



Research Paper

Inferior outcome of bone metastasis in non-small-cell-lung-cancer patients treated with epidermal growth factor receptor inhibitors



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ABSTRACT

Background: Targeted therapy has been established as the standard-of-care for patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations. Among patients with advanced lung cancer, 30–40% have bone metastases (BoM) at first diagnosis. However, little is known on the clinical characteristics and prognostic factors of BoM in patients with NSCLC harboring EGFR mutations.

Methods: Treatment-naïve patients with advanced NSCLC harboring EGFR mutations who were prescribed tyrosine kinase inhibitors (TKIs) were screened and enrolled between June 2009 and April 2019 from West China Hospital. Patients were dichotomized according to whether they had BoM. The demographic characteristics, gene mutation status and therapeutic efficacy, including objective response rate (ORR), progression-free survival (PFS) and overall survival (OS), were collected.

Results: A cohort of 604 patients were enrolled. The BoM group had worse PFS (11.7 vs. 14.0 months, HR = 0.73, $p = 0.00013$) and OS (32.8 vs. 46.1 months, HR = 0.54, $p < 0.0001$) compared with the non-BoM group. No significant differences were observed in disease control rate ($p = 0.407$) or ORR ($p = 0.537$) between the two groups. The metastatic sites in the two groups exhibited obvious differences. In multivariate analysis, BoM was found to be an independent factor of worse prognosis.

Conclusion: BoM was identified as an independent inferior prognostic factor for EGFR-TKI treatment, and may have complex biological implications.

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1. Introduction

Lung cancer is the most common type of cancer and the leading cause of cancer-related mortality worldwide [1]. The 5-year survival rate for metastatic lung cancer is ~ 5%. Compared with traditional chemotherapy, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have demonstrated superior efficacy in selected patients harbouring sensitive EGFR mutations [2–5]. Targeted therapy has been the standard first-line treatment for patients with advanced non-small cell lung-cancer (NSCLC) with EGFR mutations. Although the majority of the patients with EGFR-mutant cancer benefit from TKI treatment, clinical response varies and additional factors affecting TKI efficacy must be explored.

Bone is a common site of metastasis of advanced NSCLC. Among patients with advanced lung cancer, 30–40% have bone metastases (BoM) at the time of diagnosis [6]. BoM is closely associated with

compromised quality of life and shortened survival of the patients [7,8]. The median survival of patients with BoM is 6–8 months, even after aggressive treatment [10]. Multidisciplinary treatment of BoM is recommended, including both systemic (targeted therapy, chemotherapy, bisphosphonates, painkillers and psychosocial support) and local therapy (radiotherapy and surgery). NSCLC with EGFR mutations is associated with a higher incidence of BoM [14,15]. However, little is known on the clinical characteristics and prognostic factors of BoM in NSCLC harboring EGFR mutations. The aim of the present study was to compare the clinical characteristics between NSCLC patients harboring EGFR mutations, with or without BoM (non-BoM).

2. Methods

2.1. Study population

This was a retrospective study where 3,389 patients were screened through the Hospital Information System in West China Hospital between June 2009 and April 2019. A total of 604 enrolled patients had pathologically confirmed, metastatic, treatment-naïve

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NSCLC, harboring EGFR mutations and were prescribed EGFR-TKI as first-line therapy. A total of 300 and 304 patients were grouped into the BoM and non-BoM groups, respectively, according to the presence or absence of BoM at presentation. The median age of the patients in the BoM group was 58.1 years and in the non-BoM group 60.6 years.

The present study was undertaken to explore the relationship between the therapeutic efficacy of EGFR-TKIs and the prognosis of NSCLC patients with BoM harboring EGFR mutations. Patients treated with TKIs combined with chemotherapy, either synchronous or intercalated, or those who had mixed small-cell lung cancer, were excluded from the present study.

2.2. Diagnosis of BoM

BoM were diagnosed using methods according to the treating physicians' discretion. Patients were screened by bone scanning for possible metastases, and those with suspected BoM were confirmed by CT scan of the involved sites. When CT scans were deemed insufficient to establish the presence of BoM, magnetic resonance imaging (MRI) was prescribed as a supplementary diagnostic method. For a proportion of patients, ¹⁸F¹⁸FDG PET-scan was employed. Patients had different diagnostic approaches, but all were based on the current recommendations and guidelines, and were consistent during the period of observation.

2.3. Treatments

Each patient was treated as per the treating physicians' discretion. Either gefitinib (250 mg once a day, AstraZeneca, UK), or erlotinib (150 mg once a day, Roche, Switzerland), or icotinib (125 mg 3 times per day, Beta, China) was administered. Treatment contin-

ued until disease progression, or unacceptable toxicity, or death from any cause. In treatment-resistant patients harboring T790M mutation, osimertinib (80 mg once a day, AstraZeneca, UK) was prescribed as salvage therapy.

2.4. Genetic testing

Genetic testing was performed on tumor tissues. EGFR mutation was detected by ARMS using a commercially available kit (AmoyDx, Shameng, China) at the College of American Pathologists-certified lab of West China Hospital. Tumor content was assessed by board-certified pathologists using hematoxylin and eosin staining. All specimens contained > 10% of tumor content. DNA was extracted using the QIAamp DNA mini kit (Qiagen). In some patients, comprehensive genomic profiling was performed by next generation sequencing (NGS) with 56 cancer-related gene panels covering the whole exons of the EGFR gene at a mean coverage depth of > 800X. The genomic alterations, including single base substitutions, insertions/deletions, copy number variations, as well as gene rearrangement and fusions, were assessed.

2.5. Outcome measures

Tumors were assessed every 2 months radiographically, including CT of the chest and upper abdomen, MRI of the head and bone scintigraphy. Tumor response was evaluated as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to RECIST 1.1. The PFS was defined as the time interval from the initiation of therapy to the date of disease progression, intolerable side effects, or death from any cause. The OS was defined as the time interval from the initiation of the therapy to the date of death from any cause.

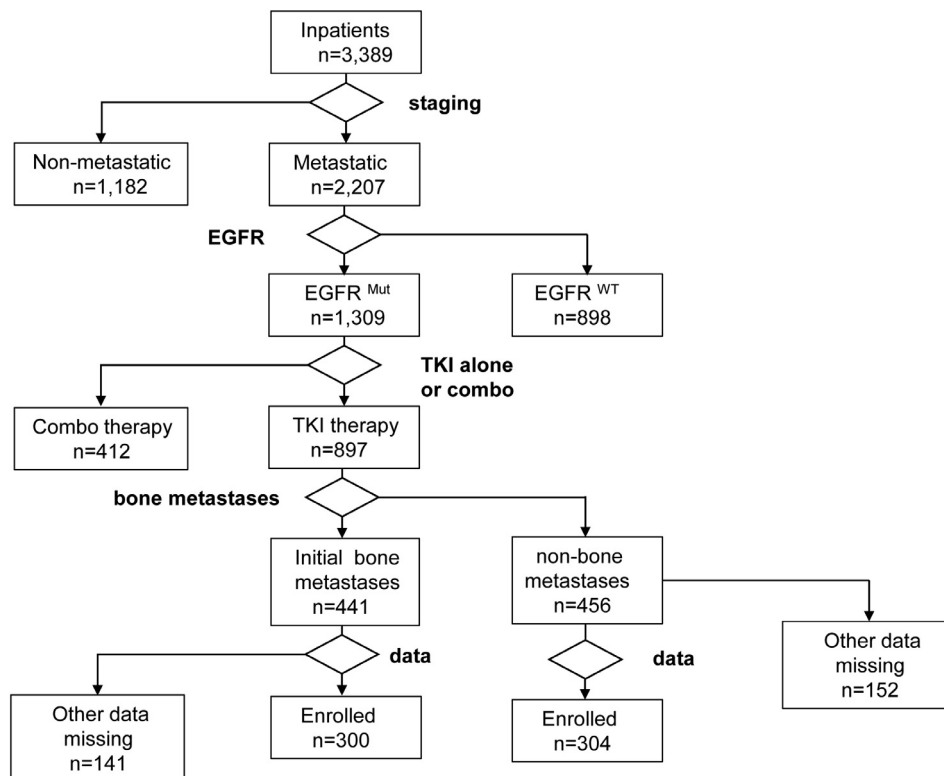


Fig. 1. The flow chart of patients screening.

2.6. Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Chicago, IL) and R version 4.0.3. The quantitative data were compared using Chi-squared test and Fischer’s exact test according to Cochran’s rule. Kaplan-Meier curves WERE used to compare survival. Multivariate analysis was performed by using a Cox proportional hazard model. All P-values were based on a two-tailed hypothesis, and statistical significance was assumed if $p < 0.05$.

3. Ethics statement

The Ethics Committee of Sichuan University reviewed and approved the study protocol and the study was performed in accordance with the principles outlined in the Declaration of Helsinki. Since this was a retrospective study of an anonymized database and had no influence on patient care, patient consent was not required. The study was performed with respect to the confidentiality of individual patient data.

4. Results

4.1. Baseline characteristics

In this study, a total of 3,389 patients were screened, and 604 patients were enrolled, of whom 300 and 304 patients were grouped into the BoM and non-BoM groups, respectively (Fig. 1). Both groups had comparable demographic characteristics, other than age and EGFR mutations. The patients in the BoM group (median age, 58.1 years) were younger compared with those in the non-BoM group (median age, 60.6 years), although the difference was non-significant. Meanwhile, fewer patients aged ≥ 60 years were in the BoM group ($n = 131, 43.7\%$) compared with the non-BoM group ($n = 171, 56.3\%, p = 0.003$). L858R point mutation was more commonly found in the BoM group, while other mutations (mostly exon 19 deletion) occurred at higher frequencies in the

Table 1
The demographic features of population.

Characteristic	Bone metastasis	Non-bone metastasis	P value
Total N (%)	300(49.7%)	304(50.3%)	
Gender			
Female	183(61.0%)	173(56.9%)	0.348
Male	117(39.0%)	131(43.1%)	
Age group			
<60 year	169(56.3%)	133(43.7%)	0.003
≥ 60 year	131(43.7%)	171(56.3%)	
Smoking history			
Yes	75(25.0%)	80(26.3%)	0.782
No	225(75.0%)	224(73.7%)	
ECOG			
0	163(54.3%)	175(57.6%)	0.473
≥ 1	137(45.7%)	129(42.4%)	
EGFR mutation			
Exon 19 deletion	129(43.0%)	140(46.1%)	0.022
L858R mutation	138(46.0%)	110(36.2%)	
Other	33(11.0%)	54(17.7%)	
Histological type			
Adenocarcinoma	289(96.3%)	291(95.7%)	0.891
Non-adenocarcinoma	11(3.7%)	13(4.3%)	
Targeted drugs			
Icotinib	82(27.3%)	86(28.3%)	0.210
Gefitinib	169(56.3%)	153(50.3%)	
Erlotinib	49(16.4%)	65(21.4%)	
≥ 3 mutations(available)			
Yes	29(58%)	13(29.5%)	0.006
No	21(42%)	31(70.5%)	

non-BoM group ($p = 0.022$). Finally, the presence of ≥ 3 gene mutations in patients with BoM for whom such data were available was more common than in the non-BoM group ($p = 0.006$, Table 1).

4.2. The BoM group was prone to multiple organ metastases

The data on organ metastasis in this cohort of patients were collected and analyzed. In the BoM group, the most common metastatic organs were the lung (46%), brain (34.7%), pleura (34.7%), distant lymph nodes (25.7%), liver (13.7%) and adrenal gland (8.7%). The brain ($p = 0.003$), liver ($p \leq 0.001$) and adrenal gland ($p = 0.001$) were more commonly involved in the BoM group, while lung ($p = 0.003$) and pleural ($p = 0.05$) involvement was more common in the non-BoM group. Distant lymph node metastasis occurred in similar frequency in the two groups ($p = 0.509$). Of note, multi-organ metastases (≥ 3) were more common in the BoM group ($p \leq 0.001$; Fig. 2).

4.3. Genetic aberrations in the two groups

Targeted sequencing results were collected for our patients. Data were available for 50 and 29 patients in the BoM and non-BoM groups, respectively (Fig. S2A). The L858R, TP53 and CDK4 mutations were more frequent in the BoM group. In addition, re-occurring genetic aberrations (defined as occurrence ≥ 3 in this cohort) were more commonly seen in the BoM group (Fig. S2B). Complex aberrations (defined as ≥ 3 parallel aberrations in 1 patient) were more common in the BoM group (Fig. S2C).

4.4. Worse outcomes in the BoM group

To explore the effect of BoM on TKI therapeutic efficacy, PFS and OS curves of the two groups were constructed and compared. The BoM group exhibited a shorter PFS (11.7 months, 95% CI: 10.9–12.5 months) and OS (32.8 months, 95% CI: 29.8–35.8 months) compared with the non-BoM group (PFS:14.0 months, HR = 0.73, 95% CI: 0.61–0.86, $p = 0.00013$; OS: 46.1 months, HR = 0.54, 95% CI:0.43–0.67, $p < 0.0001$; Fig. 3A and B).

To test whether the negative impact of BoM could be improved by osimertinib, information of salvage therapy with osimertinib after initial treatment failure was collected. In the BoM group, a total of 59 patients received subsequent osimertinib, compared with 64 patients in the non-BoM group. In this subgroup, unfavorable PFS and OS were still observed in the BoM group (PFS: 10.2 vs. 16.0 months, HR = 0.66, 95% CI: 0.42–1.04, $p = 0.059$; OS: 44.8 vs. 66.6 months, HR = 0.47, 95% CI: 0.26–0.85, $p = 0.0066$, Fig. S1A and B). Hence, the worse treatment efficacy with TKIs could not be rescued by osimertinib.

No CR was observed in the BoM group, while 1% CR was achieved in the non-BoM group. The BoM group achieved a similar DCR (95.7 vs. 97.7%, respectively) and ORR (71.7 vs. 67.8%) compared with the non-BoM group (Fig. 3C-E).

4.5. Multivariate cox regression analysis

Multivariate analysis indicated that bone and brain metastases and PS score influenced PFS independently (Fig. 4A), while bone, liver and brain metastases, PS score and sex influenced OS independently (Fig. 4B). Bone and brain metastases, as well as PS score, were proven to be independent factors for both PFS and OS ($p = 0.001$).

4.6. Subgroup analysis of metastatic organs

Subgroup analysis indicated that certain factors, including lung, brain, liver, adrenal gland, distant lymph node and pleural metas-

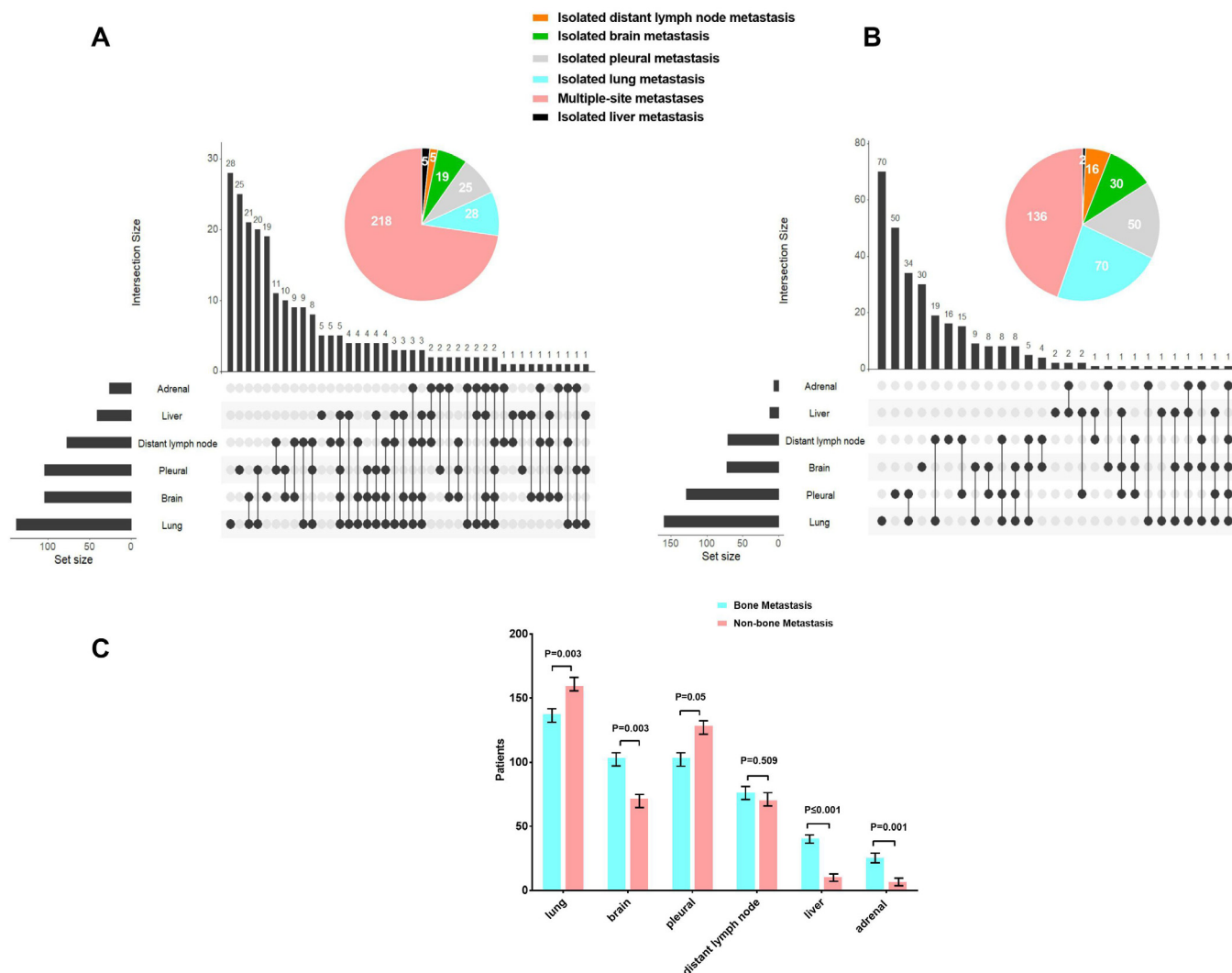


Fig. 2. Summary of metastatic sites in BoM (A) and Non-BoM group (B). Multi-organ metastases (≥ 3) were more common in BoM group ($p \leq 0.001$). In BoM group, brain ($p = 0.003$), liver ($p \leq 0.001$), and adrenal gland ($p = 0.001$) were more common, while lung ($p = 0.003$) and pleural ($p = 0.05$) were more significant in Non-BoM group. Distant lymph node metastases were similar in 2 groups ($p = 0.509$, C).

tases, all influenced PFS and OS. The non-BoM group was always superior to BoM group, regardless of the presence of organ metastases (Fig. 5).

4.7. Characteristics of patients with BoM

In the present study, the majority of the patients received treatment with bisphosphonates ($n = 214$, 71.3%). This treatment was not significantly associated with PFS (12.0 vs. 11.7 months, HR = 1.08, $p = 0.538$) or OS (31.7 vs. 33.2 months, HR = 0.86, $p = 0.393$). Only 3 patients received denosumab due to inaccessibility. A total of 67 (22.3%) and 19 (6.3%) patients received radiotherapy and surgery, respectively. Only a small number of patients experienced skeletal-related events (SRE, $n = 35$, 11.7%), including pathological fractures ($n = 24$, 8.0%), spinal cord compression ($n = 6$, 2.0%) and hypercalcemia ($n = 5$, 1.7%). The onset of SRE was associated with worse OS (33.5 vs. 26.1 months, HR = 1.84, $p = 0.005$).

5. Discussion

The present study described the association between BoM and therapeutic efficacy of TKIs in patients with advanced NSCLC. It

was demonstrated that BoM was associated with poor PFS and OS, and the inferior treatment efficacy could not be rescued by osimertinib as salvage therapy. In addition, the BoM group was prone to multi-organ metastases, and had more frequent re-occurring mutations and more complex aberrations. Finally, BoM was identified as an independent prognostic factor for both PFS and OS.

The mechanism of tumor metastasis to specific organs remains unknown. Chen et al. discovered that osteopontin (a SIBLING glycoprotein) was a predictive biomarker that was significantly associated with prognosis of NSCLC patients with BoM [9], while Hsiao et al. reported that lumican (a protein of the leucine-rich proteoglycan family and a main proteoglycan component of bone matrix) can promoted lung cancer cell migration to the bone via an auto-crine regulatory mechanism [10]. The results of the present study also indicated the metastasis to the bone was not random, but a highly regulated event.

The fact that BoM is associated with worse outcome in lung cancer has been well established [11–15]. Sugiura et al. reported that EGFR-TKIs may improve treatment efficacy in patients with BoM compared with other therapies [16]. Subsequent studies also confirmed that patients with BoM could benefit from treatment with TKIs [17,18]. However, no studies have described the prognos-

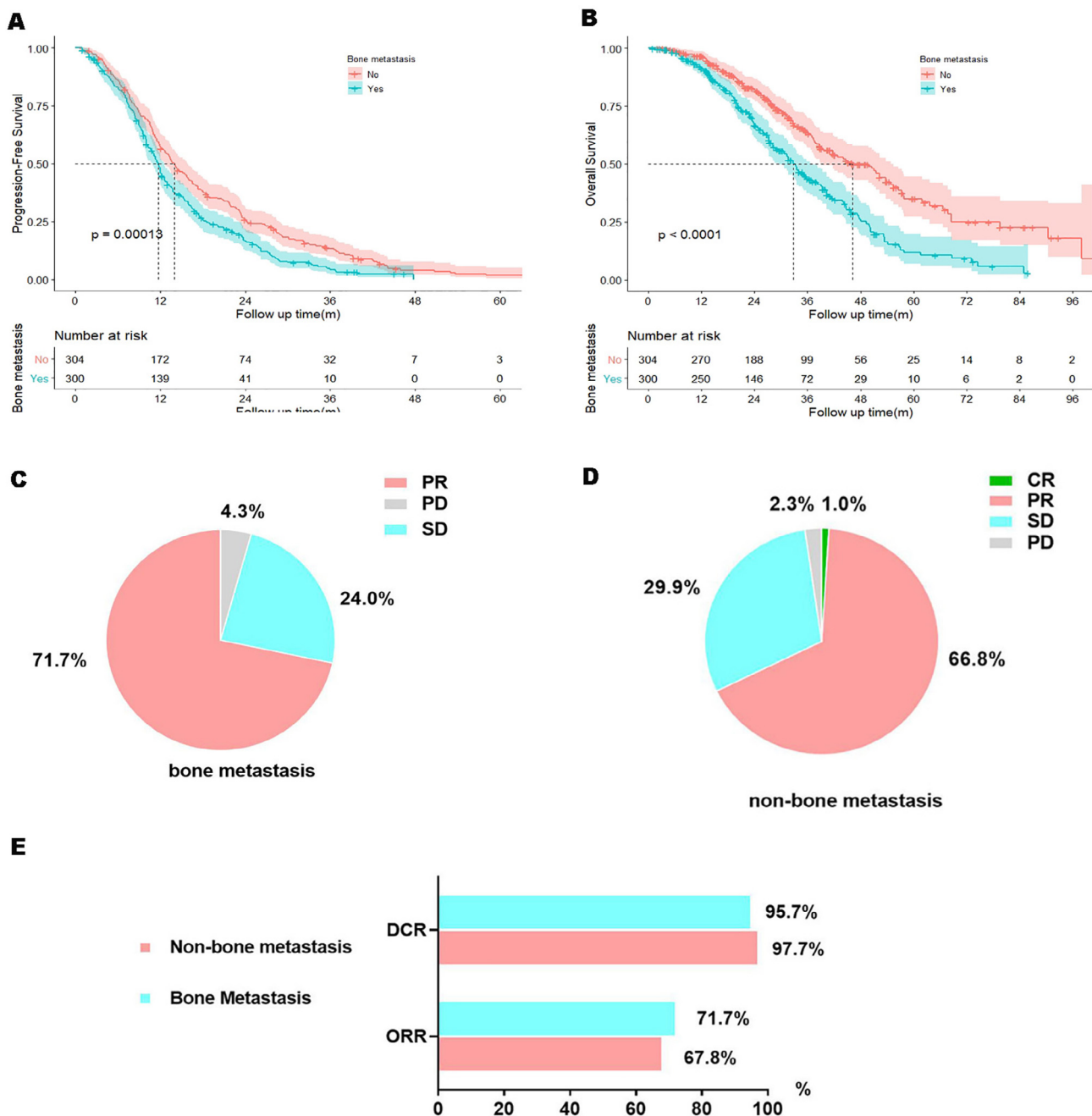


Fig. 3. Shorter PFS (A) or OS (B) in BoM group compared to Non-BoM group. Little difference in ORR (C bone metastasis, D non-bone metastasis, $p = 0.537$, E) was observed.

sis in NSCLC patients with BoM at the time of diagnosis and TKIs administered as initial therapy. To the best of our knowledge, our study was the first to demonstrate that BoM was linked to poor prognosis in patients receiving TKIs. Although osimertinib was recommended as salvage therapy for patients with T790M mutation after treatment with TKIs [19,20], the inferior efficacy of BoM could not be improved by osimertinib as second-line therapy in the present study. These results again validated that BoM was an independent factor for unfavorable outcome.

At present, the precise mechanism underlying the negative prognostic effect of BoM in NSCLC remains unclear. In this study, it was found that BoM was associated with propensity for multi-organ metastases, including brain and liver metastases, both of which are well-known factors associated with dismal prognosis [21,22]. A recent study based on the SEER database demonstrated

that the prognosis of lung cancer worsened with increasing number of metastatic sites [23]. Our study revealed that multi-organ involvement was more commonly observed in the BoM group.

In addition, several studies demonstrated that NSCLC patients with more gene mutations had a higher rate of organ metastases [24–31]. In the present study, the BoM group exhibited a higher frequency of mutations, which may be related to cancer cell transfer to other sites. Whether the genetic aberrations contributed to the selection of the organ metastasis pattern remains largely unknown, but there is evidence the genomic heterogeneity is associated with the clinical unresponsiveness to treatment [32–34].

There were certain limitations to the present study. First, due to the retrospective design of the study, potential biases were inevitable. The treatments were performed as per the physicians' discretion, and were not based on randomization, which may lead to

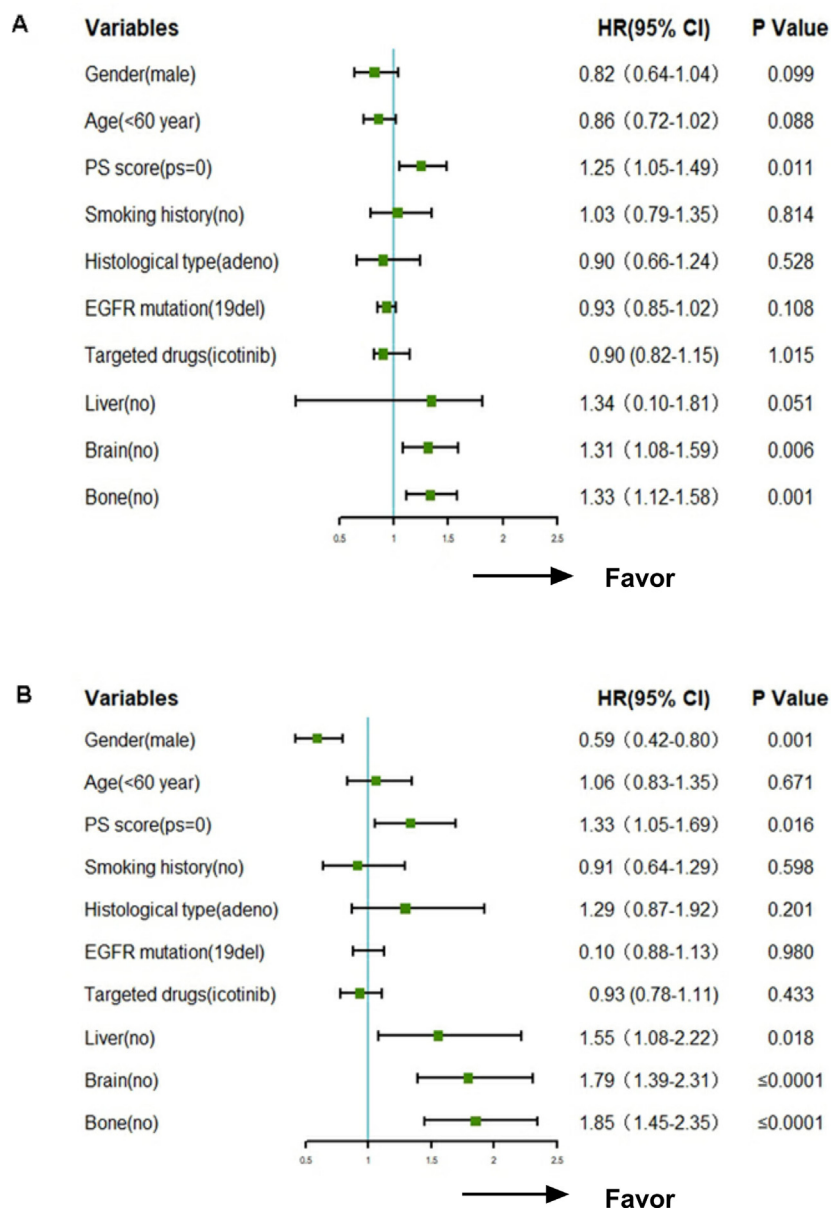


Fig. 4. Multivariate cox regression analysis (A: PFS, B: OS).

selection bias. In addition, subsequent therapies varied, which may affect survival. Furthermore, the presence of BoM was based on different radiographic examinations, each with different sensitivity and specificity. Second, genetic profiles were available in only a small fraction of our patients. This was because an NGS targeted sequencing platform was not available prior to 2017. Those without information on their genetic mutation landscape may possibly confound the present analysis. Third, the comparison of the BoM and non-BoM groups was not based on randomization.

In summary, the present study demonstrated that BoM was an independent poor prognostic factor for patients with advanced NSCLC harboring EGFR mutations after TKI treatment, and the outcome could not be improved by subsequent osimertinib therapy. Such patients were more likely to develop multiple organ metastasis and exhibited a higher frequency of gene mutations, which may be one of the reasons for the worse outcome observed among NSCLC patients with BoM. These findings may help to further improve our current understanding of the clinical and prognostic characteristics

of BoM, and they may also guide the design of more aggressive treatment for these patients.

6. Author Statement

None.

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None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

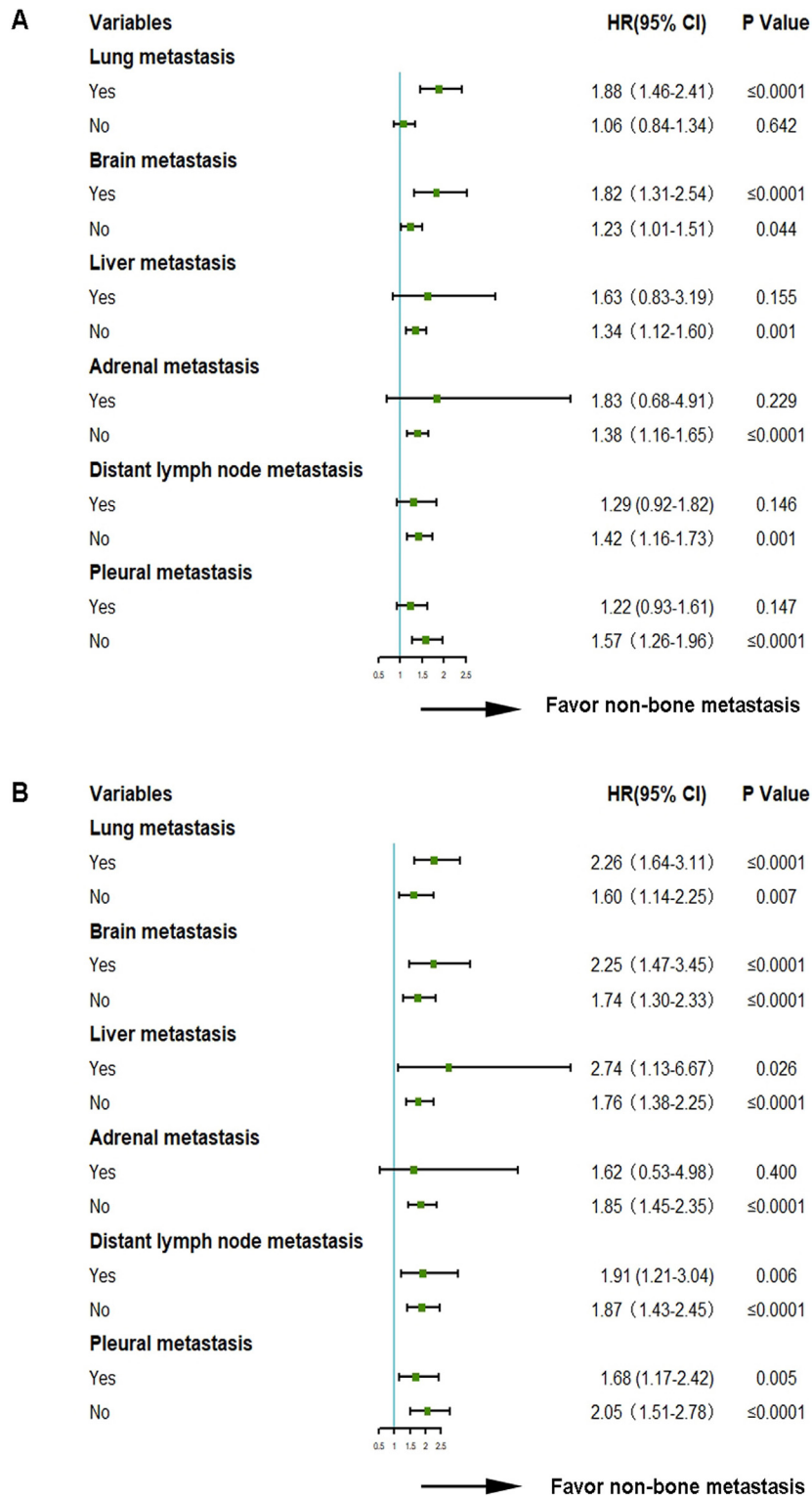


Fig. 5. Different metastatic organs were associated with PFS (A) or OS (B).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbo.2021.100369>.

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