



ASSESSMENT OF PAIN RESPONSE AND IMPACT ON COMPLICATION IN SKELETAL METASTASES AMONG BREAST CANCER PATIENTS TREATED WITH PALLIATIVE RADIATION THERAPY ALONG WITH INJECTION ZOLEDRONIC ACID - PROSPECTIVE STUDY

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ABSTRACT

Background: Bone metastases (BM) are a common cause of pain and morbidity in breast cancer (BC) patients. Zoledronic acid combined with palliative radiotherapy helps to reduce bone resorption, relieve pain, and delay skeletal-related events. The present study aims to assess pain response and observe the nature of impact on skeletal related events after palliative radiotherapy along with injection zoledronic acid for painful BM in patients with BC. **Methods:** Fifty adult female patients (≥ 18 years) with histologically confirmed breast cancer and painful bone metastases were enrolled in the study. Baseline assessment included demographic data, Eastern Cooperative Oncology Group (ECOG) performance status, stage of disease, radiotherapy technique, site of bone metastasis, pain severity using the Numeric Rating Scale (NRS), and laboratory parameters. All patients received palliative external beam radiotherapy (20 Gy in 5 fractions) along with intravenous zoledronic acid (4mg every 4 weeks). Follow-up assessments were performed at 4 and 8 weeks. **Results:** The majority of patients were aged 41–50 years (36%), with a mean age of 51.08 ± 8.96 years. Most patients had an ECOG score of 1 (60%) and were treated using the posterior radiotherapy technique (84%). All patients had bone metastases at presentation, most commonly involving the thoracic spine (42%). A significant reduction in mean serum calcium levels ($p < 0.0001$) and NRS pain scores ($p < 0.0001$) was observed over 8 weeks, while serum alkaline phosphatase levels showed no significant change ($p = 0.639$). There was no significant increase in fractures or spinal cord compression during follow-up. **Conclusion:** Palliative radiotherapy combined with zoledronic acid provides significant pain relief and maintains a low incidence of skeletal-related events in breast cancer patients with painful bone metastases over short-term follow-up.

KEYWORDS : Breast cancer, bone metastases, palliative radiotherapy, zoledronic acid, pain score, skeletal-related events.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide and represents a major public health burden, with its global incidence expected to approach nearly 2 million cases by 2030.¹ In India, breast cancer is the leading cause of cancer-related incidence and mortality, accounting for 13.6% of all cancer cases and 10.7% of cancer deaths as per GLOBOCAN 2022.² Patients with advanced breast cancer frequently develop bone metastases, which may be asymptomatic or present with significant morbidity such as pain, pathological fractures, spinal cord compression, impaired mobility, hypercalcemia, and reduced survival.³ Bone metastases arise from complex interactions between tumor cells and the bone microenvironment, disrupting the normal balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation.⁴ Tumor-derived factors enhance osteoclast activity, leading to bone destruction, release of growth factors and calcium from the bone matrix, further tumor proliferation, osteopenia, increased fracture risk, and hypercalcemia of malignancy.⁵

Skeletal metastasis is a multifactorial process in which several biologic processes play a role leading to interaction between tumor cells and the host microenvironment, including cellular invasion and migration, cell–matrix adhesion, endothelial interactions, growth factor regulation, and stimulation of osteoclasts and osteoblasts.⁵ Up to 80% of patients with metastatic BC develop bone metastases (BMs), leading to increased osteoclast activity, local bone destruction, and complications such as pain, hypercalcemia, and skeletal-related events (SREs).⁶ These SREs include pathological fractures, spinal cord compression, and the need for radiotherapy or surgery to prevent or manage skeletal complications. However, SREs occur in up to 64% of patients

with metastatic BC when they are not treated with bisphosphonates, and the burden of SREs contributes to a substantial erosion in quality of life (QOL) for many patients with advanced BC.⁷

Intravenous bisphosphonates, particularly zoledronic acid (ZA), play a key role in preventing SREs in BC patients with BMs and are recommended by the American Society of Clinical Oncology for those with radiological evidence of bone destruction.⁸ Although ZA effectively reduces and delays SREs and improves bone density, skeletal complications may still occur despite therapy, and its use is associated with potential adverse effects such as nephrotoxicity and acute-phase reactions, necessitating careful patient selection and monitoring.^{9,10} ZA is a third-generation bisphosphonate shown to be superior to other agents in reducing skeletal complications and improving clinical outcomes.³ When combined with palliative radiotherapy, ZA has demonstrated significant benefits in pain relief, quality of life, and biochemical and radiological parameters in patients with painful bone metastases.¹¹ Given the substantial morbidity associated with skeletal metastases, the present study was undertaken to assess pain response and observe the nature of impact on skeletal related events after palliative radiotherapy along with injection zoledronic acid for painful BM in patients with BC.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee and written informed consent from all participants, this prospective observational study was conducted in the Department of Radiation Oncology at a tertiary care hospital in Central India over a period of 18 months, from July 2022 to December 2023. A total of 50 adult female patients aged 18

years or older with histologically confirmed breast cancer and bone metastases were enrolled using a convenient sampling technique. Eligible patients included those receiving radiotherapy for the first time, willing to participate and comply with the study protocol, and available for regular follow-up. Patients with pathological fractures, spinal cord compression, asymptomatic bone metastases, hypocalcemia, or those unwilling to provide written informed consent were excluded. At the time of enrollment, demographic characteristics such as age and gender were recorded. Clinical parameters assessed included Eastern Cooperative Oncology Group (ECOG) performance status, stage of breast cancer, radiotherapy technique, site of bone metastasis, pain severity assessed using the Numeric Rating Scale (NRS), and disease progression at 8 weeks. Laboratory investigations included measurement of serum alkaline phosphatase and serum calcium levels. All patients were followed up at 4 weeks and 8 weeks after initiation of treatment for clinical and laboratory reassessment.

The patients with histologically diagnosed breast cancer and presence of bone metastases were recruited from the outpatient department of Radiation Oncology of a tertiary care teaching institute. The patients were screened by the clinician. Those found meeting the inclusion criteria were briefed about the trial. Screening investigations were carried out and the eligible candidates were included in the study.

After initial screening, the data regarding age, gender, ECOG status, diagnosis, and breast cancer stage were recorded. Evaluation of bone metastases was done by clinical and radiological investigation (bone scan or computed tomography) and the sites of bone metastasis were noted. NRS was used for the assessment of baseline pain (0 week). NRS was a 11-point scale ranging from 0 to 10, with 0 and 10 suggesting no and maximum pain, respectively.

After detection of bone metastases clinically and by radiological investigation, the patients were irradiated with Cobalt 60 Teletherapy Machine (Figure 1). According to general condition of the patient and ECOG score, external beam radiotherapy fractionation dose 20Gy in 5 fractions was given. Along with irradiation, injection zoledronic acid (4 mg iv q4 weekly) was administered. Before giving injection zoledronic acid, renal function test and serum calcium level was checked. Additionally, serum alkaline phosphatase levels were evaluated in all the patients (0 week). All patients were treated by standard departmental protocol for radiotherapy.

Serum alkaline phosphatase and serum calcium levels were assessed again at 4 and 8 weeks. Moreover, at similar follow-up intervals, NRS was used to assess bone metastases-associated pain. The disease progression was assessed at 8 weeks in terms of fracture and cord compression. All the study findings were recorded in a specifically designed the case record form.

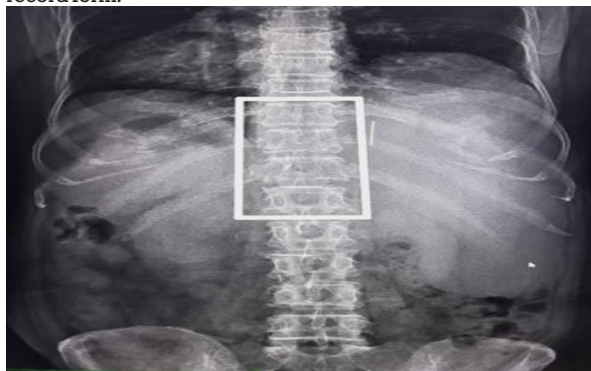


Figure 1: Treatment Field For T11-T12 Vertebrae

Statistical Analysis

Data was collected and graphics were designed by Microsoft Office Excel 2019. The data was analyzed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows. The categorical and continuous variables are represented as frequency (percentage) and mean ± standard deviation, respectively. Chi-square test was used to assess the association between categorical variables. Repeated measures ANOVA followed by post-hoc analysis with Bonferroni's test were performed to assess change in outcome measures over the study duration. A two-tailed probability value of < 0.05 was considered as statistically significant.

OBSERVATIONS AND RESULTS

A total of 50 adult breast cancer patients with painful bone metastases were enrolled from the Radiation Oncology Department over an 18-month period. Most patients belonged to the 41–50-year age group (36%), followed by 51–60 years (30%). The mean age was 51.08 ± 8.96 years, with an age range of 35 to 72 years, (Table 1).

Table 1: Distribution Of Patients According To Age

Age group (Years)	No. of patients	Percentage
31-40	08	16.0
41-50	18	36.0
51-60	15	30.0
61-70	08	16.0
71-80	01	2.0

The majority of the patients had an ECOG score 1 (30; 60%), while remaining had ECOG score 2 (20; 40%), (figure 2).

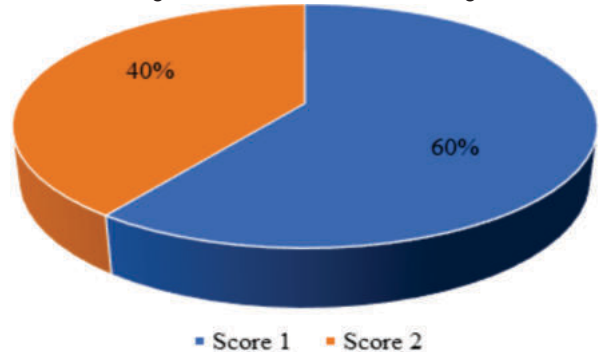


Figure 2: Distribution Of Patients According To ECOG Score

The majority of patients were treated with posterior fields (42; 84%), followed by anterior fields (7; 14%), while only one patient (2%) received both fields (Figure 3).

All 50 patients (100%) had metastatic disease at the time of presentation

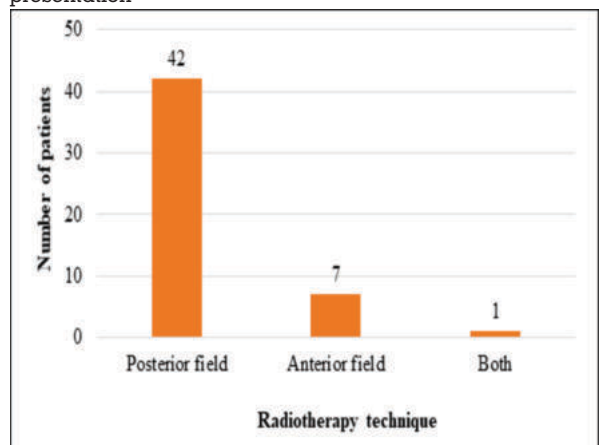


Figure 3: Distribution Of Patients According To Radiotherapy Technique

Among the 50 patients, bone metastases most commonly involved the thoracic vertebrae (42%), followed by combined lumbar and thoracic involvement (24%) and lumbar vertebrae alone (20%). The sternum was the least frequently involved site (14%) (Table 2).

Table 2: Distribution Of Patients According To Site Of Bone Metastasis

Site of bone metastasis	No. of patients	Percentage
Lumber	10	20.0
Thoracic	21	42.0
Sternum	07	14.0
Lumber + Thoracic	12	24.0

Repeated measures ANOVA showed a significant reduction in mean serum calcium levels and NRS pain scores over the study period (both $p < 0.0001$). Post-hoc Bonferroni analysis demonstrated a significant decrease in serum calcium from baseline to 8 weeks, while no significant change was observed between 4 and 8 weeks. In contrast, serum alkaline phosphatase levels did not show a significant change over time ($p = 0.639$). A significant and progressive reduction in NRS pain scores was observed from baseline to 4 and 8 weeks, as well as between 4 and 8 weeks ($p < 0.0001$), (Table 3).

Table 3: Changes In Biochemical Parameters And Pain Scores Over The Study Period

Variables	Baseline	4 weeks	8 weeks	p
Sr. calcium levels	11.15 ± 0.64	11.03 ± 0.68	9.53 ± 0.54	<0.0001
Sr. alkaline phosphatase levels	137.24 ± 13.50	137.92 ± 13.09	137.58 ± 12.26	0.639
NRS score	5.22 ± 1.13	3.18 ± 1.02	1.7 ± 1.01	<0.0001

Chi-square analysis showed no statistically significant difference in the incidence of fractures or spinal cord compression over the study duration. Fractures were absent at baseline and 4 weeks, with only one case observed at 8 weeks ($p = 0.365$). No cases of spinal cord compression were reported at any time point during the study ($p = 1.000$), (Table 4).

Table 4: Incidence Of Skeletal-related Complications During The Study Period

Complications		Baseline	4 weeks	8 weeks	p
Incidence of fracture	Present	00 (0.0%)	00 (0.0%)	01 (2.0%)	0.365
	Absent	50 (100%)	50 (100%)	49 (98%)	
Incidence of cord compression	Present	00 (0.0%)	00 (0.0%)	00 (0.0%)	1.000
	Absent	50 (100%)	50 (100%)	50 (100%)	

DISCUSSION

In the present study, most of the patients were middle-aged, with the highest proportion in the 41–50-year age group, and mean age of 51.08 ± 8.96 years. These findings are consistent with previous studies by Weinfurt et al¹² and Broom et al¹³, who reported mean ages of 57.5 ± 12.6 years and 58 years, respectively. The most patients had good performance status, with 60% having an ECOG score of 1 and 40% having a score of 2 which is comparable with the study done by Weinfurt et al¹⁰ where they reported the majority of patients had an ECOG score of 1, while Hortobagyi et al¹⁴ observed that most patients had ECOG scores of 0–1. Similarly, studies by Stopeck et al⁷ and Kohno et al¹⁵ also demonstrated a predominance of ECOG scores of 0–1 among patients receiving zoledronic acid.

Most of the patients received radiotherapy by posterior

technique (84%) followed by anterior technique (14%) and the least number of patients received radiotherapy by both the techniques (2%). To the best of our knowledge, previous studies have not specifically reported the radiotherapy techniques employed for painful bone metastases. Therefore, these findings provide additional insight and contribute novel information to the existing literature. All patients in the present study had bone metastases at the time of presentation. This finding is consistent with reports by Stopeck et al⁷, Kohno et al¹⁵, and Nie et al¹⁶ in which 100% of enrolled patients had bone metastases. All these studies specifically included patients with breast cancer-related bone metastases, explaining the consistent observation across studies.

The bone metastases predominantly involved the thoracic vertebrae (42%), followed by combined thoracic and lumbar vertebrae (24%) and lumbar vertebrae (20%), with the sternum being the least affected site (14%). These findings are in concordance with previous studies conducted by Nie et al¹⁶ and Chen et al¹⁷ reported the spine as the most commonly involved site, particularly the thoracic and lumbar vertebrae, while Wang et al¹⁸ also observed a higher frequency of metastases in load-bearing bones, including the spine.

In the present study, mean serum calcium levels showed a significant reduction over the study period (baseline: 11.15 ± 0.64 mg/dL; 4 weeks: 11.03 ± 0.68 mg/dL; 8 weeks: 9.53 ± 0.54 mg/dL; $p < 0.0001$). The decrease was significant from baseline to 8 weeks, while no significant change was observed between 4 and 8 weeks, and it was not associated with clinical sequelae. These findings are consistent with Stopeck et al⁷ and Fidan et al¹⁹ who reported mild and transient reductions in serum calcium with zoledronic acid. The serum alkaline phosphatase levels did not show a significant change during follow-up (baseline: 137.24 ± 13.50 IU/L; 4 weeks: 137.92 ± 13.09 IU/L; 8 weeks: 137.58 ± 12.26 IU/L; $p = 0.639$). This finding is in agreement with Fidan et al¹⁹, who also reported no significant change. In contrast, Stopeck et al⁷ demonstrated a reduction in alkaline phosphatase with ZA, suggesting that biochemical response may vary among patient populations.

In the present study, combined palliative radiotherapy and ZA resulted in a significant and progressive reduction in pain scores. The mean NRS score decreased from 5.22 ± 1.13 at baseline to 3.18 ± 1.02 at 4 weeks and 1.70 ± 1.01 at 8 weeks ($p < 0.0001$). Significant reductions were observed from baseline to both follow-up points and between 4 and 8 weeks. These results are consistent with previous study done by Kohno et al¹⁵, which demonstrated significant pain reduction with ZA. The findings support the effectiveness of combined radiotherapy and ZA in achieving meaningful pain relief in patients with breast cancer-related bone metastases.

In the current study, the incidence of skeletal-related events was low during follow-up. Only one patient (2%) developed a pathological fracture at 8 weeks, and there was no statistically significant change in fracture incidence over the study period ($p = 0.365$). Importantly, no cases of spinal cord compression were observed. These findings suggest that zoledronic acid (ZA), when used alongside standard care, may contribute to a reduced occurrence of SREs in the short term. Our results are consistent with existing literature demonstrating the protective role of ZA against SREs. Kohno et al¹⁵ reported a significant reduction in the risk of SREs over long-term follow-up, while Coleman et al⁶ observed a lower fracture rate in patients receiving ZA. Similar reductions in SRE risk have also been reported by Wang et al¹⁸ and supported by the meta-analysis by Valachis et al²⁰. Although the short duration of follow-up in the present study limits long-term conclusions, the low incidence of SREs observed supports the beneficial role of ZA in preventing skeletal complications in breast cancer patients with bone metastases.

The present study has certain limitations. The small sample size may restrict the generalizability of the findings. Additionally, the short follow-up period of 8 weeks limited the assessment of long-term outcomes, particularly the sustained effect on skeletal-related events following combined palliative radiotherapy and zoledronic acid therapy. Furthermore, bone mineral density was not evaluated, which could have provided additional insight into the effect of treatment on bone health.

CONCLUSION

The present study effectively assessed the pain response and impact on skeletal-related events following palliative radiotherapy combined with zoledronic acid injection for painful bone metastases in breast cancer patients. The results indicate a significant reduction in serum calcium and pain, suggesting substantial improvement over 8 weeks. This was highlighted by no significant increase in incidence of SREs, with only one patient developing pathological fracture over 8 weeks and none of the patients had cord compression. These findings suggest that the treatment regimen is effective in alleviating pain and reducing the incidence of SREs.

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