A Comparative Study Between Two Multi-Fraction Radiation Schedules; 20 Gy in 5 Fractions versus 30Gy in 10 Fractions in Palliative Management of Painful Bone Metastases

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Abstract:

Background: Bone metastases (BM) are a painful complication of advanced malignancies, significantly reducing patients' quality of life. Radiotherapy (RT) is a cornerstone in the palliative treatment of BM, with different fractionation schedules used globally. This study compared two multi-fractionated RT regimens -30 Gy/10 and 20 Gy/5 fractions- focusing on pain control, re-irradiation rates, relapse, toxicity, and overall survival (OS).

Methods: This prospective, randomized controlled trial was conducted at the South Egypt Cancer Institute, Assiut University, including 100 patients with confirmed painful BM. Patients received either 30 Gy/10 fractions (n=50) or 20 Gy/5 fractions (n=50). Pain relief was assessed using the Visual Analogue Scale at 1- and 3-months post-treatment. Re-irradiation rates, relapse, acute toxicity, pathological fractures, spinal cord compression, and 1-year OS were evaluated.

Results: At 1 month, the overall response rate was 88% in the 30 Gy group and 82% in the 20 Gy group (p=0.9), with similar results at 3 months (76% vs. 72%, p=0.991). Although both regimens provided effective pain control, patients in the 30 Gy group had a lower rate of pain progression (1.6% vs. 6.5%) and re-irradiation (6% vs. 12%) compared to the 20 Gy group. Acute toxicity was significantly higher in the 30 Gy group, with 25% experiencing Grade 1-2 toxicity compared to 5% in the 20 Gy group (p<0.0001). Skin reactions and fatigue were the most common side effects. Pathological fractures and spinal cord compression were observed in 4% and 6% of patients in the 20 Gy group, compared to 2% in both categories in the 30 Gy group. 1-year OS was comparable between groups (35% for 20 Gy and 39% for 30 Gy, p=0.527).

Conclusion: Both regimens offered high rates of pain relief, but the 30 Gy regimen provided more durable pain control, reflected in lower re-irradiation rates and pain progression. However, this came at the cost of higher acute toxicity. The 20 Gy might be more appropriate for patients with a lower performance status or in high-volume centers where shorter treatment times and fewer side effects were prioritized.

Key Words: Palliative Care; Bone Metastases; Radiotherapy; Pain Management.

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Introduction:

Bone metastases (BM) are a frequent and distressing complication of advanced malignancies, often leading to significant pain and reduced quality of life for patients. The management of painful BM is primarily palliative, aiming to alleviate symptoms and improve functional outcomes. Radiation therapy (RT) is a cornerstone in the treatment of these patients, providing effective and rapid pain relief and improved quality of life for cancer patients. [1]

Various radiation schedules have been employed to manage painful BM, with single-fraction and multi-fraction regimens being the most used. Single-fraction treatments, such as 8 Gray (Gy) delivered in one fraction, offer convenience and cost savings. However, concerns about the durability of pain relief and the potential need for re-irradiation have led to the

preference for multi-fraction schedules, which may offer prolonged palliation and improved outcomes. [2]

The question of which dose and fractionation schedule provides the best balance between pain relief, and treatment-related side effects remains a subject of debate and active research. While both single- and multi-fraction regimens have demonstrated similar efficacy in controlling pain, multi-fraction schedules are often favored for maintaining longer-term pain control, especially in patients with a more extended prognosis. [3,4,5]

The choice between single-fraction and multi-fraction RT often depends on various clinical factors, including the patient's overall condition, the extent of metastatic disease, and the expected duration of pain relief. Studies comparing different fractionation regimens have highlighted that both approaches can be effective, with no significant differences in overall survival (OS) observed between the two strategies. [6] However, the ongoing debate about the optimal fractionation schedule underscores the need for further research to refine treatment protocols and improve patient outcomes.

Considering these factors, the primary aim of this study was to provide a comparative analysis of two commonly used multi-fraction radiation schedules -20 Gy in 5 fractions and 30 Gy in 10 fractions- focusing on their efficacy in pain control, analgesic requirements, and associated side effects. Additionally, the study sought to compare secondary outcomes such as OS, response duration, acute toxicity, need for re-irradiation, and the development of skeletal-related events, including spinal cord compression and pathological fractures, between the two treatment regimens. This analysis is especially important in our high-volume center, where optimizing machine time is critical for ensuring efficient patient care and managing high treatment demand.

Methodology:

Study Design

This study was structured as a hospital-based, prospective, randomized controlled trial aimed at comparing the efficacy and safety of two multi-fraction RT schedules -20 Gy in 5 fractions and 30 Gy in 10 fractions- for the palliative treatment of painful BM. Eligible participants included patients with confirmed painful BM who were referred for palliative RT. Patients were randomly allocated to one of the two treatment groups, with key outcomes, including pain relief and treatment-related toxicity, being closely monitored and analyzed over a predefined follow-up period.

The study was conducted in the Department of Radiation Therapy at the South Egypt Cancer Institute (SECI), Assiut University, Assiut, Egypt. Data collection and analysis followed a rigorous and systematic approach, adhering to ethical guidelines with approval from the institutional ethics committee. The study spanned two years, from October 2021 to September 2023, ensuring sufficient follow-up time to assess long-term outcomes and treatment effectiveness.

Inclusion Criteria

The study included adult patients aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or lower. Participants had histopathologically confirmed malignancies with symptomatic BM and an initial pain score of 5 or higher on the Visual Analogue Scale (VAS).

Exclusion Criteria

Exclusion criteria included patients with an ECOG performance status greater than 3, those under the age of 18, or patients whose bone pain was at more than one site or could be effectively managed with medical treatment alone. Additionally, patients who lacked histopathological confirmation of their primary malignancy or had previously received RT at the same site of BM were also excluded from the study. Patients who had features of spinal cord compression, existing pathological bone fractures or impending fractures following Mirels' criteria, or any contraindications to RT, such as severe radiation hypersensitivity, pregnancy, or poor general condition precluding the safe administration of RT, were also excluded from the study.

Radiotherapy

Patients enrolled in the study were randomly assigned to one of two treatment groups. Arm A received 30 Gy of radiation delivered in 10 fractions, with each fraction consisting of 3 Gy over two weeks. Arm B received 20 Gy delivered in 5 fractions, with each fraction consisting of 4 Gy over one week. Informed consent was obtained from all patients before treatment allocation, ensuring they fully understood the study objectives and treatment protocols.

Pain Assessment

Pain levels were assessed before the initiation of treatment using the VAS, which rates pain intensity on a scale from 0 to 10, with 0 indicating no pain and 10 representing the worst possible pain. Painful sites were identified through a comprehensive approach involving clinical history, a detailed physical examination focusing on points of maximum tenderness, and imaging studies such as X-rays, MRI, or CT scans, ensuring accurate localization of metastatic lesions requiring treatment.

Treatment and Follow-Up

After identifying the painful sites, patients underwent a computed tomography-based simulation for precise treatment planning. Three-dimensional conformal RT was delivered using 6/15 megavoltage photons from a linear accelerator. Vertebral metastases were treated with a single direct posterior field, while metastases in the pelvis and long bones were treated using parallel opposed fields to optimize dose distribution. For vertebral metastases, the radiation dose was prescribed to the mid-vertebral body, whereas for

long bones and pelvic metastases, the dose was delivered to the mid-plane to ensure optimal coverage while minimizing exposure to surrounding healthy tissues. Analgesics were administered according to the World Health Organization (WHO) cancer pain ladder and principles of pain management for adults.

Patients were carefully monitored throughout the treatment period and during follow-up assessments conducted at 1, 2-, 3-, 6-, and 12-months post-RT, or until relapse or death occurred. Follow-ups were performed either through in-person outpatient visits or telephone consultations. Data on pain relief, analgesic usage, ECOG Performance Status, acute toxicity measured using the Radiation Therapy Oncology Group criteria (RTOG), retreatment rates, and skeletal-related events were systematically collected during these follow-up visits.

Response Assessment

The treatment response was evaluated based on pain relief and categorized into four groups: complete response (CR), partial response (PR), intermediate response (IR), and pain progression (PP). A CR was defined as a pain score of 0 at the treated site with no increase in analgesic use. A PR was defined as a reduction of 2 or more points on the pain scale (0 to 10) without any increase in analgesic use or a reduction of analgesic use by at least 25% from baseline without an increase in pain. PP was characterized by an increase of 2 or more points in the pain score above baseline, either with stable analgesic use or an increase of 25% or more in analgesic consumption, with either stable or worsened pain by 1 point. IR referred to any response that did not meet the criteria for CR, PR, or PP.

The overall response (OR) was defined as the combination of CR and PR. Patients who showed IR or PP at the one-month follow-up were classified as non-responders. Relapse was defined as a return to baseline pain levels or higher, without any corresponding reduction in analgesic use after an initial improvement. The decision to re-irradiate was made by the treating physician, and patients requiring re-irradiation were classified as relapsed. The response before re-irradiation was not recorded.

Response duration was measured from the time of the first documented or (assessed at one month) to the occurrence of relapse, or, if no relapse occurred, until the date of the last follow-up or death. The degree of pain control was determined by subtracting the post-treatment pain score from the pre-treatment score. A positive value indicated an increase in pain, while a negative value indicated a decrease.

Ethical Considerations:

The study was conducted in accordance with the principles outlined in the Declaration of SECI at Assuit University and adhered to all relevant local ethical guidelines. Approval from the Institutional Review Board (IRB) was obtained prior to the commencement of the study (No:581). Informed consent was secured from all participants, ensuring that they were fully aware of the study's aims and their rights. Confidentiality of personal information was strictly maintained throughout the study. Participants were informed of their right to withdraw from the study at any point, without any impact on their medical care or treatment.

Competing interests:

All publishers have no conflict of interest concerning publishing this paper.

Statistical Analysis:

Data was entered and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was applied to assess the normality of data distribution. For normally distributed quantitative variables, a paired t-test was used to compare two time periods, while analysis of variance (ANOVA) with repeated measures was employed to compare multiple time points. Post hoc analysis with Bonferroni adjustments was applied for pairwise comparisons. The Pearson correlation coefficient was used to examine relationships between normally distributed quantitative variables. Statistical significance was determined at the 5% level ($p \leq 0.05$).

Results:

The analysis included 100 patients, divided evenly between the two treatment groups, with 50 patients in each. Initially, 120 patients with painful BM fulfilling inclusion and exclusion criteria were included in the study (60 in each arm) between January 2022 and January 2023. Unfortunately, 6 patients died before 1-month follow-up during the follow-up period, and 14 patients experienced treatment or follow-up interruptions, leading to their exclusion from the study. Hence, 100 patients (50 in arm A and 50 in arm B) were included in the final assessment. Patient follow-up was at 1 month, 3 months, 6 months, 9 months, and 12 months after the onset of treatment. The demographic comparison of patients receiving two different palliative RT regimens: 20 Gy delivered in 5 fractions and 30 Gy delivered in 10 fractions was shown in Table 1.

The age distribution of patients across the two RT groups was relatively similar. The largest proportion of patients fell within the 50-70 years age range, accounting for 51% of the total cohort. Specifically, 54% of patients in the 20 Gy/5 fractions group and 48% in the 30 Gy/10 fractions group were in this age category. Meanwhile, 40% of the overall patient population was under the age of 50, with a nearly even distribution between the two groups (38% in the 20 Gy/5 fractions group and 42% in the 30 Gy/10 fractions group). Only 9% of patients were over the age of 70, with similar representation in both treatment groups (8% and 10%, respectively).

The mean age across all patients was approximately 55.7 years, with a standard deviation of around 11.2 years. The comparison between the two groups showed a mean age of 55.7 years in the 20 Gy/5 fractions group and 54.16 years in the 30 Gy/10 fractions group. The statistical analysis revealed no significant difference in

the age distribution between the groups, with a p-value of 0.146.

Gender distribution among the study participants was nearly equal, with 55% females and 45% males in the total cohort. The distribution was almost identical between the two treatment groups. In the 20 Gy/5 fractions group, 54% of patients were female and 46% were male, while in the 30 Gy/10 fractions group, 56% were female and 44% were male. The statistical analysis confirmed that there was no significant difference in gender distribution between the two groups, with a p-value of 0.989.

Table 2 provided a detailed comparison of several clinical and demographic variables between the two groups of patients undergoing palliative RT. The analysis covered factors such as ECOG performance status, primary tumor site, location of radiation, baseline pain score, and pain medications before RT.

The ECOG performance status, which assessed patients' level of functioning, was evenly distributed between the two groups. Around 20% of patients in both groups had a performance status of 0-1, indicating full activity. The majority, 57%, had a status of 2, with nearly equal distribution between the groups (56% in the 20 Gy/5 fractions group and 58% in the 30 Gy/10 fractions group). A smaller proportion of patients (23%) had a performance status of 3, again with a similar distribution between the groups. The p-value of 0.97 indicated no significant difference in performance status between the groups.

According to the primary tumor location, breast cancer was the most common, comprising 34% of the total cohort, with a slightly higher percentage in the 20 Gy/5 fractions group (36%) compared to the 30 Gy/10 fractions group (32%). Lung cancer and prostate cancer were also common, with a distribution of approximately 20% and 17%, respectively, again with similar distributions across the two groups. The "Others/unknown" category, which included various other cancer types, made up 29% of the cohort. The p-value of 0.938 suggested that there were no significant differences in the cancer staging distribution between the two treatment groups.

The table also categorized patients based on the primary location of RT. The thoracic spine was the most common site (35%), followed by the sacrum or pelvis (31%) and the lumbar spine (21%). The distribution of radiation sites was similar across the two groups, with no significant differences noted (p-value 0f 0.937). Baseline pain scores, recorded before the initiation of RT, ranged from 5 to 10 on a pain scale. The distribution of pain scores was similar between the two groups, with 48% of patients reporting a pain score of 7, which was the most common score. The p-value of 0.993 indicated no significant differences in baseline pain levels between the treatment groups.

Patients' use of pain medications before RT was categorized into three groups: no pain medication, non-opioid medications, and opioid medications. This classification was based on pain severity score using VAS and the corresponding use of pain medications, following standard clinical guidelines for pain management in BM. No medication or non-opioid medications (such as NSAIDs or acetaminophen) were used for mild pain (score 5-6), while non-opioid or opioid medications were used for moderate to severe pain (score 7-10). Most patients (71%) were using opioid pain relief, with an almost equal distribution between the two treatment groups. A p-value of 0.85 suggested that there was no significant difference in the use of pain medications between the groups.

At one-month post-treatment, 85% of the total cohort exhibited an OR, combining CR and PR. The 20 Gy group had an 82% OR rate, while the 30 Gy group had an 88% rate, with no significant difference (p-value of 0.9). The results were consistent at three months, with a 74% OR rate in the entire cohort, and slightly higher in the 30 Gy group (76%) compared to the 20 Gy group (72%), but again, this difference was not statistically significant (p-value of 0.991).

49% of patients relapsed within one year, with slightly more relapses in the 20 Gy group (52%) compared to the 30 Gy group (48%). The p-value of 0.841 suggested that this difference was not statistically significant, indicating comparable relapse rates between the two treatment schedules, as shown in Table 3.

The retreatment rate was notably higher in the 20 Gy/5 fraction group, with 12% of patients (6 out of 50) requiring additional treatment, compared to only 6% in the 30 Gy/10 fraction group (3 out of 50). Although this difference did not reach statistical significance ($p = 0.2945$), the clinical implication remained clear: the higher dose regimen (30 Gy/10 fractions) appeared to provide more sustained pain relief, and superior long-term efficacy reducing the likelihood of retreatment. In terms of the response duration, patients in the 30 Gy group experienced slightly longer pain relief, with an average response duration of 5.75 months (23 weeks), compared to 5.25 months (21 weeks) in the 20 Gy group. Nevertheless, these differences were not statistically significant, as indicated by p-values of 0.5851 for months and 0.4622 for weeks, which implies that both treatment regimens provided similar durations of pain control. Evaluating the mean degree of pain control, patients in the 30 Gy group reported a slightly higher average pain relief score of 4, compared to 3.5 in the 20 Gy group. However, this difference was also not statistically significant ($p = 0.3922$), suggesting that both groups achieved comparable levels of pain relief as shown in Table 4.

The incidence of pathological fractures was slightly higher in the 20 Gy/5 fraction group, with 4% of patients (2 out of 50) experiencing fractures, compared to 2% (1 out of 50) in the 30 Gy/10 fraction group. Although this difference did not reach statistical significance ($p = 0.5862$), suggesting a comparable impact of both regimens on pathological fractures, the clinical implications are noteworthy. The 30 Gy/10 fraction regimen may provide better bone stability, potentially lowering the risk of pathological fractures in patients with BM. This highlights the potential advantage of the higher dose regimen in maintaining skeletal integrity, which may become more evident with larger study populations as shown in Table 5.

Regarding spinal cord compression as assessed by motor and bladder function impairment, the 20 Gy group had a higher incidence of 6% (3 out of 50 patients), compared to 2% (1 out of 50 patients) in the 30 Gy group. Despite this difference, the p-value of 0.3074 indicates that the results were not statistically significant, suggesting that both regimens have a comparable risk of causing or exacerbating spinal cord compression.

Acute toxicities were assessed at regular intervals: during treatment, at the end of treatment, and at follow-up visits 1 month and 3 months post-radiation. The RTOG classification was used to grade acute toxicity from Grade 1 (mild) to Grade 4 (severe). The overall incidence of acute toxicity was higher in the 30 Gy group, with 25% of patients experiencing side effects, compared to just 5% in the 20 Gy group. Grade 1 toxicity was more frequent in the 30 Gy group (20.3% vs. 8.7%), as was Grade 2 toxicity (5.7% vs. 2.6%) with a significant p-value of <0.0001.

Skin reactions and fatigue were the most reported toxicities in both treatment arms, with Grade 1 and 2 toxicities being more frequent in the 30 Gy group. In the 30 Gy arm, 22% of patients experienced Grade 1 or 2 skin reactions, with 7 patients (14%) experiencing Grade 1 and 4 patients (8%) experiencing Grade 2 reactions. In contrast, in the 20 Gy group, 6% of patients experienced skin reactions, with 2 patients (4%) experiencing Grade 1 and 1 patient (2%) experiencing Grade 2. These skin reactions were managed with topical emollients and corticosteroid creams to reduce inflammation. Patients were advised to avoid irritating the affected skin by using gentle soaps and avoiding direct sunlight.

Fatigue was another prevalent symptom, affecting 20% of patients in the 30 Gy group, with 16% (8 patients) experiencing Grade 1 fatigue and 4% (2 patients) experiencing Grade 2. In comparison, 6% of patients in the 20 Gy group reported fatigue, with 4% (2 patients) experiencing Grade 1 and 2% (1 patient) experiencing Grade 2. Fatigue management involved lifestyle advice, including rest periods, gentle physical activity, and nutritional support to help maintain energy levels. In cases of Grade 2 fatigue, patients were also offered psychological support and counseling to help cope with the impacts on daily life.

Gastrointestinal and hematologic toxicities were less common but still observed more frequently in the 30 Gy group. 8% of patients (4 patients) in the 30 Gy group experienced Grade 1 (3 patients) or 2 (1 patient) gastrointestinal toxicity, while 2% (1 patient) in the 20 Gy group reported Grade 1 toxicity, no Grade 2 toxicity. Gastrointestinal side effects, such as nausea and mild diarrhea, were managed with antiemetic medications and dietary modifications to prevent dehydration and malnutrition. Hematologic toxicity was also mild in both groups, with 6% (3 patients) of the 30 Gy group experiencing Grade 1 or 2 toxicities, compared to 2% (1 patient) in the 20 Gy group. Muscle pain, a common side effect in palliative RT, affected 10% of patients in the 30 Gy group, with 6% (3 patients) experiencing Grade 1 and 4% (2 patients) experiencing Grade 2. In the 20 Gy group, 4% of patients (2 patients) reported muscle pain, with 2% (1 patient) having Grade 1 and 2% (1 patient) having Grade 2. Other toxicity, though rare, was observed in 2% of patients in the 30 Gy group, with 1 patient experiencing Grade 1 toxicity, presenting as a mild cough. This was managed conservatively with cough suppressants and close monitoring for any worsening symptoms. No significant lung toxicity was observed in the 20 Gy group.

Importantly, no Grade 3 or 4 toxicities were observed in either treatment group, indicating that the treatments were generally well-tolerated. Additionally, late toxicity (which typically occurs months or years after treatment) was not assessed in this study, as the focus was on acute side effects occurring during and shortly after the course of RT. A comparison of the incidence of treatment-related acute toxicity in two RT schedules for painful BM was shown in Table 6. Overall, the findings suggested that the 30 Gy in 10 fractions regimen was associated with a higher rate of acute toxicity compared to the 20 Gy in 5 fractions regimen. Although the higher dose provided potential benefits in pain relief and disease control, it was also linked to an increased risk of side effects, particularly in terms of skin reactions and fatigue. Management of these toxicities involved standard care protocols, focusing on symptom relief and close monitoring to ensure patient safety. These assessments and interventions were critical to minimizing patient discomfort and preventing the progression of side effects during and after treatment.

The 1-year OS rates were 35% in the 20 Gy arm and 39% in the 30 Gy arm. Mean survival was 6.8 months (± 2.36) and 7.24 months (± 2.23) for the 20 Gy and 30 Gy schemes, respectively. Median OS was 7.3 months in the 20 Gy arm and 7.4 months in the 30-Gy arm. There were no significant differences between schedules in terms of survival probability (p-value of 0.527). The Chi-square statistic was 0.400, reinforcing that conclusion (Table 7 and Figure 1). The findings indicated that there was no substantial evidence to suggest that the 30 Gy regimen offered a significant survival advantage over the 20 Gy regimen in this patient population.

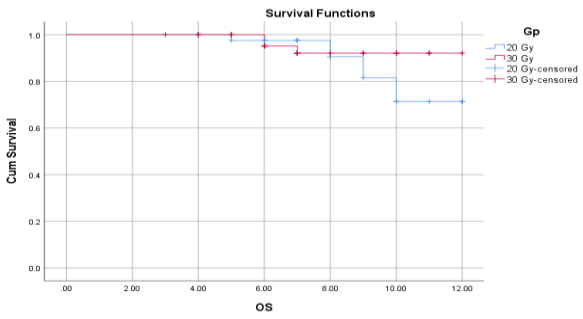

Figure 1: Kaplan-Meier Curve of One-Year Overall Survival

Table 1: Comparison of demographic characteristics in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases

	Total N=100	20 Gy/5fr N=50	30 Gy/10fr N=50	p-value
Age (years)				
< 50	40(40%)	19(38%)	21(42%)	0.824
50 - 70	51(51%)	27(54%)	24(48%)	
> 70	9(9%)	4(8%)	5(10%)	
Mean± SD	55.7±11.2	55.7±11.21	54.16±11.36	0.146
Range (Min-Max)	34-83	35-80	34-83	
Gender				
Female	55(55%)	27(54%)	28(56%)	0.989
Male	45(45%)	23(46%)	22(44%)	
Statistical test used: Chi-square test & Tow sample T-test				

p-value≤0.05 considered statistically significant (95% confidence interval

Table 2: Detailed comparison of several clinical and demographic variables in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases

	Total N=100	20Gy/5r N=50	30 Gy/10fr N=50	p-value
Eastern Cooperative Oncology Group; ECOG performance status				
0-1	20(2%)	10(20%)	10(20%)	0.97
2	57(57%)	28(56%)	29(58%)	
3	23(23%)	12(24%)	11(22%)	
Primary tumor				
Breast cancer	34(34%)	18(36%)	16(32%)	0.938
Lung cancer	20(20%)	9(18%)	11(22%)	
Prostate cancer	17(17%)	8(16%)	9(18%)	
Others/unknown	29(29%)	15(13%)	14(28%)	
Location of radiation				
Thoracic Spine	35(35%)	19(38%)	16(32%)	0.937
Lumbar spine	21(21%)	10(20%)	11(22%)	
Sacrum or pelvis	31(31%)	15(30%)	16(32%)	
Others	13(13%)	6(12%)	7(14%)	
Baseline pain score				
5	4(4%)	2(4%)	2(4%)	0.993
6	9(9%)	5(10%)	4(8%)	
7	48(48%)	23(46%)	25(50 %)	
8	22(22%)	12(24%)	10(20%)	
9	8(9%)	4(8%)	4(8%)	
10	9(9%)	4(8%)	5(10%)	
Pain medications before radiotherapy				
None	9(10%)	5(10%)	4(8%)	0.85
Non-opioid	20(20%)	9(18%)	11(22%)	
Opioid	71(71%)	36(72%)	35(70%)	

Table 3: Comparison of treatment responses and relapse rate characteristics in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases.

	Total N=100	20 Gy/5fr N=50	30 Gy/10fr N=50	p-value
Response 1m				
Complete response 1m	15(15%)	7(14%)	8(16%)	0.9
Partial response 1m	70(70%)	34(68%)	36(72%)	
Overall response 1m	85(85%)	41(82%)	44(88%)	
Intermediate response 1m	9(9%)	5(10%)	4(8%)	
Pain progression 1m	6(6%)	4(8%)	2(4%)	
No response 1m	15(15%)	9(18%)	6(12%)	
Response 3m				
Complete response 3ms	17(17%)	8(16%)	9(18%)	
Partial response 3ms	57(57%)	28(58%)	29(58%)	0.991
Overall response 3ms	74(74%)	36(72%)	38(76%)	
Intermediate response 3ms	21(21%)	11(22%)	10(20%)	
Pain progression 3ms	5(5%)	3(6%)	2(4%)	
No response 3ms	26(29%)	14(28%)	12(24%)	
Relapse				
Relapse within 1 year mostly	49(49%)	26(52%)	24(48%)	0.841

Statistical test used: Chi-square test
p-value≤0.05 considered statistically significant (95% confidence interval).

Table 4: Efficacy and retreatment outcomes in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases.

	20 Gy/5fr N=50	30 Gy/10fr N=50	p-value
Retreatment rate	6(12%)	3(6%)	0.2945
Response duration			
months	5.25	5.75	0.5851
weeks	21	23	0.4622
The mean degree of pain control	3.5	4	0.3922

Table 5: Comparison of pathological fractures, and spinal cord compression in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases.

	20 Gy/5fr N=50	30 Gy/10fr N=50	P-value
Pathological fracture	2(4%)	1(2%)	.5862
spinal cord compression			
Motor/ bladder Function impairment post-radiation	3 (6%)	1 (2%)	.3074

Table 6: Comparison of the incidence of treatment-related acute toxicity in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases.

Toxicity Type	20 Gy/5fr N=50			30 Gy/10fr N=50			p-value
Grade	0	1	2	0	1	2	
Skin Reactions	47	2	1	39	7	4	
Fatigue	47	2	1	40	8	2	
Gastrointestinal	49	1	0	46	3	1	
Hematologic	49	1	0	47	2	1	
Muscle Pain	48	1	1	45	3	2	
other	50	0	0	49	1	0	
Total % of each grade	88.7%	8.7%	2.6%	74%	20.3%	5.7%	<0.0001 *
Total acute toxicity %	5%			25%			

Table 7: Comparison of one-year overall survival in patients treated with 20 Gy and 30 Gy radiotherapy for bone metastases.

	20 Gy/5fr N=50	30 Gy/10fr N=50	P value	Chi-Square	Statistically significant
One-year overall survival Rate	35%	39%			
Mean survival ± SD (month)	6.8±2.36	7.24±2.23	0.527	0.400	N. S
Median survival (month)	7.3	7.4			

Statistical test used: Kaplan-Meier Test (Log Rank (Mantel-Cox))
p-value≤0.05 considered statistically significant (95% confidence interval).

Discussion:

Pain Relief and Response Rates:

Several studies have evaluated the efficacy of various fractionation schedules in the management of painful BM. The biological effective dose (BED) was calculated to compare the various fractionated schedules. The BED10 (BED calculated using an alpha-beta ratio (α/β) of 10 Gy) was calculated using the equation: n x d (1 + d/(α/β)), where d is the fraction dose, n is the number of fractions, and α/β is 10 Gy. Our study compared two commonly used regimens: 30 Gy delivered in 10 fractions (39.0 Gy BED10) and 20 Gy delivered in 5 fractions (28.0 Gy BED10).

At one-month post-treatment, our study found that 85% of the total cohort exhibited an OR, which included both CR and PR. The 20 Gy/5 fractions regimen resulted in an 82% OR rate, while the 30 Gy/10 fractions regimen demonstrated an 88% OR, with no statistically significant difference (p = 0.9). This was in line with several studies in the literature. For instance, Niewald et al. reported no significant difference in pain relief between the 20 Gy and 30 Gy regimens, with a CR rate of 14% for the 20 Gy group and 22% for the 30 Gy group. [7] El-Shenshawy et al. found comparable response rates between the two regimens, although the 30 Gy arm had a higher CR rate at 32% compared to 20 Gy's CR rate of 28%, which was consistent with our study's observations. [8]

Valeriani et al. further corroborated our findings, reporting an OR rate of 89.6% for the 20 Gy group and 87.3% for the 30 Gy group, with a p-value of 0.669, indicating no significant difference in pain control between the two regimens. However, the 30 Gy group did exhibit a slightly higher CR rate, as observed in our study. This suggested that both regimens offered

effective pain relief, but the 30 Gy schedule might provide a slight advantage in terms of CR. [9]

Other studies have shown similar findings. For example, Foro Arnalot et al. reported an OR rate of 85% in their cohort, with no statistically significant difference between single-dose (8 Gy) and multifraction regimens (20 Gy and 30 Gy). [10] Similarly, Hartsell et al. found no significant difference in CR rates between 8 Gy and 30 Gy regimens, although the re-irradiation rates were higher in the 8 Gy arm. [11]

The response rates remained consistent for three months, with a 74% OR rate across the entire cohort. The 30 Gy group showed a slightly higher response rate (76%) compared to the 20 Gy group (72%), although this difference was not statistically significant ($p = 0.991$). These findings were in line with previous research, which has also demonstrated sustained pain palliation with both 20 Gy and 30 Gy schedules. Studies like that of Makita et al. highlighted the long-term efficacy of these treatment protocols in managing pain from BM, with similar response rates observed in various patient populations. The study evaluated the local control (LC) of BM treated with fractionated RT. At 2 and 3 years, LC rates were high (90-83%) for doses ≤39 Gy, and similar for doses >39 Gy (87-85%). There was no significant difference between the dose groups. In favorable prognosis cases, the LC rate was slightly better (95% vs. 91%), while in unfavorable cases, LC rates were lower but still comparable between both dose levels (67-73%). [12]

Relapse and Re-irradiation:

Regarding relapse within one year, our study observed a 49% relapse rate overall, with slightly more relapses in the 20 Gy group (52%) compared to the 30 Gy group (48%). The p-value of 0.841 suggested that this difference was not statistically significant, indicating that both treatment schedules had comparable relapse rates. This finding was in line with other studies that have reported similar relapse rates for different fractionation schedules. For example, research by Kubota et al. showed no significant differences in long-term outcomes between different RT doses, further supporting the notion that both 20 Gy and 30 Gy schedules were effective for the long-term management of BM without a significant difference in relapse rates. El-Shenshawy et al. also observed slightly higher relapse rates in the 20 Gy arm compared to the 30 Gy arm. [8]

Re-irradiation was a potential concern for patients receiving palliative radiation, as recurrent pain often necessitated additional treatment. In our study, the retreatment rate was higher in the 20 Gy/5 fractions group, with 12% of patients requiring further treatment, compared to only 6% in the 30 Gy/10 fractions group, which was in line with findings from the TROG 9605 study, where patients treated with shorter RT schedules had higher retreatment rates. Our result was also consistent with findings from Niewald et al. and Foro Arnalot et al., where re-irradiation rates were higher in shorter-course regimens. This suggested that while shorter regimens provide adequate initial pain relief, they might not offer the same durability of response as longer courses of RT, making the 30 Gy regimen more appropriate for patients with longer life expectancies or those requiring more durable pain control. [7,10] Similar trends have been observed in other studies, where higher dose schedules have been associated with prolonged symptom control and fewer retreatments. For instance, this was consistent with the observations made in studies like Kowalchuk et al., where small sample sizes necessitated careful interpretation of data and highlighted the need for larger, more robust trials to confirm these findings. [13]

In terms of the response duration, our study showed that patients in the 30 Gy/10fr group experienced slightly longer periods of symptom relief, with an average response duration of 5.75 months (23 weeks), compared to 5.25 months (21 weeks) in the 20 Gy/5fr group. This difference suggested that the higher dose schedule may offer more prolonged symptom control, which could contribute to the reduced retreatment rate observed in this group. These findings were in line with those reported in other research, such as the study by Kubota et al., which demonstrated that higher dose regimens could provide longer-lasting relief for patients with BM. [14]

Acute Toxicity:

In your study, acute toxicity was significantly higher in the 30 Gy arm, with 25% of patients experiencing side effects, compared to 5% in the 20 Gy group. This result was in line with previous studies, such as those by Roos et al. and Hartsell et al., which also reported increased acute toxicity in higher-dose regimens. [15,11] Foro Arnalot et al. similarly observed higher rates of toxicity in the 30 Gy arm compared to lower-dose regimens, reinforcing the idea that although more effective in certain cases, the 30 Gy regimen presented a higher risk of side effects, which must be weighed against its potential benefits. [10] Valeriani et al. also reported that the incidence of acute toxicity was significantly higher in the 30 Gy arm (23.8%) compared to the 20 Gy arm (2.6%), highlighting that the 20 Gy regimen tended to have a lower toxicity profile [9], which was similar to the findings of El-Shenshawy et al., who reported a higher rate of acute toxicity in patients receiving 30 Gy compared to those treated with 20 Gy. [8] This increase in toxicity with higher doses was a common concern, particularly in patients with a limited prognosis, where the goal was to provide maximum comfort with minimal side effects.

Pathologic Fractures and Spinal Cord Compression:

The incidence of our pathologic fractures was slightly higher in the 20 Gy group (4%) compared to the 30 Gy group (2%). While this result did not reach statistical significance, it was consistent with the study by Nielsen et al., who reported a higher rate of pathologic fractures in patients receiving 20 Gy which might reflect reduced bone stability over time compared to higher doses of radiation. [16] Giuliani et al. discussed the cost-effectiveness of denosumab in preventing skeletal-related events in BM, highlighting

the importance of effective treatment strategies to prevent such complications. [17] However, other studies, such as those by Roos et al. have reported similar rates of pathologic fractures between different regimens. [15] Gillespie et all. observed that stereotactic body RT became more popular between 2016 and 2018, especially in patients with higher performance status. [18]

Similarly, the incidence of spinal cord compression was higher in the 20 Gy group, but the difference was not statistically significant. This supported the view that higher doses might provide more stability to the irradiated bone, as suggested by Rades et al., although further research is needed to establish this link definitively. [19]

Survival Outcomes:

Our study found no significant difference in one-year OS between the two regimens (35% in the 20 Gy group vs. 39% in the 30 Gy group, p-value of 0.527). This was in line with the findings from Roos et al. and Hartsell et al., who also observed no significant difference in survival outcomes between different dose regimens. [15,11] Similarly, Fischer-Valuck et al. reported that although higher doses were sometimes associated with improved survival in certain cancers, there was no significant difference in survival between 37.5 Gy and either 20 Gy in 5 fractions or 8 Gy in one fraction for BM, reaffirming that higher doses might not always confer a survival benefit. [20] Ignat et al. analyzed prognostic factors influencing survival, identifying poor performance status, primary site of cancer (lung and urologic), and specific irradiation sites as significant predictors of survival. [21] Sprave et al. reported that the median OS was significantly different between patients receiving long-course RT and short-course RT for unstable spinal BM, with long-course RT showing better survival outcomes. [22]

Conclusion:

Based on our results and those from the literature, both the 20 Gy and 30 Gy regimens provided effective pain palliation in patients with bone metastases and offered similar survival outcomes with manageable toxicity profiles. The 30 Gy regimen might offer slightly better pain control, bone stability, lower incidence of spinal cord compression, and lower relapse rates, making it more suitable for patients with longer life expectancies or those who require more durable pain control. However, this came at the cost of increased acute toxicity. In contrast, the 20 Gy regimen was well-suited for patients with shorter life expectancies or those who prioritized a shorter treatment duration with fewer side effects. Ultimately, the choice of regimen should be tailored to the individual patient's clinical situation and prognosis. These findings were consistent with existing literature, that emphasized the importance of personalized treatment strategies and using advanced RT techniques to optimize patient outcomes in palliative care for bone metastases. Future studies should continue to explore the balance between efficacy, safety, and quality of life to further refine palliative RT protocols.

List of abbreviations:

BM	Bone Metastases
RT8	Radiotherapy
Gy	Gray
OS	Overall Survival
SECI	South Egypt Cancer Institute
ECOG	Eastern Cooperative Oncology Group
VAS	Visual Analogue Scale
WHO	World Health Organization
RTOG	Radiation Therapy Oncology Group
CR	Complete Response
PR	Partial Response
IR	Intermediate Response
PP	Pain Progression
OR	Overall Response
IRB	Institutional Review Board
BED	Biological Effective Dose
α/β	Alpha-Beta Ratio
LC	Local Control

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