Risk factors for brain metastases in locally advanced non-small cell lung cancer patients treated with radical radiotherapy

Xiaohong Xu[1#], Gang Chen[1#], Shaonan Fan[1#], Qi Zhang[1], Wenhan Huang[1], Jingyao Chen[2], Weixing Ji[1], Jintao Ma[1], Jian He[1]

[1]Department of Radiation Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Contributions: (I) Conception and design: J He, X Xu, G Chen, S Fan; (II) Administrative support: J He, G Chen; (III) Provision of study materials or patients: J He, G Chen, W Ji; (IV) Collection and assembly of data: X Xu, S Fan, Q Zhang, W Huang, J Chen, J Ma; (V) Data analysis and interpretation: X Xu, S Fan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jian He, MD, PhD. Department of Radiation Oncology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China. Email: hejian62@163.com.

Background: Brain metastases (BM) happen frequently in lung cancer patients and lead to a poor prognosis as well as a lower quality of life. The aim of this study was to identify risk factors for BM in locally advanced non-small cell lung cancer (LA-NSCLC) patients receiving radical radiotherapy, which will be useful for selecting appropriate patient population for further intervention and future trial design.

Methods: This was a retrospective cohort study. Patients with inoperable stage IIB–IIIC NSCLC were treated consecutively with definitive thoracic radiotherapy from January 2018 to December 2021, and were retrospectively reviewed and enrolled. Patients with various clinical variables were analyzed to clarify their impact on BM with competing risk models by Fine and Gray.

Results: A total of 134 patients were enrolled in this study. The median follow-up for all patients was 37 months [95% confidence interval (CI): 30.5–43.5 months]. BM occurred in 25 patients at the time of analysis. The 1-year and 3-year cumulative BM incidence were 10.5% and 19.9%, respectively. Patients with BM had worse overall survival than those without BM [stratified hazard ratio (HR) for death: 2.83; 95% CI:1.31–6.11; P<0.001]. Based on univariate analyses, non-squamous cell carcinoma (non-SCC), biological effective dose (BED) and planning target volume (PTV) were used as input variables in multivariable analysis (P<0.01). According to multivariate analysis, non-SCC (P<0.001; HR: 6.08; 95% CI: 2.26–16.37), BED <72 Gy (P=0.017; HR: 2.81; 95% CI: 1.20–6.57), and PTV >157.73 cm³ (P=0.043; HR: 2.56; 95% CI: 1.03–6.35) were independent risk factors for BM. In subgroup analysis of adenocarcinoma with known epidermal growth factor receptor (*EGFR*) mutation status, PTV >157.73 cm³ and positive *EGFR* mutation were independent predictors for BM.

Conclusions: In this retrospective study, we found that BED <72 Gy and PTV >157.73 cm³ were significantly associated with BM development and we validated that non-SCC and positive *EGFR* mutation were risk factors for BM. More research is required to screen the high-risk patient population.

Keywords: Non-small cell lung cancer (NSCLC); lung cancer; brain metastases (BM); risk factors

Introduction

Lung cancer remains the leading cause of cancer-related mortality all over the world (1). The brain is one of the most frequent sites for lung cancer patients to develop metastases, and this prevalence has been rising over the past years because of wide application of brain imaging in initial staging procedures, and improved survival owing to advances in therapeutic approaches (2,3). Patients with brain metastases (BM) typically have declining quality of life and a poor prognosis, with a median overall survival (OS) of 12 months (4,5). Prophylactic cranial irradiation (PCI) has been used to reduce the incidence of BM in small cell lung cancer (SCLC) patients. However, it remains controversial for non-SCLC (NSCLC) patients, primarily because the decreased incidence of BM obtained with PCI does not provide a survival benefit (6-9). Appropriate populations for additional care need to be identified. Inoperable locally advanced NSCLC (LA-NSCLC) patients often have a large disease burden and develop BM frequently. However, risk factors in this patient population, particularly those linked to radiation therapy, have not been thoroughly investigated. This study aimed to identify risk factors associated with BM in patients with unresectable LA-NSCLC receiving radical radiotherapy, which may be helpful in selecting the appropriate patient population that would benefit from further prevention strategies such as PCI and imaging

monitoring. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1435/rc).

Methods

Patient selection

This was a retrospective cohort study. Patients with LA-NSCLC who were treated with radical radiotherapy at Fudan University, Zhongshan Hospital from January 2018 to December 2021 were included. The survival data, BM outcome, patient-related factors and treatment-related factors were collected. The criteria for inclusion were as follows: (I) NSCLC confirmed by histology (World Health Organization) (10); (II) complete examinations, especially brain magnetic resonance imaging (MRI) or computed tomography (CT) with contrast (if MRI was contraindicated), were performed prior to treatment, and the disease was diagnosed as stage IIB–IIIC [American Joint Committee on Cancer (AJCC) 8th] (11); (III) the total radiation dose was no less than 50 Gy with or without the combination of chemotherapy; (IV) patients followed up for at least 12 months unless they died before that; (V) patients with available complete medical records. The criteria for exclusion were as follows: (I) patients who were treated with PCI following radical thoracic radiotherapy; (II) patients with a diagnosis of malignant tumors within two years before LA-NSCLC; (III) other antitumor therapy was given prior to radiotherapy or chemoradiotherapy; (IV) patients whose radiotherapy plan was not performed in full. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhongshan Hospital (No. 2023-246), and the requirement of informed consent was waived since this was a retrospective analysis.

Chemoradiotherapy

Patients who received chemotherapy underwent at least two cycles of platinum-based doublet treatment. Radiotherapy was implemented either by intensity modulated radiotherapy (IMRT) or tomography (TOMO). The target volumes were defined in accordance with the European Society for Therapeutic Radiology and Oncology Advisory Committee in Radiation Oncology Practice (ESTRO-ACROP) guidelines published in 2018 (12). For patients who received chemotherapy before radiotherapy,

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Highlight box

Key findings

- Non-squamous cell carcinoma (non-SCC), biological effective dose (BED) <72 Gy and planning target volume (PTV) >157.73 cm^3 were significantly associated with brain metastases (BM) development in locally advanced non-small cell lung cancer (LA-NSCLC). Positive epidermal growth factor receptor (*EGFR*) mutation was a risk factor for BM in lung adenocarcinoma with known *EGFR* mutation status.

What is known and what is new?

- BM happens frequently in LA-NSCLC patients and leads to poor prognosis. Predictive factors reported previously include histology, age, *EGFR* mutation status, serum tumor marker level, etc.
- This retrospective observational study is the first to demonstrate the predictive value of BED and PTV.

What is the implication, and what should change now?

- Patients with non-SCC, BED <72 Gy, PTV >157.73 cm^3 or positive *EGFR* mutation may require additional attention. Our work provides information for future trial design for BM prevention.

the residual primary tumor volume was contoured as gross tumor volume (GTV), and clinical target volume (CTV) included initially involved lymph node stations. Planning target volume (PTV) was created by expanding CTV by 6 mm axially and 9 mm cranio-caudally.

Follow-up

The follow-up evaluations, including history, physical examination, and radiologic examinations, were performed every 3 months for the first two years following the treatment, then every 6 months for the next two years, and then once a year. Brain imaging was not routinely performed during follow-up and was only done when BM or a recurrence was suspected. Disease progression and failure sites were identified by radiologic examination. Cytological or histological confirmation of progressive disease was not obligatory, but only in cases in which it was suspected but not verified by imaging. The last follow-up was in May 2023.

Variables

Progression-free survival (PFS) was defined as time from diagnosis to disease progression or death; OS was defined as the time from diagnosis to death. Patient-related variables were age, sex, and smoking history. Tumor-related variables included pathology, epidermal growth factor receptor (EGFR) mutation status, T-stage, N-stage, tumor-node-metastasis (TNM) stage, and serum levels of tumor markers [carcinoembryonic antigen (CEA), cytokeratin fragment antigen 21-1 (CYFRA21-1), neuron-specific enolase (NSE), and squamous cell carcinoma antigen (SCC-Ag)] prior to the treatment. Treatment-related variables were radiotherapy technology, biological effective dose (BED), PTV, chemotherapy, and consolidation immune checkpoint inhibitors (ICI). *EGFR* mutation status was analyzed through a polymerase chain reaction-based assay at the time of first diagnosis. The histologic subtypes and *EGFR* mutation status were retrospectively collected from pathological report. Staging was based on the 8th version of the AJCC TNM staging system. The cutoff values for the serum tumor markers CEA, CYFRA21-1, NSE, and SCC-Ag, respectively, were 5, 3.3, 16.3, and 3.0 ng/mL, according to the standards of our institute. Radiotherapy technology was IMRT or TOMO. We chose 72 Gy as cutoff because it is BED of the standard conventional fractionated radiotherapy regimen (60 Gy in 30 fractions).

Patients with consolidation immunotherapy were those who received at least one cycle of anti-programmed cell death 1 (PD-1) or anti-PD-ligand (L)1 treatment. The cutoff value of PTV for BM was determined by survival receiver operating characteristic (ROC) curve analysis.

Statistical analyses

The OS and PFS were estimated using the Kaplan-Meier method. Log-rank test was used to test the difference in OS between groups that with BM and the group without BM. Cox regression has often been used in most previous studies for statistical analysis of BM. However, it may underestimate the risk of BM of patients who arrive at the competing event first. We used competing risk analysis in this study so that the competing risk of death caused by other reasons was considered. Distribution of cumulative incidence of BM was estimated using the competing-risks regression method by Fine and Gray in the overall population and in various groups. The ending event was the occurrence of BM. Death without the development of BM was regarded as a competing event. Patients were censored at the last follow-up date if they were lost to follow-up or were alive without development of the ending event or the competing event. Risk factors for BM were analyzed with the univariate and multivariate competing-risks regression method. Risk factors with a P value <0.1 in univariate analysis were included in the multivariate competing-risks regression analysis.

Statistical analyses were performed with IBM SPSS 26 and R version 4.2.1 (http://www.r-project.org/). All statistical tests were bilateral tests, and P<0.05 was considered statistically significant.

Results

Baseline characteristics

From January 2018 to December 2021, a total of 161 patients with LA-NSCLC were treated consecutively by radical radiotherapy. Twenty-seven patients were excluded because of the following reasons: lost to follow-up within 12 months after diagnosis (n=9), immunotherapy in combination of chemotherapy before radiotherapy (n=1), radiotherapy not completed (n=1), and incomplete records (n=16). A hundred and thirty-four patients were included in the final study population (*Figure 1*). Baseline characteristics are shown in *Table 1*. The median age was 65 years (range, 41–82 years).
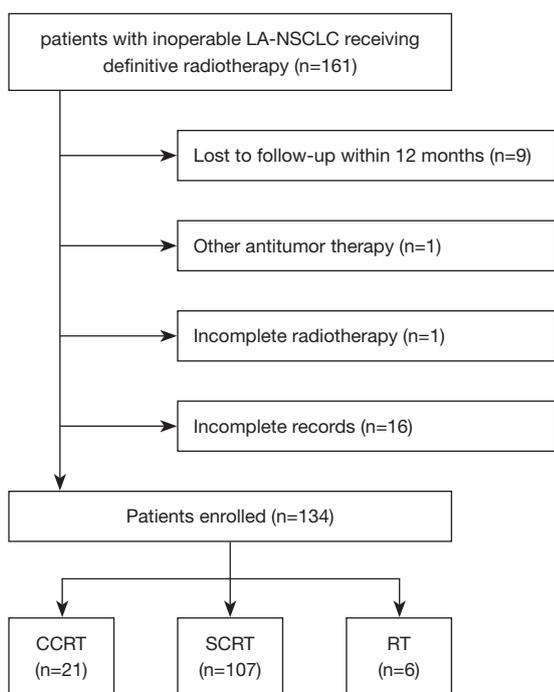
Figure 1 Flow chart of patient enrollment. LA-NSCLC, locally advanced non-small cell lung cancer; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; RT, radiotherapy alone.

Most patients were male (85%) and had smoking history (66%). Fifty patients were diagnosed with adenocarcinoma, while 70 patients as squamous cell carcinoma (SCC). Of 50 patients with adenocarcinoma, 48 patients were tested for *EGFR* mutation with 17 being *EGFR* mutation positive. Exon 19 deletion and L858R point mutation were detected in 8 and 7 patients, respectively. Uncommon mutations were detected in 2 patients (1 with exon 20 insertion and 1 with G719X). Most patients were treated with sequential chemotherapy (107/134), while concurrent chemoradiotherapy was implemented in 21 patients. Six patients received radiotherapy alone. The radiotherapy was delivered with IMRT and helical TOMO in 89 patients and 45 patients, respectively. The median total dose was 60.00 Gy (range, 50.00–64.80 Gy in 20–30 fractions), the median dose per fraction was 2.4 Gy (range, 2.0–3.1 Gy), and the median BED was 74.40 Gy (range, 60.00–81.22 Gy). Thirty patients received BED of less than 72.00 Gy due to normal tissue limits or poor lung function. Following chemoradiotherapy, consolidation ICI were applied to 17 patients.

Survival and failure pattern

The median follow-up for all patients was 37 months [95% confidence interval (CI): 30.5–43.5 months]. The 1- and 3-year OS rates for all patients were 90.2% (95% CI: 85.3–95.4%) and 57.9% (95% CI: 49.2–68.2%), respectively. The median PFS for all patients was 17.0 months (95% CI: 12.9–21.1 months). The 1-year and 3-year PFS rates were 59.7% (95% CI: 52.0–68.6%) and 33.6% (95% CI: 26.1–43.3%), respectively. Eighty-eight patients in total experienced disease progression; 42 patients only experienced local-regional recurrence, 33 patients only experienced distant metastases, and 13 patents experienced local-regional recurrence along with distant metastases as their first sites of relapse.

BM

Twenty-five patients (18.7%) developed BM, and 19 of them experienced BM as the first site of failure, including 11 patients who experienced BM only, and 8 patients who experienced BM together with extracranial disease progression (*Figure 2A*). Only two patients experienced local-regional failure and four patients experienced extracranial metastases before BM developed. The 1- and 3-year cumulative incidence of BM were 10.5% (95% CI: 5.3–15.7%) and 19.9% (95% CI: 12.8–27.0%), respectively. Patients with BM had worse OS than those who were not [stratified hazard ratio (HR) for death: 2.83; 95% CI: 1.31–6.11; P<0.001] (*Figure 2B*). The 1-year OS rate in the non-BM group and BM group was 92.7% (95% CI: 87.9–97.7%) and 79.5% (95% CI: 64.9–97.3%), and the 3-year OS rate was 66.0% (95% CI: 56.8–76.7%) and 26.0% (95% CI: 12.4–54.3%), respectively.

The cumulative incidence of BM in various subgroups was analyzed. Patients with non-SCC had a higher cumulative BM incidence (P<0.001) (shown in *Figure 3A*). According to survival ROC curve analysis, the cut-off value of PTV for BM was 157.73 cm^3 (shown in Figure S1). The cumulative incidence of BM of patients with BED less than 72 Gy (P=0.065) or PTV >157.73 cm^3 (P=0.074) tended to increase although the difference was not significant (shown in *Figure 3B,3C*).

Risk factors for BM

According to the univariate analysis, histology, BED, and PTV were included in the multivariate analysis (P<0.01). In

Table 1 Baseline characteristics

Variables	N [%]
Age, years	
≤60	38 [28]
>60	96 [72]
Sex	
Male	114 [85]
Female	20 [15]
Smoking history	
No	46 [34]
Yes	88 [66]
PS	
0	98 [73]
1	30 [22]
2	6 [4]
Pathology	
LUAD	50 [37]
SCC	70 [52]
Other/NOS	14 [10]
EGFR mutation	
Exon 19 deletion	8 [6]
L858R	7 [5]
Uncommon	2 [1]
Negative	31 [23]
Unknown	86 [64]
T-stage	
T1	19 [14]
T2	43 [32]
T3	21 [16]
T4	51 [38]
N-stage	
N0	7 [5]
N1	21 [16]
N2	57 [43]
N3	49 [37]
TNM stage	
IIB	3 [2]
IIIA	53 [40]
IIIB	57 [43]
IIIC	21 [16]

Table 1 (*continued*)

Table 1 (*continued*)

Variables	N [%]
CEA	
Normal	88 [66]
Elevated	46 [34]
CYFRA21-1	
Normal	52 [39]
Elevated	82 [61]
NSE	
Normal	87 [65]
Elevated	47 [35]
SCC-Ag	
Normal	109 [81]
Elevated	25 [19]
RT technology	
IMRT	89 [66]
TOMO	45 [34]
BED, Gy	
60.00–<72.00	30 [22]
≥72.00	104 [78]
Chemotherapy	
Concurrent	21 [16]
Sequent	107 [80]
None	6 [4]
Consolidation ICI	
No	117 [87]
Yes	17 [13]

PS, performance status; LUAD, adenocarcinoma; SCC, squamous cell carcinoma; NOS, not otherwise specified; *EGFR*, epidermal growth factor receptor gene; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; SCC-Ag, squamous cell carcinoma antigen; RT, radiotherapy; IMRT, intensity modulated radiation therapy; TOMO, helical tomotherapy; BED, biological effective dose; ICI, immune checkpoint inhibitors.

multivariate analysis, non-SCC (P<0.001; HR: 6.08; 95% CI: 2.26–16.37), BED <72 Gy (P=0.017; HR: 2.81; 95% CI: 1.20–6.57), and PTV >157.73 cm^3 (P=0.043; HR: 2.56; 95% CI: 1.03–6.35) were independent predictors for BM (*Table 2*).

Considering that BED of 60–<72 Gy is a suboptimal dose for radical treatment, a subgroup analysis was performed for patients who received BED of 72 Gy or higher (n=104). Sixteen patients developed BM. Pathology and PTV were

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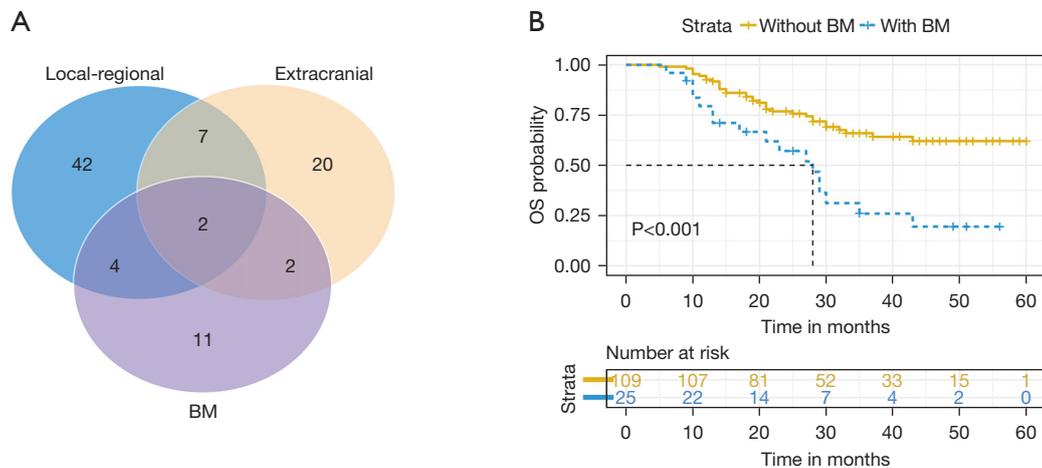
Figure 2 First failure pattern (A) and OS in patients with and without brain metastases (B). BM, brain metastases; local-regional, local-regional relapse; extracranial, extracranial metastases; OS, overall survival.
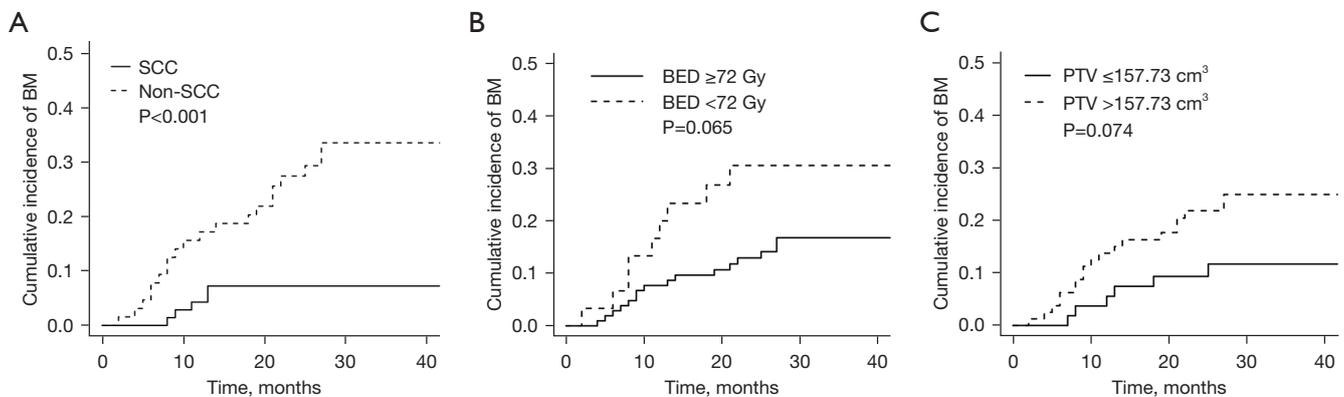
Figure 3 The cumulative incidence of BM in various groups. BM, brain metastases; SCC, squamous cell carcinoma; BED, biological effective dose; PTV, planning target volume.

used as input variables in multivariable analysis based on univariate analysis. The multivariable analysis showed that non-SCC (P=0.006; HR: 8.55; 95% CI: 1.87–39.10) and PTV >157.73 cm³ (P=0.044; HR: 3.70; 95% CI: 1.04–13.20) remained as the risk factors for BM (*Table 3*).

We also performed a subgroup analysis in patients with adenocarcinoma with known *EGFR* mutation status to determine the role of *EGFR* mutation status in BM development. Of the 48 patients whose *EGFR* mutation status was known, 16 experienced BM. Based on univariate analysis, *EGFR* mutation status and PTV were used as input variables in multivariable analysis. Positive *EGFR* mutation (P=0.049; HR: 2.65; 95% CI: 1.00–7.01) and PTV >157.73 cm³ (P=0.021; HR: 4.10; 95% CI: 1.24–13.50) were found significantly

associated with BM in multivariate analysis (*Table 4*).

PTV and survival outcomes

To further explore the correlation between PTV and prognosis, we analyzed the OS and PFS of patients with PTV >157.73 cm³ (PTV-high) and PTV ≤157.73 cm³ (PTV-low) and found patients in the PTV-high group had poorer PFS (P=0.001; HR: 2.05; 95% CI: 1.35–3.12) and OS (P=0.002; HR: 2.60; 95% CI: 1.50–4.52) (*Figure 4*).

Discussion

PCI and MRI surveillance are two management strategies

Table 2 Univariate and multivariate competing risk model analyses of brain metastases in all patients

Variables	Univariate competing risk model			Multivariate competing risk model		
	HR	95% CI	P value	HR	95% CI	P value
Age, years						
≤60	1					
>60	0.55	0.25–1.22	0.140			
Sex						
Male	1					
Female	1.40	0.55–3.56	0.480			
Smoking history						
No	1					
Yes	1.17	0.51–2.66	0.710			
Pathology						
SCC	1			1		
Non-SCC	4.93	1.85–13.10	0.001	6.08	2.26–16.37	<0.001
T-stage						
T1–2	1					
T3–4	0.73	0.53–2.49	0.730			
N-stage						
N0–2	1					
N3	1.17	0.53–2.59	0.700			
TNM stage						
IIB–IIIA	1					
IIIB–IIIC	1.63	0.72–3.72	0.240			
CEA						
Normal	1					
Elevated	1.26	0.57–2.77	0.570			
CYFRA21-1						
Normal	1					
Elevated	1.17	0.53–2.62	0.690			
NSE						
Normal	1					
Elevated	1.82	0.83–3.99	0.130			
SCC-Ag						
Normal	1					
Elevated	0.83	0.29–2.35	0.730			

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate competing risk model			Multivariate competing risk model		
	HR	95% CI	P value	HR	95% CI	P value
RT technology						
IMRT	1					
TOMO	0.63	0.25–1.56	0.310			
BED, Gy						
≥72.00	1			1		
60.00–<72.00	2.16	0.96–4.87	0.063	2.81	1.20–6.57	0.017
PTV, cm³						
≤157.73	1			1		
>157.73	2.26	0.91–5.57	0.078	2.56	1.03–6.35	0.043
Chemotherapy						
Concurrent	1					
Sequent	0.63	0.23–1.76	0.380			
None	0.58	0.07–4.76	0.610			
Consolidation ICI						
No	1					
Yes	0.27	0.04–2.09	0.210			

HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; SCC-Ag, squamous cell carcinoma antigen; RT, radiotherapy; IMRT, intensity modulated radiation therapy; TOMO, helical tomotherapy; BED, biological effective dose; PTV, planning target volume; ICI, immune checkpoint inhibitors.

for BM, but both have not been recognized as standards of care for LA-NSCLC (13). The lack of an OS benefit from PCI in recent studies is due to various reasons, such as slow accrual, low statistical power, most patients getting extracranial metastases, relatively low BM incidence in NSCLC compared to SCLC, and treatment of BM in control groups which also prolongs OS (14). However, in RTOG 0214 trial, the nonsurgical group showed a higher incidence of BM compared to the surgery group, probably owing to the higher disease burden of nonsurgical patients, and PCI was associated with increased OS and reduced BM incidence according to the multivariate analysis in nonsurgical group (9). These findings suggest that patients with inoperable LA-NSCLC may be at higher risk of BM and likely to benefit from BM prevention; therefore, further

Table 3 Univariate and multivariate competing risk model analyses of brain metastases in subgroup of BED ≥72 Gy (n=104)

Variables	Univariate competing risk model			Multivariate competing risk model		
	HR	95% CI	P value	HR	95% CI	P value
Pathology						
SCC	1			1		
Non-SCC	7.57	1.71–33.50	0.008	8.55	1.87–39.10	0.006
PTV, cm³						
≤153.73	1			1		
>153.73	3.04	0.88–10.50	0.079	3.70	1.04–13.20	0.044

BED, biological effective dose; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; PTV, planning target volume.

Table 4 Univariate and multivariate competing risk model analyses of brain metastases in subgroup of adenocarcinoma with known *EGFR* mutation status (n=48)

Variables	Univariate competing risk model			Multivariate competing risk model		
	HR	95% CI	P value	HR	95% CI	P value
EGFR mutation status						
Negative	1			1		
Positive	2.78	1.06–7.26	0.038	2.65	1.00–7.01	0.049
PTV, cm³						
≤153.73	1			1		
>153.73	4.26	1.27–14.20	0.019	4.10	1.24–13.50	0.021

HR, hazard ratio; CI, confidence interval; *EGFR*, epidermal growth factor receptor gene; PTV, planning target volume.
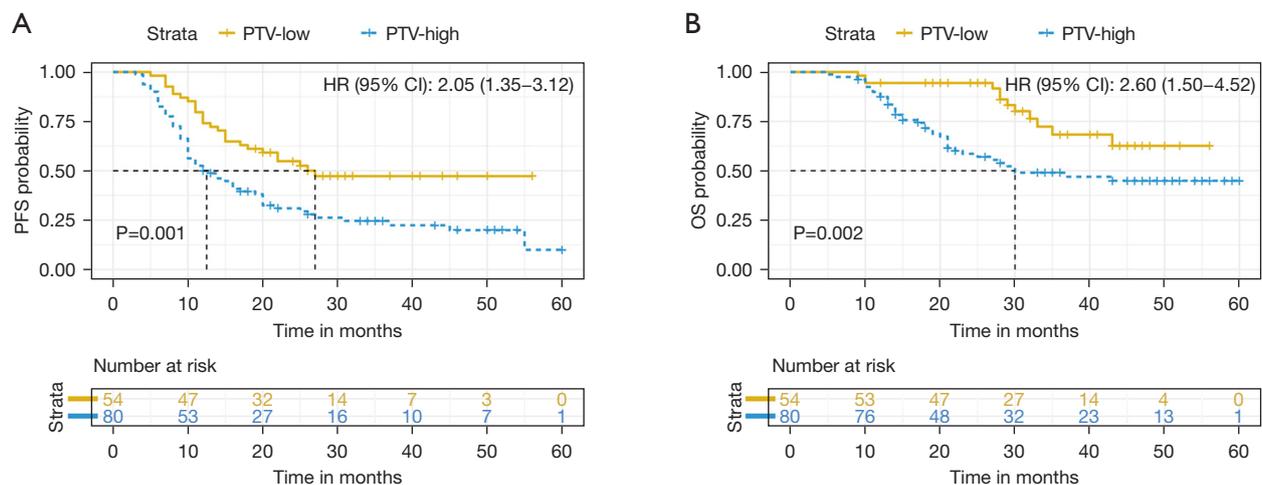
Figure 4 PFS (A) and OS (B) in patients with PTV-high (PTV >153.73 cm³) and PTV-low (PTV ≤153.73 cm³). PFS, progression-free survival; OS, overall survival; PTV, planning target volume; HR, hazard ratio; CI, confidence interval.

screening of high-risk patients in this subgroup is needed. As a result, we concentrated on BM risk factors for LA-NSCLC patients who underwent radical radiotherapy, a field in which there is relatively little research. In our study, the OS of patients in our study who experienced BM was significantly worse than that of patients who did not, highlighting the importance of BM prevention. We found that non-SCC, BED <72 Gy and PTV >153.73 cm³ were predictive factors for BM, while positive *EGFR* mutation and PTV >153.73 cm³ were associated with occurrence of BM for patients with adenocarcinoma with known *EGFR* mutation status.

It has been widely reported that patients with non-SCC or adenocarcinoma had a higher risk for developing BM than patients with SCC (9,15-18). We confirmed that non-SCC was an independent predictive factor for BM in our study (P<0.001; HR: 6.08; 95% CI: 2.26–16.37). A possible explanation is that the major histology of non-SCC is adenocarcinoma and the property of invasive growth of adenocarcinoma increases its likelihood to migrate to the brain through blood vessels. Besides, the highly aggressive micropapillary subtype in adenocarcinoma with strong proliferation and migration ability was found to be associated with an increased BM risk (19,20). Recently,

positive *EGFR* mutation in NSCLC patients was reported to have an impact on BM incidence in several studies (21-23). We also performed subgroup analysis in adenocarcinoma patients with known *EGFR* mutation status in our study and similar results were found. Even though the correlation between positive *EGFR* mutation and BM was observed, the underlying mechanism is not very clear. Positive *EGFR* mutation may be involved in the occurrence of BM or prolong survival, leading to an increased risk of BM. Li *et al.* found overexpression of *WNT5A*, which belongs to Wnt family and exerts a critical role in cancer progression, was associated with less BM in *EGFR*-mutant NSCLC while the activation of ERK1/2-E2F1-WNT5A pathway contributed to the development of BM (24).

In 2014, Ji *et al.* analyzed 346 patients with stage III NSCLC treated with conventional fractionated thoracic radiotherapy, showing that patients treated with a radiation dose of 61–72 Gy had a lower BM incidence than patients treated with 60 and 50–59 Gy, yet the difference was not significant (25). In our study, patients treated with various total doses and fractionations were included, therefore we chose to analyze BED rather than the total dose. We found a BED <72 Gy was significantly associated with an increased BM incidence (HR: 2.81; 95% CI: 1.20–6.57; P=0.017). The possible explanation is that these patients received insufficient radiation doses, which raised their likelihood of developing BM. Based on our findings, additional care should be given to patients receiving suboptimal BED due to poor lung function or organ at risk limitation.

Increasing tumor volumes have long been thought to indicate a poor prognosis. Previous studies found that PTV and GTV had an impact on prognosis of inoperable LA-NSCLC patients (26-29). There were also reports that primary tumor size was associated with BM incidence (30-32). However, no significant association between GTV or PTV and risk for BM had been reported. Ji *et al.* reported that patients with GTV of 65.45 cm^3 or more had higher BM incidence (3-year BM rate, 31.4% *vs.* 26.0%), but the difference was not significant (25). Zeng *et al.* analyzed 327 patients with stage III NSCLC treated with radical chemoradiotherapy and found no significant association between GTV and BM risk (33). We analyzed the impact of PTV on BM as an indicator of tumor burden, which considered the primary tumor volume, the CTV, and the safety margin. We found that patients with PTV >157.73 cm^3 had significantly higher BM incidence and worse OS and PFS. Our results validated the argument that high-volume

tumors are more likely to develop BM and suggest PTV could be considered as a stratification factor in clinical trials of BM prevention for unresectable LA-NSCLC in the future.

We failed to demonstrate the influence of chemotherapy on BM risk. Similar results have been reported previously. There was no significant association between chemoradiotherapy regimen (concurrent, sequential, or no chemotherapy) and BM risk in Ji's study (25). Hendriks *et al.* analyzed 838 patients in a retrospective study and found that treatment schedule (concurrent or sequential chemoradiotherapy) did not influence symptomatic BM development, and they believed that it was possible that patients already had subclinical BM at initial staging and that concurrent or sequential chemoradiotherapy was just as effective in eliminating these tumor deposits (17). This rationale was reasonable considering that concurrent chemoradiotherapy mainly enhances locoregional control compared to sequential chemoradiotherapy (34). This reason also applies to explain why the addition of chemotherapy cannot reduce BM incidence given that chemotherapy drugs have difficulty penetrating the blood-brain barrier. However, in our study, most patients were treated with sequential chemoradiotherapy, and the number of patients receiving concurrent chemoradiotherapy or radiotherapy alone is considerably small, which seems to be a more possible explanation for the results in our study. Although it has been proven to be inferior to concurrent chemotherapy (34), sequential chemoradiotherapy still represents an important treatment modality in China. One important factor that results in this phenomenon is the inherent belief that intensifying both radiotherapy and concurrent chemotherapy may result in excessive toxicity or incomplete treatment, and that sequential chemoradiotherapy may be more appropriate for fragile patients who are less tolerant of concurrent chemoradiotherapy (35).

In the PACIFC study, patients treated with consolidation durvalumab had improved PFS and OS as well as lower BM incidence than patients in the placebo group (6.3% *vs.* 11.8%) (36,37). However, due to its expensive price, consolidation immunotherapy has not been widely used in clinical practice. In our study, only 17 patients were treated with consolidation ICI, and it showed a trend of positive impact on a lower BM risk, but no significant difference was found. Given the small number of patients receiving consolidation immunotherapy, this result should be interpreted with caution. More studies are needed to investigate the role of ICI in preventing BM development.

Our study has several limitations. First, this is a

retrospective study with a relatively small sample size. Second, since brain imaging scans were not routinely performed but only when BM or recurrence was suspected, asymptomatic BM may have been neglected, and the time and incidence of BM may have been underestimated. Third, more than half of the patients with BM had preceding or concurrent extracranial disease progression, which may have been the source of BM. Considering the small number of patients who developed BM as the first and only site of relapse and that a subset of them may also have undetected extracranial progression, additional analyses of these patients were not done. What is more, for the six patients who experienced extracranial relapse before BM, subsequent treatment may also affect the development of BM. However, this impact was uncertain due to incomplete detailed data on subsequent therapy in our study. Finally, various chemotherapy regimens, radiation doses and fractionations caused heterogeneity in treatment. Well-designed prospective trials with a larger sample size are needed to validate our results.

Conclusions

In this retrospective study, non-SCC, BED less than 72 Gy, and PTV >157.73 cm^3 were significantly associated with increased BM risk, providing information for clinical decision and future trial design. In the subgroup of adenocarcinoma with known *EGFR* mutation status, PTV >157.73 cm^3 and positive *EGFR* mutation were predictors for occurrence of BM. More research is required to screen appropriate patient population that can benefit from further intervention, and to optimize the management strategies for BM in LA-NSCLC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1435/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1435/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1435/coif). The 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). The study was approved by the Ethics Committee of Zhongshan Hospital (No. 2023-246), and the requirement of informed consent was waived since this was a retrospective analysis.

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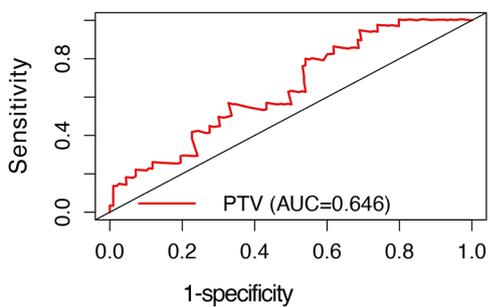
Figure S1 Survival ROC curve analysis for optimal cut-off value of PTV.