DOI: 10.7860/JCDR/2025/79353.21051

Original Article

Oncology Section

Efficacy of External Beam Radiotherapy with Concurrent Capecitabine versus Radiotherapy alone for the Treatment of Painful Bone Metastasis in Primary Breast Cancer Patients: A Prospective Interventional Study

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ABSTRACT

Introduction: The development of widespread distant metastasis, including skeletal metastasis, is common among breast carcinoma patients, irrespective of multimodal treatment. Symptomatic skeletal metastasis is usually treated with External Beam Radiotherapy (EBRT). Capecitabine can act as a radiosensitiser antineoplastic drug and can be added concurrently with EBRT.

Aim: To compare the safety and efficacy of EBRT with concurrent capecitabine against EBRT alone in pain control of painful bone metastasis.

Materials and Methods: This prospective interventional study was conducted in the Department of Radiation Oncology at Acharya Harihar Postgraduate Institute of Cancer, Cuttack, Odisha, India from September 2022 to March 2024. Histologically proven breast cancer patients with painful bone metastasis were included and randomly assigned to group A, receiving palliative radiotherapy only (n=20), and group B, receiving palliative radiotherapy with concurrent capecitabine (n=22). Radiotherapy was administered at a dose of 30 Gy in 10 fractions at 3 Gy per fraction over two weeks. The patients were assessed once weekly during the treatment and at the end of the treatment, patients were evaluated every four weeks until 12 weeks. Response to treatment was evaluated using the Visual Analog Scale (VAS) and analgesic score. Statistical Package for the Social Sciences (SPSS) Version 21.0 (Armonk, NY: IBM Corp) was used for data analysis.

Results: The mean age was 49.90 years for group A and 46.36 years for group B, respectively. The median pain score was 7 (4-10) in group A and 8 (5-9) in group B at baseline; at the end of 12 weeks, it was 2.5 (0-9) for group A and 0 (0-5) for group B (p-value=0.024). All the patients exhibited some level of response at the end of 12 weeks, with a Complete Response (CR) observed in 4 (20%) patients in group A, whereas it was seen in 14 (63.6%) patients in group B (p-value=0.004). Furthermore, there was a decrease in the consumption of analgesics in both groups from week 0 to week 4, with the median analgesic score changing from 2 (1-4) to 1 (0-3) in group A and from 3 (1-4) to 1 (0-2) in group B, without any significant difference between the groups (p-value=0.786).

Conclusion: In comparison to radiotherapy alone, concurrent chemoradiation offers superior pain control and response rates in breast cancer patients with painful bone metastasis. Therefore, capecitabine administered concurrently with radiotherapy is safe for managing painful bone metastasis.

Keywords: Breast malignancy, Chemoradiation, Response, Skeletal metastasis, 5-flouracil prodrug

INTRODUCTION

Skeletal metastasis is the most common site of distant metastasis in breast cancer patients, with about 70% of patients who die from breast cancer experiencing bone metastasis [1]. Factors predisposing to the high incidence of bone metastasis include increased blood flow in the red bone marrow and the production of adhesive molecules [2]. Pain is the most common presentation of bone metastasis and the response to systemic treatments-such as chemotherapy, hormone therapy and targeted therapy-typically takes several weeks to months. The administration of local radiotherapy to painful bone metastatic sites is necessary to achieve rapid control of pain and improve quality of life; this should be initiated before the administration of chemotherapy [3]. Palliative radiotherapy to symptomatic bony sites can be given either as a single fractionation or as multiple fractionation schedules, both yielding almost similar responses to pain [4,5]. It is known that nearly all patients experience some form of pain relief within four weeks [6]. The range of complete pain response in a meta-analysis was reported to be between 23% and 24%, with many patients requiring reirradiation due to symptom progression during the disease course [4,5].

Concurrent chemoradiation is frequently employed in several malignancies in different settings, such as adjuvant therapy, to enhance local control of the primary disease and for the palliation of local symptoms such as pain, bleeding and compression by the primary tumour [7,8]. It may be utilised as a mainstay of treatment for organ preservation or in neoadjuvant or adjuvant settings. Capecitabine, an oral prodrug of 5-fluorouracil, is frequently used in a concurrent setting with radiotherapy for anorectal carcinoma as neoadjuvant treatment and for adenocarcinoma of the stomach as adjuvant therapy [9-12]. Capecitabine, in combination with adjuvant radiotherapy, can be safely administered in breast cancer, with comparable toxicity to that seen with radiotherapy alone [13].

Due to its potential as a radiosensitiser, capecitabine may improve the biologically effective dose of radiation therapy [14]. However, the concurrent use of capecitabine with radiotherapy as a radiosensitiser for the treatment of painful bone metastasis in breast cancer patients has been less studied, with only a few publications to date [15,16]. The study conducted by Kundel Y et al., on concurrent capecitabine-based chemoradiation for pain control of bone metastasis was a single-arm study and did not compare results with

radiotherapy alone to determine the superiority of chemoradiation [15]. Additionally, data in an Indian context are lacking. Hence, the present study was conducted to analyse the safety and efficacy profile of concurrent capecitabine plus radiotherapy compared to radiotherapy alone for the treatment of painful bone metastasis among breast cancer patients in an Indian setting.

MATERIALS AND METHODS

The present prospective interventional study was conducted in the Department of Radiation Oncology at Acharya Harihar Postgraduate Institute of Cancer, Cuttack, Odisha, India, from September 2022 to March 2024. Institutional Ethics Committee (IEC) approval for the study was obtained via letter number 056 IEC AHPGIC.

Inclusion criteria: Patients aged ≥18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, histologically proven breast cancer patients with painful bone metastasis and radiological evidence, an estimated life expectancy of ≥3 months, Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST) levels not exceeding three times the normal level, serum bilirubin and creatinine levels not greater than 1.5 times the normal level, an absolute neutrophil count of ≥1500/mL, and a platelet count of >100,000/mm^3 were included in the study.

Exclusion criteria: Patients with an ECOG score of ≥3, those who had received previous radiation or undergone palliative surgery to the same painful site planned for treatment and those who had previously received capecitabine within the last six months were excluded from the study.

Sample size: Assuming the efficacy of capecitabine alongside palliative radiotherapy to be 42.9% and that of palliative radiotherapy alone to be 19%, as determined in the study conducted by Ahmed S et al., at the South Egypt Cancer Institute and considering a power of 80% and a 95% confidence level, the calculated sample size was 90 for a one-sided test (45 in each arm) using nMaster (developed by CMC Vellore) [16]. However, the required sample size could not be achieved due to the limited study period.

Study Procedure

Histologically proven breast cancer patients with painful bone metastasis were randomly assigned to group A, receiving palliative radiotherapy only (n=20) and group B, receiving palliative radiotherapy with concurrent capecitabine (n=22). In both arms, palliative radiotherapy was administered as external beam radiation with a total dose of 30 Gy in 10 fractions to the planning target volume at a rate of 3 Gy per fraction, delivered in five fractions per week for two weeks, using either conventional techniques or three-dimensional conformal radiotherapy (3DCRT) as required. Radiotherapy was delivered either using a Bhabatron machine for conventional techniques or a linear accelerator machine for the conformal technique. Concurrent tablet capecitabine was administered alongside radiotherapy at a dose of 825 mg/m^2 of body surface area in twice-daily doses, starting from the first day of radiotherapy (five days a week) until the completion of the treatment. Radiotherapy planning was performed using a computer-based manual technique for conventional planning or through the Oncentra system for the conformal technique.

Patients were simulated using a CT simulator in a comfortable position, ensuring proper immobilisation according to the site of metastasis. During contouring, the treatment volume included the radiographic abnormality with at least a 2 cm margin. In cases of vertebral metastasis, the treatment volume was determined by including the upper and lower vertebrae adjacent to the affected vertebra.

Response to treatment was evaluated using VAS and analgesic score. Patients were followed-up for 12 weeks, with toxicity assessed once weekly during treatment. At the end of the treatment, patients were evaluated every four weeks until the completion of 12 weeks according to Common Terminology Criteria for Adverse Events (CTCAE) version 5 [17].

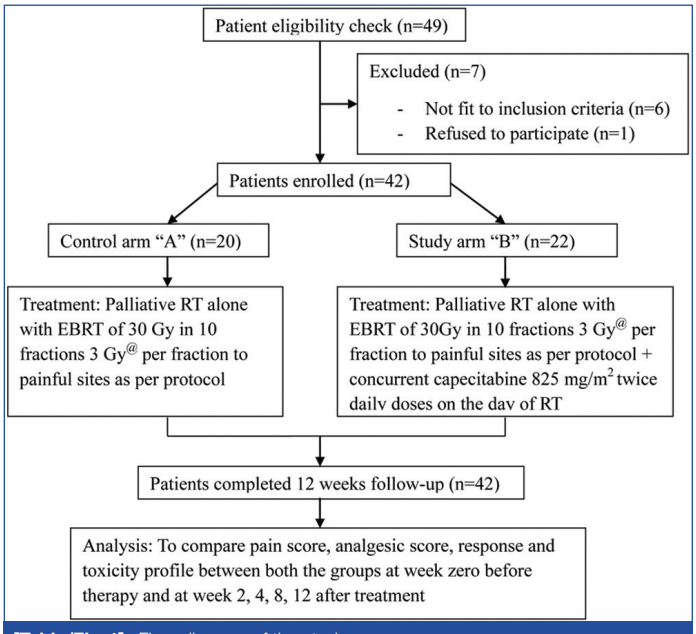
In this study, patients' pain was rated using the VAS, which has a scoring range from 0 to 10, with 0 representing "no pain" and 10 representing "worst possible pain." A VAS score of 1-4 was categorised as mild pain, 5-6 as moderate pain, 7-8 as extreme pain and 9–10 as severe pain [18]. The most painful site was selected as the index site and pain scores were recorded before treatment began (week zero) and at weeks 1, 2, 4, 8 and 12 after the completion of treatment in both groups.

Study used the five-point World Health Organisation (WHO) scale to measure analgesic use based on the patients' medication intake [15]:

1) Level 0 indicates no analgesic use;
2) Level 1 requires non narcotic analgesics occasionally;
3) Level 2 requires non narcotic analgesics regularly;
4) Level 3 requires narcotic analgesics occasionally;
5) Level 4 requires narcotic analgesics regularly.

The response evaluation considered both the patient's pain score and analgesic score. CR was defined as a zero pain score at the treated site, with no increase in analgesic intake. Partial Response (PR) was defined as a reduction in pain score by 2 or more at the treated site without an increase in analgesic need. Stable Pain (SP) was characterised by no change in pain score or a one-point change. Progressive Pain (PP) was indicated by a 2 or more-point increase in pain score alongside stable analgesic use. Patients with CR or PR were considered to have Overall Response rates (OR), while those with stable pain or PP were regarded as non responders.

The flow diagram for the study is detailed in [Table/Fig-1].



[Table/Fig-1]: Flow diagram of the study.

STATISTICAL ANALYSIS

IBM SPSS Statistics for Windows, Version 21.0, (Armonk, NY: IBM Corp) was used for the analysis of the study. Continuous variables were presented as mean±SD and median (range), while frequency and percentage were used for categorical variables. The mean values of variables were compared between the two groups using an independent sample t-test. The median pain score and analgesic score were compared between the two groups using the Mann-Whitney U Test. Response to treatment between the two

groups was compared using the Chi-square test. Fisher's exact test and the Fisher-Freeman-Halton test were employed to determine associations for 2×2 and larger contingency tables, respectively. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients at presentation was 49.90 years for group A and 46.36 years for group B [Table/Fig-2]. According to the sites of painful bone metastasis, the patients were distributed as follows: axial (n=26) and appendicular (n=16). For axial sites, the cases were distributed as follows: dorsal spine (n=10), dorso-lumbar spine (n=8), lumbar spine (n=2), cervical spine (n=1), lumbo-sacral spine (n=3) and cervico-dorsal spine (n=2). For the appendicular sites, the distribution included the pelvic bone (n=14), shoulder (n=1) and humerus (n=1). In addition to bone metastasis, three patients in group A had liver metastasis, two patients had lung metastasis and one patient had both lung and brain metastasis, while one patient in group B had lung metastasis. All patients completed the treatment protocol.

Parameters	Overall (n=42)	Group-A (n=20)	Group-B (n=22)	p-value
Age (years)				
Mean±SD	48.05±8.92	49.90±9.170	46.36±8.561	0.205
Range	33-68	36-68	33-65	
Sex, n (%)				
Female	40 (95.2)	18 (90)	22 (100)	0.221*
Male	2 (4.8)	2 (10)	0	
Histology, n (%)				
Lobular carcinoma	4 (9.5)	2 (10)	2 (9.1)	1.0*
Invasive ductal carcinoma	38 (90.5)	18 (90)	20 (90.9)	
ER, n (%)				
Positive	23 (54.8)	11 (55)	12 (54.5)	0.976
Negative	19 (45.2)	9 (45)	10 (45.5)	
PR, n (%)				
Positive	11 (26.2)	6 (30)	5 (22.7)	0.592
Negative	31 (73.8)	14 (70)	17 (77.3)	
HER2, n (%)				
Positive	25 (59.5)	10 (50)	15 (68.2)	0.231
Negative	17 (40.5)	10 (50)	7 (31.8)	
Molecular subtypes, n (%)				
Luminal A	6 (14.3)	3 (15)	3 (13.6)	0.420#
Luminal B	17 (40.5)	8 (40)	9 (40.9)	
HER2 enriched	14 (33.3)	5 (25)	9 (40.9)	
Triple negative	5 (11.9)	4 (20)	1 (4.6)	

[Table/Fig-2]: Basic characteristics of the patient's profile.
ER: Oestrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth receptor
*Fisher's-exact test; #Fisher-Freeman-Halton test

There was no statistically significant difference between the two groups regarding treatment-related toxicity, specifically in terms of nausea, diarrhoea, mucositis, weakness and radiation dermatitis. Ten patients in group B developed hand and foot syndrome, which was graded as 1. Within two weeks of the end of treatment, all toxicities had improved [Table/Fig-3].

Variable	Group A (N=20)	Group B (N=22)	p-value
Nausea, n (%)			
Grade 0	12 (60)	16 (72.7)	0.382
Grade 1	8 (40)	6 (27.3)	
Grade 2	0	0	
Diarrhea, n (%)			
Grade 0	14 (70)	11 (50)	0.133#
Grade 1	2 (10)	8 (36.4)	
Grade 2	4 (20)	3 (13.6)	
Hand foot syndrome, n (%)			
Grade 0	20 (100)	12 (54.5)	0.001*
Grade 1	0	10 (45.5)	
Grade 2	0	0	
Mucositis, n (%)			
Grade 0	19 (95)	21 (95.5)	1.0*
Grade 1	1 (5)	1 (4.5)	
Grade 2	0	0	
Weakness, n (%)			
Grade 0	12 (60)	11 (50)	0.186#
Grade 1	6 (30)	11 (50)	
Grade 2	2 (10)	0 (0)	
Radiation dermatitis, n (%)			
Grade 0	14 (70)	17 (77.3)	0.730
Grade 1	6 (30)	5 (22.7)	
Grade 2	0	0	

[Table/Fig-3]: Comparison of treatment related toxicity as per CTCAE version 5 in both groups.
*Fisher's exact test; #Fisher-Freeman-Halton test

There was no significant difference in the median pain score between the two groups at weeks 0, 1, 2, 4 and 8. However, a significant difference was observed in the median pain score between the two groups at week 12 (p-value=0.024) [Table/Fig-4].

Pain score	Group-A	Group-B	p-value*
Week 0	7 (4-10)	8 (5-9)	0.167
Week 1	5 (1-7)	5 (0-7)	0.848
Week 2	4 (0-8)	3 (0-6)	0.177
Week 4	3 (0-8)	2 (0-5)	0.061
Week 8	3 (0-8)	1.5 (0-5)	0.070
Week 12	2.5 (0-9)	0 (0-5)	0.024

[Table/Fig-4]: Median pain score comparison between both groups during weekly follow-up.
*Mann-Whitney U test

The use of analgesics decreased over time. There was no significant difference in the median value of analgesic scores between the two groups at weeks 0, 1, 2, 4, 8 and 12 [Table/Fig-5].

Analgesic score	Group A	Group B	p-value*
Week 0	2 (1-4)	3 (1-4)	0.103
Week 1	2 (0-4)	2 (0-3)	0.664
Week 2	1 (0-3)	2 (0-3)	0.599
Week 4	1 (0-3)	1 (0-2)	0.786
Week 8	1 (0-3)	1 (0-2)	0.297
Week 12	1 (0-2)	1 (0-2)	0.383

[Table/Fig-5]: Comparison of median analgesic score between two groups during follow-up.
*Mann-Whitney U test

At the end of 12 weeks, CR was observed in 20% of patients in the radiotherapy-only group, whereas it was 63.6% in the radiotherapy plus concurrent capecitabine group and this difference was statistically significant with a p-value of 0.004 [Table/Fig-6].

The OR rates observed among molecular subtypes revealed no significant difference (p-value >0.05). CR was achieved in three out of six (50%) luminal A, six out of 17 (35.3%) luminal B, seven out of 14 (50%) HER2-enriched and two out of five (40%) triple-negative breast cancer patients.

Follow-up	Response	Group A (N=20) n (%)	Group B (N=22) n (%)	p-value
Week 1	Complete Response (CR)	0	1 (4.5)	0.174#
	Partial Response (PR)	16 (80)	20 (91)	
	Stable Pain (SP)	4 (20)	1 (4.5)	
Week 2	CR	3 (15)	4 (18.2)	0.445#
	PR	15 (75)	18 (81.8)	
	SP	2 (10)	0	
Week 4	CR	4 (20)	8 (36.4)	0.241*
	PR	16 (80)	14 (63.6)	
	SP	0	0	
Week 8	CR	4 (20)	10 (45.5)	0.081*
	PR	16 (80)	12 (54.5)	
	SP	0	0	
Week 12	CR	4 (20)	14 (63.6)	0.004*
	PR	16 (80)	8 (36.4)	
	SP	0	0	

[Table/Fig-6]: Week wise response to treatment in both the groups.
#Fisher-Freeman-Halton test; *Chi-square test

DISCUSSION

Present study observed no significant differences in side-effects between the groups and there was an absence of any grade 3 or 4 toxicity. Both groups tolerated the treatment well and the median pain score decreased significantly from week 1 to week 12 in the concurrent capecitabine plus radiotherapy arm compared to the radiotherapy-only arm. Local radiotherapy is effective in alleviating pain from bone metastasis by promoting ossification and reducing the osteoclast activity of tumour cells. Several studies have investigated different dose schedules of local radiotherapy for bone metastasis and found no differences in response rates between single- and multiple-fractionation schedules, suggesting that changes in dose fractionation of local radiotherapy will not significantly improve pain control [19-21]. The addition of chemotherapy concurrent with radiotherapy may act as a radiosensitiser, enhancing the effects of radiotherapy.

Present study observed only grade 1 and grade 2 treatment-related toxicity in both arms and all toxicities resolved within two weeks after the end of treatment. There were no grade 3 or 4 toxicities in either arm. Hand-foot syndrome occurred in the chemoradiation arm due to capecitabine. Kundel Y et al., in a phase II single-arm prospective study, noted only grade 1 or 2 toxicities, without any grade 3 or 4 toxicities [15]. Ahmed S et al., in a prospective comparative study, reported no significant difference in early treatment toxicity between capecitabine-based chemoradiation and radiotherapy alone; both treatment groups showed no grade 3 or 4 toxicity [16]. Both of these studies support present study findings. Therefore, authors suggest that the addition of capecitabine concurrent with local radiotherapy can be considered safe.

A greater decrease in the median pain score was observed at week 12 after treatment in the chemoradiation arm compared to radiotherapy alone (p-value=0.024). Authors noted that analgesic use decreased over time, although no significant difference was evident between the groups. A possible explanation for this finding may be the limited sample size of the study. Kundel Y et al., in their analysis of capecitabine-based chemoradiotherapy for treating painful bone metastasis in breast cancer patients, observed a significant decrease in pain from week 1 to week 12 (p-value <0.001), with no progression of pain after 12 weeks and an improvement in analgesic scores up to week 4, followed by stabilisation of the score [15]. Ahmed S et al., found that the decrease in median pain score from week 1 to week 12 was greater in the capecitabine-based chemoradiation group compared to radiotherapy alone (p-value=0.001) and there was a significant difference in median analgesic scores between the two groups from week 2 to week 12 after treatment, particularly at week 4 (p-value=0.001) [16].

In the present study, a CR of 63.6% was achieved at 12 weeks after treatment in the chemoradiation arm. Present study data are supported by Kundel Y et al., and Ahmed S et al., who reported CR values of 42.9% and 48%, respectively [15,16]. In present study, the addition of capecitabine concurrent with radiotherapy provided superior pain control and response, with no difference in the toxicity profile compared to radiotherapy alone in breast cancer patients with painful bone metastasis. Therefore, it can be safely administered alongside radiotherapy for improved outcomes.

Limitation(s)

In this study, the major limitations were the small sample size and the limited follow-up period of only 12 weeks. Therefore, long-term pain control, recurrence rates of pain and long-term toxicities cannot be thoroughly evaluated in this study. Consequently, further large-scale studies with extended follow-up are needed for more comprehensive validation.

CONCLUSION(S)

Concurrent capecitabine with local radiotherapy is well tolerated and safe for the treatment of painful bone metastasis of breast cancer origin, demonstrating a higher response rate, particularly in terms of CR and pain palliation, compared to radiotherapy alone. The toxicity observed was mild and comparable to that seen with radiotherapy alone. A large, randomised prospective study is necessary for further validation of this approach.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 17, 2025
- Manual Googling: Mar 21, 2025
- iThenticate Software: Apr 17, 2025 (22%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 14, 2025**
Date of Peer Review: **Mar 23, 2025**
Date of Acceptance: **Apr 19, 2025**
Date of Publishing: **Jun 01, 2025**