

ORIGINAL RESEARCH ARTICLE

Planning target volume, biological dose, and radiological response following radiotherapy for bone metastases: An exploratory analysis

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Abstract

Planning target volume (PTV) is routinely used in radiotherapy planning, but its relationship with treatment response in bone metastases remains insufficiently characterized. This retrospective single-center study evaluated associations of PTV and biologically effective dose (BED10) with objective radiological response and pain reduction in 40 patients treated with radiotherapy between 2024 and 2025. Radiological response was evaluable in 28 patients; complete and partial responses were classified as response. Associations with objective response were assessed using Firth penalized logistic regression, the relationship between PTV and BED10 using Spearman correlation, and PTV discrimination using receiver operating characteristic analysis with bootstrap confidence intervals. Fifteen patients were responders and 13 were non-responders. PTV and BED10 were inversely correlated (Spearman’s $\rho = -0.471$, $p = 0.011$). In multivariable Firth regression, larger PTV was associated with lower odds of objective response after adjustment for BED10 (OR per 100-cm³ increase, 0.752; 95% CI, 0.532–0.978; $p = 0.032$), whereas BED10 was not independently associated with response (OR per 10-Gy increase, 0.827; 95% CI, 0.347–1.995; $p = 0.661$). PTV showed modest discrimination (AUC = 0.685; bootstrap 95% CI, 0.462–0.882), and an exploratory cutoff of 427.4 cm³ yielded 93.3% sensitivity and 53.8% specificity. PTV was not significantly associated with pain reduction. These exploratory findings suggest that treatment volume and biological dose should be considered jointly and that radiological and symptomatic outcomes represent distinct dimensions of treatment efficacy. Prospective validation is required.

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1. Introduction

Bone metastases are among the most common complications of advanced malignancies and are associated with pain, impaired mobility, pathological fractures, and reduced quality of life. Radiotherapy is one of the main treatment modalities for patients with symptomatic bone metastases, providing effective pain relief and local tumor control

while contributing to preservation of function and quality of life. Current clinical guidelines from American Society for Radiation Oncology (ASTRO) and European Society for Radiotherapy and Oncology (ESTRO) continue to support external beam radiotherapy as a standard treatment option for both uncomplicated and complicated bone metastases.¹⁻³

Advances in radiotherapy techniques have expanded treatment possibilities, enabling highly conformal irradiation and, in appropriately selected patients, delivery of higher biological doses while limiting exposure of surrounding normal tissues. Contemporary systematic reviews and meta-analyses indicate high rates of local control after SBRT for appropriately selected spinal and non-spinal bone metastases, although outcomes vary according to treatment regimen, metastatic site, and patient selection.^{4,5} Biologically effective dose (BED) provides a radiobiological framework for comparing different fractionation schedules by incorporating total dose and dose per fraction.⁶ BED-based comparisons are therefore widely used when evaluating conventional, hypofractionated, and stereotactic radiotherapy regimens.^{7,8}

Alongside dose and fractionation, increasing attention has been directed toward the potential influence of treatment volume on radiotherapy outcomes. Larger tumor volumes have been associated with inferior outcomes after radiotherapy in several malignancies, including lung and head and neck cancers.⁹⁻¹¹ Importantly, a volume-outcome relationship has also been reported specifically in patients undergoing stereotactic body radiotherapy (SBRT) for bone metastases. Erler *et al.*¹² demonstrated an association between larger planning target volume (PTV) and local recurrence following SBRT for non-spine bone metastases. In a subsequent larger series of 505 non-spine bone metastases, larger PTV was independently associated with local failure, while dose-related parameters also contributed to treatment outcome.¹³ More recent evidence evaluating gross tumor volume has further supported an association between increasing target volume and inferior local outcomes after SBRT for bone oligometastases.¹⁴

These observations are clinically relevant because PTV and BED represent different but potentially interrelated aspects of radiotherapy. BED characterizes the biological effect of a fractionation regimen, whereas PTV is a treatment-planning construct incorporating the delineated target and margins required for treatment delivery.^{15,16} PTV should therefore not be regarded as synonymous with gross tumor volume or total tumor burden. At the same time, target volume may capture clinically relevant information related to lesion extent, anatomical complexity,

and treatment geometry. The relative and combined associations of PTV and BED with treatment response in heterogeneous populations receiving radiotherapy for bone metastases remain insufficiently characterized.

Moreover, treatment efficacy in bone metastases is multidimensional. Radiological tumor response and pain relief are both clinically relevant outcomes but may not necessarily occur in parallel. Pain response is influenced not only by tumor regression but also by mechanical, inflammatory, neurological, and patient-related factors.^{17,18} Randomized evidence comparing stereotactic and conventional radiotherapy further illustrates that treatment effects on pain-related outcomes may vary according to treatment approach and clinical setting.¹⁹ Evaluation of radiological and symptomatic outcomes as separate endpoints may therefore provide a more complete assessment of treatment response.

Accordingly, the aim of the present study was to investigate the associations of PTV and BED10 with objective radiological response in patients undergoing radiotherapy for bone metastases and to examine the relationship between PTV and BED10. We additionally evaluated the association of treatment volume with pain reduction to explore whether radiological and symptomatic responses demonstrated similar relationships with PTV.

2. Materials and methods

2.1. Study design and patients

This retrospective single-center study included all 40 eligible patients with bone metastases who underwent radiotherapy between 2024 and 2025 at the State Institute “Shalimov’s National Scientific Center of Surgery and Transplantation” of the National Academy of Medical Sciences of Ukraine. Eligibility required available treatment-planning data, dosimetric parameters, and clinical follow-up information. As the study comprised all eligible patients treated during the predefined study period, no formal *a priori* sample size calculation was performed.

Clinical data were retrieved from medical records, including age, sex, primary tumor type, anatomical site of bone metastases, pain intensity, radiotherapy characteristics, PTV, and follow-up information. Objective radiological response could be evaluated in 28 of the 40 patients. The remaining 12 patients lacked sufficient or comparable post-treatment imaging for reliable objective response assessment and were therefore excluded from response-based analyses but retained in analyses of baseline characteristics and other available clinical variables.

To assess potential selection bias associated with unavailable radiological response data, baseline

characteristics of patients with and without evaluable objective response were compared in a sensitivity analysis.

This retrospective study analyzed anonymized clinical data from patients who received radiotherapy as part of routine clinical care during 2024–2025. All patients provided voluntary informed consent for treatment, and no additional interventions were performed for the purposes of this study. The retrospective study protocol was reviewed and approved by the Bioethics Committee of the State Institution “Shalimov’s National Scientific Center of Surgery and Transplantation” of the National Academy of Medical Sciences of Ukraine (Protocol No. 4, May 22, 2026). The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable national regulations.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2. Radiotherapy treatment and dosimetric parameters

All patients underwent computed tomography (CT)-based treatment planning with appropriate immobilization, target delineation, individualized treatment planning, and image-guided radiotherapy (IGRT). Target delineation and treatment planning followed institutional practice and contemporary recommendations for radiotherapy of bone metastases.^{1–3,8}

PTV was defined as the treatment-planning volume encompassing the delineated target, with margins to account for treatment setup and geometric uncertainties.^{15,16} PTV therefore represents a radiotherapy planning parameter and should not be interpreted as a direct measurement of gross tumor volume or total systemic tumor burden.

Fractionation schedules were selected individually according to lesion characteristics, anatomical location, treatment intent, expected normal-tissue constraints, and multidisciplinary clinical assessment. The cohort included both conventional/hypofractionated radiotherapy and stereotactic body radiotherapy (SBRT) approaches.

For comparison of different fractionation schedules, the biologically effective dose for tumor tissue (BED10) was calculated using the linear-quadratic model.⁶

$$\text{BED10} = nd [1 + d/(\alpha/\beta)]$$

where n is the number of fractions, d is the dose per fraction in Gy, and α/β was set at 10 Gy for tumor tissue. BED10 values ranged from 28.0 to 60.0 Gy in the study cohort.

For patients with more than one irradiated metastatic lesion, the lesion selected for response analysis was matched to its corresponding PTV, fractionation schedule, BED10, and radiological outcome. Thus, treatment parameters and objective response used in the analysis referred to the same irradiated target.

2.3. Assessment of objective radiological response

Objective radiological response was evaluated during follow-up performed approximately 3–6 months after completion of radiotherapy. Follow-up imaging timing varied according to the treatment program, primary tumor histology, clinical status, and patient availability.

Response assessment was based on available imaging, including CT, magnetic resonance imaging (MRI), bone scintigraphy, and, where available, positron emission tomography/computed tomography (PET/CT). When feasible, we used the same imaging modality at baseline and follow-up (e.g., CT-to-CT, MRI-to-MRI, or bone scintigraphy-to-bone scintigraphy) to improve longitudinal comparability. PET/CT was not routinely repeated in all patients because of limited availability and cost considerations.

Radiological response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST 1.1 principles, where applicable to the evaluated lesion.²⁰ Patients with CR or PR were classified as responders, whereas those with SD or PD were classified as non-responders.

Radiologists at the diagnostic centers where examinations were performed provided the initial imaging reports. Imaging findings were subsequently reviewed within the treating department by a radiologist together with a radiation oncologist in the context of clinical follow-up. Formal blinded independent central radiological review was not performed.

Of the 40 patients, 28 had sufficient radiological information for objective response classification: 9 achieved CR, 6 achieved PR, 5 had SD, and 8 had PD. Accordingly, the response analysis included 15 responders and 13 non-responders.

2.4. Assessment of pain response

Pain intensity was assessed using the Visual Analogue Scale (VAS) before radiotherapy and during clinical follow-up. The change in pain intensity (ΔPain) was defined as the absolute reduction in VAS score:

$$\Delta\text{Pain} = \text{Baseline VAS} - \text{Post-treatment VAS}.$$

Thus, ΔPain represents the absolute number of VAS points by which pain decreased rather than a percentage change. The relationship between PTV and pain reduction was analyzed separately from objective radiological response because symptomatic and radiological outcomes may reflect different aspects of treatment benefit.

2.5. Statistical analysis

Continuous variables were summarized using the mean $\pm$ standard deviation when appropriate and the median with interquartile range or range, as specified. Categorical variables were presented as frequencies and percentages. Between-group comparisons were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Because objective radiological response was evaluable in only 28 patients and the number of outcome events was limited, conventional maximum-likelihood multivariable logistic regression was considered potentially susceptible to small-sample bias and model instability. Therefore, Firth penalized logistic regression was used as the primary regression approach to evaluate associations between treatment parameters and objective response.²¹ Objective response (CR + PR versus SD + PD) was the binary dependent variable, with PTV and BED10 entered as explanatory variables.

To facilitate clinical interpretation of effect estimates, PTV was scaled per 100-cm³ increase and BED10 per 10-Gy increase. Univariable Firth models were first fitted for PTV and BED10, followed by a multivariable Firth model including both variables. Odds ratios (ORs) with 95% confidence intervals (CIs) and two-sided p -values were reported. Given the limited sample size and absence of an independent validation cohort, regression analyses were considered exploratory and hypothesis-generating.

The relationship between PTV and BED10 was assessed using Spearman's rank correlation coefficient in both the entire cohort and the radiologically evaluable cohort to investigate potential interdependence between target volume and prescribed biological dose.

Receiver operating characteristic (ROC) analysis was performed to explore the discriminative ability of PTV for objective radiological response. The area under the ROC curve (AUC) was calculated, and an exploratory PTV cutoff was identified. The uncertainty of the AUC estimate was evaluated using bootstrap resampling to obtain a 95% CI. Because the cutoff was derived and evaluated within the same small cohort and was not externally validated, it was considered exploratory and was not interpreted as a clinically established threshold.

The discriminative performance of PTV alone was also descriptively compared with that of the combined PTV + BED10 Firth model. Given the sample size and absence of model validation, differences in AUC were interpreted descriptively rather than as evidence of superiority of one predictive model over another.

Spearman's rank correlation coefficient was also used to assess the association between PTV and ΔPain . To explore possible selection bias resulting from unavailable radiological follow-up, baseline characteristics were compared between patients with evaluable ($n = 28$) and non-evaluable ($n = 12$) objective response.

All statistical analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Firth penalized logistic regression was performed using the `logistf` package, and ROC analyses with bootstrap 95% CIs for AUC were performed using the `pROC` package. All statistical tests were two-sided, and a p -value < 0.05 was considered statistically significant.

3. Results

3.1. Patient and treatment characteristics

The study included 40 patients with bone metastases treated with radiotherapy. The cohort's mean age was 67.2 ± 10.8 years (range, 32–85 years), and 25 patients (62.5%) were male. Prostate cancer was the most common primary malignancy, accounting for 22 cases (55.0%), followed by lung and breast cancers, with four cases (10.0%) each.

The most frequently irradiated sites were mixed or multiple skeletal lesions (30.0%) and the spine or sacrum (27.5%). The median PTV was 325.5 cm³ (range, 30.1–1380.8 cm³), and the median BED10 was 37.5 Gy (range, 28.0–60.0 Gy). Median baseline pain intensity was 8 points on the VAS.

Table 1 presents detailed baseline patient and treatment characteristics.

3.2. Objective radiological response

Objective radiological response could be evaluated in 28 of the 40 patients. Complete response (CR) was observed in 9 patients, partial response (PR) in 6, stable disease (SD) in 5, and progressive disease (PD) in 8. Accordingly, 15 patients were classified as responders (CR + PR) and 13 as non-responders (SD + PD).

Responders had a lower median PTV than non-responders (228.7 vs 559.1 cm³), although the difference was not statistically significant in the unadjusted comparison ($p = 0.102$). Median BED10 was 37.5 Gy among responders and 31.2 Gy among non-responders; this difference was also not statistically significant ($p = 0.239$).

Table 1. Baseline patient and treatment characteristics (*n* = 40)

Variable	Value
Age (years)	67.2 ± 10.8 (range, 32–85)
Male sex	25 (62.5%)
Female sex	15 (37.5%)
Primary tumor type	
Prostate cancer	22 (55.0%)
Lung cancer	4 (10.0%)
Breast cancer	4 (10.0%)
Melanoma	2 (5.0%)
Renal cell carcinoma	1 (2.5%)
Multiple myeloma	1 (2.5%)
Other tumors	6 (15.0%)
Site of irradiated metastasis	
Mixed/multiple lesions	12 (30.0%)
Spine/sacrum	11 (27.5%)
Ribs/sternum/clavicle	7 (17.5%)
Pelvis	6 (15.0%)
Long bones	4 (10.0%)
PTV (cm ³)	325.5 (range, 30.1–1380.8)
BED10 (Gy)	37.5 (range, 28.0–60.0)
Baseline pain score, VAS	8 (range, 2–10)

Abbreviations: BED10: Biologically effective dose calculated using $\alpha/\beta = 10$ Gy; PTV: Planning target volume; VAS: Visual Analogue Scale.

No significant between-group differences were observed in age, sex, primary tumor grouping, baseline pain intensity, absolute pain reduction, or SBRT use. [Table 2](#) summarizes the clinical and treatment characteristics of responders and non-responders.

3.3. Relationship between PTV and BED10

PTV and BED10 were significantly inversely correlated in the overall cohort (Spearman's $\rho = -0.494$, $p = 0.0012$). The association remained significant when the analysis was restricted to the 28 patients with evaluable objective radiological response ($\rho = -0.471$, $p = 0.011$).

Thus, larger treatment volumes tended to be associated with lower BED10 values in this cohort. Because PTV and BED10 were interrelated, both variables were subsequently included in the penalized multivariable regression model to assess their respective associations with objective radiological response.

3.4. Firth penalized logistic regression analysis

In univariable Firth analysis, increasing PTV was associated with lower odds of objective radiological response. For each 100-cm³ increase in PTV, the odds of achieving CR or PR decreased (OR, 0.767; 95% CI, 0.564–0.970; $p = 0.026$). In contrast, BED10 was not significantly associated with objective response when evaluated per 10-Gy increase (OR, 1.256; 95% CI, 0.621–2.762; $p = 0.528$).

In the multivariable Firth model including both PTV and BED10, the inverse association between PTV and objective response remained statistically significant (OR per 100-cm³ increase, 0.752; 95% CI, 0.532–0.978; $p = 0.032$). BED10 was not independently associated with objective response in the same model (OR per 10-Gy increase, 0.827; 95% CI, 0.347–1.995; $p = 0.661$).

These results correspond to an approximately 25% reduction in the odds of objective response per 100-cm³ increase in PTV after adjustment for BED10. Given the small number of evaluable patients and the width of the confidence intervals, these findings should be interpreted as exploratory rather than as evidence of a validated predictive model.

The results of the Firth regression analyses are presented in [Table 3](#).

3.5. ROC analysis

ROC analysis was performed to explore the ability of PTV to discriminate between responders and non-responders. The AUC for PTV was 0.685 (bootstrap 95% CI, 0.462–0.882), indicating modest discrimination with substantial uncertainty around the estimate.

The exploratory ROC-derived PTV cutoff was 427.4 cm³, corresponding to a sensitivity of 93.3% and specificity of 53.8% for objective radiological response ([Figure 1](#)). Importantly, because this threshold was derived and evaluated within the same small cohort, it should not be interpreted as a validated clinical cutoff.

Table 2. Clinical and treatment characteristics according to objective radiological response ($n = 28$)

Variable	Responders (CR + PR) ($n = 15$)	Non-responders (SD + PD) ($n = 13$)	<i>p</i> -value
Age (years)	69 (59–72)	68 (62–72)	0.817
Male sex, n (%)	11 (73.3%)	7 (53.8%)	0.433
Prostate primary, n (%)	11 (73.3%)	6 (46.2%)	0.246
PTV (cm^3)	228.7 (89.2–373.0)	559.1 (137.6–816.3)	0.102
BED10 (Gy)	37.5 (31.2–43.2)	31.2 (28.0–39.0)	0.239
Baseline VAS	8 (6.5–8)	8 (7–9)	0.306
Δ Pain (VAS points)	5 (4–6)	5 (4–5)	0.422
SBRT, n (%)	11 (73.3%)	5 (38.5%)	0.125

Notes: Continuous variables are presented as median (interquartile range). Δ Pain = Baseline VAS – Post-treatment VAS, and represents absolute VAS-point reduction. Continuous variables were compared using the Mann–Whitney U test; categorical variables using Fisher's exact test. Abbreviations: CR: Complete response; PD: Progressive disease; PR: Partial response; SBRT: Stereotactic body radiotherapy; SD: Stable disease.

Table 3. Firth Penalized logistic regression analysis of objective radiological response

Variable	Univariable OR (95% CI)	<i>p</i> -value	Multivariable OR (95% CI)	<i>p</i> -value
PTV, per 100 cm^3	0.767 (0.564–0.970)	0.026	0.752 (0.532–0.978)	0.032
BED10, per 10 Gy	1.256 (0.621–2.762)	0.528	0.827 (0.347–1.995)	0.661

Notes: The outcome variable used was objective radiological response (CR + PR vs SD + PD), $n = 28$. Odds ratios are scaled per 100- cm^3 increase in PTV and per 10-Gy increase in BED10. Penalized logistic regression using Firth's bias-reduction method was used because of the small number of outcome events. Estimates are exploratory and hypothesis-generating.

The combined PTV + BED10 Firth model yielded an AUC of 0.715, compared with 0.685 for PTV alone. This numerical difference was considered descriptive only because of the limited sample size and absence of internal or external model validation.

3.6. Comparison of patients with and without evaluable radiological response

Because objective radiological response was unavailable in 12 of the 40 patients, we compared baseline characteristics between patients with evaluable ($n = 28$) and non-evaluable ($n = 12$) response to assess potential selection bias.

No statistically significant differences were observed in PTV (median, 325.5 vs 336.1 cm^3 ; $p = 0.384$), BED10 (37.5 vs 37.5 Gy; $p = 0.891$), baseline VAS score (8 vs 8; $p = 0.306$), sex ($p = 0.736$), SBRT use ($p = 0.494$), or prostate versus non-prostate primary tumor status ($p = 0.315$).

Patients without evaluable radiological response tended to be older than evaluable patients (median, 73.5 vs 68.5 years), although this difference did not reach statistical significance ($p = 0.074$).

These comparisons are summarized in [Table 4](#).

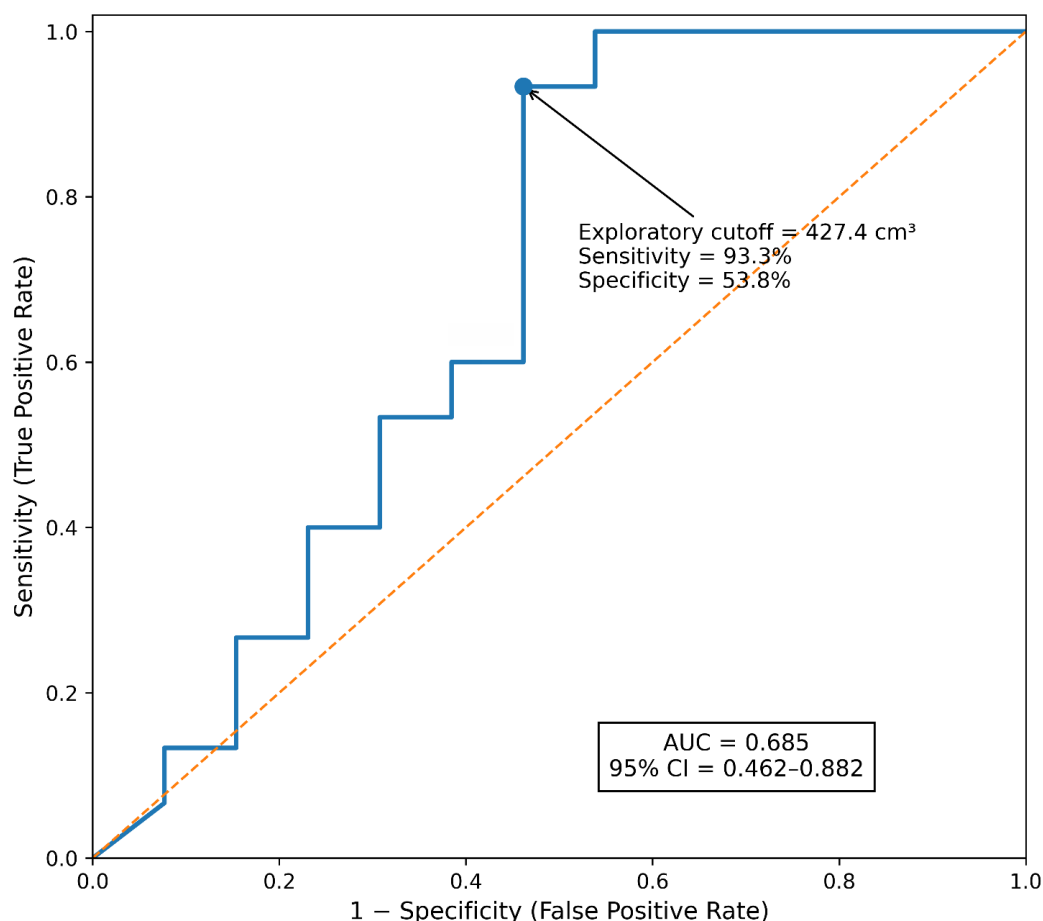


Figure 1. Receiver operating characteristic (ROC) curve of planning target volume (PTV) for discrimination of objective radiological response after radiotherapy for bone metastases. The area under the curve (AUC) was 0.685 (bootstrap 95% CI, 0.462–0.882). The exploratory ROC-derived PTV cutoff of 427.4 cm³ yielded a sensitivity of 93.3% and a specificity of 53.8%.

Table 4. Comparison of baseline characteristics between patients with and without evaluable radiological response

Baseline characteristic	Evaluable (n = 28)	Non-evaluable (n = 12)	p-value
Age (years)	68.5 (60.5–72.0)	73.5 (68.0–76.8)	0.074
Male sex, n (%)	18 (64.3%)	7 (58.3%)	0.736
Prostate primary, n (%)	17 (60.7%)	5 (41.7%)	0.315
PTV (cm ³)	325.5 (106.8–590.1)	336.1 (167.3–635.5)	0.384
BED10 (Gy)	37.5 (28.0–43.2)	37.5 (28.0–40.1)	0.891
Baseline VAS	8 (6.8–9.0)	8 (5.8–8.0)	0.306
SBRT, n (%)	16 (57.1%)	5 (41.7%)	0.494

Notes: Continuous variables are presented as median (interquartile range). Continuous variables were compared using the Mann–Whitney *U* test; categorical variables using Fisher's exact test. No statistically significant baseline differences were identified between evaluable and non-evaluable patients.

3.7. Pain response

PTV was not significantly correlated with absolute pain reduction in the overall cohort (Spearman's $\rho = 0.185$, $p = 0.252$). No significant association was observed among the 28 patients with evaluable radiological response ($\rho = 0.131$, $p = 0.507$). Similarly, absolute pain reduction did not differ significantly between radiological responders and non-responders (median Δ Pain, 5 vs 5 VAS points; $p = 0.422$).

These findings indicate that the association observed between PTV and objective radiological response was not paralleled by a corresponding association between PTV and pain reduction.

4. Discussion

The present study demonstrated an inverse association between planning target volume (PTV) and objective radiological response following radiotherapy for bone metastases. In Firth penalized logistic regression, increasing PTV remained associated with lower odds of response after adjustment for BED10, whereas BED10 itself was not significantly associated with response. PTV and BED10 were also significantly inversely correlated, indicating that treatment volume and prescribed biological dose were interrelated rather than independent characteristics in this cohort. In contrast, PTV was not associated with pain reduction, suggesting that radiological response and symptomatic benefit capture different aspects of treatment efficacy.

Although the present cohort was small, the observed volume-response association is consistent with an emerging body of evidence linking larger treatment or tumor volumes with inferior local outcomes after radiotherapy for bone metastases. Erler *et al.* reported a significant association between larger PTV and local recurrence after SBRT for non-spine bone metastases.¹² In a larger subsequent series of 505 non-spine bone metastases, larger PTV was independently associated with local failure, while dose-related parameters also contributed to outcome prediction.¹³ More recent data evaluating gross tumor volume have similarly demonstrated poorer local control with increasing tumor volume after SBRT for bone oligometastases.¹⁴ Although these studies primarily addressed local control or recurrence rather than short-term objective radiological response, their findings support the clinical relevance of treatment volume as an outcome-related variable.

4.1. PTV and the volume–response relationship

The inverse association between PTV and objective radiological response is biologically and clinically plausible. Larger tumor volumes may contain a greater

absolute number of clonogenic tumor cells and may exhibit greater intratumoral heterogeneity, hypoxic subregions, heterogeneous perfusion, and variable radiosensitivity. Tumor volume has been associated with radiotherapy outcomes in several malignancies, including lung and head and neck cancers.^{9–11} The similar direction of association observed in studies of bone metastases suggests that a volume effect may also be relevant in metastatic skeletal disease.^{12–14}

However, PTV should not be equated directly with biological tumor burden. PTV is a treatment-planning construct derived from the delineated target, with margins added to account for setup and geometric uncertainties. Its magnitude therefore depends not only on lesion extent but also on anatomical site, target-definition strategy, immobilization, image guidance, and institutional planning practice. Contemporary consensus recommendations for spinal and non-spinal bone metastases emphasize the importance of standardized target delineation and treatment margins.^{8,15,16,22}

The prognostic information associated with PTV may consequently reflect a combination of lesion extent, treatment geometry, anatomical complexity, and clinical planning decisions rather than a purely biological measure of metastatic burden. This distinction is important when interpreting the present findings and when comparing volume–outcome relationships between institutions.

Nevertheless, the persistence of the inverse association between PTV and objective response after adjustment for BED10 suggests that treatment volume deserves explicit consideration in studies evaluating radiotherapy outcomes in bone metastases. Our ROC analysis yielded an exploratory PTV cutoff of 427.4 cm³, but discrimination was modest (AUC 0.685), and the bootstrap confidence interval was wide. Importantly, because this threshold was derived and evaluated in the same small cohort, it should not be interpreted as a validated clinical cutoff.

4.2. Interrelationship between PTV and BED10

The significant inverse correlation between PTV and BED10 represents an important finding of the present study. Larger treatment volumes tended to receive lower biologically effective doses, both in the entire cohort and among patients with evaluable radiological response.

This relationship is clinically plausible because dose and fractionation in bone-metastasis radiotherapy are selected within a broader therapeutic context. Treatment intent, lesion size, anatomical location, proximity to organs at risk, expected survival, primary tumor histology, previous treatment, and technical feasibility all influence prescription decisions. Current ASTRO and ESTRO

recommendations emphasize individualized treatment selection and provide several acceptable conventional and stereotactic dose-fractionation approaches rather than a single optimal schedule.^{1-3,8} The achievable dose may also be constrained by target location, surrounding organs at risk, treatment geometry, and requirements for safe stereotactic delivery.^{23,24}

The inverse PTV-BED10 relationship also has methodological implications. In retrospective studies, a simple association between BED and outcome may partly reflect treatment selection processes rather than an isolated biological dose effect. Conversely, apparent volume effects may also be influenced by the doses technically achievable in larger or anatomically complex targets. The two variables should therefore be considered jointly rather than treated as competing predictors.

Larger observational series support this interpretation, in which both target volume and dose-related parameters contributed to local outcome after SBRT for bone metastases.¹³ Such findings reinforce the concept that volume and biological dose represent complementary components of treatment rather than mutually exclusive explanations of response.

4.3. BED10 and objective response

Biologically effective dose (BED) remains a useful radiobiological framework for comparing different fractionation schedules,⁶ and dose escalation is central to modern stereotactic radiotherapy.^{7,8} Contemporary evidence from clinical series, systematic reviews, and meta-analyses demonstrates high local control rates after SBRT for selected spinal and non-spinal bone metastases, while also indicating that outcomes depend on dose, fractionation, anatomical site, and patient selection.^{4,5,25,26} Clinical series have further demonstrated that local control after SBRT may vary according to disease characteristics and treatment approach, including primary tumor biology and metastatic site.^{27,28}

Recent data further support a dose-response relationship in selected disease settings. In a large retrospective cohort of differentiated thyroid cancer bone metastases, higher BED10 was associated with a lower cumulative incidence of progression, illustrating that dose can remain clinically relevant even when other tumor and treatment characteristics are considered.²⁹ Dose-response relationships have also been demonstrated in disease-specific SBRT series. In patients with metastatic sarcoma, higher BED was associated with improved local control, supporting the potential relevance of biological dose even in relatively radioresistant histologies.³⁰ Long-term prospective data on dose-intensified fractionated SBRT

for painful spinal metastases likewise demonstrate durable local control and symptomatic benefit after high-dose treatment.³¹

In the present cohort, BED10 was not significantly associated with objective radiological response in either univariable or multivariable Firth regression. However, this finding should not be interpreted as evidence that BED10 lacks biological or clinical importance. The confidence intervals were wide, the BED10 range was relatively limited, treatment selection was non-randomized, and BED10 was significantly correlated with PTV.

The combined PTV + BED10 model showed a numerically higher AUC than PTV alone (0.715 vs 0.685), but this difference cannot be interpreted as evidence of superior predictive performance because of the small sample size and lack of validation. Taken together, these results suggest that the respective contributions of target volume and biological dose cannot be reliably separated in this cohort.

Accordingly, our findings neither argue against dose escalation nor establish PTV as a replacement for dose-related parameters. Rather, they support a more integrated approach in which target volume, dose, anatomical site, tumor histology, and treatment intent are evaluated together when studying radiotherapy outcomes.

4.4. Radiological response and pain relief as distinct endpoints

Planning target volume (PTV) was not significantly associated with pain reduction, and absolute pain reduction did not differ significantly between radiological responders and non-responders. This suggests that radiological tumor response and analgesic benefit should not be considered interchangeable endpoints.

Pain arising from bone metastases is multifactorial and may reflect periosteal involvement, inflammatory mediators, mechanical instability, neurological involvement, tumor location, and individual pain perception. Radiotherapy may therefore provide clinically meaningful analgesia without producing measurable tumor regression during the same observation period.^{17,18}

Pain response remains one of the principal endpoints of palliative radiotherapy for bone metastases, and contemporary guidelines emphasize symptom relief alongside local disease control.¹⁻³ Randomized trials comparing stereotactic and conventional radiotherapy have demonstrated that the effects of dose escalation on pain response are not uniform across treatment regimens and patient populations.^{19,32-34} This heterogeneity is also reflected in systematic reviews and meta-analyses

comparing SBRT with conventional radiotherapy for painful bone metastases.^{18,35-37}

Recent prospective and real-world studies continue to evaluate pain response as a distinct clinical endpoint in patients receiving radiotherapy for bone metastases.^{38,39} Evidence from non-spinal bone metastases further illustrates the complexity of treatment endpoints: in a propensity score-matched analysis, SBRT was associated with higher 3-month pain response and a lower 1-year local failure rate than conventional external beam radiotherapy.⁴⁰ These data support assessing both radiological and patient-reported outcomes rather than assuming one serves as a surrogate for the other.

4.5. Clinical and research implications

These findings suggest that future studies of radiotherapy response in bone metastases should explicitly consider treatment volume. This is particularly relevant when comparing conventional radiotherapy with SBRT or when evaluating dose-response relationships across heterogeneous patient populations.^{4,5,12-14}

The available literature indicates that target volume is associated with local outcome in bone metastases, while higher biological dose may also improve local control in appropriately selected patients.^{5,7,12-14,25-31} Rather than identifying a single dominant predictor, these observations support a multidimensional model in which volume, biological dose, target definition, anatomical site, histology, and treatment technique interact to determine outcome.

Future prospective multicenter studies should therefore evaluate PTV together with gross tumor volume and clinical target volume, BED, primary tumor histology, metastatic site, treatment intent, and standardized radiological and pain-response endpoints. Such studies would help determine whether the volume-response association observed in the present cohort primarily reflects lesion biology, treatment geometry, clinical selection, or a combination of these factors.

5. Limitations

Several limitations should be considered when interpreting these findings. First, this was a retrospective single-center study with a small overall cohort and only 28 patients evaluable for objective radiological response. Although Firth penalized logistic regression was used to reduce small sample bias, the sample size limits the precision of the effect estimates, and the findings should therefore be regarded as exploratory. In addition, the single-center design may reflect institution-specific patterns of patient selection, treatment planning, and clinical decision-making; consequently, the observed associations cannot

be assumed to be directly generalizable to other patient populations or radiotherapy settings without external validation.

Second, objective radiological response was unavailable in 12 of the 40 patients, creating the potential for selection bias. Baseline comparisons between evaluable and non-evaluable patients showed no significant differences in PTV, BED10, baseline pain intensity, sex, SBRT use, or prostate versus non-prostate primary tumor status, reducing concern for obvious differential selection by the principal treatment variables. Nevertheless, residual selection bias cannot be excluded.

Third, the cohort was heterogeneous with respect to primary tumor histology, anatomical site of metastases, treatment intent, and radiotherapy fractionation. In particular, bone metastases from different primary tumors may differ in intrinsic radiosensitivity and biological behavior. These factors may influence both treatment response and treatment selection; however, histology-specific stratified analyses and reliable multivariable adjustment for these factors were not feasible because of the limited sample size. The observed inverse correlation between PTV and BED10 further indicates that treatment volume and prescribed biological dose were not independent, and residual confounding related to primary tumor histology and clinical treatment selection therefore cannot be excluded.

Fourth, PTV is a treatment-planning construct rather than a direct biological measure of tumor burden. Its magnitude depends on target delineation, treatment margins, anatomical site, immobilization, and image-guidance practice. Therefore, these findings should not be extrapolated directly to gross tumor volume, clinical target volume, or total metastatic burden.

Fifth, objective response assessment was based on retrospective clinical imaging obtained during routine follow-up. Although the same imaging modality was used before and after treatment whenever feasible and radiologists and radiation oncologists reviewed the images, examinations were not performed according to a prospectively standardized imaging protocol, and no blinded independent central review was available. Variation in imaging modality and follow-up timing may therefore have introduced measurement variability.

Finally, the ROC-derived PTV cutoff of 427.4 cm³ was identified and evaluated in the same small cohort. The modest AUC and wide bootstrap confidence interval indicate substantial uncertainty, and the cutoff should be considered hypothesis-generating rather than clinically validated. External validation in an independent cohort is

required before considering any threshold-based clinical application.

6. Conclusions

In patients treated with radiotherapy for bone metastases, larger planning target volume (PTV) was associated with lower odds of objective radiological response, and this association persisted after adjustment for BED10 using Firth penalized logistic regression. Together with previous reports linking larger treatment volumes to inferior local outcomes, these findings support treatment volume as a potentially informative component of radiotherapy outcome assessment.

The observed inverse relationship between PTV and BED10 further indicates that volume and biological dose should be considered jointly rather than as competing determinants of response. In contrast, the lack of association between PTV and pain reduction emphasizes that radiological and symptomatic outcomes represent distinct dimensions of treatment efficacy.

These findings are exploratory and require prospective validation, but they provide a rationale for incorporating treatment volume into future multidimensional models that combine target geometry, biological dose, tumor characteristics, and clinical factors to predict radiotherapy outcomes in patients with bone metastases.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

This retrospective study analyzed anonymized clinical data from patients who received radiotherapy as part of routine medical care during 2024–2025. All patients

provided voluntary informed consent for treatment, and no additional interventions were performed for the purposes of this study. The retrospective study protocol was reviewed and approved by the Bioethics Committee of the State Institution “Shalimov’s National Scientific Center of Surgery and Transplantation” of the National Academy of Medical Sciences of Ukraine (Protocol No. 4, May 22, 2026). The study was conducted in accordance with the Declaration of Helsinki and applicable national regulations.

Consent for publication

Not applicable.

Availability of data

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional requirements.

Further disclosure

During the preparation and revision of this manuscript, the authors used ChatGPT (OpenAI, GPT-5.6 Sol) to assist with language editing, improvement of scientific writing and manuscript organization, preparation and revision of tables and figures, formatting of references, and interpretation and presentation of statistical results. No generative AI tools were used for study design, data collection, or generation or modification of the underlying clinical data. Statistical analyses reported in the manuscript were performed using the statistical software and methods specified in the Methods section. All AI-assisted content was critically reviewed, verified, revised, and proofread by the authors. The authors take full responsibility for the final content of the manuscript, including its scientific accuracy, originality, and integrity.

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