Original Article

Prognostic significance of bone metastasis and clinical value of bone radiotherapy in metastatic non-small cell lung cancer receiving PD-1/PD-L1 inhibitors: results from a multicenter, prospective, observational study

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Background: Bone metastasis (BoM) is a prevalent occurrence in patients with non-small cell lung cancer (NSCLC), significantly impacting prognosis and diminishing both survival rates and patients' quality of life. More and more studies have demonstrated that immunotherapy can improve the prognosis of NSCLC patients with bone metastases. Previous investigations pertaining to BoM in NSCLC have generally suffered from small sample sizes, absence of propensity score matching (PSM) to equate baseline characteristics, and an omission of the examination of patterns of treatment failure. This study aims to evaluate the prognostic significance of BoM and potential clinical value of bone radiation in metastatic NSCLC patients receiving immunotherapy.

Methods: Metastatic NSCLC patients receiving programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors from three academic centers were enrolled in a prospective, observational trial (https://clinicaltrials.gov/study/NCT04766515) and those with measurable disease and adequate follow-up were retrospectively reviewed. Propensity score matched (PSM) patients with and without BoM were included in this study. Treatment efficacy, pattern of failure and clinical value of bone radiotherapy were extensively evaluated.

Results: A total of 544 out of 1,451 immunotherapy-treated NSCLC patients were included after PSM, including 272 with BoM and 272 without. Patients with baseline BoM had a median progression-free survival (PFS) of 7.8 months [95% confidence interval (CI): 7.0–8.7], lower than those without it (9.5 months; 95% CI: 8.9–10.0) (P<0.001). Patients with baseline BoM had a median overall survival (OS) of 14.5 months (95% CI: 12.6–16.4), lower than those without 27.6 months (95% CI: 25.1–30.1) (P<0.001). Patients with BoM also had lower objective response rate than those without it (11.1% *vs.* 15.8%, P<0.001). Initial disease progression in the bone was more common in those with BoM (56.5%) compared to those without it (31.7%) (P<0.001). Meanwhile, among patients with BoM, no significant difference of PFS was found between those

receiving bone radiation or not, possibly due to a dominant use of palliative radiotherapy.

Conclusions: Baseline BoM correlated with worse prognosis and palliative bone radiation did not improve PFS in metastatic NSCLC patients receiving PD-1/PD-L1 inhibitors.

Keywords: Non-small cell lung cancer (NSCLC); bone metastasis (BoM); programmed cell death protein 1/programmed cell death-ligand 1 inhibitors (PD-1/PD-L1 inhibitors); bone radiotherapy; progression-free survival (PFS)

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Introduction

Lung cancer remains the leading cause of cancer-related death and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases. The emergence of immunotherapy has brought new hope to patients with advanced NSCLC (1) and incorporating programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors with conventional systemic therapy has dramatically improved treatment efficacy and patient's survival (2). For patients with PD-L1 positive untreated metastatic NSCLC, PD-1/PD-L1 inhibitor monotherapy was demonstrated to be associated with prolonged overall survival (OS) and less toxicities than conventional chemotherapy (3-5). Meanwhile, combining PD-1/PD-L1 inhibitors with chemotherapy significantly improved patient's long-term survival in treatment naive advanced NSCLC, regardless of PD-L1 expression (6-9). Based on the recently updated survival outcomes from the Keynote-189 and Keynote-407 studies, the 5-year OS rate among those treated with first-line pembrolizumab and chemotherapy reached about 20% (10,11).

Approximately 20–30% of patients with NSCLC present with bone metastases at diagnosis, and 35–60% will develop them during their disease course (12). Bone metastases stemming from solid tumors can substantially augment bone resorption, resulting in skeletal-related events (SREs), thereby compromising the physical and psychological quality of life to varying degrees (13). Moreover, a mounting body of evidence underscores the pivotal role of BoM in the distal prognosis associated with immunotherapy (14-16). A retrospective study encompassing 330 NSCLC patients subjected to immune checkpoint inhibitor (ICI) treatment revealed that patients harboring baseline bone metastases exhibited shorter survival durations in comparison to those without bone metastases, with a median OS of 5.9 months [95% confidence interval (CI), 4.2–7.8] versus 13.4 months (95% CI, 10.8–17.0; P<0.001) (17). Previous investigations pertaining to BoM in NSCLC have generally suffered from small sample sizes, absence of propensity score matching (PSM) to equate baseline characteristics, and an omission of the examination of patterns of treatment failure. Therefore, further research endeavors are warranted to address this issue comprehensively.

Palliative radiotherapy is frequently mandated for patients afflicted with bone metastases. The clinical value of bone radiotherapy remains controversial. Recently,

Highlight box

Key findings

- Baseline bone metastasis (BoM) correlated with worse prognosis in metastatic non-small cell lung cancer (NSCLC) patients receiving programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors.
- BoM had a higher risk developing their initial progressive disease in the bone.
- Palliative bone radiotherapy could not improve progression-free survival (PFS) in those with baseline BoM.

What is known and what is new?

- BoM was found to be associated with compromised prognosis, which was reconfirmed in the current study including patients from a prospectively maintained database.
- To the best of our knowledge, palliative bone radiotherapy was found to be not associated with patient's PFS.

What is the implication, and what should change now?

- This study clarifies the recurrence pattern of bone metastasis in the context of immunotherapy for advanced NSCLC, proves that bone metastasis reduces the efficacy of immunotherapy, reminds clinicians to pay attention to the prevention, diagnosis and treatment of bone metastasis, and explores more effective methods for the treatment of bone metastasis.

in a multicenter randomized controlled trial conducted in the United States that encompassed 78 adult patients diagnosed with metastatic solid tumor malignancies, bone radiation reduced the incidence of SREs at the 1-year mark from 29% to 1.6% when compared to the standard of care. Additionally, the use of bone radiation therapy extended the OS, with a median of 1.7 *vs.* 1.0 years (18). However, in the era of immunotherapy, while there are studies demonstrating that immunotherapy in conjunction with bone radiotherapy can protract OS in patients afflicted with melanoma BoM (19), scarcely any investigations have explored the impact of immunotherapy combined with bone radiotherapy on the treatment efficacy and survival of lung cancer patients with BoM. Consequently, this study endeavors to elucidate the influence of immunotherapy in conjunction with bone radiotherapy on survival rates and identify risk factors in NSCLC patients grappling with BoM. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-441/rc).

Methods

Patients

A prospective observational study database, registered under https://clinicaltrials.gov/study/NCT04766515, cataloged patients with metastatic NSCLC who underwent treatment with PD-1/PD-L1 inhibitors in clinical settings. The study aimed to evaluate the efficacy and safety of immunotherapy in treating advanced NSCLC within the real-world population. Patients included in our retrospective analysis were sourced from this database, covering the period from September 1, 2020, to May 30, 2023. These patients were affiliated with institutions, including Fudan University Shanghai Cancer Center, Zhongshan Hospital affiliated to Fudan University, and the Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology. Inclusion criteria were as follows: (I) all patients had a pathological confirmation of metastatic NSCLC with measurable lesions; (II) patients received PD-1/PD-L1 inhibitor treatment and underwent regular follow-up imaging examinations; (III) BoM diagnosis was evaluated by two experienced radiologists, with or without pathological confirmation. Additionally, patients who underwent follow-up imaging either at our facility or at local hospitals, with detailed results recorded in our electronic health system, were included. The main exclusion criteria comprised: (I) second primary tumors; (II) incomplete data; (III) lack of measurable lesions at baseline; (IV) presence of *EGFR* or *ALK* mutations; (V) loss to follow-up. Clinical data for enrolled patients, including gender, age, pathological type, number of immunotherapy lines, treatment regimen (PD-1/PD-L1 inhibitors monotherapy *vs.* combination therapy), PD-L1 expression, smoking history, and Eastern Oncology Collaborative Group presentation status (ECOG-PS), were retrieved from their medical records. Dates of first immunotherapy, last follow-up, disease progression, and death were also collected for patients with advanced NSCLC. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the Fudan University Shanghai Cancer Center (No. 090977-1). All participating hospitals/institutions were informed of and agreed to participate in the study. The requirement for informed consent from individual patients was waived in this retrospective analysis.

Follow-up

Patients underwent regular follow-up evaluations every 6–12 weeks during PD-1/PD-L1 inhibitors treatment. Each follow-up visit included a review of medical history, physical examination, and imaging studies such as chest computed tomography (CT) and abdominal ultrasound or CT scan. Additional tests like bone scans and positron emission tomography were conducted based on clinical discretion, particularly upon the onset of indicative symptoms, and the decision for bone scans was made by the attending physician. Evaluation of bone metastases was performed by experienced radiologists using imaging techniques (20). Moreover, for lesions with ambiguous radiographic findings, tumor biopsies were performed and the differential diagnosis of progressive disease (PD) in the bone was determined after comprehensive review of all available clinical data, such as symptoms, lab examinations, disease status of extra-skeletal tumor lesions and disease evolution. Follow-up telephone consultations were also utilized as a supplementary measure.

Statistical analysis

PSM at a ratio of 1:1 was used to analyze patients with advanced NSCLC, stratified according to the BoM status prior to immunotherapy, to adjust for possible selection bias due to the retrospective non-randomized design. PSM matched gender, age, pathological type, number of

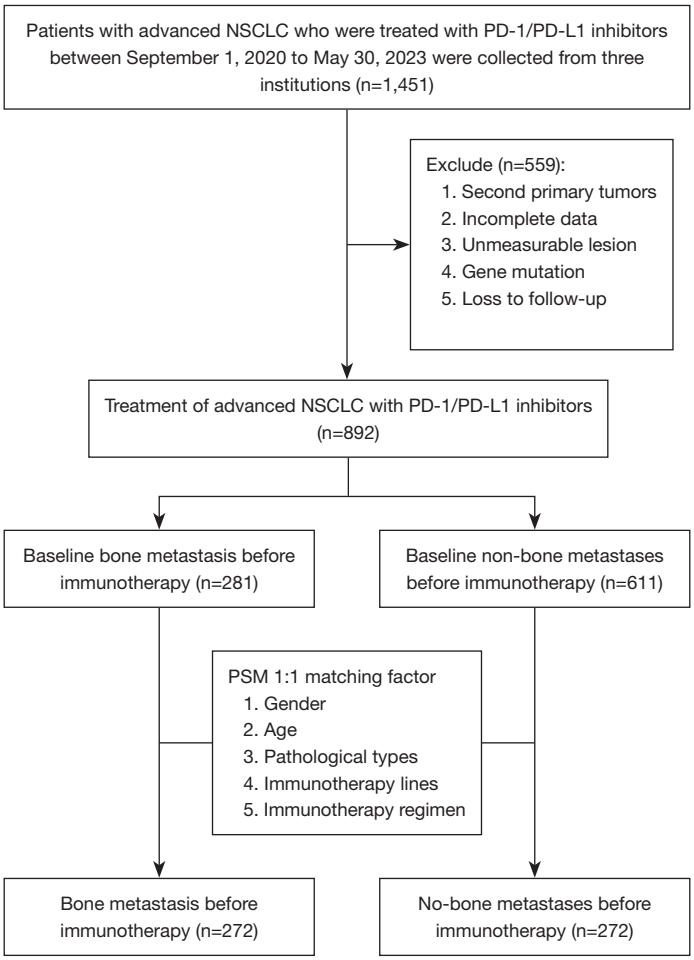

Figure 1 Flowchart of patient enrollment. NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PSM, propensity score matching.

immunotherapy lines, immunotherapy regimen (PD-1/PD-L1 inhibitors monotherapy *vs.* combination therapy), PD-L1 expression, smoking history, and ECOG-PS to establish two matched cohorts with balanced baseline demographics and disease characteristics. Baseline clinical features are presented by number and percentage. Progression-free survival (PFS) is defined as the time from the date of immunotherapy initiation to disease progression or death from any cause. OS is defined as the time from the date of immunotherapy initiation to death from any cause. Tumor response and disease progression were assessed following the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) (21). The Chi-square test was employed to measure the correlation between patient characteristics and objective response rate (ORR). The patients' survival was plotted using the Kaplan-Meier method, and the differences in the variables were estimated by log-rank test. Cox proportional hazard models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analysis was carried out using SPSS version 27.0 (IBM, Armonk, NY, USA).

Results

Patient's characteristics

Initially, 1,451 patients diagnosed with metastatic NSCLC were initially identified, from whom 829 individuals meeting the specified inclusion and exclusion criteria were subsequently selected, as illustrated in *Figure 1*. Among them, 281 had BoM prior to immunotherapy while 611 did not. Following PSM, 272 patients with baseline BoM were paired with an equal number of patients without

Table 1 Baseline features stratified by group (BoM and non-BoM) for all matched patients and data

Characteristic	BoM (N=272), n (%)	Non-BoM (N=272), n (%)	P value
Sex			0.99
Female	219 (80.5)	218 (80.1)	
Male	53 (19.5)	54 (19.9)	
Age (years)			0.28
≤60	101 (37.1)	123 (45.2)	
>60	171 (62.9)	149 (54.8)	
Pathological type			0.77
Scc	80 (29.4)	84 (30.9)	
Non-Scc	192 (72.6)	188 (69.1)	
Number of immunotherapy lines			0.73
First-line treatment	129 (47.4)	134 (49.3)	
Non-first-line treatment	143 (52.6)	138 (50.7)	
Immunotherapy regimen			0.41
Monotherapy	47 (17.3)	39 (14.3)	
Combination therapy	225 (82.7)	233 (85.7)	
Smoking history			0.91
Yes	216 (79.4)	214 (78.7)	
No	56 (20.6)	58 (21.3)	
PD-L1			0.54
<1%	52 (19.1)	51 (18.8)	
≥1%	105 (38.6)	117 (43.0)	
Unknown	115 (42.3)	104 (38.2)	
ECOG			0.45
0–1	247 (90.8)	248 (91.2)	
≥2	25 (9.2)	24 (8.8)	

BoM, bone metastasis before immunotherapy; non-BoM, no bone metastasis before immunotherapy; Scc, squamous cell carcinoma; non-Scc, non-squamous cell carcinoma; PD-L1, programmed cell death-ligand 1; ECOG, Eastern Cooperative Oncology Group.

baseline BoM, resulting in a final study cohort comprising 544 individuals. Patient's characteristics were summarized in *Table 1*. The median age of participants was 62 years, with squamous cell carcinoma representing 30.1% of cases, PD-L1 expression exceeding 1% in 40.8% of cases, first-line immunotherapy administered in 48.3% of cases, and monotherapy utilized in 15.8% of cases.

Prognostic significance of baseline BoM

In the entire study cohort, 73 individuals (13.4%) achieved partial response (PR), 274 individuals (50.4%) maintained stable disease (SD), and 197 individuals (36.0%) developed PD, with no instances of complete response (CR). The ORR stood at 13.4%, while the disease control rate (DCR) reached 63.8%. Within the subgroup of patients presenting with baseline BoM, 30 individuals (11.0%) exhibited PR, 127 individuals (46.7%) maintained SD, and 115 individuals (42.3%) manifested PD, with no occurrences of CR. The ORR and DCR were recorded at 11.0% and 57.7%, respectively. In contrast, among patients devoid of baseline BoM, 43 individuals (15.8%) attained PR, 147 individuals

(54.1%) sustained SD, and 82 individuals (30.2%) encountered PD, without any instances of CR (P<0.001). The ORR and DCR were notably higher, reaching 15.8% and 69.9% (*Table 2*), respectively.

Meanwhile, the median PFS for the entire cohort was 9.5 months (95% CI: 9.12–9.87). Patients with baseline BoM exhibited a median PFS of 7.8 months (95% CI: 7.0–8.7), compared to 9.5 months (95% CI: 8.9–10.0) (*Figure 2A*) for those without baseline BoM (P<0.001). The median OS for the entire cohort was 20.4 months (95% CI: 17.6–23.1). The median OS of patients with baseline bone metastases was 14.5 months (95% CI: 12.6–16.4), while the median OS of patients without baseline bone metastases was 27.6 months (95% CI: 25.1–30.1) (P<0.001) (*Figure 2B*).

Table 2 Prognostic significance of baseline bone metastasis versus non-bone metastasis

Efficacy evaluation	BoM (N=272), n (%)	Non-BoM (N=272), n (%)
CR	0	0
PR	30 (11.0)	43 (15.8)
SD	127 (46.7)	147 (54.1)
PD	115 (42.3)	82 (30.1)
ORR	30 (11.0)	43 (15.8)
DCR	157 (57.7)	190 (69.9)

BoM, bone metastasis before immunotherapy; non-BoM, no bone metastasis before immunotherapy; CR, complete response; PR, partial response; SD, standard deviation; PD, progress disease; ORR, objective response rate; DCR, disease control rate.

Pattern of treatment failure

To date, 197 individuals have developed PD in the whole population. Among those with baseline BoM, 115 individuals experienced PD. Of these, 31 individuals (26.9%) had PD localized only to the bones, 50 individuals (43.5%) experienced PD occurring exclusively outside of the bones, and 34 individuals (29.6%) had PD involving both bone and other sites. In patients without baseline BoM, 82 individuals experienced PD. Among them, 24 individuals (29.3%) had PD confined solely to the bones, 56 individuals (68.3%) experienced PD occurring exclusively outside of the bones, and 2 individuals (2.4%) had PD involving both bone and other sites. The proportion of bone-only PD among patients with baseline BoM (56.5%) exceeded that among patients without baseline BoM (31.7%) (*Figure 3A*), indicating a higher tendency for bone-only PD in the former group (P<0.001).

Furthermore, in patients without baseline BoM, the cumulative incidence rate of subsequent BoM after immunotherapy was 6.8% at 3 months, 15.8% at 6 months and 39.6% at 9 months (*Figure 3B*). Cox univariate analysis determined that initial ECOG-PS and smoking history

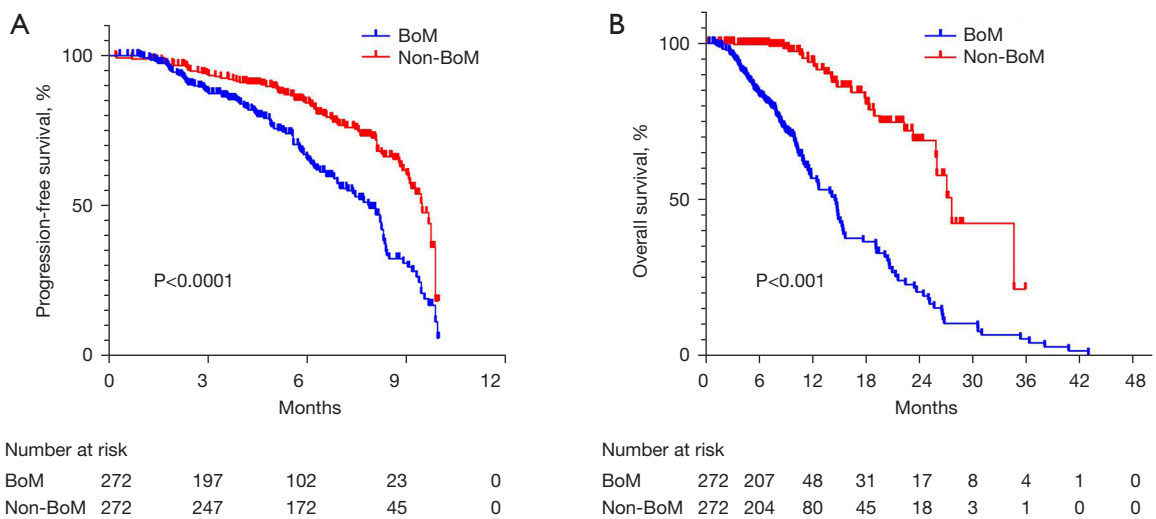

Figure 2 Kaplan-Meier analysis of progression-free survival and overall survival. (A) Kaplan-Meier plots of PFS in patients with BoM and non-BoM. (B) Kaplan-Meier plots of OS in patients with BoM and non-BoM. BoM, bone metastasis before immunotherapy; non-BoM, no bone metastasis before immunotherapy; PFS, progression-free survival; OS, overall survival.

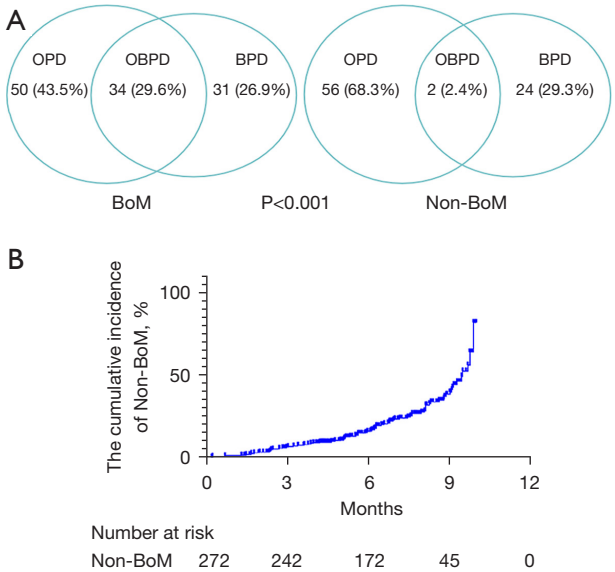

Figure 3 Treatment failure and cumulative incidence of bone metastasis. (A) PD pattern of immunotherapy failure in patients with baseline bone metastasis and no bone metastasis. (B) Kaplan-Meier analysis of cumulative incidence of bone metastasis following immunotherapy in patients without bone metastasis at baseline. PD, progressive disease; OPD, metastasis to other sites outside the bone leads to disease progression; OBPD, metastasis of bone and other parts leading to disease progression; BPD, bone metastasis led to disease progression; BoM, bone metastasis before immunotherapy; non-BoM, no bone metastasis before immunotherapy.

were significant risk factors for BoM, while other factors did not reach statistical significance (*Table 3*).

Clinical value of bone radiotherapy

Among patients with baseline BoM, 82 patients received bone radiotherapy before their initial disease progression during immunotherapy, including palliative bone radiotherapy in 67 patients and stereotactic body radiotherapy (SBRT) in 15 patients. The baseline characteristics of patients with BoM, who received or did not receive bone radiotherapy, are presented in (*Table 4*). Notable differences between the radiotherapy and non-radiotherapy groups were observed in the number of immunotherapy lines, the presence of bone pain, the incidence of high-risk bone metastases, and the occurrence of bone oligo-metastasis. The median PFS was 8.2 months (95% CI: 7.84–8.63) for those without bone radiotherapy and 7.2 months (95% CI: 5.58–8.88) for those with bone radiotherapy. No significant difference of PFS was found between these two subgroups (P=0.68) (*Figure 4A*). Additionally, the median PFS of patients receiving bone SBRT and palliative bone radiotherapy, were 7.4 months (95% CI: 4.94–9.86) and 7.2 months (95% CI: 5.58–8.88), respectively. Again, no significant difference of PFS was found between those without bone radiotherapy, with bone SBRT and with palliative bone radiotherapy (P=0.36) (*Figure 4B*). After Cox analysis, there was no significant association between bone radiation therapy and PFS, except for immunotherapy regimens, bone pain, high-risk bone metastases (*Table 5*).

Discussion

Bone metastases are a prevalent occurrence in patients with NSCLC, significantly impacting prognosis and diminishing both survival rates and patients' quality of life (22). Existing investigations into immunotherapy for bone metastases have primarily centered on assessing its influence on patient survival. However, these studies have rarely delved into the patterns of relapse among NSCLC patients with bone metastases, nor have they explored the potential benefits of combining immunotherapy with radiotherapy. Our dataset comprises information gleaned from a prospective study involving 1,451 patients. To mitigate potential selection bias in our retrospective design, we employed a 1:1 PSM technique to match patients with and without bone metastases prior to immunotherapy. In total, 544 patients were successfully included in our analysis. We found that patients without pre-existing bone metastases prior to commencing immunotherapy exhibited longer PFS compared to their counterparts with bone metastases, which aligns with previously reported data. Furthermore, our study revealed that in patients with baseline bone metastases, disease recurrence was primarily driven by the progression of bone metastases. Conversely, among patients without baseline bone metastases, the progression of other metastatic sites played a more dominant role in disease recurrence. However, it should be noted that the underlying molecular mechanisms responsible for these observations remain elusive and require further investigation.

Notably, bone metastases have been documented to exert a detrimental influence on the efficacy of immunotherapy. A retrospective analysis of 270 patients across 10 European institutions receiving ICIs indicated that the presence of bone metastases was associated with poorer prognoses (23).

Table 3 Cox proportional hazards model analysis of risk factors for bone metastasis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex		0.09		
Female	1			
Male	0.648 (0.39–1.07)			
Age (years)		0.69		
≤60	1			
>60	1.091 (0.70–1.69)			
Pathological type		0.91		
Scc	1			
Non-Scc	1.026 (0.63–1.67)			
Number of immunotherapy lines		0.58		
First-line treatment	1			
Non-first-line treatment	1.15 (0.70–1.89)			
Immunotherapy regimen		0.42		
Monotherapy	1			
Combination therapy	1.194 (0.77–1.85)			
Smoking history		0.01		0.01
Yes	1		1	
No	0.561 (0.35–0.91)		0.587 (0.38–0.96)	
PD-L1		0.18		
<1%	1			
≥1%	0.728 (0.46–1.16)			
Unknown	1			
ECOG		0.001		0.001
0–1	1		1	
2	3.97 (2.29–6.89)		4.03 (2.32–7.01)	

HR, hazard ratio; CI, confidence interval; Scc, squamous cell carcinoma; non-Scc, non-squamous cell carcinoma; PD-L1, programmed cell death-ligand 1; ECOG, Eastern Cooperative Oncology Group.

A multicenter retrospective study involving 330 patients revealed that patients with bone metastases had a shorter OS compared to those without bone metastases. The median OS for patients with bone metastases was 5.9 months (95% CI, 4.2–7.8), whereas for those without bone metastases, it was 13.4 months (95% CI, 10.8–17.0; P<0.001). Regardless of BoM status at baseline, the occurrence of bone-related events was associated with a shorter OS. Specifically, the median OS for patients experiencing bone-related events was 7.5 months (95% CI, 4.6–10.0) compared to 10.6 months (95% CI, 8.4–12.8) for those without such events (P=0.04) (17). Another prospective study conducted in 153 centers in Italy demonstrated that OS for non-squamous NSCLC patients with BoM+ was 7.4 months, significantly shorter than the 15.3 months observed for those BoM– (P<0.0001). Similarly, among squamous cell patients, BoM+ individuals exhibited a significantly reduced OS of 5.0 months compared to 10.9 months for BoM–

Table 4 Baseline characteristics of patients with bone metastases receiving bone radiation or not

Characteristic	Without bone radiotherapy (N=190), n (%)	With bone radiotherapy (N=82), n (%)	P value
Sex			0.09
Female	158 (83.2)	61 (74.4)	
Male	32 (16.8)	21 (25.6)	
Age (years)			0.34
≤60	67 (35.3)	34 (41.5)	
>60	123 (64.7)	48 (58.5)	
Pathological type			0.88
Scc	55 (28.9)	25 (30.5)	
Non-Scc	135 (71.1)	57 (69.5)	
Number of immunotherapy lines			0.046
First-line treatment	98 (51.6)	31 (37.8)	
Non-first-line treatment	92 (48.4)	51 (62.2)	
Immunotherapy regimen			0.60
Monotherapy	31 (16.3)	16 (19.5)	
Combination therapy	159 (83.7)	66 (80.5)	
Smoking history			0.32
Yes	154 (81.1)	62 (75.6)	
No	36 (18.9)	20 (24.4)	
PD-L1			0.33
<1%	37 (19.5)	15 (18.3)	
≥1%	78 (41.1)	27 (32.9)	
Unknown	75 (39.5)	40 (48.8)	
ECOG			0.49
0–1	174 (91.6)	73 (89.0)	
2	16 (8.4)	9 (11.0)	
Bone pain			0.047
Yes	97 (51.1)	53 (64.6)	
No	93 (48.9)	29 (35.4)	
High-risk bone metastases			0.03
Yes	94 (49.5)	52 (63.4)	
No	96 (50.5)	30 (36.6)	
Bone oligo-metastasis			0.02
Yes	98 (51.6)	32 (39.0)	
No	92 (48.4)	50 (61.0)	

Scc, squamous cell carcinoma; non-Scc, non-squamous cell carcinoma; PD-L1, programmed cell death-ligand 1; ECOG, Eastern Cooperative Oncology Group; High-risk bone metastases, giant tumors (with a maximum diameter of ≥2 cm), borderline spinal or posterior component diseases, diseases involving the hip or sacroiliac joints, or long bone diseases involving 1/3–2/3 cortical thickness; Oligo-metastasis, refers to the condition where the number of metastatic organs is ≤3 and the number of metastatic lesions is ≤5.

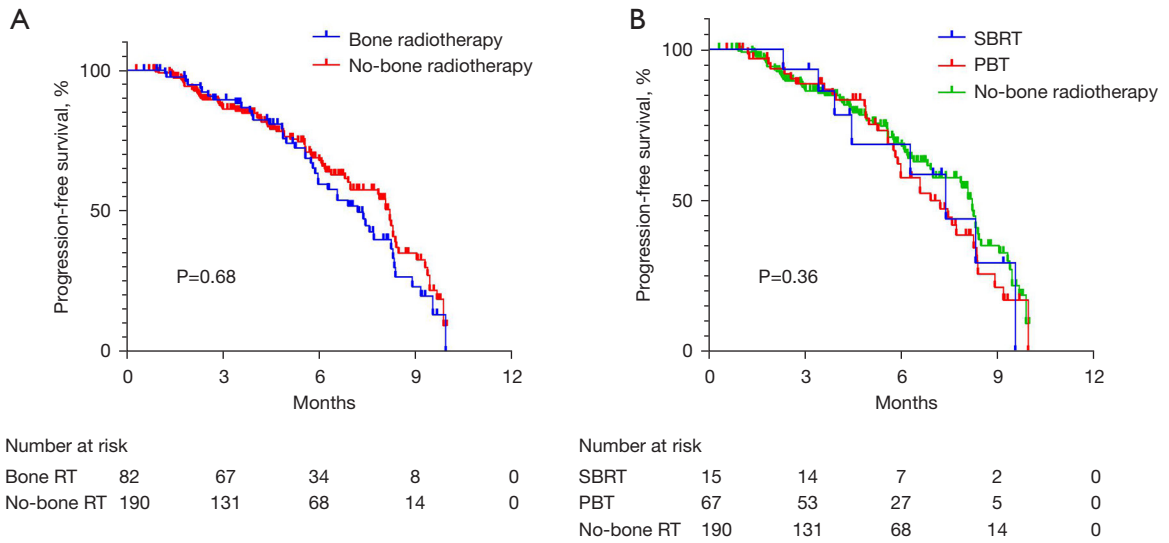

Figure 4 Kaplan-Meier analysis of progression-free survival in those with baseline bone metastasis. (A) Kaplan-Meier plots of PFS in patients with bone radiotherapy and no bone radiotherapy. (B) Kaplan-Meier plots of PFS in patients with SBRT, PBT and no bone radiotherapy. SBRT, stereotactic body radiotherapy; PBT, palliative bone radiotherapy; RT, radiotherapy; PFS, progression-free survival.

patients (P<0.001) (14). Our study further reinforces these findings by revealing that patients with bone metastases experience lower treatment efficacy, shorter survival, and an elevated risk of disease progression associated with bone lesions when compared to those without bone metastases. Previous studies have suggested that the bone marrow plays a pivotal role in modulating the immune response and influencing the outcome of immunotherapy (24,25). Consequently, it is plausible that the immune response elicited by bone metastases differs from that generated in response to primary tumors, potentially accounting for the diminished efficacy of immune checkpoint inhibitors in patients with bone metastases. Nevertheless, it is important to underscore that this hypothesis warrants further exploration, and the underlying mechanisms remain to be elucidated.

Our study additionally ascertains that in NSCLC patients with baseline bone metastases, recurrences predominantly manifest as bone progression, while in patients devoid of baseline bone metastases, recurrences primarily occur in other anatomical sites. Currently, there is a paucity of literature elucidating the recurrence patterns of bone metastases in the context of immunotherapy. Consequently, further research is imperative to comprehensively understand this phenomenon. Although the precise mechanisms governing bone metastases remain incompletely elucidated, mounting evidence suggests that the bone microenvironment provides a conducive milieu for the homing, proliferation, and colonization of circulating cancer cells, culminating in metastatic lesion formation. Metastatic cancer cells that infiltrate the bone also possess unique characteristics that enable them to exploit the bone microenvironment. Consequently, communication between cancer cells and the bone milieu is postulated to play a pivotal role in facilitating the development and progression of bone metastases (26). The enduring validity of Stephen Paget's "seed and soil" hypothesis, propounded over a century ago, posits that a particular tumor cell can only thrive and proliferate within a compatible microenvironment. Thus, the molecular attributes of malignant cells (the "seed") and their reciprocal interactions with the bone microenvironment (the "soil") assume paramount importance in enabling the metastatic dissemination of tumors (27,28). These factors collectively contribute to the heightened propensity of patients with bone metastases to experience bone progression.

In this study, our evaluation of advanced NSCLC patients with bone metastases who received combined immunotherapy and radiotherapy did not reveal a substantial improvement in PFS. Similarly, in the FORCE study, which bifurcated advanced NSCLC patients into two groups—one receiving nivolumab combined with radiotherapy and the other receiving nivolumab alone—failed to demonstrate an enhanced ORR in the cohort receiving combination

Table 5 Cox proportional hazards model analysis of bone radiotherapy factors

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value		P value
Sex		0.07		
Female	1			
Male	0.687 (0.46–1.04)			
Age (years)		0.59		
≤60	1			
>60	0.904 (0.62–1.31)			
Pathological type		0.70		
Scc	1			
Non-Scc	0.928 (0.63–1.37)			
Number of immunotherapy lines		0.11		
First-line treatment	1			
Non-first-line treatment	0.695 (0.44–1.09)			
Immunotherapy regimen		0.007		0.33
Monotherapy	1		1	
Combination therapy	1.716 (1.16–2.55)		1.314 (0.76–2.28)	
Radiation therapy				
Non-RT	1	0.29		
RT	1.225 (0.84–1.79)			
Smoking history		0.71		
Yes	1			
No	1.073 (0.74–1.56)			
PD-L1		0.44		
<1%	1			
≥1%	1.160 (0.79–1.70)			
Unknown	1			
ECOG		0.19		
0–1	1			
2	1.514 (0.80–2.85)			
Bone pain		0.03		0.58
Yes	1		1	
No	0.619 (0.39–0.98)		1.655 (0.27–10.03)	
High-risk bone metastases		0.01		0.26
Yes	1		1	
No	0.578 (0.37–0.91)		0.358 (0.06–2.14)	
Bone oligo-metastasis		0.16		
Yes	1			
No	1.372 (0.88–2.15)			

HR, hazard ratio; CI, confidence interval; Scc, squamous cell carcinoma; non-Scc, non-squamous cell carcinoma; RT, radiotherapy; non-RT, non-radiation therapy; PD-L1, programmed cell death-ligand 1; ECOG, eastern cooperative oncology group.

therapy. More than half of the patients in the study received palliative radiotherapy for bone metastases. Consequently, when assessing the efficacy of immunotherapy, clinical attributes must be taken into account (29). Previous preclinical investigations and retrospective analyses have furnished evidence indicating that the concurrent administration of immunotherapy and radiotherapy can mutually potentiate the radiation associated abscopal effect (30). A retrospective study that we previously conducted examined the influence of brain metastases on OS among patients with metastatic NSCLC undergoing treatment with PD-1/PD-L1 inhibitors. Out of the 461 patients included in that study, 110 (23.9%) presented with brain metastases at baseline. Patients who received upfront cranial radiotherapy (uCRT) exhibited a significantly extended median OS compared to those who did not (HR =0.29–0.91, P=0.04) (31). Given the pivotal role of local treatment, particularly radiotherapy, in managing bone metastases, the relative contributions of bone radiotherapy and anti-PD-1/PD-L1 therapy have garnered considerable interest in shaping the optimal therapeutic approach for bone metastases in NSCLC. A burgeoning body of literature suggests that the amalgamation of radiotherapy and PD-1/PD-L1 inhibitors may confer superior benefits compared to radiotherapy in isolation or systemic therapy alone, particularly with regard to enhancing local disease control and OS (30,32). However, the precise optimization of this combination strategy remains an area of active research, necessitating further exploration of parameters such as the appropriate radiotherapy dosage. Moreover, researchers have begun to recognize the potent immunomodulatory effects of SBRT, which possesses the capability to transform recalcitrant "cold" tumors into "hot" tumors that are amenable to immunotherapeutic interventions (33). For instance, the incorporation of SBRT with immunotherapy in advanced NSCLC patients not only extended OS but also significantly increased cytotoxic T cell infiltration within the tumor microenvironment (TME) (34). Thus, it is pertinent to investigate whether this approach could be effectively harnessed to enhance local tumor control, minimize recurrence, and mitigate metastasis in patients with advanced NSCLC featuring bone metastases. However, it is important to note that our study results indicated that radiotherapy, when combined with immunotherapy, did not confer a survival advantage. This outcome may be attributed to the relatively small number of patients who underwent radiotherapy for bone metastases in our study cohort. Moreover, the majority of these radiotherapy recipients received symptomatic palliative bone radiotherapy, with only a minority undergoing SBRT. Consequently, our findings suggest that further research is warranted to evaluate the potential benefits of radiotherapy, particularly employing advanced techniques like SBRT, in combination with immunotherapy to enhance survival.

Our study is not without limitations. Although we endeavored to address potential selection bias through the utilization of PSM and COX regression analysis, it is possible that some degree of bias may still persist. Furthermore, our retrospective design did not enable the collection of data pertaining to toxicities and side effects associated with treatment. It is worth noting that a substantial proportion of patients in the radiotherapy group were symptomatic and received palliative radiotherapy, potentially reflecting a greater disease burden and poorer overall health status. Consequently, their natural efficacy and survival outcomes were inherently disadvantaged. Importantly, the absence of a survival benefit in this study should not be misconstrued as evidence that radiotherapy for bone metastases lacks a synergistic effect with immunotherapy. To address these limitations and provide more conclusive insights, future investigations should embrace prospective study designs and incorporate radiotherapy approaches that encompass advanced techniques such as SBRT.

Conclusions

Patients with baseline BoM exhibit a worse prognosis and a higher risk for bone PD compared to those without. Combining immunotherapy with bone radiotherapy did not yield improved survival outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-441/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-441/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 Institutional Ethics Committee of the Fudan University Shanghai Cancer Center (No. 090977-1). All participating hospitals/institutions were informed of and agreed to participate in the study. The requirement for informed consent from individual patients was waived in this retrospective analysis.

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