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A PROSPECTIVE INTERVENTIONAL STUDY COMPARING PALLIATIVE RADIOTHERAPY WITH AND WITHOUT CONCURRENT CAPECITABINE IN BONE METASTASES OF CARCINOMA BREAST ORIGIN

Radiotherapy

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ABSTRACT

Background: Painful bone metastases are common in Breast cancer. Radiotherapy to painful sites is the mainstay of treatment. However, pain control and local response is low with radiotherapy alone. Use of concurrent chemotherapy is a viable option to improve symptomatic outcomes in painful bone metastases. The purpose of this study was to compare the efficacy of concurrent Capecitabine with EBRT vs EBRT alone for palliation of painful bone metastases and the toxicity profile of the two regimens. **Materials And Methods:** Sixty patients with painful bone metastases from breast cancer participated in this prospective study. We randomized the patients into two groups: group A treated with radiotherapy 30 Gy in 10 fractions and group B treated with radiotherapy 30 Gy in 10 fractions with concurrent Capecitabine 825 mg/m2 every 12 hrs. **Results:** There was no statistically significant difference between the two groups regarding early treatment toxicity. Most of the toxicity was gastrointestinal (diarrhea and nausea) and mild (grade I or II). The median pain score decreased from week one, and there was a marked response in week 4. The difference in median pain score between both groups was statistically significant with p-value =0.0001. The median analgesic score in both groups was statistically significant with a p-value = 0.004 at week 12. A complete response to pain in week 4 was 6 and 12 in groups A and B, respectively with a p-value of 0.029. **Conclusion:** Concurrent chemoradiation in painful bone metastases from breast cancer origin was tolerable and safe; it had a higher overall response rate and pain palliation than radiotherapy alone.

KEYWORDS

Breast cancer, Bone metastases, Palliative Radiotherapy, Capecitabine, Pain Score, Analgesic Score, Toxicity

INTRODUCTION:

Breast cancer is a major public health problem among women all over the world. According to GLOBOCAN 2022, it is the second most diagnosed cancer globally accounting for 2,296,840 (11.5%) newly diagnosed cancer cases, after lung cancer (12.4%) mainly due to high prevalence in low- and middle-income countries. It is the 4th leading cause of cancer mortality accounting for 666,103 cancer related deaths in 2022. It is the most diagnosed malignancy with an incidence of 23.8% and the leading cause of cancer related deaths among women in 2022. Breast cancer is the most common cancer overall as well as among women in India accounting for 13.6% of all newly diagnosed cancer cases among both sexes and 26.6% of all cancers in women with incidence being 1,92,020. It is also the most common cause of cancer related deaths in the country and also among females causing 98,337 deaths in 2022.[1] The major risk factors include early menarche, late menopause, nulligravida status, combined OCP use, postmenopausal Hormone Replacement therapy, obesity etc. that lead to high oestrogen exposure, exposure to thoracic irradiation, family history and Genetic factors like mutations in BRCA1 and BRCA2 genes. Breast cancer has a high survival rate if diagnosed early but unfortunately, about 50-80% of cases present in advanced stages. Approximately 5-10% of cases present with metastases at the time of diagnosis ("de novo" metastatic Breast cancer).

Bone is the most common site of metastasis in Carcinoma Breast. Seventy percent of patients with advanced breast cancer have bone metastases and about one-third of metastatic breast cancer patients have only bone metastases. Bone metastases cause significant morbidity due to pain and skeletal related events or SREs (pathological fractures, Radiotherapy to bone, Surgery to bone, Spinal cord compression and hypercalcemia) affecting quality of life and decreasing overall survival. Bone metastases related to Carcinoma Breast have the highest incidence of SREs.[2] Greater blood flow to red bone marrow; higher manufacturing of adhesion molecules involved in binding of tumor cells to bone marrow stroma; latent tumor cells within the hematopoietic stem cells that escape the effects of chemotherapy leading to formation of definite metastatic colonies: are some of the factors causing such high incidence of bone metastases.

The preferred site in hematogenous spread of Breast cancer is the trabecular bone being highly vascular. The interaction of tumor cells with bone microenvironment stimulates osteoclasts leading to increased bone turnover and release of bone activating growth factors and cytokines. Bone metastases can be either osteoblastic or osteolytic. The most common type of bone metastases in Carcinoma Breast is osteolytic.

Pain, slowly progressive, insidious, and fairly well localized, is the most common presenting symptom of bone metastases. The standard and most effective treatment is conventional radiotherapy, which improves bone integrity, reduces risk of fractures, preserves physical function, and palliates pain with few side effects. This is always combined with pharmacological analgesia which include nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, opioids, and bisphosphonates. The class of pain medication used is dictated by the WHO recommendations based on the severity of pain rated on a scale of 0-10.[3][4]

Local EBRT is effective in alleviating pain due to bone metastases with about 60-80% patients responding to RT and 25-30% showing complete response. Pain relief occurs rapidly with 40% of responders benefiting as early as within 10 days.[5] Various Radiotherapy regimens have been used for palliation of painful bone metastases, using both single and multiple fractionations. Single fractionation though having similar response rates to multiple fractionations have been found to have more frequent need for reirradiation and more pain flare up at the treated site.[6] Therefore, the most used regimen in our setting is a total dose of 30 Gy given over 10#, i.e., 3 Gy per fraction over 2 weeks.

Over the years concurrent chemotherapy and radiation have become the mainstay of treatment of most malignancies, both metastatic and locally advanced to improve local control of primary tumor and palliation of local symptoms like pain.

Capecitabine, an oral fluoropyrimidine and a prodrug of 5-FU is a potent radiosensitizer thus enhancing the biological effectiveness of radiotherapy. Compared to 5-FU it has enhanced efficacy on tumor tissue and reduced gastrointestinal and bone marrow toxicity. Due to the ease of administration and limited toxicity profile, it is a good option for many patients with better acceptance and compliance.

Capecitabine combined with radiotherapy in adjuvant treatment of

metastatic breast cancer was found to be safe with comparable toxicity to radiotherapy alone.[7] In a phase II study, combining Capecitabine with EBRT in treatment of painful bone metastases originating from Ca Breast conducted by Kundel et al, it was found to have better response rates with comparable toxicities to radiotherapy alone.[8]

However, the efficacy of concurrent Capecitabine in the treatment of bone metastases from Breast cancer is yet to be studied among Indian population. The purpose of this study is to compare the efficacy of concurrent Capecitabine with EBRT and EBRT alone for palliation of painful bone metastases and the toxicity profile of the two regimens.

MATERIALS AND METHODS

This was a prospective, comparative study conducted among a total of 60 patients of Ca Breast with Bone metastases presenting at Department of Radiation Oncology at a tertiary care hospital in North India.

Inclusion Criteria:

1. Histologically proven Adenocarcinoma Breast irrespective of previous exposure to Chemotherapy except Capecitabine.
2. Age ≥18 years.
3. Patients with radiographic evidence of bone metastasis including plain radiographs, Bone scans, or MRI.
4. Patients with normal hemogram and metabolic parameters.
5. ECOG performance status 0-3.
6. Patients willing to participate in the study and sign informed written consent.

Exclusion Criteria:

1. Patients previously treated with either surgery, radiotherapy, or chemotherapy for bone metastases.
2. Any uncontrolled comorbidities, pregnancy, lactating mothers, immunocompromised state.
3. Patients having previously received Capecitabine.
4. Double malignancy.

Initial Patient Evaluation:

This included history and complete physical examination; histopathology; Complete hemogram, Liver and Kidney function tests; Viral markers (HIV, HBsAg, Anti HCV); CECT/MRI of concerned site; CXR/CECT Chest; USG Whole Abdomen; Bone scan/PET CT (optional).

Methodology:

Patients were randomly assigned to the study and control arms each having 30 patients. Patients in ARM A (Control arm) received a total radiation dose of 30 Gy (3 Gy per fraction delivered over 5# a week for 2 weeks) while those in ARM B (Study arm) received the same radiation dose with concurrent Capecitabine in dose of 825 mg/m^2 orally every 12 hours.

Radiation Technique:

Radiation was delivered by Cobalt-60 in anterior-posterior or posterior-anterior fields according to site with proper immobilization. Pre-treatment 2-D planning was done to demarcate the treatment volume which included the radiographic abnormality with at least 2 cm margin. In the case of vertebral metastases, this was done by adding the vertebrae above and below the area involved. The total dose delivered was 30 Gy given in 10 fractions, 5 days a week.

Chemotherapy:

Patients in Arm B received concurrent Capecitabine 825 mg/m^2 orally every 12 hours through the course of radiotherapy.

Assessment:

1. Pain Assessment:

It was done by asking the patients to describe their pain on the Visual Analogue Scale (VAS) which ranges from a score of 0 to 10 with 0 being no pain and 10 being indicative of the worst possible pain.
Mild pain = Score of 1-4
Moderate pain = Score 5-6
Extreme pain = Score 7-8
Heavy pain = Score 9-10.

Pain score was assessed before the onset of treatment, followed by weeks 2, 4, 8 and 12 after end of treatment in both arms.

2. Analgesic Use Assessment:

The 5-point WHO Scale was used to measure analgesic score.
Level 0 – No analgesics required.
Level 1 – Non-narcotic analgesics required occasionally.
Level 2 – Non-narcotic analgesics required regularly.
Level 3 – Narcotic analgesics required occasionally.
Level 4 – Narcotic Analgesics required regularly.

3. Response To Treatment:

Response to treatment was evaluated by the international bone consensus [] which takes into account both patient's pain score and analgesic consumption.

- Complete response (CR) = 0 pain score at treated site with no increase in analgesic intake.
- Partial response (PR) = Reduction in pain score by ≥2 at the treated site without increase in analgesic requirement.
- Stable pain (SP) = No change in pain score or a change of 1 point.
- Progressive pain (PP) = Increase in pain score by ≥2 with stable analgesic use or increased analgesic use with stable pain score or increase by 1 point.

Patients with CR and PR were considered as Overall response rates (OR) and those with SP and PP as non-responders.

4. Toxicity Evaluation:

Toxicity was assessed weekly during treatment. At the end of treatment, it was assessed every 4 weeks for 12 weeks according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Statistical Analysis: Continuous variables were summarized in the form of mean ± SD and Median (range). Mann Whitney U Test was used to compare median pain score and analgesic score between groups A and B at each point of time. Nominal/ Categorical variables were summarized in the form of proportions. Chi-Square test was used to compare the proportion of response to treatment between groups A and B. All data was analyzed using SPSS version 26. P-value <0.05 was taken as significant.

RESULTS

Baseline Characteristics

- **Age:** Group A (Mean: 46.40 years, SD: 9.42) vs. Group B (Mean: 51.57 years, SD: 11.69). The p-value of 0.062 suggests no statistically significant difference in age between the groups.

Hormonal Receptor Status

- **Hormonal Receptor**: Group A (Negative: 10, Positive: 20) vs. Group B (Negative: 11, Positive: 19). The p-value of 0.787 indicates no significant difference in hormonal receptor status between the groups.

Her2neu Status

- **Her2neu**: Group A (Negative: 20, Positive: 10) vs. Group B (Negative: 17, Positive: 13). The p-value of 0.424 indicates no significant difference in Her2neu status between the groups.

Molecular Status

- **Molecular Status**: Distribution across various receptor profiles (ER-/PR-/Her2neu-, ER-/PR-/Her2neu+, ER+/PR-/Her2neu-, ER+/PR+/Her2neu-, ER+/PR+/Her2neu+) shows similar patterns in both groups. The p-value of 0.782 suggests no significant difference in molecular status between the groups.

Toxicity Analysis

1. Nausea:

- At Week 2, Group A (Mean: 0.17, SD: 0.379) vs. Group B (Mean: 0.27, SD: 0.450) with a p-value of 0.356, indicating no significant difference.
- No nausea reported in Weeks 4, 8, and 12.

2. Diarrhoea:

- At Week 2, Group A (Mean: 0.13, SD: 0.346) vs. Group B (Mean: 0.27, SD: 0.521) with a p-value of 0.248, indicating no significant difference.
- No diarrhoea reported in Weeks 4, 8 and 12.

3. Dermatitis:

- At Week 2, Group A (Mean: 0.17, SD: 0.379) vs. Group B (Mean: 0.27, SD: 0.450) with a p-value of 0.356, indicating no significant

difference.
- At Week 4, both groups had identical mean scores (0.03, SD: 0.183) with a p-value of 1, indicating no significant difference.
- No dermatitis reported in Weeks 8 and 12.

Pain Score
- **Baseline:** Both Group A (radiotherapy alone) and Group B (radiotherapy with Capecitabine) had a similar median pain score of 7, with no statistically significant difference (p = 0.689).
- **Week 2:** Group B experienced a significant reduction in pain (median score 5) compared to Group A (median score 6), with a p-value of 0.019.
- **Week 4:** The median pain score in Group B continued to improve (4) compared to Group A (5), with a p-value of 0.027.
- **Week 8:** Group B's median pain score dropped to 2, while Group A's was 4, with a highly significant p-value of 0.001.
- **Week 12:** Group B's median pain score decreased to 1, significantly lower than Group A's score of 3 (p = 0.0001).

Group B showed significantly better pain relief over time compared to Group A.

Analgesic Score
- **Baseline:** Both groups had comparable analgesic scores (Group A: 4, Group B: 3), with no significant difference (p = 0.397).
- **Week 2:** Group B's analgesic scores were significantly higher (p = 0.026), indicating higher usage of analgesics initially.
- **Week 4 to Week 12:** Group B consistently showed lower analgesic scores compared to Group A, with significant differences:
- Week 4: p = 0.005
- Week 8: p = 0.002
- Week 12: p = 0.004

Over time, Group B required less analgesic medication compared to Group A.

Response to Treatment

In the study, treatment responses were assessed at 2, 4, 8, and 12 weeks across two groups (Group A and Group B), with a focus on complete response (CR), partial response (PP), partial remission (PR), and substantial progression (SP).
- **Week 2**: Group B had significantly more complete responses (CR) than Group A (p = 0.007).
- **Week 4**: Group B again showed more CRs, with a statistically significant difference (p = 0.029).
- **Week 8**: Group B had a higher number of CRs compared to Group A, with a significant difference (p = 0.014).
- **Week 12**: The trend continued, with Group B having more CRs, maintaining a significant difference (p = 0.014).

Overall, Group B consistently outperformed Group A in achieving complete responses throughout the study.

The results demonstrated that the addition of concurrent Capecitabine to palliative radiotherapy significantly improved pain relief compared to palliative radiotherapy alone. Patients in Group B (receiving Capecitabine) reported a greater reduction in pain scores, indicating enhanced pain control.

The analgesic requirement was notably lower in Group B, suggesting that patients receiving concurrent Capecitabine experienced better pain management with reduced reliance on additional analgesics.

The toxicity profiles, as evaluated by the CTCAE v5.0 criteria, revealed an increase in certain adverse effects in the Capecitabine group. However, these toxicities were generally manageable and did not outweigh the benefits of improved pain relief.

In conclusion, the addition of concurrent Capecitabine to palliative radiotherapy significantly improved pain relief and reduced analgesic use in patients with painful bone metastases from breast cancer. Despite manageable toxicities, the combination therapy showed superior clinical outcomes compared to radiotherapy alone, with greater pain control and more complete treatment responses.

Table 1: Characteristics Of The Studied Groups.

VARIABLES	GROUP A (n=30)	GROUP B (n=30)
1. Age	46.40±9.423	51.57±11.688
2. Molecular Classification:		
ER-/PR-/Her2neu-	3 (10%)	4 (13.3%)
ER-/PR-/Her2neu+	7 (23.3%)	7 (23.3%)
ER+/PR-/Her2neu-	7 (23.3%)	6 (20%)
ER+/PR+/Her2neu-	10 (33.3%)	7 (23.3%)
ER+/PR+/Her2neu+	3 (10%)	6 (20%)

Table 2: Median Pain Score

Pain score	Group A		Group B		P value
	Median	IQ range	Median	IQ range	
Base line	7	6.00 - 8.00	7	4.75 - 8.00	0.689
Week 2	6	5.00 - 7.00	5	4.00 - 7.00	0.019
Week 4	5	3.75 - 5.00	4	3.00 - 4.25	0.027
Week 8	4	2.00 - 5.00	2	0.75 - 3.00	0.001
Week 12	3	1.00 - 4.00	1	0.00 - 1.00	0.0001

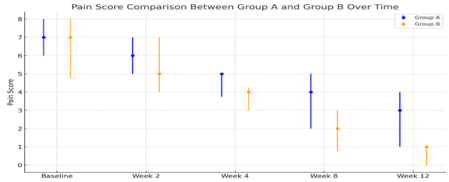

Table 3: Analgesic Score.

Analgesic score	Group A		Group B		P value
	Median	IQ range	Median	IQ range	
Base line	4	3.00 - 4.00	3	2.00 - 4.00	0.397
Week 2	2	2.00 -2.25	3	2.00 – 3.00	0.026
Week 4	2	1.00 - 2.00	1	1.00 - 2.00	0.005
Week 8	2	0.00 - 2.00	1	0.00 – 1.00	0.002
Week 12	1	0.00 - 1.00	0	0.00 - 1.00	0.004

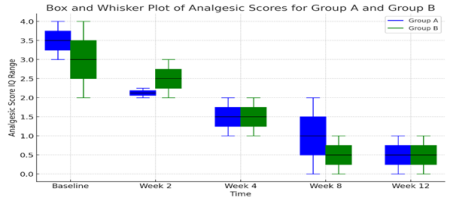

Table 4: Response to treatment.

RESPONSE	ARM A (n=30)	ARM B (n=30)	TOTAL	p-value
Week 2				
CR	4	9	13	0.007
PR	8	16	24	
SP	13	4	17	
PP	5	1	6	
Week 4				
CR	6	12	16	0.029
PR	8	13	21	
SP	12	4	16	
PP	4	1	5	
Week 8				
CR	6	14	50	0.014
PR	7	11	18	
SP	13	4	17	
PP	4	1	6	
Week 12				
CR	6	14	20	0.014
PR	7	11	18	
SP	13	4	17	
PP	4	1	5	

Table 5: Toxicities at Week 2.

VARIABLES	ARM A (n=30)	ARM B (n=30)	p-value
1. DIARRHOEA			
Grade 0	26	23	0.453
Grade 1	4	6	
Grade 2	0	1	
2. NAUSEA			
Grade 0	25	22	0.347
Grade 1	5	8	
Grade 2	0	0	
3. RADIATION DERMATITIS			
Grade 0	25	22	0.347

Grade 1	5	8	
Grade 2	0	0	

DISCUSSION

A large number of breast cancer patients develop metastases despite the advances in screening and treatment over the years. Due to the interactions between tumour cells and hematopoietic stem cells, bone is the most common site of distant metastasis and is the cause of severe morbidity in patients.

Radiotherapy is the standard and the most effective treatment modality for painful bone metastases due to its ability to improve bone integrity, reduction in risk of fractures, preservation of physical function and effective palliation of pain with minimal side effects. Several fractionation schedules have been used over the course of years, both single and multiple fractionation regimens with both having similar rates of local control but higher rates of re-irradiation with single fraction regimens. The most used schedule is a radiotherapy dose of 30 Gy over 10 fractions as it causes effective symptom control with reduced risk of pain flare and re-irradiation. Thus, this is the schedule that was used in this study.

Concurrent chemoradiation has become the mainstay in treatment of many primary and metastatic tumours as addition of a radio-sensitizing chemotherapy enhances the biological effect of radiotherapy thus improving symptom control. Capecitabine is one such radiosensitizer which also has use in treatment of metastatic breast cancer. Therefore, our study aimed to compare the efficacy and toxicity profile of radiotherapy alone and concurrent chemoradiation with Capecitabine in the treatment of painful bone metastases of carcinoma breast origin.

This study intended to compare the efficacy and toxicity profile of local radiotherapy with and without concurrent Capecitabine in the palliation of painful bone metastases in breast cancer patients. The radiotherapy regimen used was total dose of 30 Gy in 10# and the dose of Capecitabine in the concurrent chemoradiation arm was 825 mg/m^2 given 12th hourly for the duration of radiotherapy regimen.

Baseline characteristics in terms of age distribution and molecular status including hormone receptors and Her-2-neu receptors were comparable between the two groups.

A retrospective analysis by **Doval et. al.** assessed 1284 patients with breast cancer for evaluation of ER, PR and Her2neu receptor status. Hormone receptor positivity (ER and/or PR) was seen in 63.4% while Her2neu positivity was seen in 23.8%. Similarly, in our study Hormone receptor positivity (ER+/PR+/Both) was present in approximately 65% patients while Her2neu receptor positivity was seen in 38% patients.[9]

Kulkarni et. al. conducted a meta-analysis of 34 studies for the prevalence of triple negative breast cancer among Indian patients. They computed a pooled prevalence of 27% with the lowest prevalence being at 7% and 11.8% and the highest being at 47% and 50%. 11.6% of patients in our study had triple negative breast cancer which is within the range of the studies included in the meta-analysis.[10]

The patients were evaluated for development of acute toxicities during the course of treatment in both arms. There was no statistically significant difference in toxicity between the two arms. These results are consistent with a study conducted by **Ahmed et. al.** who studied the efficacy of concurrent Capecitabine with palliative radiotherapy for treatment of painful bone metastases of carcinoma breast origin. Concurrent Capecitabine was tolerated well in this study. Most toxicities reported were gastrointestinal and there were no Grade III-IV toxicities.[11]

In our study, among the 30 patients in each arm, 5 patients in the control arm and 8 in the study arm developed Grade 1 nausea during Week 2 of treatment. There were no incidents of nausea >Grade 1 in either arm.

The analysis of diarrhoea grades in the two arms revealed that 4 individuals in the control arm developed Grade 1 diarrhoea while in the study arm, 6 patients developed Grade 1 diarrhoea, and 1 patient developed Grade 2 diarrhoea during Week 2. There were no cases reported of diarrhoea >Grade 2.

At Week 2, 5 patients in the control group and 8 patients in the study group developed Grade 1 radiation dermatitis while at Week 4, 1 patient of each group developed Grade 1 radiation dermatitis. There were no incidents of radiation dermatitis of >Grade 1 in either arm.

Several studies have shown the efficacy of palliative radiotherapy alone in decreasing the mean pain score and analgesic use in patients with painful bone metastases and thus improving their quality of life. This is similar to the response of patients included in the control group in our study.

In our study, the median pain score of patients in the study arm decreased from 7 to 5 in 2 weeks and further to 1 at 3 months. This is similar to the findings of **Ahmed et. al.** which reported a decrease in median pain score from 7 to 2 at week 2 and to 1 at week 12 with a p-value of 0.001.

Ahmed et. al. documented a median analgesic score of 2 and 3 respectively in the control and study arms at the beginning of treatment. This decreased to 1 and 0 respectively at 12 weeks with a p-value of 0.002. This is similar to the results of our study where the median analgesic score in the control and study arm were 4 and 3 respectively at the beginning which decreased to 1 and 0 at week 12.

Our study found that in the control group the CR at week 12 was 20% and the OR was 43%. The same in the study group were 46% and 83% respectively with a p-value of 0.014 which indicates a statistically significant difference in the treatment response. These results are similar to those found by Ahmed et. al. where the CR and OR at 12 weeks were 19% and 42.8% respectively in the control group while those in the study group were 42.9% and 81% respectively. This was also consistent with the results reported by a Phase II study conducted by **Kundel et. al.** who found CR and OR at 12 weeks to be 48% and 86% respectively in patients who received concurrent Capecitabine along with palliative radiotherapy.

CONCLUSION

The addition of Capecitabine to palliative external beam radiotherapy for treatment of painful bone metastases of carcinoma breast origin is a feasible and tolerable option in terms of pain relief and thus may aid in betterment of quality of life in these patients.

However, further studies with larger sample sizes and longer follow up duration is required in order to study if this can be included in standard practice in the treatment of carcinoma breast patients with painful bone metastases.

REFERENCES

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [02 April 2024].
2. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006 Oct 15;12(20 Pt 2):6243s-6249s. doi: 10.1158/1078-0432.CCR-06-0931. PMID: 17062708.
3. Ahles TA, Ruckdeschel JC, Blanchard EB. Cancer-related pain--II. Assessment with visual analogue scales. J Psychosom Res. 1984;28(2):121-4. doi: 10.1016/0022-3999(84)90004-7. PMID: 6737324.
4. Anekar AA, Hendrix JM, Cascella M. WHO Analgesic Ladder. [Updated 2023 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554435/
5. Hoskin PJ. Scientific and clinical aspects of radiotherapy in the relief of bone pain. Cancer Surv. 1988;7(1):69-86. PMID: 3289744.
6. Howell DD, James JL, Hartsell WF, Suntharalingam M, Machtay M, Suh JH, Demas WF, Sandler HM, Kachnic LA, Berk LB. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. Cancer. 2013 Feb 15;119(4):888-96. doi: 10.1002/cncr.27616. Epub 2012 Nov 16. PMID: 23165743; PMCID: PMC5746185.
7. Sherry AD, Mayer IA, Ayala-Peacock DN, Abramson VG, Rexer BN, Chakravarthy AB. Combining Adjuvant Radiotherapy With Capecitabine in Chemotherapy-resistant Breast Cancer: Feasibility, Safety, and Toxicity. Clin Breast Cancer. 2020 Aug;20(4):344-352.e1. doi: 10.1016/j.clbc.2020.02.010. Epub 2020 Mar 6. PMID: 32234364.
8. Kundel Y, Nasser NJ, Purim O, Yerushalmi R, Fenig E, Pfeffer RM, Stemmer SM, Rizel S, Symon Z, Kaufman B, Sulkes A, Brenner B. Phase II study of concurrent capecitabine and external beam radiotherapy for pain control of bone metastases of breast cancer origin. PLoS One. 2013 Jul 10;8(7):e68327. doi: 10.1371/journal.pone.0068327. PMID: 23874586; PMCID: PMC3707893.
9. Doval DC, Sharma A, Sinha R, Kumar K, Dewan AK, Chaturvedi H, Batra U, Talwar V, Gupta SK, Singh S, Bhole V, Mehta A. Immunohistochemical Profile of Breast Cancer Patients at a Tertiary Care Hospital in New Delhi, India. Asian Pac J Cancer Prev. 2015;16(12):4959-64. doi: 10.7314/apjcp.2015.16.12.4959. PMID: 26163622.
10. Kulkarni A, Kelkar DA, Parikh N, Shashidhara LS, Koppiker CB, Kulkarni M. Meta-Analysis of Prevalence of Triple-Negative Breast Cancer and Its Clinical Features at Incidence in Indian Patients With Breast Cancer. JCO Glob Oncol. 2020 Jul;6:1052-1062. doi: 10.1200/GO.20.00054. PMID: 32639876; PMCID: PMC7392736.
11. Ahmed S, M Kamal S, Salah T, Fawzy Sedik M, Youssief AA. Concurrent capecitabine

with external beam radiotherapy versus radiotherapy alone in painful bone metastasis of breast cancer origin. J Bone Oncol. 2021 Oct 16;31:100395. doi: 10.1016/ j.jbo. 021. 100395. PMID: 34712554; PMCID: PMC8529095.
12. Hartsell WF, Desilvio M, Bruner DW, Scarantino C, Ivker R, Roach M 3rd, Suh J, Demas WF, Movsas B, Petersen IA, Konski AA. Can physicians accurately predict survival time in patients with metastatic cancer? Analysis of RTOG 97-14. J Palliat Med. 2008 Jun;11(5):723-8. doi: 10.1089/jpm.2007.0259. PMID: 18588404
13. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007 Apr 10;25(11):1423-36. doi: 10.1200/JCO.2006.09.5281. PMID: 17416863.
14. Korkolis DP, Boskos CS, Plataniotis GD, Gontikakis E, Karaitianos IJ, Avgerinos K, Katopodi A, Xinopoulos D, Dimitroulopoulos D, Beroukas K, Vassilopoulos PP. Pre-operative chemoradiotherapy with oral capecitabine in locally advanced, resectable rectal cancer. Anticancer Res. 2007 Jan-Feb;27(1B):541-5. PMID: 17348439.
15. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol. 1999 Aug;52(2):111-21. PMID: 10577696.