

# Combination of immune checkpoint inhibitors and radiotherapy for bone metastases induces an abscopal effect and improves outcomes in non-small cell lung cancer

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**Abstract.** The combination of immune checkpoint inhibitors (ICIs) and radiotherapy (RT) improves outcomes in non-small cell lung cancer (NSCLC). However, the potential abscopal effect of RT for bone metastases (BoMs) remains unclear. The present retrospective study aimed to evaluate the impact of RT for BoMs on lung lesion response and survival in patients with NSCLC receiving ICIs. A total of 108 patients with NSCLC with BoMs treated with ICIs between March 2016 and January 2024 were included and divided into two groups based on whether they received RT for BoMs. Primary outcomes included the lung lesion response rate, overall survival (OS), progression-free survival (PFS) and incidence of immune-related adverse events (irAEs). Among 33 patients who received RT for BoM (RT-BoM group), the dose/fraction ranged from 2 to 8 Gy/1 to 15 fx (total 8–39 Gy). The lung lesion response rate was significantly higher in the RT-BoM group than in the non-RT-BoM group (n=75; 42.4 vs. 21.3%; P=0.03). The median OS and PFS times were significantly longer in the RT-BoM group (24.9 vs. 16.3 months, P=0.01; 11.0 months vs. 6.2 months, P=0.03), while the incidence of irAEs was comparable (21.2 vs. 21.3%; P=0.99). The group that received

RT before ICI initiation (n=22) had a significantly higher lung lesion response rate than the group that received RT after ICI initiation (n=11; 54.5 vs. 9.1%; P=0.02), with a trend toward prolonged OS and PFS. Multivariate analysis identified RT for BoMs as an independent predictor of lung response (P=0.02), OS (P=0.03) and PFS (P=0.02). RT for BoMs was associated with improved lung response and prognosis in patients with NSCLC receiving ICIs, suggesting a possible abscopal effect. Further validation in prospective studies with larger patient groups is warranted.

## Introduction

Recent advances in immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway have significantly improved treatment outcomes in non-small cell lung cancer (NSCLC), with improvements in overall survival (OS) and progression-free survival (PFS) (1–6). ICIs can yield favorable clinical outcomes even in patients with NSCLC and bone metastases (BoMs) (7–11), a condition traditionally associated with poor prognosis (12–14). However, not all patients respond favorably, highlighting a need for continued research to enhance the therapeutic efficacy of ICIs.

In our clinical experience, we have observed several cases of NSCLC with BoMs where bone-targeted radiotherapy (RT) combined with ICIs achieved lung tumor shrinkage and prolonged survival. This phenomenon, where tumors shrink at sites distant from the irradiated area, is known as the abscopal effect (15). RT promotes an antitumor immune response by inducing antigen release and immunogenic cell death, enhancing maturation and antigen presentation by antigen-presenting cells, mobilizing T cells, and sensitizing tumor cells to immune-mediated cell death, which may underlie the abscopal effect (15,16). Although the abscopal effect is rare and its mechanisms are unclear (17), ICIs may enhance immune responses induced by RT, suggesting a potential synergistic effect that could improve ICI efficacy (16–20). Notably, increased infiltration and enhanced cytotoxic function

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**Abbreviations:** BoM, bone metastasis; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RT, radiotherapy; SRE, skeletal-related event; TPS, tumor proportion score

**Key words:** NSCLC, BoM, ICI, RT, abscopal effect

of CD8<sup>+</sup> T cells within the tumor immune microenvironment have been reported to play a crucial role in augmenting the abscopal effect (21,22). However, the relationship between RT for BoMs and the abscopal effect in ICI-treated NSCLC has not been elucidated. The study aimed to determine whether RT for BoMs induces an abscopal effect in ICI-treated NSCLC and the clinical benefits of this effect.

## Patients and methods

**Study design and patient population.** This retrospective study included patients with advanced NSCLC diagnosed with BoMs before receiving ICI treatment between January 2016 and March 2024 at Kanazawa University Hospital. The ICIs used in this study were PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitors (atezolizumab and durvalumab). For patients with negative driver-gene mutations and a PD-L1 tumor proportion score (TPS) >50%, first-line treatment was PD-1/PD-L1 inhibitor monotherapy or combination therapy with platinum-based agents. In other cases, ICIs were employed as second-line or later therapy following failure of conventional chemotherapy or molecular-targeted treatments. To accurately evaluate the effects of RT on BoMs, patients who had received RT for lung lesions or brain metastases, as well as those who had been treated with bone-modifying agents for BoMs, were excluded. Additionally, patients with a performance status of 3 or higher and those who received combination therapy with PD-1/PD-L1 inhibitors and cytotoxic T-lymphocyte-associated protein-4 inhibitors were excluded. This study was approved by the Medical Ethics Committee of Kanazawa University (approval number: 3339-1) and was conducted in accordance with relevant laws and institutional guidelines as well as with the tenets enunciated in the Declaration of Helsinki. Written informed consent was waived due to the retrospective design. Instead, consent was obtained via an opt-out method approved by the ethics committee, with study information provided publicly to allow patients to decline participation.

**Data analysis.** The medical records used in this study were collected from the Kanazawa University Hospital database. Data included patient characteristics such as age, sex, histological type, Eastern Cooperative Oncology Group performance status, PD-L1 TPS, number of BoM, visceral metastasis, and ICI and RT history, including timing and site of BoM. All data were reviewed independently by at least two investigators to ensure accuracy and consistency. Patients who received RT to treat multiple bone lesions were excluded to evaluate the therapeutic effect of radiation on a single metastatic bone lesion. Participants were divided into two groups: irradiated (RT-BoM) and non-irradiated BoMs (non-RT-BoM), and clinical outcomes were evaluated by assessing responses in lung lesions, OS, PFS, and the incidence of immune-related adverse events (irAEs, grade  $\geq 3$  based on Common Terminology Criteria for Adverse Events version 5.0). To evaluate local control of BoMs with and without irradiation, spinal paralysis and pathological fractures during ICI treatment were assessed. Lung lesion response was assessed based on Response Evaluation Criteria in Solid Tumors version 1.1, with size changes measured via computed tomography between ICI initiation and the final follow-up. This radiological evaluation

was performed by at least two physicians, including radiologists, to ensure accuracy and reliability.

**Statistical analysis.** OS and PFS from ICI treatment initiation were assessed using the Kaplan-Meier curve analysis. All clinical data were used as variables, with Fisher's exact and log-rank tests to compare between the two groups. In addition, logistic regression and the COX proportional hazards models were used in multivariate analysis to assess correlations between clinical data and outcomes and identify independent predictive factors. Cases with missing data for key variables or primary outcomes were excluded from the analysis. However, PD-L1 TPS was not assessed in some patients; these cases were included in the analysis as a separate unknown category. A P-value <0.05 was considered significant, and EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for all statistical analyses.

## Results

**Clinical characteristics.** In total, 108 patients with NSCLC having BoMs were enrolled, and their clinical characteristics are summarized in Table I. This study included 80 men and 28 women, with a mean age of 66.6 $\pm$ 8.6 years. The median follow-up time from initiation of ICI treatment was 21.8 (2-101) months. The RT-BoM and non-RT-BoM groups included 33 and 75 patients, respectively, with no significant difference observed for clinical characteristics (Table I). In the RT-BoM group, the dose/fraction was 2-8 Gy/1-15 fx (total dose 8-39 Gy) and the most frequently irradiated site was the spine. Additionally, 66.7% of cases received radiation before initiating ICI (Table I).

**Clinical outcomes between RT-BoM vs. non-RT-BoM groups.** The overall response rate of lung lesions in the RT-BoM group was 42.4%, which was significantly better than that in the non-RT-BoM group (21.3%, P=0.03). The median OS and PFS in the RT-BoM group were 24.9 (17.6-NA) and 11.0 (4.9-29.6) months, respectively, significantly longer than those in the non-RT-BoM group [16.3 (11.6-20.4) months, P=0.01; 6.2 (4.4-9.8) months, P=0.03] (Fig. 1A and B). The incidence of irAEs in the RT-BoM group was 21.2%, similar to that in the non-RT-BoM group (21.3%), with no significant difference (P=0.99). No skeletal-related events (SREs) were observed after radiation in the RT-BoM group; however, two cases of pathological fracture were observed in the non-RT-BoM group during ICI treatment (both cases required surgery for vertebral pathological fractures and paralysis).

Furthermore, subgroup analyses were performed for the RT-BoM group. The group that received radiation before ICI initiation (n=22) had a significantly better lung lesion response rate than the group that received radiation after ICI initiation (n=11) (54.5 vs. 9.1%, P=0.02). Although no significant difference was observed in OS [24.9 (18.9-NA) vs. 21.0 (3.3-NA) months, P=0.58] or PFS [18.2 (5.1-NA) vs. 6.4 (1.4-64.9) months, P=0.45] between the two groups, a trend toward prolonged OS and PFS was noted in the group that received radiation before initiating ICIs. Irradiation sites of BoM were analyzed in the spine (n=22) and pelvis (n=11), where case numbers were high. No significant differences were observed

Table I. Clinical characteristics of participants.

| Clinical characteristic       | RT-BoM, n (n=33) | Non-RT-BoM, n (n=75) | P-value |
|-------------------------------|------------------|----------------------|---------|
| Sex                           |                  |                      | 0.63    |
| Male                          | 26               | 54                   |         |
| Female                        | 7                | 21                   |         |
| Age, years                    |                  |                      | 0.52    |
| ≥70                           | 21               | 42                   |         |
| <70                           | 12               | 33                   |         |
| Histology                     |                  |                      | 0.81    |
| Adenocarcinoma                | 25               | 59                   |         |
| Non-adenocarcinoma            | 8                | 16                   |         |
| PD-L1 TPS, %                  |                  |                      | 0.98    |
| <50                           | 15               | 34                   |         |
| ≥50                           | 7                | 17                   |         |
| Unknown                       | 11               | 24                   |         |
| PS                            |                  |                      | 0.51    |
| ≤1                            | 28               | 68                   |         |
| 2                             | 5                | 7                    |         |
| ICIs                          |                  |                      | 0.98    |
| PD-1 inhibitor                | 22               | 51                   |         |
| PD-L1 inhibitor               | 11               | 24                   |         |
| Treatment line of ICIs        |                  |                      | 0.19    |
| 1st                           | 18               | 51                   |         |
| ≥2nd                          | 15               | 24                   |         |
| Number of BoM                 |                  |                      | 0.81    |
| Monostotic                    | 9                | 18                   |         |
| Multiple                      | 24               | 57                   |         |
| Visceral metastasis           |                  |                      | 0.62    |
| Yes                           | 27               | 57                   |         |
| No                            | 6                | 18                   |         |
| Radiation to BoM timing       |                  |                      |         |
| Pre-ICI treatment             | 22               |                      |         |
| Post-ICI treatment            | 11               |                      |         |
| Site                          |                  |                      |         |
| Spine                         | 20               |                      |         |
| Pelvis                        | 11               |                      |         |
| Long bones of the extremities | 2                |                      |         |

BoM, bone metastasis; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PS, performance status; RT, radiotherapy; TPS, tumor proportion score.

between lung lesion response (22.7 vs. 36.3%,  $P=0.61$ ), OS [24.8 (8.6-NA) vs. 22.6 (8.6-NA) months,  $P=0.44$ ], and PFS [8.9 (3.6-NA) vs. 18.1 (4.8-NA) months,  $P=0.27$ ]. However, due to the limited number of cases in each group, these findings should be interpreted with caution.

*Predictive factors of clinical outcomes.* Univariate analysis identified predictors of lung lesion response, revealing significant differences in sex [odds ratio and 95% confidence interval: 0.23 (0.06-0.85),  $P=0.02$ ] and radiation for BoM (2.72 (1.12-6.58),  $P=0.01$ ). Multivariate analysis incorporating these

factors revealed that radiation for BoM was an independent predictor [3.69 (1.20-11.40),  $P=0.02$ ] (Table II). Univariate analysis for OS predictors showed significant differences in visceral metastasis [hazard ratio and 95% confidence interval: 2.72 (1.12-6.58),  $P=0.02$ ] and radiation for BoM [2.21 (1.22-3.97),  $P<0.01$ ]. Multivariate analysis confirmed radiation for BoM as an independent predictor of OS [2.22 (1.23-4.01),  $P<0.01$ ] (Table III). For PFS, univariate analysis showed significant differences in sex [1.68 (1.05-2.70),  $P=0.03$ ], treatment line of ICIs [1.73 (1.12-2.67),  $P=0.01$ ], and radiation for BoM [0.60 (0.36-0.97),  $P=0.04$ ]. Multivariate analysis incorporating these

Table II. Univariate and multivariate analyses of lung lesion response.

| Variable               | Comparison                         | Univariate analysis |         | Multivariate analysis |         |
|------------------------|------------------------------------|---------------------|---------|-----------------------|---------|
|                        |                                    | OR (95% CI)         | P-value | OR (95% CI)           | P-value |
| Sex                    | Male vs. female                    | 0.23 (0.06-0.85)    | 0.02    | 0.48 (0.11-2.17)      | 0.34    |
| Age                    | ≥70 vs. <70 years                  | 1.11 (0.46-2.58)    | 0.82    |                       |         |
| Histology              | ADC vs. non-ADC                    | 2.29 (0.88-5.94)    | 0.09    |                       |         |
| PD-L1 TPS              | <50 vs. ≥50                        | 1.25 (0.43-3.58)    | 0.67    |                       |         |
| PS                     | ≤1 vs. 2                           | 2.03 (0.59-6.97)    | 0.26    |                       |         |
| ICIs                   | PD-1 inhibitor vs. PD-L1 inhibitor | 0.42 (0.15-1.15)    | 0.09    |                       |         |
| Treatment line of ICIs | 1st vs. ≥2nd                       | 0.43 (0.16-1.14)    | 0.09    |                       |         |
| Number of BoMs         | Monostotic vs. multiple            | 1.65 (0.59-4.59)    | 0.33    |                       |         |
| Visceral metastasis    | Yes vs. no                         | 2.50 (0.77-8.02)    | 0.12    |                       |         |
| Radiation to BoM       | Yes vs. no                         | 2.72 (1.12-6.58)    | 0.02    | 3.69 (1.20-11.40)     | 0.02    |

ADC, adenocarcinoma; BoM, bone metastasis; ICI, immune checkpoint inhibitor; OR, odds ratio; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PS, performance status; TPS, tumor proportion score.

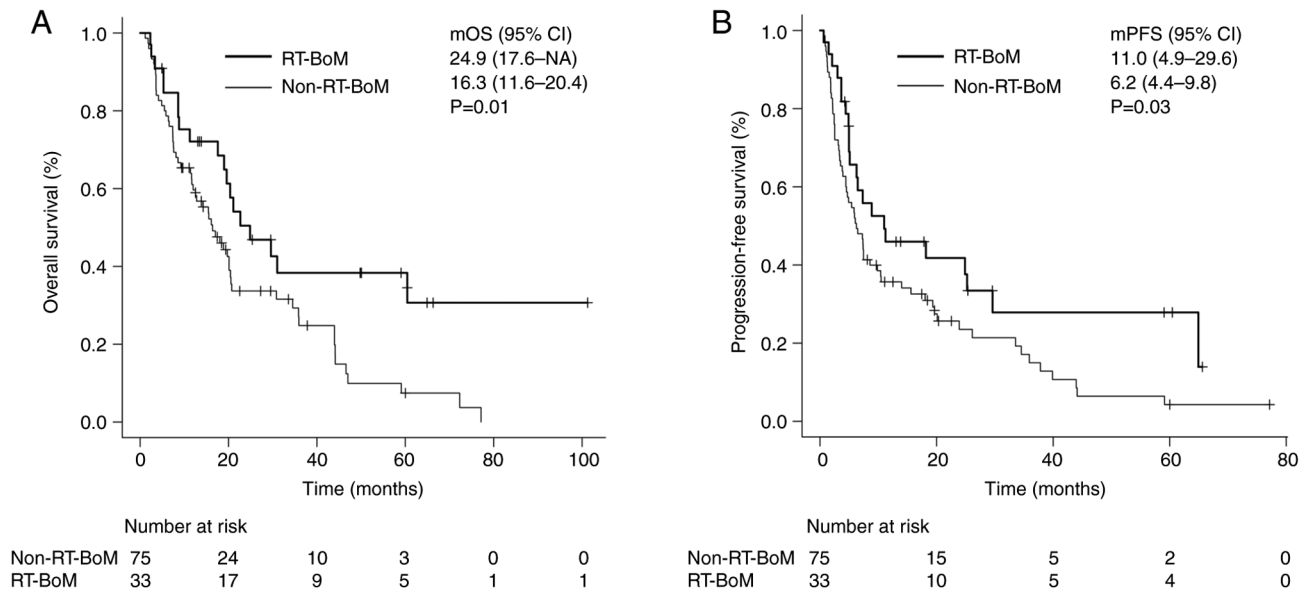


Figure 1. (A) Overall survival and (B) progression-free survival in the RT-BoM and non-RT-BoM groups. BoM, bone metastasis; mOS, median overall survival; mPFS, median progression-free survival; RT, radiotherapy.

factors revealed that treatment line of ICIs (1.84 [1.16-2.91],  $P=0.01$ ) and radiation for BoM (0.56 [0.33-0.93],  $P=0.02$ ) were independent predictors of PFS (Table IV).

## Discussion

Our study found that combined therapy with ICIs and RT for BoM in advanced NSCLC may induce a favorable response in lung lesions, considered an abscopal effect, and prolong prognosis, in addition to providing good local control of BoMs.

Recent, large-scale studies on immunotherapy combining ICIs and RT (23-32) have demonstrated that ICI treatment enhances the immune response induced by RT, whereas RT enhances the therapeutic effect of ICIs, confirming the existence of the abscopal effect (18-20). Several systematic

reviews and meta-analyses have reported the occurrence of the abscopal effect at distant sites, alongside prolonged OS and PFS with the combination of ICIs and RT (20,33-36). However, the abscopal effect remains rare, and its underlying mechanism is not yet fully understood (17). Additionally, the relationship between irradiation of BoMs and abscopal effect in NSCLC has rarely been studied.

BoM is a poor prognostic factor in lung cancer (12-14), and SREs, such as severe pain, pathological fracture, and spinal cord compression, significantly reduces daily activity and quality of life (37,38). Therefore, early management of BoMs is crucial to prevent SREs. Generally, RT and bone-modifying agents are commonly used in combination to avoid interfering with systemic therapy (39-41). This study focused on RT for BoMs and explored its potential to improve ICI treatment

Table III. Univariate and multivariate analyses of overall survival.

| Variable               | Comparison                         | Univariate analysis |         | Multivariate analysis |         |
|------------------------|------------------------------------|---------------------|---------|-----------------------|---------|
|                        |                                    | HR (95% CI)         | P-value | HR (95% CI)           | P-value |
| Sex                    | Male vs. female                    | 1.33 (0.82-2.17)    | 0.23    |                       |         |
| Age                    | ≥70 vs. <70 years                  | 1.42 (0.91-2.23)    | 0.11    |                       |         |
| Histology              | ADC vs. non-ADC                    | 1.01 (0.57-1.74)    | 0.99    |                       |         |
| PD-L1 TPS              | <50 vs. ≥50                        | 1.01 (0.53-1.86)    | 0.98    |                       |         |
| PS                     | ≤1 vs. 2                           | 1.17 (0.61-2.29)    | 0.63    |                       |         |
| ICIs                   | PD-1 inhibitor vs. PD-L1 inhibitor | 1.31 (0.81-2.11)    | 0.28    |                       |         |
| Treatment line of ICIs | 1st vs. ≥2nd                       | 1.56 (0.99-2.46)    | 0.06    |                       |         |
| Number of BoMs         | Monostotic vs. multiple            | 1.54 (0.90-2.61)    | 0.11    |                       |         |
| Visceral metastasis    | Yes vs. no                         | 2.72 (1.12-6.58)    | 0.02    | 1.28 (0.80-2.04)      | 0.31    |
| Radiation to BoM       | Yes vs. no                         | 2.21 (1.22-3.97)    | <0.01   | 2.22 (1.23-4.01)      | <0.01   |

ADC, adenocarcinoma; BoM, bone metastasis; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PS, performance status; TPS, tumor proportion score.

Table IV. Univariate and multivariate analyses of progression-free survival.

| Variable               | Comparison                         | Univariate analysis |         | Multivariate analysis |         |
|------------------------|------------------------------------|---------------------|---------|-----------------------|---------|
|                        |                                    | HR (95% CI)         | P-value | HR (95% CI)           | P-value |
| Sex                    | Male vs. female                    | 1.68 (1.05-2.70)    | 0.03    | 1.51 (0.93-2.45)      | 0.08    |
| Age                    | ≥70 vs. <70 years                  | 0.91 (0.59-1.41)    | 0.69    |                       |         |
| Histology              | ADC vs. non-ADC                    | 0.87 (0.52-1.47)    | 0.62    |                       |         |
| PD-L1 TPS              | <50 vs. ≥50                        | 0.85 (0.47-1.51)    | 0.58    |                       |         |
| PS                     | ≤1 vs. 2                           | 1.45 (0.76-2.74)    | 0.25    |                       |         |
| ICIs                   | PD-1 inhibitor vs. PD-L1 inhibitor | 1.31 (0.82-2.11)    | 0.24    |                       |         |
| Treatment line of ICIs | 1st vs. ≥2nd                       | 1.73 (1.12-2.67)    | 0.01    | 1.84 (1.16-2.91)      | 0.01    |
| Number of BoMs         | Monostotic vs. multiple            | 1.56 (0.93-2.61)    | 0.08    |                       |         |
| Visceral metastasis    | Yes vs. no                         | 1.43 (0.83-2.44)    | 0.18    |                       |         |
| Radiation to BoM       | Yes vs. no                         | 2.21 (1.22-3.97)    | <0.01   | 2.22 (1.23-4.01)      | <0.01   |

ADC, adenocarcinoma; BoM, bone metastasis; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PS, performance status; TPS, tumor proportion score.

efficacy. This favorable treatment effect, which can be considered an abscopal effect, may improve clinical outcomes for patients with NSCLC presenting BoMs, who typically have a poor prognosis.

Our study found that irradiation of BoMs improved the response rate of lung lesions and prolonged prognosis, consistent with reports of the abscopal effect induced by RT of lung or brain lesions (20,33-36), as well as recent findings by Facilissimo *et al* (42) demonstrating similar benefits of RT to BoMs in NSCLC patients receiving ICIs. In addition, no spinal paralysis and pathological fractures occurred at the irradiated site, and good local control was achieved. The incidence of grade 3 or higher irAEs, evaluated as a safety measure, was similar between the RT-BoM and non-RT-BoM groups and consistent with previous studies (36,43,44). Subgroup analysis for investigating optimal RT strategy suggested that RT prior

to ICI treatment may result in better clinical outcomes. Our results aligned with the suggestion that the optimal timing for RT is either concomitant with or prior to ICI administration (19,45). Based on these results, irradiated BoMs before initiating ICIs may provide good local control, pulmonary response, and prolonged prognosis, which can be considered an abscopal effect, for advanced NSCLC. Our analysis found no significant differences in clinical outcomes among different irradiated BoM sites, suggesting that therapeutic benefits may apply broadly. However, due to limited sample size and site heterogeneity, further studies are needed to explore site-specific effects and optimize treatment. While our results are promising, the retrospective nature and heterogeneity in RT protocols preclude definitive clinical recommendations. Further prospective studies are needed to determine the optimal timing, dosage, fractionation, and the role of irradiated

sites to establish standardized treatment protocols for clinical practice.

This study had several limitations. First, it was a retrospective analysis conducted at a single center without randomization or a control group, which may have introduced selection bias and limited generalizability. Second, the RT-BoM group included a small number of patients ( $n=33$ ), and RT regimens varied in dose, fractionation, and treatment site, limiting the evaluation of specific RT parameters. Third, although a possible abscopal effect was suggested, its underlying mechanisms remain unclear. Notably, we did not assess changes in the tumor immune microenvironment or PD-L1 expression, which limits interpretation of the immunological response. Further prospective, multi-center studies, including randomized controlled trials with standardized RT protocols and immune profiling, are necessary to validate and expand upon these findings.

In conclusion, in ICI treatment of NSCLC with BoMs, irradiation of BoMs was associated with improved lung lesion response and prolonged prognosis, suggesting a possible abscopal effect. In addition to local control of BoMs, systemic clinical benefits were observed. However, due to the limitations of this study, including its retrospective single-center design, small sample size, and heterogeneity in RT protocols, these findings should be interpreted with caution. Further prospective, multi-center studies and mechanistic investigations are warranted to confirm and better understand the observed effects and to develop an optimized immunoradiotherapeutic strategy.

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## Availability of data and materials

The data generated in the present study are not publicly available due to privacy or ethical restrictions but may be requested from the corresponding author.

## Authors' contributions

YA, KH, MO, IM, SY and SD conceptualized the study. YA, KH, SM, YT, MO, IM and SY developed the methodology. YA performed the formal analysis. YA, KH, SM, YT, MO, IM and SY conducted the investigation and data acquisition. KH, SY and SD confirm the authenticity of all the raw data. YA wrote the original draft. KH, MO, IM, SY and SD performed review and editing. KH and SD supervised the study. All authors have read and approved the final version of the manuscript.

## Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Kanazawa University (no. 3339-1; Kanazawa, Japan). The requirement for written informed consent was

waived due to the retrospective design. Instead, consent was obtained via an opt-out method approved by the ethics committee, with study information provided publicly to allow patients to decline participation.

## Patient consent for publication

Written informed consent for publication was not required for the present study because all data were fully anonymized and contained no identifiable patient information.

## Competing interests

The authors declare that they have no competing interests.

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