

Comparative Evaluation of Two Different Single-Session Radiotherapy Regimens along with Zoledronic Acid in Painful Bone Metastases

Research Article

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Abstract: Background: Bone metastases frequently occur in various types of cancer. External beam radiotherapy (EBRT) effectively alleviates the pain associated with these metastases. Various experimental studies have been conducted to see the effectiveness of single-session radiation along with bisphosphonates to control the pain of bone metastasis. In the present study, we compared two schedules of palliative EBRT in painful bony metastasis.

Patients and methods: We conducted a prospective study involving patients with bone metastases from any primary cancer. Patients were randomly assigned to receive palliative EBRT at either 8 Gy single session (group I) or 6 Gy single session (group II), along with zoledronic acid administered to the involved site in both groups. The primary objective was to evaluate overall pain response using the Glasgow pain scale and improvement in performance status measured by the Eastern Cooperative Oncology Group (ECOG) performance status score. Secondary objectives included assessing complete pain relief and the duration of overall pain response.

Results: A total of 60 patients were equally randomized into two groups. Group I showed the highest degree of pain relief. In both groups, there was a significant reduction in mean baseline pain score, and the mean ECOG performance status improved at the 1-month post-EBRT assessment.

Conclusion: Our analysis showed that both single-session schedules of EBRT with zoledronic acid effectively alleviate painful bone metastases, offering viable options based on individual patient tolerability and compliance.

Keywords: Bone metastases • external beam radiation • single session • zoledronic acid

1. Background

The skeletal system ranks as the third most frequent site for metastatic disease, following lungs and the liver.^[1] Typically, the identification of bone metastases occurs subsequent to the diagnosis of the primary location in the majority of instances.^[2] However, bone metastases can be the initial indication of the disease in approximately 10%–15% of cases.^[2] Bone metastases are frequently detected in the advanced stages of different types of cancer,

especially breast, prostate, and lung cancers.^[3] Pure osteoblastic lesions are seen in prostate malignancies, while pure lytic lesions are seen in multiple myeloma.^[3] However, most bone metastases are of mixed variety.^[4] Skeletal metastases typically present as multiple lesions, with solitary metastases observed in just 10% of cases.^[5] The most common site of bone metastases is the axial skeleton.^[6] Although the majority of individuals with bone metastases experience bone pain, a subset of patients may exhibit various complications, such as pathologic

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fractures, hypercalcemia, and spinal cord compression.^[3] Several potential causes for the bone pain resulting from metastatic disease have been proposed, such as the infiltration of the highly innervated periosteum, mechanical stress, nerve entrapment, pain receptors activation in local nerves, micro fractures, and bone destruction or collapse.

^[7] A comprehensive approach involving radiologists, radiation oncologists, medical oncologists, surgeons, pain physicians, and palliative care professionals is essential for the appropriate management of bone metastases.

^[8] The treatment is usually palliative, except in case of solitary metastasis, with goals of pain alleviation, function, and mobility preservation to allow better quality of patient survival time.^[5]

The World Health Organization (WHO) has outlined a three-step approach for managing cancer pain based on its severity.^[9] Initially, nonopioid medications such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol are recommended.^[9] If the pain persists, mild opioids like codeine can be considered.^[9] Finally, if necessary, strong opioids such as morphine may be prescribed.^[9] This progressive treatment strategy aims to effectively address cancer-related pain while minimizing the use of opioids.^[9] Nevertheless, opioids and NSAIDs may not consistently offer effective pain relief due to insufficient analgesic response, and they have negative side effects and low patient compliance.^[10]

External beam radiotherapy (EBRT) is the most effective treatment and gold standard for pain relief in symptomatic bone metastases.^[11] EBRT provides effective and time-efficient pain control and also avoids the adverse systemic effects of opioids.^[11] Approximately 60%–80% of patients exhibit a positive response to EBRT, while around 25%–30% of patients achieve complete response.^[12] Pain flare or transient worsening of pain in the irradiated site is a well-known side effect of EBRT, which can be prevented by giving steroids before commencement of radiotherapy.^[13] Bisphosphonates are standard treatment for the medical management of bone metastases.^[14] They reduce pain in osteolytic metastasis and are proven to prevent other skeletal-related events (SREs) or delay them by their powerful inhibition of osteoclastogenesis and osteoclast-mediated bone resorption.^[15] The preclinical safety characteristics of zoledronic acid are typically comparable to those of other bisphosphonates, but it seems to result in fewer and milder adverse reactions at therapeutically effective doses.^[16] Various studies and trials showed that single-fraction radiation regimens (8–10 Gy) have comparable effectiveness to multifraction radiation schedule (20–30 Gy in 5–10 fractions) in achieving relief of pain.^[17,18] Single-fraction radiation therapy has evident advantage for the patient as fewer visits to the hospital and use of

a single fraction mean a more economical use of limited resources for the radiation oncology department.^[17] The present study is designed to evaluate the optimal single dose of radiotherapy (8 vs. 6 Gy) along with zoledronic acid in painful bone metastasis.

2. Patients and Methods

This was a prospective and randomized trial which involved 60 patients who had histopathologic confirmation of malignancy with bone metastases from any primary solid tumor. We first received approval for this study from our Institutional Review Board (IRB). After receiving written informed consent from the participants, they were split into two groups, with each group containing 30 cases by draw of lots by free Internet service website <https://www.random.org/lists/>. The study excluded patients who had undergone radiotherapy in the concerned region previously, had any coexisting conditions that could explain their symptoms, or were pregnant, or patients with solitary metastases and curable primary tumor.

The initial assessment of all patients encompassed a comprehensive review of their medical history, a thorough physical examination, and systematic evaluation of their entire bodily system. Radiologic assessment, including X-ray of the involved site, was done in all patients. Computed tomography scan, magnetic resonance imaging, bone scan, and positron emission tomography scan were done in those patients requiring them. Patient's functional outcome assessment was done by Eastern Cooperative Oncology Group (ECOG) performance scale, and pain score was calculated using the Glasgow pain scale.

All the patients received radiation treatment using a telecobalt machine by two-dimensional modality. Vertebral metastases were treated with the patient in a prone position, while long bone and pelvic bone metastases were treated with the patient in a supine position. The field placement was determined through clinical examination and radiologic investigations. Treatment fields were carefully planned to ensure sufficient margins from the identified skeletal abnormalities. Patients in group I and group II received palliative external radiation therapy single dose 8 and 6 Gy, respectively, to the involved site, followed by treatment with zoledronic acid, 4 mg administered in 100 ml normal saline over 15-min intravenous infusions 7 days after radiation and every 4 weeks thereafter for a maximum of 6 months.

Follow-up and assessment measures: Patients were monitored for a duration of 6 months, with weekly

assessments conducted for the initial month following radiotherapy, followed by monthly evaluations for the subsequent 5 months. During each follow-up session, patients' pain relief was evaluated using the Glasgow pain scale, while their functional progress was measured using the ECOG performance scale. Patients were assessed for any adverse reaction due to radiation therapy or zoledronic acid at each follow-up.

Overall pain response was defined as decrease in pain score by at least two points with respect to the pretreatment value. Performance status improvement was characterized as a reduction in the ECOG functional outcome score by a minimum of one grade compared to the value before treatment.

Statistical analysis: The data thus obtained was entered in Microsoft Excel spreadsheet and analyzed with IBM Statistical Package for Social Sciences (SPSS) software version 21.0. The quantitative data was displayed using the mean and standard deviation, while the qualitative data was shown using ratios and proportions. Quantitative data was compared using paired and unpaired *t*-test following confirmation of data normality, while qualitative data was analyzed using Chi-square test and Fisher's exact test for comparisons involving two or more groups. $P < 0.05$ was considered significant.

Table 1: Demographic profile and tumor characteristics.

Parameters	Group I (n= 30)	Group II (n= 30)
Age		
Mean	60.47	53.83
Range	27-85 years	30 to 76 years
Gender		
Male	14	15
Female	16	15
Residence		
Rural	19	20
Urban	11	10
Primary		
Breast	12	13
Lung	10	06
Prostrate	06	07
Others	02	04

Table 2: Patients with overall pain relief after radiotherapy.

Patients with overall pain relief after radiotherapy	1 st week	2 nd week	3 rd week	4 th week	2 nd month	3 rd month	4 th month	5 th month	6 th month
Group I (n= 30)	12	12	20	24	24	24	24	24	24
Group II (n= 30)	8	9	9	23	23	23	23	23	23

3. Results

The present study involved a total of 60 patients randomized into two groups. In group I, patients' age ranged from 27 to 85 years (mean 60.47 years), while in group II, patients' age ranged from 30 to 76 years (mean 53.83 years), which were comparable ($P = 0.03$). Group I comprised 14 males and 16 females, while group II comprised an equal number (i.e., 15) of male and female patients ($P = 0.79$). Out of a total 60 patients, 39 patients (65%) belonged to the rural population and the remaining 21 (35%) belonged to urban areas. The predominance of the rural population was also evident in each group (63.33% and 66.67% in group I and group II, respectively). Breast carcinoma was the most common primary overall, accounting for 41.67% of all cases, with the lung and prostate being the next most frequent sites, having 26.67% and 21.67% of cases, respectively. In group I and group II, breast remained the most common primary site comprising 40% and 43.33% of patients, respectively (Table 1). Overall, most patients presented with vertebral bony metastases (35%). In both groups, vertebra, multiple sites, and pelvis were the most common sites of metastases as depicted in figure 1.

Glasgow pain scale of patients in group I before the treatment ranged from moderate to severe, which was mild to moderate for most patients after radiotherapy. A similar pattern was observed in group II as shown in figure 2.

Maximum number of patients, that is, 80% in group I and 76.67% of patients in group II, had overall pain relief at 4 weeks post-radiotherapy and sustained it till follow-up of 6 months as shown in table 2. Some patients' general condition improved after the treatment as measured by ECOG performance status as shown in table 3. No major side effect was observed in both groups.

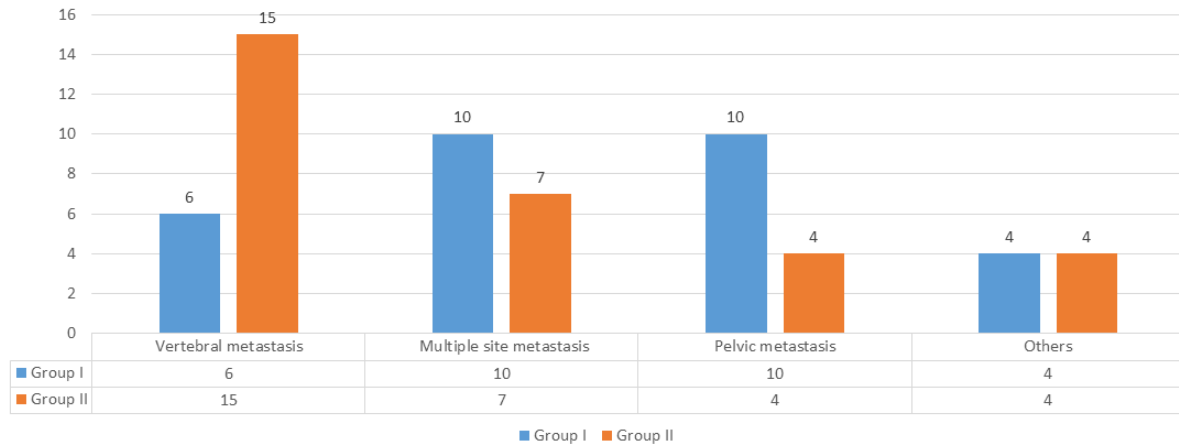
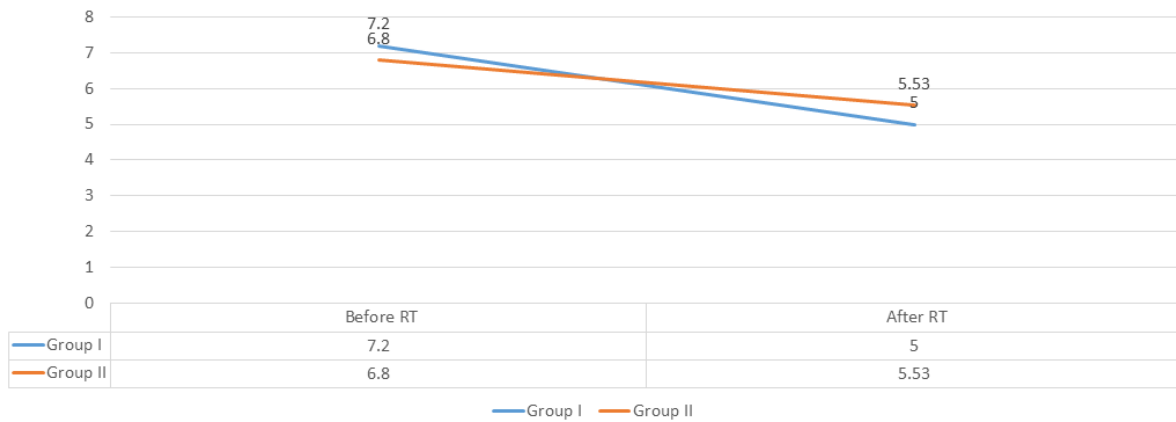


Figure 1: Sites of bone metastasis in both groups.



RT: Radiation Therapy

Figure 2: Glasgow pain scale before and after radiotherapy in both groups.

Table 3: ECOG performance status before and after radiotherapy.

ECOG performance status	Group I (n= 30)		Group II (n= 30)		Total		p value
	Before	After	Before	After	Before	After	
ECOG ≤ 2	18	22	15	17	33	39	0.351
ECOG >2	12	8	15	13	27	21	

ECOG: Eastern Cooperative Oncology Group

4. Discussion

Approximately, half of cancer patients develop bone metastases.^[19] The spread of cancer to the bone often leads to pain and other distressing symptoms that can greatly impact a person's quality of life.^[19] Radiotherapy is often

regarded as the preferred treatment option. Its primary goal is to alleviate bone pain, prevent pathologic fractures, and promote healing, ultimately leading to enhanced mobility, functionality, and improved quality of life.^[20]

Various EBRT schedules are utilized to alleviate symptoms of bone metastases; nevertheless, the most

effective radiation dose, fractionation schedule, and duration of treatment are still subjects of debate.^[15] Resource-efficient single-fraction radiotherapy is gaining popularity for alleviating painful bone metastases.^[15] Our primary aim was to evaluate the optimal single dose of radiotherapy (8 vs. 6 Gy) along with zoledronic acid in painful bone metastasis.

Wu et al. and Supportive Care Guidelines Group of Cancer Care Ontario in 2004 carried out a systematic review and meta-analysis and formulated evidence-based practice guideline.^[11] For uncomplicated cases of bone metastases, where the main goal is pain relief, they recommended using a single dose of 8 Gy as the most effective and standard used treatment schedule.^[11]

In our study, maximum patients got pain relief at the fourth week post-radiotherapy (80% and 76.67% in group I and group II, respectively). All patients had sustained pain relief (pain score less than the pretreatment pain score anytime during follow up) till the sixth month of follow up.

Our findings align with those of a similar study carried out by Jeremic et al., who compared the efficacy of three single-fraction radiation schedules in the management of painful bone metastases.^[21] The overall response rates in group I, group II, and group III were 59%, 73%, and 78%, respectively.^[15] Jilla et al. conducted a study

where the single-fraction arm achieved an overall pain relief of 78%, which was comparable to the multifraction arm, where the pain relief was 80%.^[22] The Bone Trial Working Party Study Group (BTWPG) also reported overall pain relief of 78% in the single fraction as well as the multifraction groups.^[23] Anter et al. compared 8-Gy single fraction versus 20 Gy/five fractions and found no significant statistical difference in overall pain relief (74.8% vs. 74.2%).^[24] Analysis from Indian researched also confirmed the efficacy of single session EBRT in palliation of painful bone metastasis.^[25]

5. Conclusion

It was observed that both schedules provided good palliation to the painful bone metastases. Although group I schedule (8 Gy single session with zoledronic acid) was found to give slightly better results in comparison to group II schedule (6 Gy single session with zoledronic acid) with better overall pain relief and improved performance status, the difference was found statistically insignificant. It can be stated that both schedules of palliative EBRT can be given depending upon patient tolerability and compliance.

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