Am J Cancer Res 2026;16(4):1312-1326
www.ajcr.us /ISSN:2156-6976/ajcr0171767

Original Article

Palliative radiotherapy plus multimodal analgesia for painful bone metastases: improved pain control and survival

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Received January 29, 2026; Accepted April 2, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Aims: To evaluate the synergistic effects of palliative radiotherapy combined with multimodal analgesia on pain control, quality of life, and survival in patients with painful bone metastases, and to identify prognostic factors for overall pain response. Methods: This retrospective study analyzed 205 patients with radiologically confirmed painful bone metastases treated at West China Fourth Hospital (2015-2022). Patients were divided into a control group (n = 103; conventional palliative care with clinician-directed analgesia) and an observation group (n = 102; protocolized multimodal analgesia plus palliative radiotherapy to symptomatic lesions). The primary outcome was overall pain response at week 12, assessed using consensus numeric rating scale (NRS)-opioid criteria. Secondary outcomes included longitudinal NRS scores, pain relief duration and onset, quality of life, safety, progression-free survival (PFS) and overall survival (OS). Results: The observation group achieved greater reductions in NRS pain scores at all time points (all P < 0.001), with longer pain control duration and more rapid onset of relief (both P < 0.001). Greater improvements in global health and functional domains were observed at week 12 (all P < 0.001). Overall and grade 3-4 adverse event rates were comparable between groups, though constipation was less frequent in the observation group (29.4% vs 42.7%, P = 0.047). The observation group showed longer PFS (7.2 vs 4.8 months; hazard ratio [HR] 0.68, P = 0.009) and OS (12.1 vs 9.4 months; HR 0.73, P = 0.021), greater improvements in inflammatory and nutritional markers (all P < 0.001), and higher odds of overall pain response (odds ratio 0.116, P < 0.001). Conclusion: Palliative radiotherapy combined with multimodal analgesia provided superior pain control, improved quality of life, and prolonged survival compared to standard care, without increased serious toxicity, in patients with painful bone metastases.

Keywords: Bone metastases, cancer pain, palliative radiotherapy, multimodal analgesia, prognostic factors

Introduction

Bone metastases are a common and debilitating manifestation of advanced solid malignancies, and their clinical burden is increasing in aging populations as improvements in cancer survival prolong the course of metastatic disease. Among the most disabling complications, cancer-induced bone pain remains highly prevalent in patients with advanced malignancies and exerts a persistent adverse effect on physical functioning, sleep quality, and overall quality of life, irrespective of ongoing anticancer treatment [1, 2]. Solid tumors such as breast, prostate, and lung cancers frequently metastasize to bone, giving rise to complex pain states characterized by intertwined nociceptive and neuropathic mechanisms, often in conjunction with skeletal instability and an elevated risk of pathological fracture and spinal cord compression [3-6]. In this context, pain palliation constitutes a central therapeutic priority alongside disease control and preservation of functional status [7]. However, in routine clinical practice, a substantial proportion of patients continue to experience moderate-to-severe pain despite receiving guideline-recommended therapies. This unmet need is associated with functional impairment, psychological distress, increased healthcare utilization, and considerable caregiver burden. The persistent gap between available treatment options and real-world analge-

https://doi.org/10.62347/HSZY1527

sic outcomes highlights the urgent need for a more rational, integrated, and evidence-based approach to the optimization and sequencing of multimodal pain management strategies.

Palliative radiotherapy (RT) remains a cornerstone in the management of painful bone metastases [8]. In addition to providing local tumor control, RT may modulate the bone microenvironment and attenuate nociceptive signaling, with consistently reported analgesic efficacy and a favorable toxicity profile [9]. However, pain relief following RT is often delayed, and both the onset and magnitude of analgesic benefit vary substantially across individuals; notably, a clinically meaningful proportion of patients achieve only partial relief or derive no meaningful benefit at all [10]. Meanwhile, contemporary pain medicine has progressively shifted from a predominantly opioid-centered model toward individualized, mechanism-based treatment strategies. Current standards of pain management increasingly emphasize multimodal analgesia, integrating non-opioid analgesics, adjuvant agents such as anticonvulsants, antidepressants, and corticosteroids, minimally invasive interventions, and non-pharmacological approaches [11]. From both biological and clinical perspectives, the combination of palliative RT with a structured multimodal analgesic regimen is highly compelling: RT acts primarily by reducing local tumor burden and inflammatory activity, whereas multimodal analgesia addresses peripheral and central sensitization, neuroimmune dysregulation, and psychosocial determinants of pain.

Despite this strong biological and clinical rationale, the potential synergistic benefit of combining palliative radiotherapy (RT) with multimodal analgesia has not yet been systematically evaluated in prospective, hypothesis-driven studies. The existing literature has largely examined RT and pharmacologic pain management in comparison with other treatment modalities, rather than assessing them as components of an integrated therapeutic strategy. In routine clinical practice, considerable heterogeneity persists with respect to RT fractionation schedules, the timing and intensity of analgesic escalation, the use of adjuvant analgesics, and the incorporation of interventional pain management techniques [12]. Consequently, the true additive or synergistic effects of palliative RT combined with multimodal analgesia on clinically meaningful outcomes - including pain intensity, opioid consumption, functional status, and health-related quality of life - remain insufficiently defined. In the absence of robust evidence, clinicians frequently rely on experience-based rather than data-driven decision-making when determining the timing and intensity of analgesic optimization in relation to RT. This knowledge gap hampers efforts to standardize care pathways and to develop evidence-based treatment algorithms that appropriately align analgesic strategies with RT delivery and the temporal dynamics of treatment response.

More importantly, data on prognostic factors that may modify response to this combined therapeutic approach remain scarce. Patients with bone metastases constitute a clinically and biologically heterogeneous population, in whom multiple disease- and treatment-related variables may influence both the efficacy of palliative radiotherapy (RT) and the effectiveness of analgesic interventions. These variables include primary tumor type, the burden and anatomical distribution of skeletal disease, performance status, prior systemic treatment exposure, concurrent targeted therapy or immunotherapy, and baseline pain severity. In addition, host-related factors - including comorbidities, opioid tolerance, psychological distress, and systemic inflammatory status - may shape both pain trajectories and overall survival. The identification of robust clinical and treatment-specific predictors of analgesic response and prognosis is therefore essential for improving patient stratification, facilitating shared decision-making, and tailoring treatment intensity to individual need. In particular, distinguishing patients who are likely to achieve rapid and durable pain relief with combined RT and multimodal analgesia from those at high risk of refractory pain or early mortality may support the timely integration of interventional pain procedures, systemic anticancer therapies, or best supportive care.

Against this background, we designed the present study to evaluate the potential synergistic effects and prognostic determinants of palliative radiotherapy (RT) combined with multimodal analgesia in patients with bone metastasis -

related cancer pain. Specifically, we sought to assess not only pain relief and opioid-sparing effects, but also functional outcomes and survival, while identifying baseline clinical characteristics and treatment-related factors associated with differential benefit from this combined strategy. Ultimately, these findings may inform the development of risk-adapted, evidence-based care pathways aimed at maximizing analgesic benefit, minimizing treatment burden, and improving quality of life for patients with advanced cancer and painful bone metastases.

Methods

Study population

This retrospective cohort study included 205 consecutive patients with cancer-related bone pain secondary to radiologically confirmed bone metastases who received palliative care at West China Fourth Hospital between January 2015 and December 2022. Eligible patients met all of the following inclusion criteria: (i) age ≥ 18 years; (ii) histologically confirmed malignant solid tumor; (iii) at least one radiologically confirmed bone metastasis considered by the treating physician to be the main source of cancer-related pain; (iv) moderate-to-severe pain due to bone metastases, defined as a numeric rating scale (NRS) score ≥ 4 despite ongoing analgesic therapy; (v) receipt of external-beam palliative RT to at least one symptomatic bone lesion; and (vi) availability of complete baseline and follow-up data on pain scores, analgesic intake, and RT parameters. Patients were excluded if they (i) had benign bone lesions or primary bone malignancies; (ii) had received high-dose curative-intent RT or overlapping re-irradiation to the index metastatic site; (iii) had comorbid neurologic or psychiatric disorders, cognitive impairment, or communication barriers that precluded reliable and consistent pain assessment; (iv) were enrolled in interventional clinical trials expected to substantially affect pain levels or analgesic use; (v) had uncontrolled concurrent pain from non-bone-metastatic causes that could not be clearly distinguished from bone pain; (vi) or had incomplete clinical documentation or insufficient follow-up. Based on the palliative regimen actually administered, patients were categorized into a control group (n = 103), who received conventional palliative care including routine, clinician-directed analgesic treatment without a formalized protocol, or an observation group (n = 102), who received a protocolized multimodal analgesia regimen in conjunction with palliative RT to the symptomatic bone lesion(s) (**Figure 1**). This observational study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of West China School of Public Health and West China Fourth Hospital, Sichuan University. The requirement for written informed consent was waived because of the retrospective design and anonymization of all patient data.

Data collection

Standardized case-report forms were used to record baseline demographic and clinical characteristics (including age, sex, primary tumor, Eastern Cooperative Oncology Group performance status, prior therapies, and number of bone metastases) at enrollment. Pain intensity was assessed using an 11-point NRS (0-10) at baseline and at 1, 4, 8, and 12 weeks after initiation of study treatment; these data were used to determine overall pain response at week 12. Health-related quality of life and functional status (global health, physical, role, emotional, and social functioning) were assessed at baseline and week 12 using a validated cancer-specific questionnaire, scored according to the developer's manual. All treatment-emerging adverse events (AEs) were prospectively captured at each visit, coded, and graded using the Common Terminology Criteria for Adverse Events (version 5.0). Fasting venous blood samples were collected at baseline and week 12 to measure inflammatory markers, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), white blood cell (WBC) count, procalcitonin (PCT), and neutrophil-to-lymphocyte ratio (NLR; calculated from automated differential counts), as well as nutritional indices (serum albumin, hemoglobin, and transferrin). A standardized 3-day dietary record, assessed by a dietitian, was used to estimate daily caloric intake. Electronic medical records provided dates of pain progression, death, and last follow-up; these data were supplemented by structured telephone interviews when necessary to determine pain progression-free survival (PFS) and overall survival (OS).

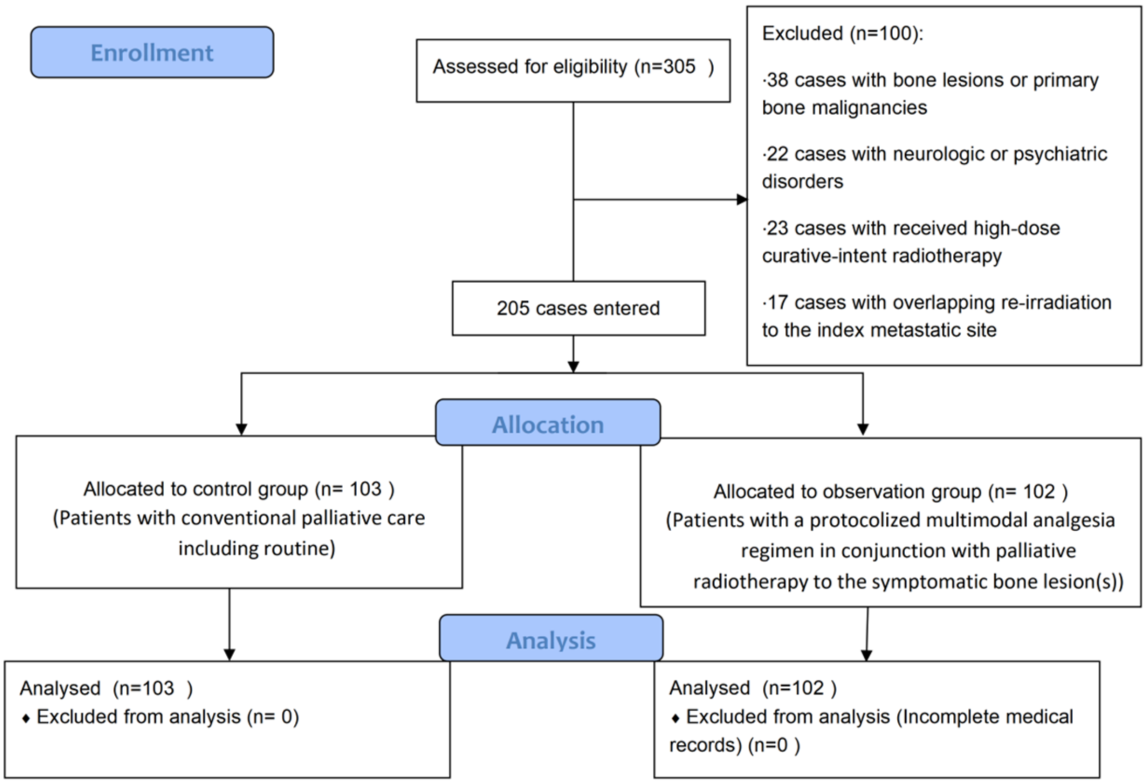


Figure 1. Flowchart of patient selection and grouping.

Outcome measures

The primary outcome was overall pain response at week 12, which was a priori defined based on consensus criteria combining changes in NRS pain scores and opioid use. Complete and partial responders were considered overall responders; stable or progressive pain defined non-response. Key secondary endpoints included the longitudinal profile of NRS scores at 1, 4, 8, and 12 weeks, duration of analgesia, and time to clinically meaningful pain relief. A validated cancer-specific questionnaire was used to measure health-related quality of life and functional status (global health status, physical, role, emotional, and social functioning) at baseline and week 12, with high scores indicating better status. The incidence, type, and severity of treatment-emergent AEs constituted the safety endpoints, which were graded according to the Common Terminology Criteria for Adverse Events (version 5.0). PFS was defined as the time from treatment initiation to documented pain progression or death, and OS were time-to-event endpoints; patients who had not experienced an event were censored at the last follow-up date. Exploratory outcomes included changes from baseline to week 12 in indicators of systemic inflammatory response (CRP, NLR, TNF-α, IL-6, WBC count and PCT) and nutritional status (serum albumin, hemoglobin, transferrin, and daily caloric intake), as well as the identification of independent predictors of overall pain response using multivariate logistic regression.

Statistical analysis

All analyses were performed according to a predetermined statistical analysis plan and conducted on the intention-to-treat population using R (R Foundation for Statistical Computing). Continuous variables were summarized as mean ± standard deviation or median (interquartile range), and categorical variables were summarized as counts and percentages. Between-group differences at baseline were assessed using Student's t-test or Mann-Whitney test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Longitudinal NRS pain scores and quality-of-life domain

Table 1. Baseline clinical characteristics

Variable	Control group (n = 103)	Observation group (n = 102)	t/X^2	*p*-value
Age, years, mean ± SD	62.02 ± 11.39	62.25 ± 11.54	0.147	0.883
Male sex, n (%)	63 (61.2)	62 (60.8)	0.003	0.955
ECOG performance status, n (%)			0.121	0.941
0-1	49 (47.6)	51 (50.0)		
2	36 (35.0)	34 (33.3)		
3-4	18 (17.5)	17 (16.7)		
Primary tumor type, n (%)			0.581	0.965
Breast	31 (30.1)	30 (29.4)		
Lung	36 (35.0)	35 (34.3)		
Prostate	18 (17.5)	17 (16.7)		
Gastrointestinal	10 (9.7)	9 (8.8)		
Other (kidney, thyroid, etc.)	8 (7.8)	11 (10.8)		
Number of bone metastases, n (%)			0.056	0.814
≤ 3 lesions	39 (37.9)	37 (36.3)		
> 3 lesions	64 (62.1)	65 (63.7)		
Dominant site of bone metastasis, n (%)			0.143	0.931
Axial skeleton (spine, pelvis, ribs)	60 (58.3)	58 (56.9)		
Appendicular skeleton	21 (20.4)	23 (22.5)		
Mixed axial and appendicular	22 (21.4)	21 (20.6)		
Spinal involvement, n (%)	67 (65.0)	68 (66.7)	0.060	0.807
Pathological fracture, n (%)	22 (21.4)	23 (22.5)	0.042	0.837
Visceral metastases present, n (%)	55 (53.4)	54 (52.9)	0.004	0.948

Note: ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

scores were analyzed using linear mixed-effects models, with fixed effects for treatment group, time, and their interaction, and a random intercept for each patient. Estimated marginal means were obtained for pairwise comparisons at each time point with Bonferroni adjustment. Analysis of covariance was used to compare changes in inflammatory and nutritional markers from baseline to week 12 between groups, with baseline values included as covariates. Time-to-event endpoints (PFS and OS) were estimated using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional-hazards models. Independent predictors of overall pain response at week 12 were identified using multivariable logistic regression, entering clinically relevant variables and those with $P < 0.10$ in univariable analyses. Mixed-model and survival analyses used all available observations under a missing-at-random assumption. All hypothesis tests were two-sided, with a significance level of $P < 0.05$.

Results

Baseline clinical characteristics

There were no significant between-group differences in age (P = 0.883), sex distribution (P = 0.955), or Eastern Cooperative Oncology Group performance status (P = 0.941). The distribution of primary tumor types was comparable between groups (P = 0.965), as were the number of bone metastases (P = 0.814), the dominant site of bone involvement (axial vs appendicular vs mixed; P = 0.931), and the prevalence of spinal involvement (P = 0.807). Similarly, the proportions of patients with pathological fractures (P = 0.837) and concurrent visceral metastases (P = 0.948) did not differ significantly, indicating that the two cohorts were clinically comparable at baseline (**Table 1**).

Comparison of pain responses between the two groups

As shown in **Figure 2**, pain responses differed markedly between the two groups. Baseline

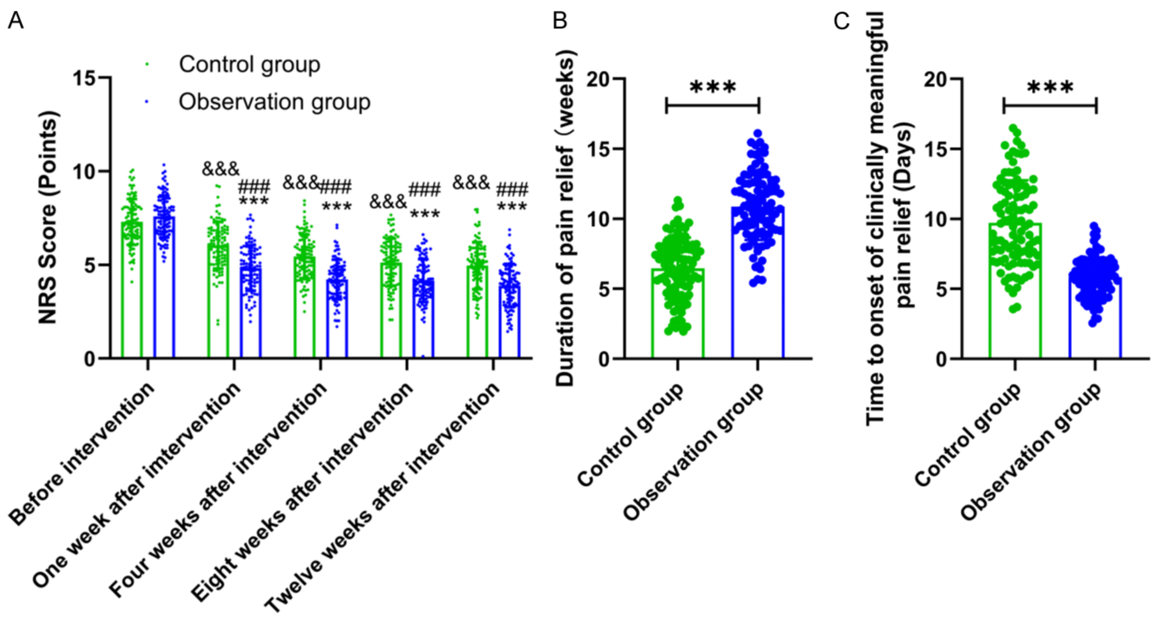


Figure 2. Comparison of pain responses between the two groups. A. NRS pain scores. B. Duration of pain relief. C. Time to onset of clinically meaningful pain relief. ***P < 0.001 for between-group comparisons at the indicated time points; &&&P < 0.001 versus before intervention within the control group; ###P < 0.001 versus before intervention within the observation group. Note: NRS: numeric rating scale.

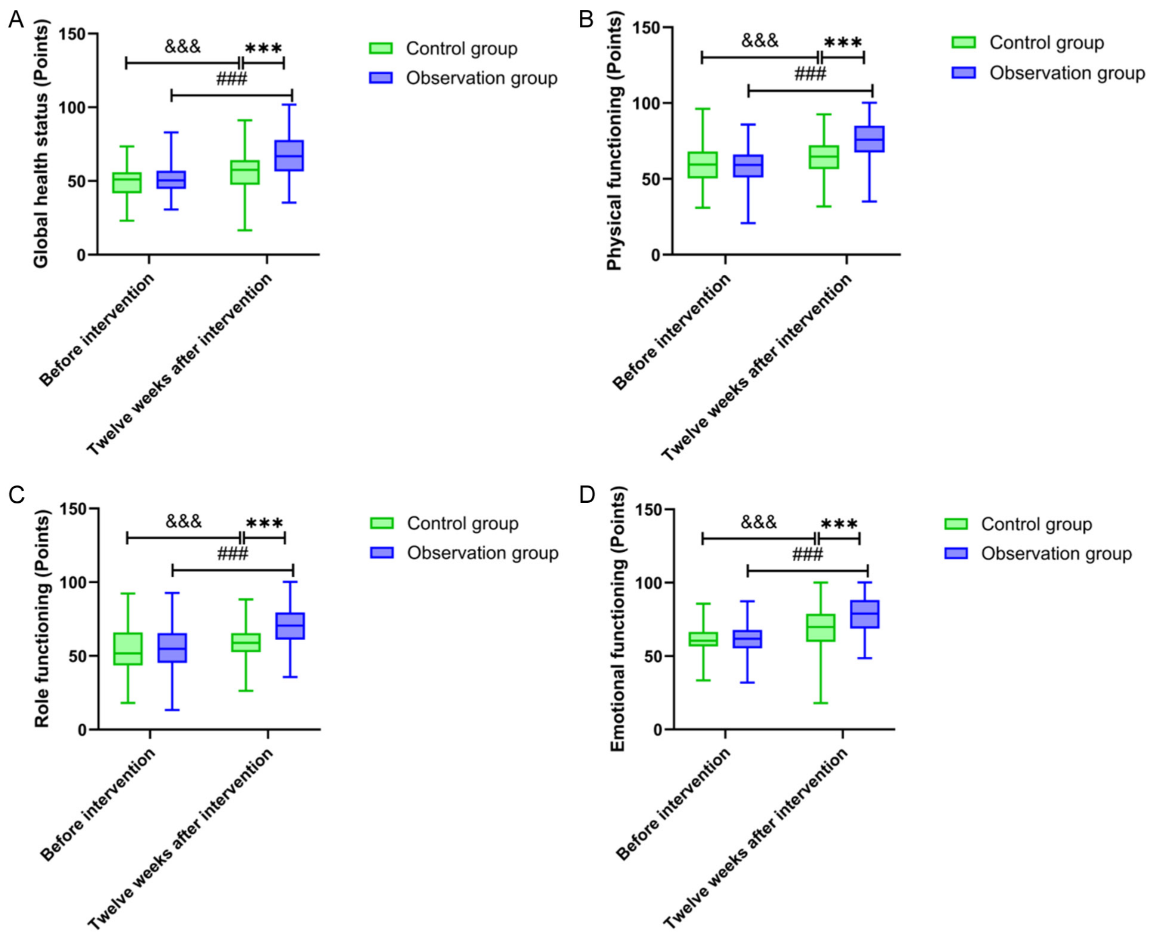
NRS scores were comparable, indicating similar initial pain intensity. Following the intervention, NRS scores declined significantly over time in both groups (all P < 0.001), but the reduction was consistently greater in the observation group than in the control group at 1, 4, 8, and 12 weeks after treatment (all P < 0.001), with significant between-group differences at all post-intervention time points (**Figure 2A**). In addition, the observation group experienced a substantially longer duration of pain relief (**Figure 2B**) and a significantly shorter time to onset of clinically meaningful pain relief (**Figure 2C**) compared with the control group (both P < 0.001). Together, these findings demonstrate that the intervention used in the observation group provided faster onset and more durable analgesic effects than the regimen administered to the control group.

Comparison of quality of life and functional status between the two groups

At baseline, scores for global health status, physical functioning, role functioning, emotional functioning, and social functioning were comparable between groups. By 12 weeks after the intervention, both groups showed significant within-group increases across all five domains relative to baseline (all P < 0.001), indicating a general improvement in health-related quality of life. However, patients in the observation group achieved markedly higher post-treatment scores than those in the control group for global health status (**Figure 3A**), physical functioning (**Figure 3B**), role functioning (**Figure 3C**), emotional functioning (**Figure 3D**) and social functioning (**Figure 3E**), as indicated by between-group comparisons (all P < 0.001). These findings suggest that, beyond alleviating pain, the therapeutic strategy applied in the observation group confers broader and more substantial gains in overall quality of life and multidimensional functional recovery.

Comparison of safety and AEs between the two groups

Any treatment-emergent AE of any grade occurred in 82 of 103 patients (79.6%) in the control group and 80 of 102 patients (78.4%) in the observation group (P = 0.836), and the incidence of grade 3-4 AEs was likewise similar (23.3% vs. 18.6%, P = 0.411). The most frequently reported AEs in both groups were gastrointestinal and neurocognitive events, including nausea and/or vomiting, constipation, somnolence or excessive sedation, and cognitive disturbance or delirium, as well as RT-related pain flare, local skin reactions in the irradiated



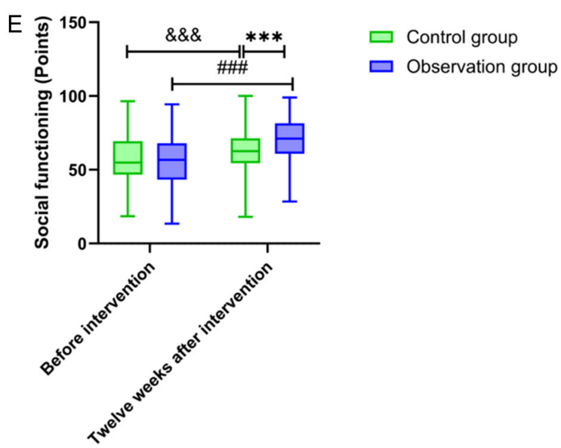


Figure 3. Comparison of quality of life and functional status between the two groups. A. Global health status. B. Physical functioning. C. Role functioning. D. Emotional functioning. E. Social functioning. ***P < 0.001 for between-group comparisons at the indicated time points; &&&P < 0.001 versus before intervention within the control group; ###P < 0.001 versus before intervention within the observation group.

field, and hematologic toxicity. Among these, only constipation differed significantly between groups, being less common in the observation group than in the control group (29.4% vs. 42.7%, P = 0.047). Trends toward lower rates of nausea/vomiting and somnolence were also observed in the observation group, although these did not reach statistical significance (P = 0.078 and P = 0.074, respectively) (**Table 2**).

Comparison of PFS and OS between the two groups

As shown in **Figure 4A**, the PFS curves separated early and remained divergent throughout follow-up, with a longer median PFS in the observation group than in the control group (7.2 vs. 4.8 months; log-rank P = 0.009). This translated into a 32% relative reduction in the

Table 2. Comparison of safety and adverse events between the two groups

	Control group (n = 103)	Observation group (n = 102)	χ^2 value	*p*-value
Any treatment-emergent AE (any grade)	82 (79.6)	80 (78.4)	0.043	0.836
Any grade 3-4 AE	24 (23.3)	19 (18.6)	0.675	0.411
Nausea and/or vomiting (any grade)	38 (36.9)	26 (25.5)	3.103	0.078
Constipation (any grade)	44 (42.7)	30 (29.4)	3.934	0.047
Somnolence/excessive sedation (any grade)	29 (28.2)	18 (17.6)	3.203	0.074
Cognitive disturbance/delirium (any grade)	12 (11.7)	7 (6.9)	1.397	0.237
Radiotherapy-related pain flare	15 (14.6)	11 (10.8)	0.661	0.416
Local skin reaction in irradiated field (any grade)	21 (20.4)	23 (22.5)	0.142	0.706
Hematologic toxicity (grade ≥ 2 anemia/leukopenia/thrombocytopenia)	14 (13.6)	13 (12.7)	0.032	0.858
Treatment discontinuation due to AE	8 (7.8)	6 (5.9)	0.286	0.593

Note: Data are presented as n (%). AE: adverse event.

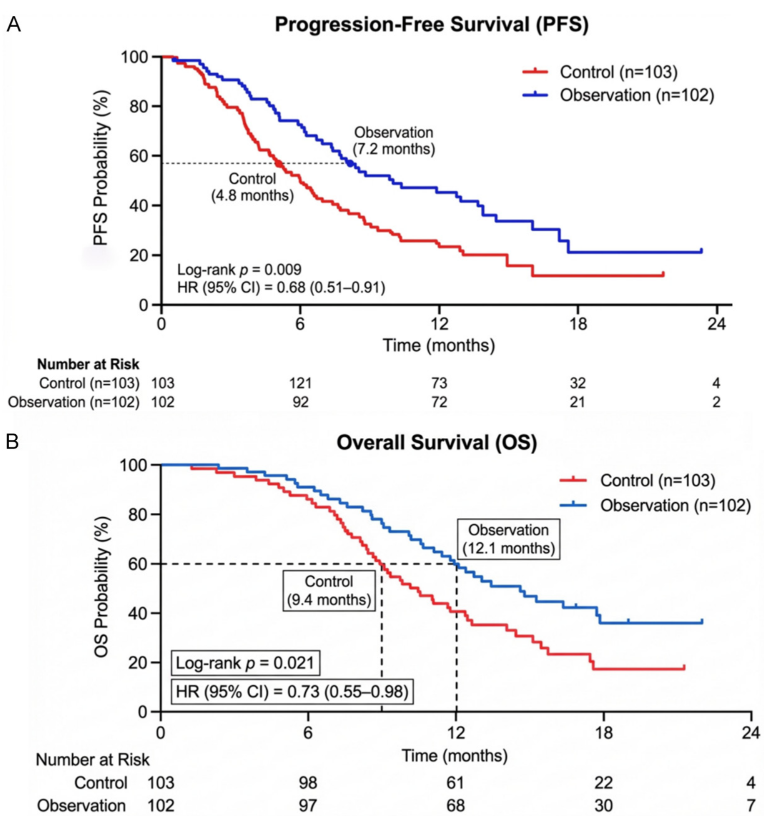


Figure 4. Survival analysis. A. PFS. B. OS. Note: PFS: progression-free survival; OS: overall survival; CI: confidence interval; HR: hazard ratio.

risk of pain progression or death (HR 0.68; 95% CI 0.51-0.91). A similar pattern was observed for OS (**Figure 4B**): patients in the observation group achieved a longer median OS compared with those in the control group (12.1 vs. 9.4 months; log-rank P = 0.021), corresponding to a 27% reduction in the risk of death (HR 0.73; 95% CI 0.55-0.98). Together, these findings indicate that the observation group strategy not only delays pain progression but also confers a clinically meaningful survival benefit.

Comparison of inflammatory indicators between the two groups

At 12 weeks after the intervention, both groups showed significant declines in CRP, TNF-α, IL-6, WBC, and PCT compared with their respective baselines (all P < 0.001), indicating an overall attenuation of systemic inflammation. However, the magnitude of reduction was consistently greater in the observation group: CRP, NLR, TNF-α, IL-6, WBC, and PCT levels were all substantially lower than those in the control group at follow-up (all P < 0.001), as reflected by the more pronounced downward shifts in the corresponding boxplots (**Figure 5**).

Comparison of nutritional indicators between the two groups

Over the 12-week treatment period, albumin, hemoglobin, and transferrin improved in both groups, but the magnitude of improvement was consistently greater in the observation group (all P < 0.05). Patients in the observation group

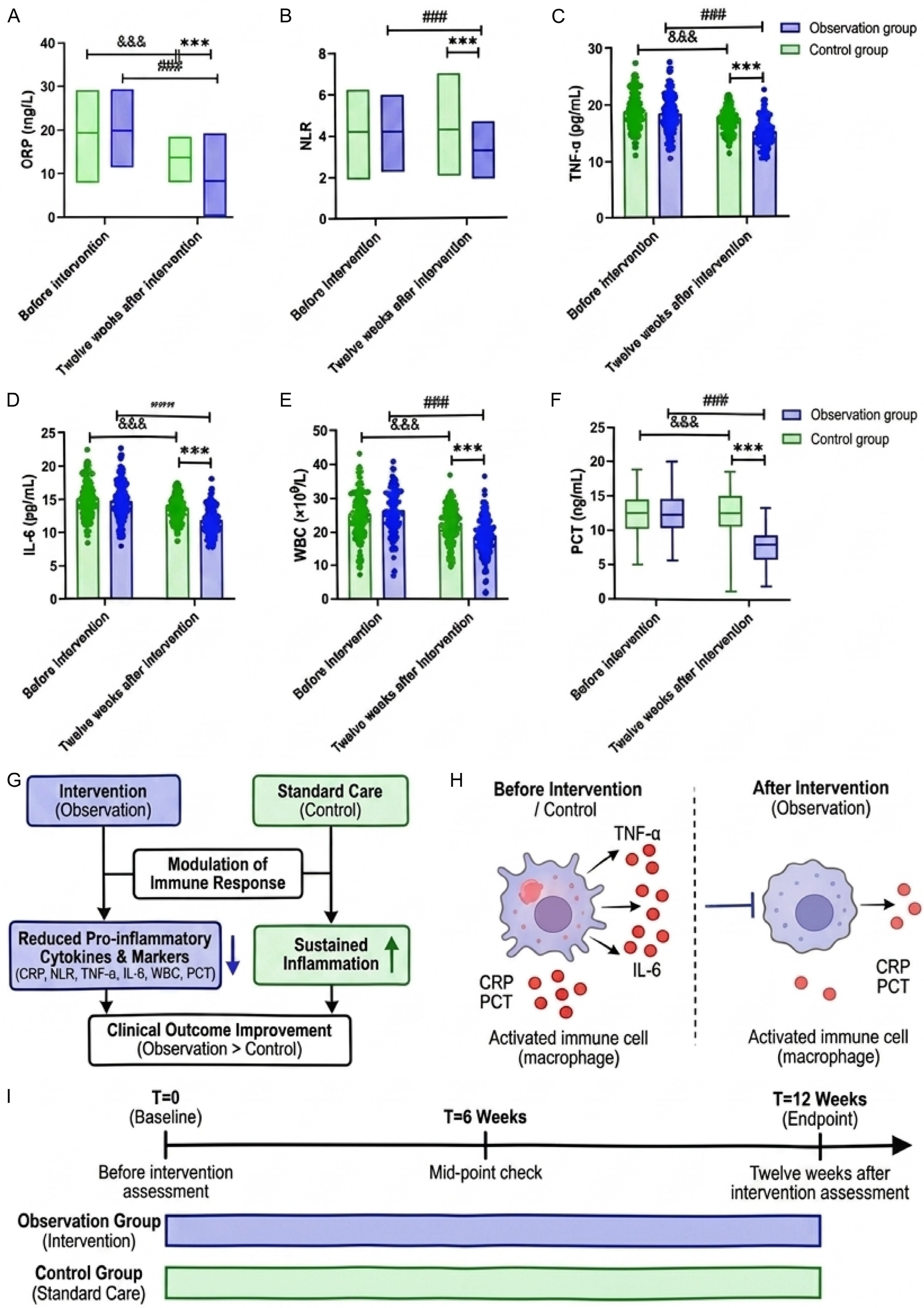


Figure 5. Comparison of inflammatory indicators between the two groups. A. CRP. B. NLR. C. TNF-α. D. IL-6. E. WBC. F. PCT. G. Proposed intervention mechanism. H. Cellular inflammatory pathway. I. Study timeline & assessment points. ***P < 0.001 for between-group comparisons at the indicated time points; &&&P < 0.001 versus before

intervention within the control group; ###P < 0.001 versus before intervention within the observation group. Note: CRP: C-reactive protein; IL-6: interleukin 6; PCT: procalcitonin; TNF-α: tumor necrosis factor alpha; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio.

exhibited larger increases in serum albumin and hemoglobin, resulting in significantly higher levels than those in the control group at week 12 (**Figure 6A**, **6B**; both P < 0.05). Likewise, transferrin levels and caloric intake rose more markedly in the observation group, with between-group differences at follow-up reaching statistical significance (**Figure 6C**, **6D**; both P < 0.05, as indicated in the figure). A schematic overview of the intervention-related improvement in nutritional and hematologic status is presented in **Figure 6E**, while the overall study workflow, including baseline assessment, the 12-week intervention period, and post-intervention assessment, is summarized in **Figure 6F**. In addition, the potential biological basis underlying these changes is illustrated in **Figure 6G**, **6H**, showing how nutritional supplementation may promote protein synthesis and contribute to increased albumin, hemoglobin, and transferrin levels.

Univariate and multivariable logistic regression for overall pain response at week 12

Patients in the observation group had approximately 0.12-fold greater odds of response compared with those in the control group (adjusted odds ratio [OR] 0.116, 95% CI 0.056-0.239; P < 0.001). In contrast, higher baseline pain intensity was an adverse prognostic factor: each 1-point increase in baseline NRS score was associated with a 268% reduction in the odds of overall pain response (adjusted OR 3.676, 95% CI 1.757-7.689; P = 0.001). Similarly, a higher skeletal tumor burden was negatively associated with treatment efficacy, with patients harboring more than three bone metastases having 53% lower odds of response than those with three or fewer lesions (adjusted OR 1.532, 95% CI 1.359-1.727; P < 0.001) (**Tables 3** and **4**).

Discussion

The present study demonstrates that a combination of palliative RT and protocolised multimodal analgesia provides clinically significant benefits over conventional clinician-directed analgesic treatment in patients with painful bone metastases. This combined approach resulted in rapid and sustained pain relief, greater improvements in health-related quality of life, suppression of systemic inflammation, enhanced nutritional status, and extended PFS and OS, without increasing the burden of serious toxicity. Moreover, we identified baseline pain intensity and skeletal tumor burden as independent predictors of overall pain response, thereby providing a useful model of risk stratification in this patient population.

Our results build upon and extend the available evidence on palliative RT for bone metastases, which has largely focused on short-term pain response rather than long-term management and patient outcomes. Other trials involving single- and multiple-fraction RT [13] or RT with systemic opioids alone [14] have demonstrated statistically significant but often transient analgesic effect, with relatively limited impact on functional recovery. In comparison, we not only observed greater improvements in NRS scores at all follow-up time points but also a longer duration of pain relief and a shorter time to clinically meaningful benefit in the observation group. These findings support the concept that RT and multimodal pharmacologic analgesia are not merely additive but rather synergetic, with optimized systemic analgesia stabilizing and reinforcing the antinociceptive effects of local RT [15]. In clinical terms, this highlights the need to move beyond the RT-or-analgesia dichotomy toward protocol-based regimens, while remaining attentive to individual differences in pain patterns.

The observed high scores for global health status and physical, role, emotional, and social functioning in the observation group demonstrate the relevance of considering quality of life as a criterion in the assessment of palliative interventions. Earlier bone-targeted therapy and RT trials have shown small functional improvements that are usually hampered by poor pain management or treatment toxicities [16, 17]. We propose that our findings indicate that, with rapid and sustained pain control, patients are able to resume daily life, continue

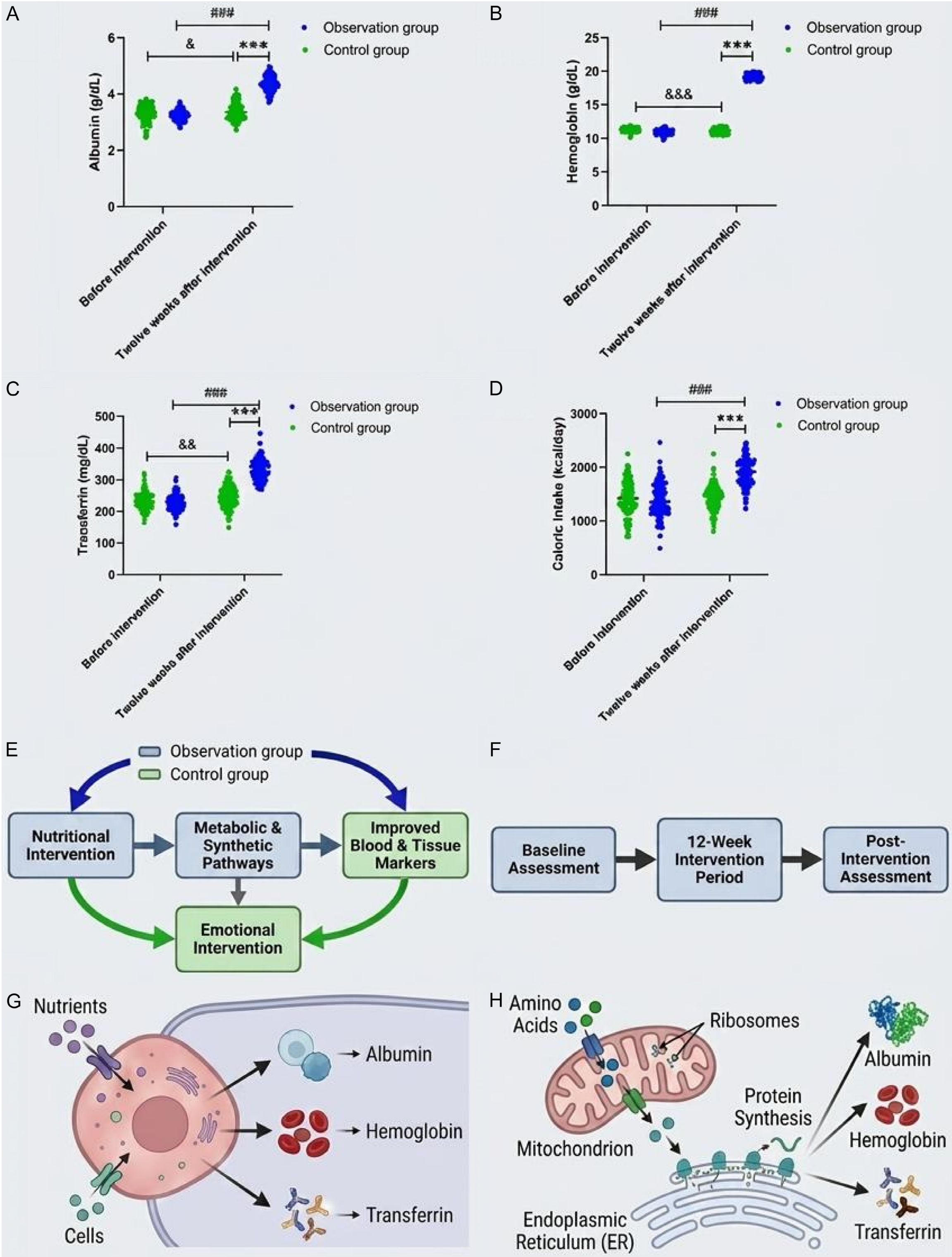


Figure 6. Comparison of nutritional indicators between the two groups. A. Albumin. B. Hemoglobin. C. Transferrin. D. Caloric intake. E. Intervention impact mechanism. F. Study timeline. G. Cellular nutrient uptake and synthesis. H. Mitochondrial and ER protein synthesis pathway. ***P < 0.001 for between-group comparisons at the indicated time points; &P < 0.05, &&P < 0.01, &&&P < 0.001 versus before intervention within the control group; ###P < 0.001 versus before intervention within the observation group. Note: ER: endoplasmic reticulum.

occupations, and experience psychological relief. The effects of pain control can mechanistically promote mobility, reduce sleep disturbance, and decrease anxiety and depressive

Table 3. Univariate logistic regression analysis for overall pain response at week 12

Variable	Responders (n = 132)	Non-responders (n = 73)	t/χ^2	*P* value
Age, years	61.84 ± 10.89	61.56 ± 10.26	0.179	0.858
Sex, n (% male)	78 (59.1)	46 (63.0)	0.303	0.582
ECOG performance status, n (%)			5.597	0.018
0-1	77 (58.3)	30 (41.1)		
2-3	55 (41.7)	43 (58.9)		
Charlson comorbidity index	5.91 ± 2.42	5.79 ± 2.17	0.337	0.737
Primary tumor type, n (%)			0.278	0.964
Breast	40 (30.3)	21 (28.8)		
Lung	44 (33.3)	27 (37.0)		
Prostate	23 (17.4)	12 (16.4)		
Other	25 (18.9)	13 (17.8)		
Number of bone metastases, n (%)			1.506	0.220
≤ 3 lesions	53 (40.2)	23 (31.5)		
> 3 lesions	79 (59.8)	50 (68.5)		
Spinal involvement, n (%)	83 (62.9)	52 (71.2)	1.459	0.227
Pathological fracture, n (%)	26 (19.7)	19 (26.0)	1.099	0.294
Visceral metastases, n (%)	64 (48.5)	45 (61.6)	3.269	0.071
Baseline NRS pain score	7.08 ± 2.29	7.96 ± 2.27	2.652	0.009
Baseline strong opioid use, n (%)	51 (38.6)	42 (57.5)	6.773	0.009
Total RT dose, n (%)			6.677	0.411
< 30 Gy	59 (44.7)	37 (50.7)		
≥ 30 Gy	73 (55.3)	36 (49.3)		
Fractionation schedule, n (%)			1.570	0.210
Single fraction	41 (31.1)	29 (39.7)		
Multiple fractions	91 (68.9)	44 (60.3)		
Treatment group, n (%)			8.230	0.004
RT alone	52 (39.4)	44 (60.3)		
RT + multimodal analgesia	80 (60.6)	29 (39.7)		

Note: ECOG: Eastern Cooperative Oncology Group; NRS: numeric rating scale; RT: radiotherapy.

Table 4. Multivariable logistic regression for overall pain response at week 12

Variable	Category/Unit	Adjusted OR	95% CI	*p*-value
Treatment group	1 = Observation group (RT + multimodal analgesia); 0 = Control group Continuous; per 1-point increase (0-10 scale) 1 = > 3 lesions; 0 = ≤ 3 lesions Continuous; per 10-year increase 1 = Male; 0 = Female 1 = Yes; 0 = No	0.116	0.056-0.239	< 0.001
Baseline NRS pain score	1 = Observation group (RT + multimodal analgesia); 0 = Control group Continuous; per 1-point increase (0-10 scale) 1 = > 3 lesions; 0 = ≤ 3 lesions Continuous; per 10-year increase 1 = Male; 0 = Female 1 = Yes; 0 = No	3.676	1.757-7.689	0.001
Number of bone metastases	1 = Observation group (RT + multimodal analgesia); 0 = Control group Continuous; per 1-point increase (0-10 scale) 1 = > 3 lesions; 0 = ≤ 3 lesions Continuous; per 10-year increase 1 = Male; 0 = Female 1 = Yes; 0 = No	1.532	1.359-1.727	< 0.001

Note: OR: odds ratio; CI: confidence interval; RT: radiotherapy; NRS: numeric rating scale.

symptoms, which further leads to a virtuous cycle of functional recovery [18]. The results caution against using analgesic response rates alone as an evaluation of palliative strategies and recommend the routine use of validated quality-of-life measures in practice and clinical studies.

The overall safety profile of the combined approach was comparable to that of conventional care, and there were no significant differences in the rates of any-grade or grade 3-4 adverse events, with constipation being less frequent in the observing group. This finding contrasts with the longstanding concern that escalating analgesic regimens inevitably increases toxicity, particularly gastrointestinal and neurocognitive events associated with opioid management [19]. We believe that our data indicate that a multimodal pain management approach - comprising protocolized non-opioid adjuvants, rational opioid titration, and early management of side effects - can achieve effective pain control with reduced reliance on high-dose opioids and, consequently, fewer dose-limiting toxicities. This observation is supported by the trends toward reduced nausea/vomiting and somnolence, although these differences did not reach statistical significance. Clinically, these findings imply that deploying more intensive palliative treatment requires structured toxicity surveillance and proactive supportive care rather than therapeutic nihilism.

Of special interest is the increased PFS and total OS associated with the observation group regimen, as palliative interventions for bone metastases have long been viewed as symptom-centric rather than survival-centric. Recent literature has proposed that optimized symptom management, particularly pain control, can have an indirect survival benefit through improved performance status, the ability to continue systemic anticancer treatment, and the mitigation of chronic stress and inflammation [20, 21]. Our findings corroborate this paradigm: the combination of RT and multimodal analgesia not only achieves better local pain control but also provides significant relative protection against pain progression or death and against all-cause mortality. These findings suggest that, in certain contexts, high-quality supportive care should be considered a disease-modifying component of oncologic care. Simultaneously, they emphasize the need for detailed characterization of concomitant systemic treatments and disease trajectories in future prospective studies to disentangle direct from indirect survival effects.

The greater improvements in CRP, NLR, TNF-α, IL-6, WBC count, and PCT, and greater improvements in serum albumin, hemoglobin, transferrin, and caloric intake, are indicative of an effect of the combined approach on the systemic inflammatory and nutritional microenvironment, rather than simply the alleviation of symptoms. Systemic inflammation is proven to be a driver of cachexia, impaired functioning, and poor survival, as it has been shown to result in chronic cancer pain and uncontrolled bone metastases [22-24]. Palliative RT along with multimodal analgesia can break this vicious cycle by transforming inflammatory signaling and enabling sufficient oral intake and nutrient utilization [25, 26]. This hypothesis is supported by the simultaneous enhancement of inflammatory and nutritional indicators in our group of patients and is consistent with past findings that ranked NLR, CRP, and hypoalbuminemia among negative prognostic indicators of metastatic cancer. These facts, clinically, argue for regular check-ups and active optimization of inflammatory and nutritional status as part of comprehensive palliative care.

This research is limited in a number of ways that should be taken into account. This retrospective, single-center study presents the risk of selection bias, unmeasured confounding, and center-specific practice patterns, which can restrict external validity. The treatment decisions were based on group allocation instead of randomization, and despite control for major covariates at baseline, residual confounding cannot be excluded. The heterogeneity of the cohort in terms of primary tumor type, previous systemic therapy, and RT parameters may have contributed to the symptom course as well as survival. Although the follow-up period is adequate to measure the main endpoint and initial survival, it might not be sufficient to comprehensively describe long-term outcomes or late toxicities. Moreover, we did not directly assess psychological distress, caregiver burden, or economic endpoints, which are regarded as increasingly important aspects of palliative care. Further and larger outcome analysis requires future multicenter randomized trials in which therapeutic protocols are unified and comprehensive outcomes were evaluated.

In conclusion, we find that a synergistic benefit is achieved with the use of palliative RT and protocolized multimodal analgesia, which offers patients with painful bone metastases better and longer-lasting pain management, more significant improvements in quality of life and functional status, better nutritional outcomes, and clinically significant increases in survival, and shows no excess serious toxicity. Baseline pain intensity and skeletal tumor burden were identified as useful prognostic predictors that can be used to make individualized treatment plans. These results justify the addition of structured multimodal analgesia to RT as a preferred option in this specific palliative care setting and support future randomized trials to streamline treatment components and understand the biological processes involved.

Disclosure of conflict of interest

None.

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