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Original Research Article

Comparing the efficacy of concurrent capecitabine with external beam radiotherapy versus radiotherapy alone in pain management of osseous metastasis from breast cancer

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ABSTRACT

Background: Breast cancer is the most common cancer in women globally, and bone metastases significantly affect the quality of life and survival. This study aimed to compare the efficacy of concurrent capecitabine with EBRT versus EBRT alone in managing pain from osseous metastases in breast cancer patients.
Methods: A quasi-experimental study was conducted with 56 breast cancer patients with bone metastases. Patients were divided into two groups: Group A received EBRT alone, while group B received concurrent capecitabine (825 mg/m^2, 5 days/week) with EBRT.
Results: In this study, group A (n=28) and group B (n=28) were compared across various parameters. The mean ages were similar (Group A: 42.9±8.4 years, group B: 42.1±12.5 years, p=0.780). ECOG performance status was significantly better in group B (e.g., 12th week: group A: 1.14±0.65, group B: 0.71±0.59, p=0.012). Treatment response showed that by the 12th week, 42.9% of group B had a complete response (CR) compared to 14.3% in group A (p=0.027). No significant differences were observed in treatment-related side effects.
Conclusions: The study found that combining capecitabine with EBRT improved pain management and reduced the need for pain medications in breast cancer patients with bone metastasis. Both treatment groups showed similar side effects, indicating good tolerance for both regimens.

Keywords: Capecitabine, Radiotherapy, Breast cancer

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related deaths in women worldwide.[1] In Bangladesh, it is the most prevalent cancer in females, according to the 2018-2020 report of the national institute of cancer research and hospital. Metastasis significantly contributes to the high mortality rate among breast cancer

patients, with 20-30% of early breast cancer recurrences involving metastatic disease.[2] Patients with metastatic breast cancer (MBC) have a median overall survival (OS) ranging from 2 to 3 years, with a 27% 5-year relative survival rate.[3] Bone metastases are common, with around 70% of advanced breast cancer patients developing them.[4] Other common metastatic sites include the liver, lungs, and brain, though bone remains the most frequently affected organ.[5] Different breast cancer subtypes, such as HER-2+ and triple-negative breast cancer (TNBC), are more aggressive and prone to metastasis, particularly to bone.[3] Bone metastasis severely impacts the quality of life through complications like pain, fractures, and neurologic deficits, leading to poor survival rates.[6,7] Patients with bone metastases, particularly those with skeletal involvement, often have longer survival rates.[8] The axial skeleton, especially the spine, pelvis, and ribs, is the primary site of bone metastasis.[9] Osteolytic and osteoblastic lesions result from osteoclast-mediated and tumor-cell-mediated destruction, influenced by various factors secreted by malignant cells.[10] Management of bone metastasis requires a multidisciplinary approach, including radiation therapy, chemotherapy, hormone therapy, surgery, and bone-targeted treatments such as bisphosphonates and denosumab. While radiation therapy has long been effective in treating bone metastasis pain, with 80-90% of patients experiencing partial relief and 50% achieving complete pain relief, some patients continue to experience persistent or recurrent pain despite treatment.[11] Studies suggest that combining systemic therapies with radiotherapy may improve outcomes by enhancing tumor control and symptom relief. Given capecitabine's radiosensitizing properties and its efficacy in MBC, combining it with radiotherapy may enhance pain control and tumor response in bone metastases. Radiation therapy also improves quality of life by reducing symptoms like anxiety, insomnia, and mobility issues.[12] Multiple fractionation regimens, such as 30 Gray in 10 fractions and 20 Gray in 5 fractions, are commonly used for pain palliation, with studies showing similar pain response rates for single and multiple fraction treatments.[13,14] Concurrent chemoradiation, such as combining capecitabine with radiotherapy, has shown promise in other cancers but has limited research in bone metastases from breast cancer. This study aimed to compare the effectiveness and safety of radiotherapy alone versus radiotherapy combined with capecitabine for managing painful bone metastases in breast cancer patients.

METHODS

This quasi-experimental study was conducted at the department of radiation oncology, NICRH, Dhaka, from May 2022 to April 2023. A total of 56 histologically confirmed breast cancer patients with radiological evidence of bone metastases were selected by purposive sampling and divided into two groups (A and B) of 28 each. Group A received external beam radiotherapy (EBRT) alone, while group B received concurrent oral capecitabine (825 mg/m^2, 5 days/week) with radiotherapy. Pretreatment evaluation included clinical history, physical examination, pain assessment, ECOG performance status, and laboratory tests. Radiotherapy was planned using 2D conventional techniques with a 6 MV linear accelerator. Supportive care, including analgesics and systemic therapy, was provided as needed. Treatment response was assessed using VAS pain scores, ECOG status, ASIA classification, and WHO analgesic use scale, with follow-ups at 1, 2, 4, 8, and 12 weeks. Data were analyzed using SPSS 25.0, with t-tests and Chi-square tests for comparison. Ethical approval was obtained from the NICRH ethical committee, and informed consent was secured.

Inclusion criteria

Patients with histologically confirmed breast carcinoma with radiological evidence of skeletal metastasis, age between 18 and 70 years and willingness to participate and complete regular pain assessments were included.

Exclusion criteria

Patients with prior radiotherapy at the index site or previous capecitabine treatment, significant neurological or psychiatric disorders, complete paralysis, or post-operative cases and pregnancy, lactation, or systemic therapy within 14 days of radiotherapy were excluded.

RESULTS

This table showed that the mean ages were similar, with group A having an average age of 42.9 years (±8.4) and group B 42.1 years (±12.5) (p=0.780). Most participants were married (92.9% in group A and 82.1% in group B), with few widows. Group A had a higher proportion of individuals with higher education, whereas group B had more participants with secondary education. Additionally, 78.6% of group B participants were housewives, compared to 50% in group A, which had more individuals in business and service sectors. Overall, p values indicated no significant differences between groups in most categories.

Both groups showed similar breastfeeding histories (around 90%), with no significant differences in family history of cancer or obesity prevalence. Group B had a higher proportion of oral contraceptive use (64.3% vs. 42.9%). Menopausal status, age at menarche, age at menopause, and age at first childbirth were comparable between the groups, with most subjects being premenopausal and having their first child at or before 30 years. Regarding the number of children, the majority in both groups had more than two children. The p values indicate that most differences were not statistically significant.

This Figure 1 showed most of the patients in both groups, 19 (67.9%) in group A and 20 (71.4%) in group B were suffering from multiple site involvement.

The Figure 2 shows that there was no significant difference in pain scores between the two groups at the baseline (pre-treatment). However, from the first week after starting the treatment, the pain score in group B was significantly lower than that in group A, and the difference became more significant over time.

This Table 3 indicates that there were no significant differences in analgesic requirement (according to the WHO analgesic ladder, grade 0-4) between the two groups at the pre-treatment stage (0 weeks) and the 1st follow-up, but significant differences were observed from the 2nd week onward, with group B exhibiting significantly lower analgesic requirement compared to group A ($p<0.001$).

This Table 4 shows that there was no significant difference in Eastern cooperative oncology group performance status (ECOG PS) between the two groups at the start of treatment. Group B showed significantly better ECOG PS scores than group A at all-time points afterward, with a decreasing trend over time. The p values were statistically significant at all-time points.

This Table 5 shows that the response to treatment between the two groups was not statistically significant in the 1st week ($p=0.625$). but continued to become significant thereafter reaching CR of 14.3% in group A and 42.9% in group B in the 12th week ($p=0.027$).

The Table 6 shows that there was no statistically significant distinction observed in early treatment toxicity between the two groups, with the majority of reported toxicities being gastrointestinal such as diarrhea, vomiting, and nausea and typically of mild intensity (grade I or II).

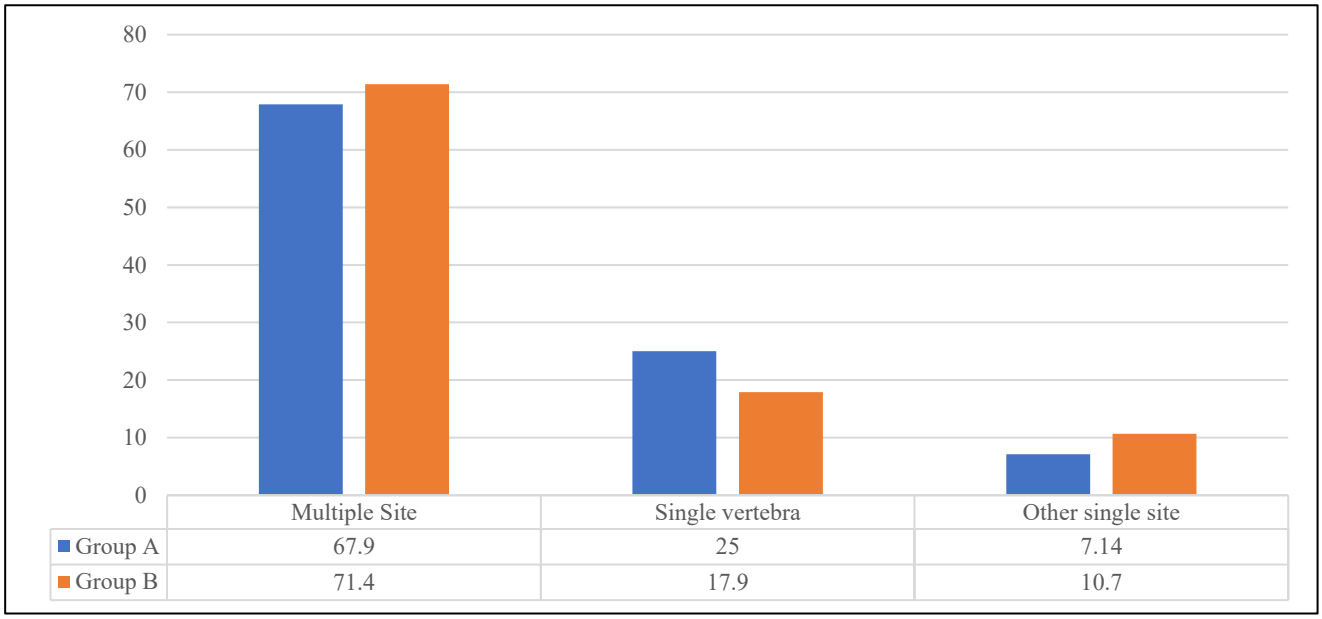

Figure 1: Distribution of the patients according to bone involvement status.

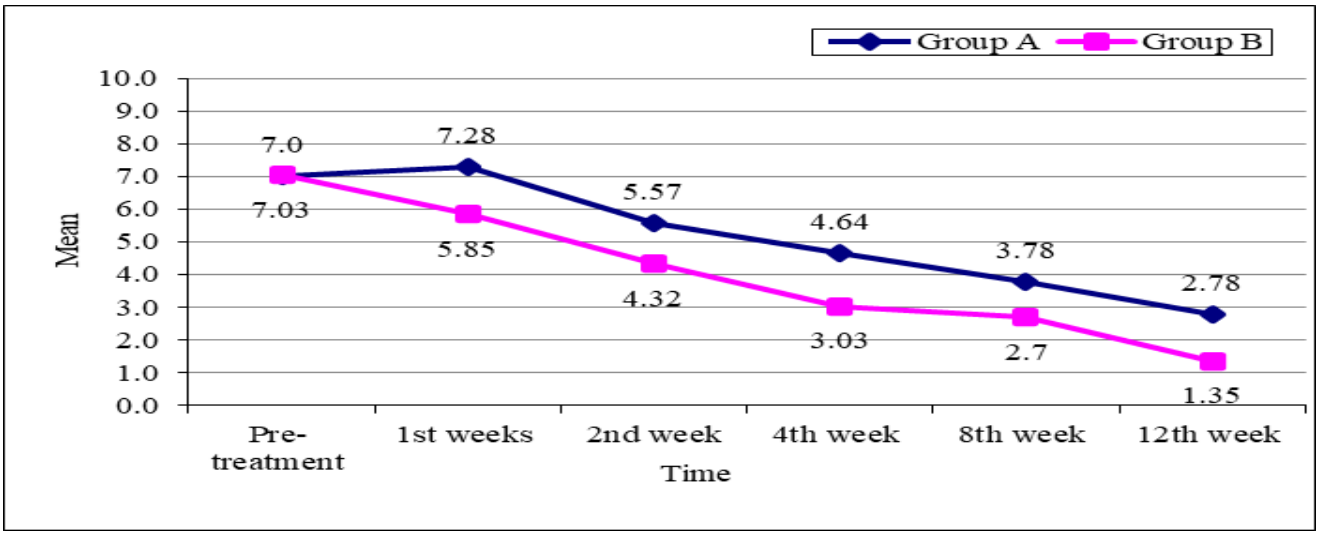

Figure 2: Change in VAS score over time of the study subjects.

Table 1: Demographic characteristics of the study subjects, (n=56).

Characteristics	Group A, (n=28)		Group B, (n=28)		P value
	N	%	N	%	
Age (in years)					
Mean±SD	42.9±8.4		42.1±12.5		0.780ns
Marital status					
Married	26	92.9	23	82.1	0.225ns
Unmarried	0	0	0	0	
Widow	2	7.1	5	17.9	
Educational status					
Illiterate	2	7.1	2	7.1	0.369ns
Primary	6	21.4	6	21.4	
SSC	2	7.1	6	21.4	
HSC	12	42.9	6	21.4	
Graduate	6	21.4	8	28.6	
Occupational status					
Housewife	14	50.0	22	78.6	0.161ns
Business	4	14.3	0	00	
Service holder	4	14.3	6	21.6	
Garments factory worker	2	7.1	0	00	
Others	4	14.3	0	00	

*Ns-p value not significant.

Table 2: Risk factors and reproductive risk factors of the study subjects, (n=56).

Factors	Group A, (n=28)	Group B, (n=28)	P value
Breastfeeding	92.9% (Yes)	89.3% (Yes)	0.693ns
Family history	85.8% (None)	92.8% (None)	0.688ns
Oral contraceptive	42.9% (Yes)	64.3% (Yes)	0.108ns
Obesity	7.1% (Yes)	7.1% (Yes)	1.000ns
Menopausal tatus	67.9% (Pre)	75.0% (Pre)	0.554ns
Age at menarche	92.9% (Normal)	96.4% (Normal)	0.698ns
Age at menopause	96.4% (Normal)	100% (Normal)	0.313ns
Age at 1st childbirth	82.1% (≤30 years)	85.8% (≤30 years)	0.600ns
Number of children	78.6% (>2 children)	71.4% (>2 children)	0.771ns

*Ns-p value not significant.

Table 3: Analgesic requirement between two groups, (n=56).

Analgesic requirement (After start of treatment)	Group A, (n=28)	Group B, (n=28)	P value
Pre-treatment (0 weeks)	2.21±0.41	2.42±0.50	0.091^{ns}
1st weeks	2.28±0.46	2.14±0.65	0.356^{ns}
2nd week	2.00±0.10	1.57±0.63	0.002^{s}
4th week	1.78±0.41	1.00±0.54	0.001^{s}
8th week	1.64±0.48	0.71±0.59	0.001^{s}
12th week	0.92±0.60	0.35±0.28	0.001^{s}

*ns=not significant, s=significant, p value reached from unpaired t test.

Table 4: ECOG PS status between two groups, (n=56).

ECOG PS (After the start of treatment)	Group A, (n=28)	Group B, (n=28)	P value
Pre-treatment (0 weeks)	2.21±0.56	2.07±0.46	0.311^{ns}
1st weeks	2.50±0.63	2.00±0.54	0.002^{s}
2nd week	1.92±0.26	1.28±0.46	0.001^{s}
4th week	1.78±0.41	1.14±0.35	0.001^{s}
8th week	1.64±0.48	0.92±0.53	0.001^{s}
12th week	1.14±0.65	0.71±0.59	0.012^{s}

*ns=not significant, s=significant, p value reached from unpaired t-test

Table 5: Response to treatment between two groups, (n=56).

Response	Group A, (n=28), (Mean±SD)		Group B, (n=28), (Mean±SD)		P value
	N	%	N	%	
1st weeks					
CR	0	00	0	00	0.625
PR	18	64.3	21	75.0	
SP	2	7.1	3	10.7	
PP	8	28.6	4	14.3	
2nd week					
CR	0	00	0	00	0.029
PR	16	57.1	24	85.7	
SP	8	28.6	4	14.3	
PP	4	14.3	0	00	
4th week					
CR	0	00	4	14.3	0.036
PR	23	100	24	85.7	
SP	4	0	0	00	
PP	1	00	0	00	
8th week					
CR	0	00	8	28.6	0.002
PR	23	100	20	71.4	
SP	5	00	0	00	
PP	0	00	0	00	
12th week					
CR	4	14.3	12	42.9	0.027
PR	22	78.6	16	57.1	
SP	0	00	0	00	
PP	2	7.1	0	00	

*ns=not significant, p reached from Fisher exact test, PR=Partial response, SP=Stable pain, PP=Pain progression.

Table 6: Treatment-related side effects between groups, (n=56).

Response	Group A, (n=28)		Group B, (n=28)		P value
	N	%	N	%	
Nausea					
No	24	85.7	21	75.0	0.034ns
Grade I	4	14.3	7	25.0	
Grade II	0	00	0	00	
Vomiting					
No	27	96.4	25	89.3	0.297ns
Grade I	1	3.6	3	10.7	
Grade II	0	0.0	0	0.0	
Mucositis					
No	28	100.0	27	96.4	0.310ns
Grade I	0	00	1	3.6	
Grade II	0	00	0	00	
Hand and foot syndrome					
No	28	100.0	27	96.4	0.310ns
Grade I	0	00	1	3.6	
Grade II	0	00	0	00	
Diarrhea					
No	25	89.3	23	82.1	0.538ns
Grade I	3	10.7	4	14.3	
Grade II	0	00	1	3.6	
Radiation dermatitis					
No	25	89.3	22	78.6	0.271ns
Grade I	3	10.7	6	21.4	
Grade II	0	00	0	00	

*ns=not significant, p-value reached from Fisher exact test.

DISCUSSION

The impact of bone metastases originating from breast cancer on patients' well-being and survival is significant. Pain, a common symptom of bone metastases, can drastically reduce a patient's quality of life. EBRT is a proven treatment for managing pain in patients with osseous metastases from breast cancer. Regarding the demographic data, most patients in this study were within the 31-40 age range, with a mean age of 42.9±8.4 years in group A and 42.1±12.5 years in group B. These findings align with the hospital-based cancer registry (HBCR) of NICRH (2018-2020), which reported a mean age of 43.8 years for breast cancer patients. This age distribution corroborates previous research indicating that breast cancer is often diagnosed in women aged 40 to 50 (Nguyen et al, Yee et al and Ahmed et al).[15-17] The majority of study participants in both groups were married, from middle-class backgrounds, and housewives. In group A, 42.9% (12/28) completed their higher secondary certificate (HSC), while 28.6% (8/28) of group B were graduates. The majority of patients in both groups had a history of breastfeeding (92.9% in group A and 89.3% in group B), with no significant difference observed (p=0.693). Regarding family history, 7.1% of group A patients and 3.6% of group B patients had a first-degree relative with cancer. This is relatively low compared to other studies (e. g., Smith et al), where a higher percentage of MBC patients report a family history of cancer.[18,19] Oral contraceptive use was reported by 42.9% of group A and 64.3% of group B patients, while the prevalence of obesity showed no significant difference between the groups (p>0.05). Other reproductive factors, such as menarche and menopause, did not show significant differences between the groups (p>0.05). Bone imaging revealed that the majority of patients had multiple bone metastases, with 67.9% of group A and 71.4% of group B patients presenting with this finding. This is consistent with research by Ahmed et al which found a similar prevalence of multiple bone metastases in patients with breast cancer.[17] At baseline (0 weeks), the pain scores were comparable between the two groups. However, group B experienced a significantly greater reduction in pain scores from the first week of treatment onward (p=0.001), with this trend continuing through the second, fourth, eighth, and twelfth weeks (p=0.001). Statistically significant pain reduction was observed in group B starting from the first week of treatment onward (p=0.001), with this trend continuing through the second, fourth, eighth, and twelfth weeks (p=0.001). These results align with previous studies, such as Ahmed et al which showed significant pain relief in patients receiving both capecitabine and EBRT compared to those receiving radiotherapy alone.[17] In terms of analgesic requirements, there was no significant difference between the groups at baseline (p=0.091). However, by the second week after treatment initiation, group B required significantly fewer analgesics than group A (p=0.002), with this trend continuing through the 12th week (p=0.001). This finding supports previous studies (Ahmed et al and Kundel et al), which observed reduced analgesic needs in patients receiving combined treatments.[17,20] Motor function at baseline was similar between the groups (p=0.424). However, group B demonstrated a significantly better motor function improvement starting from the first week of treatment (p=0.002), and this improvement continued significantly through the study period (p<0.05). These results suggest that adding capecitabine to EBRT may positively affect motor function in breast cancer patients with bone metastases, thereby enhancing their quality of life and ability to perform daily activities. The ECOG PS score, which assesses functional status, showed no significant difference at baseline between the groups. However, group B had better functional status in the first week after treatment (p=0.002) and continued to show significant improvement through the 12th week. By the end of the study, group B had a mean ECOG PS score of 0.71±0.59, compared to 1.14±0.65 in group A, indicating better overall functional status in group B. These findings were consistent with the research by Ahmed et al.[17] In terms of treatment response, group B demonstrated a significantly better response compared to group A in terms of partial response (PR) and complete response (CR) at various time points. In the 12th week, 42.9% of group B patients achieved CR, while only 14.3% of group A patients did (p=0.027). These results are consistent with findings from Ahmed et al and Kundel et al which reported higher response rates with the combination of capecitabine and radiotherapy.[17,20] Side effects were generally mild in both groups, with nausea (grade I or II) being more common in group B (25%) than in group A (14.3%) (p=0.034). However, other side effects, such as mucositis, vomiting, and diarrhea, were not significantly different between the groups. Results indicate that both treatment regimens were well-tolerated, with most side effects being grade I or II, in line with previous studies. [17,20]

Limitations

The study was limited by a small sample size and the absence of randomization, which may affect the generalizability of the results.

CONCLUSION

The results of the study indicate that combining capecitabine with EBRT significantly improved pain management in breast cancer patients with bone metastasis. This combined approach reduced the need for pain medications and resulted in better treatment responses compared to EBRT alone. Importantly, the side effects experienced by both treatment groups were nearly identical, suggesting that both regimens were well-tolerated by the patients.

Recommendations

Based on the results of this study, it is recommended that external beam radiotherapy combined with concurrent capecitabine be considered a safe and effective option for pain palliation in breast cancer patients with bone

metastasis. This combination provides better pain relief compared to EBRT alone. For future studies, it is essential to consider using a larger sample size, incorporating multiple centers, and implementing randomization to improve the reliability and applicability of the findings.

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