

## RADIATION THERAPY– AN EFFECTIVE TOOL FOR ANALGESIA IN METASTATIC BONE DISEASE IN BREAST CANCER

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### ABSTRACT

#### BACKGROUND

Radiation therapy plays an important role in the treatment of breast cancer patients with bone metastasis. Approximately 70% of patients are likely to achieve complete pain relief after palliative external beam radiotherapy (RT). The aim of current study is to determine the role of RT in palliation of symptomatic bone metastases from invasive breast cancer.

#### MATERIALS AND METHODS

Hundred and twelve breast cancer patients who received palliative RT for bone metastasis were enrolled prospectively. Baseline pain assessment using visual analogue score was done at the time of diagnosis and 3 months following completion of RT. WHO analgesic pain ladder was also used for adequate pain relief. Analgesic requirement was also assessed at the time of diagnosis and 3 months following RT.

#### RESULTS

Our results found thoracolumbar spine involvement (87%) to be the commonest site of metastasis. A reduction in severity of pain was noticed with 79.5% patients experiencing mild pain, 16% having moderate pain, and only 3.6% having severe pain after treatment with palliative RT. Approximately 36.6% patients experienced significant reduction in analgesic requirement.

#### CONCLUSION

This study provides an insight into the combined use of palliative RT and pharmacological treatment for pain relief in breast cancer patients with bone metastasis. We found palliative RT and adequate analgesic use as strong pillars in managing bone metastasis secondary to breast cancer.

#### KEYWORDS

Analgesics, Breast Neoplasms, Pain, Pain Management, Retrospective Studies.

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#### BACKGROUND

Bone is among the most common metastatic site in breast cancer patients and once distant metastases occur, breast cancer remains a treatable condition but is no longer considered curable.<sup>[1,2]</sup> Breast cancer patients with bone-only metastasis have a relatively good prognosis as compared to those with extensive disease involving multiple organs.<sup>[3,4]</sup> Various treatment modalities namely, chemotherapy, hormonal therapy, external beam radiotherapy and bisphosphonate therapy are available therapeutic options for these patients. Bone metastases represent the most frequent indication for palliative radiotherapy (RT) in these patients. The most important goals of palliative RT are pain relief, recalcification and stabilisation, reducing spinal cord compression and minimising the risk of paraplegia. Dose fractionation and the type of RT must be tailored to each

patient individually taking into account the patient's perspective, goals of treatment, and prognosis.<sup>[5]</sup> Till date, there is a continued debate over the appropriate fractionation scheme of palliative RT to treat these patients.<sup>[6]</sup> The median survival of patients after development of bone metastasis is approximately two years and 20% of these patients live longer than 5 years.<sup>[7]</sup> There is a definite lack of information regarding the best treatment approach for bone metastases leading to prolongation of survival in patients with breast cancer. Early intervention is of paramount importance to control pain and maintain the quality of life. We undertook this study to primarily shed light on the role of palliative RT in relieving pain related to skeletal metastases from breast cancer.

#### MATERIALS AND METHODS

The case report forms of all patients treated from 1999 – 2011 at Christian Medical College & Hospital, Ludhiana were reviewed.

#### Inclusion Criteria

1. Patients with histopathological diagnosis of carcinoma breast with metastatic disease limited to bone.
2. Patients who developed bone metastases as the first site of failure after completing the primary treatment for breast cancer in the form of neoadjuvant/adjvant

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chemotherapy, surgery with or without external beam radiotherapy to chest wall or intact breast.

**Exclusion Criteria**

All patients presenting with treatment failure in the form of visceral metastasis (such as liver, lung or brain).

Diagnosis of bone metastasis was confirmed with whole body bone scintigraphy. Twenty-seven percent patients presented with bone as the first site of failure. The case report form of each patient was scrutinised and demographic details (e.g. age at presentation, menopausal status), clinicopathological data (e.g. T-size, N-size, histology), and treatment details were recorded.

Assessment of the severity of pain was done using Visual analogue score<sup>9</sup> and it was documented as part of standard institutional protocol in patient record form once on presentation of bone metastasis and at 3 months following completion of palliative RT. After confirmation of bone metastatic disease by whole body bone scintigraphy, all patients received palliative RT to a dose of 30 Gy in 10 fractions using Cobalt-60 teletherapy unit (Theratron-80R). Radiotherapy planning was done on conventional simulator. All the patients were treated with two field technique i.e. two parallel opposed lateral field. All patients received appropriate pain medications as per the World Health Organization stratified three-step analgesic ladder: Step I using non-opioid analgesics (Acetaminophen or non-steroidal anti-inflammatory drugs- NSAIDS), Step II with “weak” opioids (Hydrocodone, codeine, or tramadol), and Step III with “strong” opioids (Morphine, hydromorphone, oxycodone, fentanyl, or methadone). Additional drugs (Adjuvants) were used as and when required. The patients were moved up or down the ladder based on the clinical assessment of pain. Changes in analgesic requirement pre- and 3 months post-RT were recorded. Approximately 70% patients received calcium supplementation.

The data was analysed using SPSS software version 21. For categorical data, we have calculated n (%). A paired t-test was run to determine whether there was a statistically significant mean difference between the pain score and analgesic use before and after the treatment.

**RESULTS**

The median age was 51.4 years (range, 25 – 75 years). Majority of patients had advanced T-stage disease (79.5%) and node-positive disease (75%) at presentation. Bone metastasis was present at diagnosis in 27% patients whereas 73% patients developed distant metastasis to bone after median follow-up of 54 months. Multiple sites of bone metastases were observed in 77.3% patients, while the remaining (22.7%) had solitary metastases. Among those with multiple bone metastases, spine (59.1%) was the most frequent site of metastases followed by long bones (40.9%). Largest number of patients (87%) had thoracolumbar spine involvement followed by pelvis (58.9%), femur (18.5%), humerus (13.2%), sternum (21.3%), scapula (21.5%) and ribs (10.7%) and tibia (1%). Solitary metastasis was predominantly seen in the axial skeleton (Table 1).

Patient Characteristics	No. of Patients (n=112)
<b>Age (Years)</b>	
≤ 30	5 (4.5%)
31-40	11 (9.8%)
41-50	36 (32.1%)
51-60	46 (41.1%)
≥61	14 (12.5%)
Mean (range)	45.7 years
<b>Menopausal Status</b>	
Premenopausal	37 (33%)
Postmenopausal	75 (67%)
<b>ECOG Performance Status</b>	
2	34 (30.3%)
3	49 (43.7%)
4	29 (25.9%)
<b>T-Size</b>	
T1	2 (1.79%)
T2	21 (18.8%)
T3	57 (50.9%)
T4	32 (28.6%)
<b>N-Stage</b>	
N0	28 (25%)
N1	62 (55.4%)
N2	17 (15.2%)
N3	5 (4.5%)
<b>Stage Grouping</b>	
II	25 (22.3%)
III	57 (50.9%)
IV	30 (26.8%)
<b>Histology</b>	
Ductal	111 (99%)
Lobular	1 (1%)
<b>Type of Lesion</b>	
Osteolytic	65 (58%)
Osteoblastic	25 (22.3%)
Both/Mixed	22 (19.6%)
<b>Receptor Status</b>	
ER	Positive in 64% patients
PR	Positive in 50% patients
HER2/neu	-

**Table 1. The Demographic and Oncological Characteristics**

Osteolytic bone metastasis was the most frequently observed radiological pattern accounting for 57.1%. Of 112 patients, 32.1% had mild pain at presentation, while 50.9% and 17% had moderate and severe pain, respectively. Following treatment, the severity of pain decreased with 79.5% of the patients experiencing no or mild pain, 16% having moderate pain, and 3.6% having severe pain (Table 2a). Eight (7.2%) patients presented with pathological fracture involving humerus and axial skeleton. During follow-up, 73% patients developed only bone metastases while 45% had visceral (lung, liver, brain) metastases.

VAS before Treatment	No. of Patients
1 – 3 (Mild pain)	36 (32.1%)
4 (Moderate pain)	57 (50.9%)
5 – 6 (Severe pain)	19 (17%)
<b>VAS after treatment</b>	
0 – 3	89 (79.5%)
4	18 (16%)
5 – 6	4 (3.6%)

**Table 2a. Pain Scores (VAS)**

	Mean $\pm$ S.D	t-score	p-value
VAS before treatment	1.85 $\pm$ 0.065	13.063	0.000*
VAS after treatment	1 $\pm$ 0.00		

**Table 2b. T-score and Pain scores**

VAS after treatment was very mild (1  $\pm$  0.00) as opposed to VAS before treatment (1.85  $\pm$  0.00); a statistically significant improvement of 0.848 (95% CI, 0.720 to 0.977) in pain score was noticed, t (111) = 13.063, p<0.001 (Table 2b).

As per WHO analgesic ladder, a statistically significant reduction in pain score was observed leading to decrease from 77.7% to 36.6% of patients requiring step 2 analgesia (Table 3a).

Before RT	No. of Patients
Step 1	20 (17.9%)
Step 2	87 (77.7%)
Step 3	5 (4.5%)
After RT	
Step 1	69 (61.6%)
Step 2	41 (36.6%)
Step 3	2 (1.8%)

**Table 3a. WHO Analgesic Ladder Use**

	Mean $\pm$ S.D	T-score	p-value
Before RT	1.87 $\pm$ 0.455	9.474	0.000*
After RT	1.40 $\pm$ 0.528		

**Table 3b. T-score and Analgesic Use**

As per WHO analgesic ladder use, there was a reduction in usage of analgesics after RT (1.40  $\pm$  0.528) as opposed to before RT (1.87  $\pm$  0.455); a statistically significant improvement of 0.464 (95% CI, 0.367 to 0.561) in analgesic use was noticed, t (111) = 9.474, p < 0.001 (Table 3b).

## DISCUSSION

Breast cancer is now recognised as the most common cancer in Indian women and has overtaken cervical cancer.<sup>[8]</sup> Approximately 5% of breast cancer patients have metastatic disease on diagnosis. The bones are the most frequent site of metastatic disease, both at initial diagnosis of disease and as a site of first recurrence.<sup>[9,10]</sup> We found thoracolumbar spine and pelvis to be the commonest site of bone metastasis similar to as reported in literature.<sup>[11]</sup>

Bone metastasis is a multistep process involving disturbance between bone formation and resorption as well as the inability of new bone formation in compensating the loss.<sup>[12]</sup> Imaging modalities such as plain radiography, bone scintigraphy, computed tomography, or magnetic resonance imaging are used for diagnostic workup, allowing a total skeletal assessment for evaluation of the extent of metastatic spread.<sup>[13]</sup> Majority of our patients were subjected to bone scintigraphy on diagnosis for staging purposes.

Once metastasis occurs, breast cancer is considered a treatable condition but not curable with the exception of micrometastasis.<sup>[1,14]</sup> Majority of patients with bone metastasis requires an urgent treatment, due to pain, pathological fractures, spinal cord compression, hypercalcaemia and neurologic deficits.<sup>[15]</sup> Therefore, the aim of palliative RT is to provide complete pain relief, recalcification and stabilisation of the bone, reduction in the risk of complications (e.g. bone fractures, spinal cord compression) and reduce analgesic requirements.<sup>[13]</sup> Majority

of our patients had moderate intensity pain (50.9%) with a pain score of 4 while severe pain was encountered by 17% patients. Pathological fractures commonly occur in patients with bone metastasis from breast cancer and this is mainly due to the lytic nature of bone lesions.<sup>[16]</sup> In our series, 8 (7.14%) patients presented with pathological fracture during follow-up.

Patients with the diagnosis of breast cancer with metastatic disease to bone survive longer as compared to those with visceral metastasis. In addition, painful bone metastasis leads to considerable morbidity and reduced quality of life.<sup>[17]</sup> The aim of treatment for these patients is to provide adequate pain control and good quality of life.<sup>[18]</sup> Palliative RT can relieve pain in 50 - 80% patients achieving complete pain relief in one-third of patients. Unfortunately, the role of palliative RT for alleviation of pain in bone metastatic disease is underutilised. We found palliative RT and adequate analgesic use resulted in improvement with reduction in pain scores in 79.5% of the patients experiencing no or mild pain, 16% having moderate pain, and only 3.6% having severe pain. The rates of pain relief vary from 50% to 85% with approximately one-third patients reporting complete response, worldwide. Complete to partial pain relief is said to occur within 4 weeks after RT with a mean duration of remission in 19 weeks.<sup>[15]</sup> Keeping this in mind, we re-assessed pain scores after 3 months of RT.

There is still a controversy regarding the optimal fractionation schedule of RT in bone metastasis. Multiple randomised controlled data have demonstrated similar pain relief for different regimens, including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions and a single 8-Gy fraction.<sup>[19]</sup> Until further data are available, it is suggested that short course regimens (i.e. 5 x 4 Gy or 1 x 8 Gy) can be used for patients with short life expectancy, while higher dose per fraction schedules (i.e. 10 x 3 Gy or greater) should be reserved for patients with better prognosis.<sup>[13]</sup> Rades et al<sup>[20]</sup> compared the local control of different radiotherapy schedules in patients with metastatic spinal cord compression. A total of 265 patients were randomised to short course (1 x 8 Gy or 5 x 4 Gy) versus long course (10 x 3 Gy or 15 x 2.5 Gy) irradiation pattern. Superior 1-year local control and similar survival was reported with long course RT (61% versus 81%; p = 0.005) as compared to short course. The authors concluded that patients with a relatively favourable expected survival should receive long-course RT. Despite various fractionation schedules being used in clinical practice for bone metastasis, the optimal palliative RT fractionation schedule is still controversial. All the patients in our series received palliative RT dose of 30 Gy in 10 fractions over 2 weeks.

We found that the requirement of opioid analgesia dropped from 4.5% to 1.8% following palliative RT. In addition, there are reports suggesting that the use of immediate-release morphine before initiating RT allows a higher number of patients to complete the scheduled course of RT.<sup>[21]</sup>

The present study had limitations of small sample size and bisphosphonates were not given routinely in view of deranged renal parameters, financial constraints, and poor oral hygiene.

Although the role of palliative RT for bone metastases is well-established in literature, our study provides additional

information with regard to 30 Gy in 10 fractions being quite effective in achieving symptom control in patients with metastatic bone disease from breast cancer.

#### CONCLUSION

Our results indicate that spine and pelvis are the most frequently involved metastatic sites in carcinoma breast. Treating the bone pain caused by cancer is a challenging condition. This study highlights the role of palliative external beam radiotherapy in a dose of 30 Gy in 10 fractions and analgesics in alleviating bone pain associated with bone metastasis in patients with breast cancer with minimal side effects.

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