 1.68–3.13, P<0.001), PL3 (OR: 10.05, 95% CI: 5.05–19.99, P<0.001), and PL-NOS (OR: 9.55, 95% CI: 6.64–13.74, P<0.001) were risk factors. Compared to no malignancy history, history of colorectal cancer (OR: 2.01, 95% CI: 1.01–4.00, P=0.046) were risk factor, and history of breast cancer tend to be a protective factor but without statistical significance (OR: 0.26, 95% CI: 0.06–1.07, P=0.06). Sex was not a risk factor in the multivariable analysis (OR: 1.20, 95% CI: 0.93–1.55, P=0.17). Race, tumor laterality, marital status, and income were not associated with the risk of extrathoracic metastasis.

Model development and validation

Based on the independent risk factors, we developed a model to predict the risk of extrathoracic metastasis using data of the training cohort patients. A corresponding nomogram was also developed (*Figure 1*). The ROC curves

Table 1 The baseline clinicopathological characteristics of patients with or without EM

Characteristics	Without EM (N=19,806)	With EM (N=251)	P
Age (years)			0.007
≤50	779 (3.9)	18 (7.2)	
51–60	3,110 (15.7)	37 (14.7)	
61–70	7,672 (38.7)	81 (32.3)	
71–80	6,851 (34.6)	88 (35.1)	
≥81	1,394 (7.0)	27 (10.8)	
Sex			0.03
Female	11,489 (58.0)	128 (51.0)	
Male	8,317 (42.0)	123 (49.0)	
Race			0.55
White	16,481 (83.2)	204 (81.3)	
Black	1,598 (8.1)	25 (10.0)	
Others[a]	1,727 (8.7)	22 (8.8)	
Hispanic[b]			0.004
No	18,528 (93.5)	223 (88.8)	
Yes	1,278 (6.5)	28 (11.2)	
Primary site			0.005
Bronchus	77 (0.4)	4 (1.6)	
Upper lobe	11,664 (58.9)	161 (64.1)	
Middle lobe	1,347 (6.8)	13 (5.2)	
Lower lobe	6,718 (33.9)	73 (29.1)	
Laterality			0.24
Right	11,738 (59.3)	139 (55.4)	
Left	8,068 (40.7)	112 (44.6)	
Size (cm)			<0.001
≤1	1,037 (5.2)	2 (0.8)	
(1, 2]	10,527 (53.2)	95 (37.8)	
(2, 3]	8,242 (41.6)	154 (61.4)	
Pleural invasion			<0.001
PL0	16,455 (83.1)	142 (56.6)	
PL1/2	2,792 (14.1)	58 (23.1)	
PL3	87 (0.4)	10 (4.0)	
PL-NOS[c]	472 (2.4)	41 (16.3)	
Malignancy history			0.01
No	15,385 (77.7)	205 (81.7)	
Yes, breast	644 (3.3)	2 (0.8)	
Yes, colon and rectum	336 (1.7)	9 (3.6)	
Yes, lung and bronchus	370 (1.9)	2 (0.8)	
Yes, multiple	781 (3.9)	5 (2.0)	
Yes, others[d]	2,290 (11.6)	28 (11.2)	
Marital status			0.72
Never married	2,807 (14.2)	37 (14.7)	
Married	11,569 (58.4)	151 (60.2)	
Others	5,430 (27.4)	63 (25.1)	
Income[e]			0.86
<50,000$	1,884 (9.5)	26 (10.4)	
50,000–74,999$	7,552 (38.1)	97 (38.6)	
≥75,000$	10,370 (52.4)	128 (51.0)	

Values are numbers (percentages), and percentages may not total 100 because of rounding. [a], others included Asian/Pacific Islander and American Indian/Alaska Native; [b], "Hispanic" indicated Americans from Latin America; [c], "PL-NOS" indicated pleural invasion but no other specific information about PL1/2 or PL3; [d], "Yes, others" indicated cancer history not including breast, lung and bronchus, colon and rectum, or multiple cancer history; [e], "Income" indicated median household income inflation adjusted to 2021. EM, extrathoracic metastasis.

were drawn and the AUCs were 0.727, 0.728 in the training cohort and validation cohort respectively (*Figure 2A*). The calibration curves showed good consistence of the predicted risk and the observed risk. The results of the Hosmer-Lemeshow test were P=0.47 and P=0.61 in the training cohort and validation cohort respectively (*Figure 2B*), which indicated good fitness of the model. The decision curves of the training cohort and validation cohort showed net benefit of our model, indicating good clinical meaning (*Figure 2C*).

Discussion

Extrathoracic metastasis is the most important factor influencing the prognosis of lung cancer patients and the treatment of patients with extrathoracic metastasis was very

Table 2 Results of the univariable and multivariable analyses to identify independent risk factors of extrathoracic metastasis

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)				
≤50	2.19 (1.31–3.67)	0.003	2.05 (1.19–3.53)	0.01
51–60	1.13 (0.76–1.67)	0.55	1.12 (0.75–1.66)	0.58
61–70	Reference		Reference	
71–80	1.22 (0.90–1.65)	0.21	1.20 (0.88–1.63)	0.24
≥81	1.83 (1.18–2.85)	0.007	1.65 (1.05–2.58)	0.03
Sex				
Female	Reference		Reference	
Male	1.33 (1.03–1.70)	0.03	1.20 (0.93–1.55)	0.17
Race				
White	Reference			
Black	1.26 (0.83–1.92)	0.27		
Others[a]	1.03 (0.66–1.60)	0.90		
Hispanic[b]				
No	Reference			
Yes	1.82 (1.22–2.71)	0.003	1.81 (1.20–2.71)	0.004
Primary site				
Bronchus	3.76 (1.36–10.41)	0.01	3.18 (1.08–9.35)	0.04
Upper lobe	Reference		Reference	
Middle lobe	0.70 (0.40–1.23)	0.22	0.73 (0.41–1.29)	0.28
Lower lobe	0.79 (0.60–1.04)	0.09	0.83 (0.62–1.10)	0.19
Laterality				
Right	Reference			
Left	1.17 (0.91–1.51)	0.21		
Size (cm)				
≤1	Reference		Reference	
(1, 2]	4.68 (1.15–18.99)	0.03	4.14 (1.02–16.83)	0.047
(2, 3]	9.69 (2.40–39.11)	0.001	7.70 (1.90–31.16)	0.004
Pleural invasion				
PL0	Reference		Reference	
PL1/2	2.41 (1.77–3.28)	<0.001	2.30 (1.68–3.13)	<0.001
PL3	13.32 (6.78–26.16)	<0.001	10.05 (5.05–19.99)	<0.001
PL-NOS[c]	10.07 (7.03–14.42)	<0.001	9.55 (6.64–13.74)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Malignancy history				
No	Reference		Reference	
Yes, breast	0.41 (0.10–1.64)	0.21	0.48 (0.12–1.96)	0.31
Yes, colon and rectum	0.23 (0.06–0.94)	0.04	0.26 (0.06–1.07)	0.06
Yes, lung and bronchus	2.01 (1.02–3.95)	0.04	2.01 (1.01–4.00)	0.046
Yes, multiple	0.92 (0.62–1.37)	0.67	0.90 (0.60–1.35)	0.60
Yes, others[d]	0.48 (0.20–1.17)	0.11	0.50 (0.20–1.23)	0.13
Marital status				
Never married	Reference			
Married	0.99 (0.69–1.42)	0.96		
Others	0.88 (0.59–1.32)	0.54		
Income[e]				
<50,000$	Reference			
50,000–74,999$	0.93 (0.60–1.44)	0.75		
≥75,000$	0.89 (0.59–1.37)	0.61		

[a], others included Asian/Pacific Islander and American Indian/Alaska Native; [b], "Hispanic" indicated Americans from Latin America; [c], "PL-NOS" indicated pleural invasion but no other specific information about PL1/2 or PL3; [d], "Yes, others" indicated cancer history not including breast, lung and bronchus, colon and rectum, or multiple cancer history; [e], "Income" indicated median household income inflation adjusted to 2021. OR, odds ratio; CI, confidence interval.

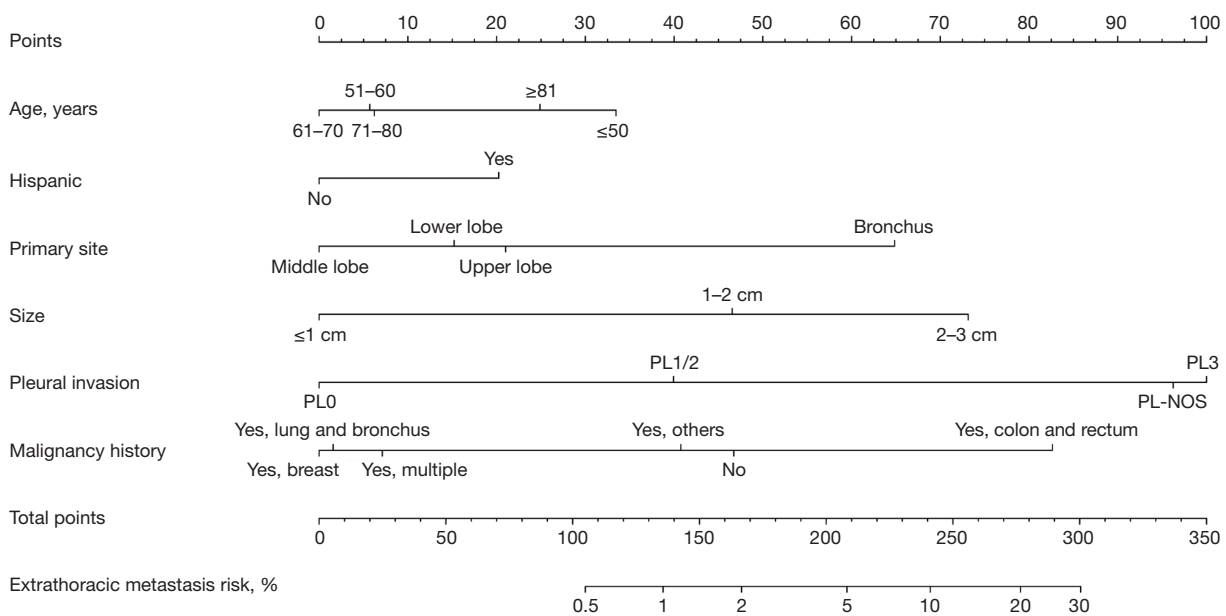

Figure 1 Nomogram of the developed model based on the independent risk factors.

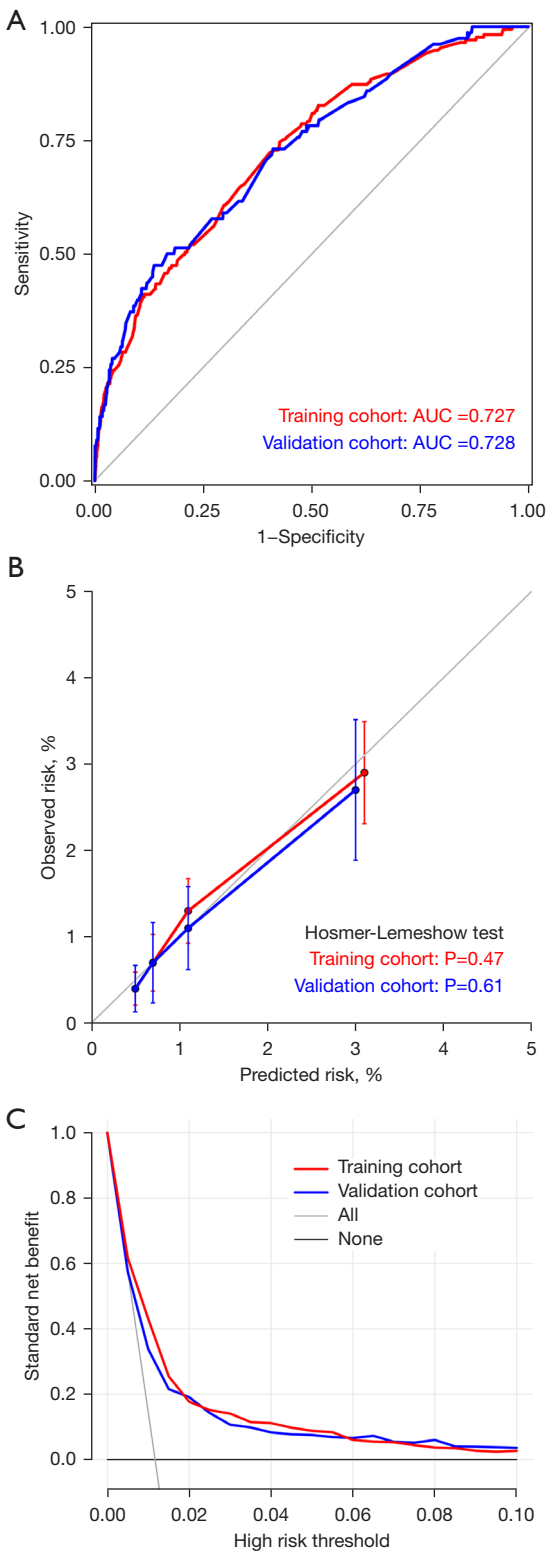

Figure 2 Assessment of the developed model. (A) ROC curves; (B) calibration curves; (C) decision curves. AUC, area under the curve; ROC, receiver operating characteristic.

different from that of early-stage patients. In this study, we identified the risk factors of extrathoracic metastasis and built a model to predict risk of extrathoracic metastasis at initial diagnosis in $T_{\leq 3cm}N_0$ patients. We found early-onset (≤50 years old) or late-onset (≥81 years old) of lung cancer, Hispanic, location of bronchus, larger tumor size, pleural invasion, and history of colorectal cancer were independent risk factors of extrathoracic metastasis. The predictive model based on the independent risk factors showed good performance in differentiating patients at different risk. A corresponding nomogram of the model was also developed.

In a study reported by Iijima *et al.*, the incidence of extrathoracic metastasis was 1% in stage IA NSCLC patients (5). In another study including stage IA lung cancer patients whose tumor size ≤2 cm, the authors reported that the incidence of extrathoracic metastasis was 6.31% (7). In our study, the incidence was 1.25%, which is more consistent with the result of Iijima *et al.* Blood vessels and lymph vessels are the two routes of distant metastasis of primary lung cancer. It was reported that intratumoral vascular invasion was found in 30.4–38.8% T_1N_0 NSCLC patients, and the intratumoral vascular invasion was a risk factor for prognosis (8,9). In the study by Shi *et al.*, 33.1% NSCLC patients with brain metastasis had N_0 disease (10). These evidences and our result indicated that extrathoracic metastasis is not rare in $T_{\leq 3cm}N_0$ patients, and appropriate strategy to screen for extrathoracic metastasis in those patients is needed.

In the study by Hu *et al.*, they built a model to predict extrathoracic metastasis, and the three main predictive factors were differentiation grade, histological subtype, and age (7). In the NCCN guideline, patients with a strong clinical suspicion of stage IA lung cancer do not require a biopsy before surgery (3), thus it might be difficult to get the differentiation grade and histological subtype information for those patients. Therefore, we did not analyze the different metastasis characteristics of different histological subtypes in this study. For the convenience of clinical practice, we only included baseline demographic information and image information which could be assessed at pretreatment evaluation, so our model could help physicians to predict the risk of extrathoracic metastasis before treatment even without the biopsy.

In our study, it was interesting that compared with aged 61–70 years old at initial diagnosis, early-onset (≤50 years old) and late-onset (≥81 years old) were both risk factors for extrathoracic metastasis. Studies have reported that early-onset lung cancer patients tend to have more stage

IV disease (11,12) and late onset has higher metastasis incidence (13). Our result is consistent with these studies. And we found that brain metastasis was less frequent than bone metastasis or liver metastasis in patients ≥81 years old, indicating that more attention could be paid to other sites except for brain when screening for distant metastasis in those patients.

It was reported that tumor-pleural relationship was associated with occult lymph node metastasis in stage IA adenocarcinoma (14). In our study, we found that pleural invasion was an independent risk factor for distant metastasis in $T_{\leq 3cm}N_0$ patients. These results indicated the important association of pleural invasion on the tumor progress. According to the 8th edition TNM system, tumor with visceral pleural invasion is classified as T2 and tumor with parietal pleural invasion was classified as T3, regardless of the tumor size. Previous studies have found that pleural signs on CT could help predict pleural invasion with good performance (15-17). Given that when evaluating $T_{\leq 3cm}N_0$ tumors before treatment without biopsy, the information a physician could collect is very limited, and pleural invasion is a significant message a physician could get from the pleural signs on CT, so we included $T_{\leq 3cm}N_0$ patients with pleural invasion into our study rather than only included stage IA patients.

To our best knowledge, our study is the first article taking into account the malignancy history when predicting extrathoracic metastasis at initial diagnosis. We found that patients with a history of colorectal cancer were at higher risk of extrathoracic metastasis. Although we only included primary lung cancer patients into our study, there was a chance that the tumor in the distant site might be a metastasis from the colorectal cancer rather than the lung cancer. However, based on reported findings, the most frequent metastasis sites of colorectal cancer were liver, peritoneum, and lung, but not bone or brain (18-20). In our study, the most frequent metastasis sites of patients with a history of colorectal cancer were bone and brain, so the chance mentioned above was possible but low. It was found that different driver mutations might be associated with different metastasis pattern (21,22). We assumed that lung cancer patients with a history of colorectal cancer and distant metastasis might have certain molecular pattern, and further studies are needed in the era of high-throughput sequencing.

Of noting, the application of this nomogram must be addressed to the situations in which the real access to advanced diagnostic technologies is difficult and must not replace the standard practice of whole-body examination (such as PET/CT) in the suspicion of lung cancer.

Though our model is more convenient and practical, there were still some limitations in our study. First, our study was retrospective and there might be selection bias in our study. Second, information such as smoking status, family history, and laboratory test result might help predict the extrathoracic metastasis, but we did not include it as SEER database did not collect the categories. Third, consolidation/tumor ratio of the tumor on the CT image might be related to lymph node metastasis (23), but we could not assess the effect of it on extrathoracic metastasis because we could not get access to this information. Forth, there might be a confounding effect resulting from the use of different examinations to detect metastasis, but as SEER database did not provide detailed information about the examinations each patient received, we could not assess the impact of different examinations on our model.

Conclusions

We found that extrathoracic metastasis at initial diagnosis in $T_{\leq 3cm}N_0$ lung cancer patients was not rare, and early-onset or late-onset of lung cancer, Hispanic, location of bronchus, larger tumor size, pleural invasion, and history of colorectal cancer were independent risk factors of extrathoracic metastasis. The model based on the independent risk factors showed good performance in predicting risk of extrathoracic metastasis at initial diagnosis in those patients.

Acknowledgments

We acknowledged the effort of the National Cancer Institute and the SEER Program tumor registries in the creation of the SEER database.

Funding: This work was supported by Sichuan Science and Technology Support Program (No. 2022NSFSC1590 to H.J.) and National Natural Science Foundation of China (No. 82102968 to J.Z.).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-338/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-338/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-338/coif). J.Z. reports receiving funding support from National Natural Science Foundation of China (No. 82102968). H.J. reports receiving funding support from Sichuan Science and Technology Support Program (No. 2022NSFSC1590). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Wang T, Wang Z, Zhou J, Jie H, Liao H, Mei J, Pu Q, Liu L. A nomogram predicting the risk of extrathoracic metastasis at initial diagnosis of $T_{\leq 3cm}N_0$ lung cancer. Transl Lung Cancer Res 2024;13(8):1841-1850. doi: 10.21037/tlcr-24-338