Original Research Article

Role of palliative radiotherapy in painful bone metastases: A prospective study

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Abstract

Background: Metastatic bone diseases is a usual cause of pain in cancer patients. Bone metastases are associated with skeletal-related events(SREs) including pathological fractures, spinal cord compression, bone pain and hypercalcemia which leads to impaired mobility and reduced quality of life. Radiation therapy plays an important role in the treatment of painful bone metastases. **Objectives:** To compare the pain relieving efficacy and improvement in quality of life by using 8 Gy in single fraction in one day versus 20 Gy in five fractions in five days in patients with painful bone metastases. **Material and Methods:** A prospective study conducted on sixty patients with painful bone metastases who were randomly assigned. By using visual analogue score, baseline pain assessment was done at day 1, day 7, day 15, 1 month and 3 months after treatment. WHO analgesic pain ladder was also used for adequate pain relief. **Results:** Majority of patients were included in age group of 51-60 yrs(46.7%), followed by 61-70 yrs of age group (35%). Majority of the patients were of carcinoma breast(48%), followed by carcinoma prostate(38.3%), followed by multiple myeloma(6.6%). Thoracolumbar spine involvement(68.3%) to be the commonest site of metastases. A reduction in severity of pain was noticed with 28% patients experiencing no pain, 52% having mild pain and only 12% having severe pain after 3 months of treatment in 8Gy in one fraction in day group while in comparison, in 20Gy in 5 fractions in 5 days group, 60% patients experienced no pain and 40% patients had mild pain after 3 months of treatment. The requirement of analgesics dropped in both the arms in comparison to pretreatment analgesics requirement, but after 3 months of follow up it was observed that Arm B required less analgesics as compare to Arm A. **Conclusion:** Both 8 Gy in single fraction and multi-fractionated regimen are effective to treatment painful metastatic bone disease but 8 Gy in single fraction in one day has greater convenience, lower cost and less duration of hospital stay with same efficacy for palliation of painful bone metastases.

Key Words: Bone metastases, painful, palliative radiotherapy, fractions, multiple.

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INTRODUCTION

Bone metastases is a commonly encountered problem in oncology practice. It is a devastating condition that can have a negative impact on the lives of patients with advanced cancer in many ways. Patients may experience limitations in the activities of daily life and hence reduces the quality of life. Approximately half of all cancer patients develop metastases in their life time and among them, more than 50% of patients develop skeletal metastases.[1] Patients who develop bone metastases, represent a major cause of morbidity in cancer patients and causes more workload on patients as well as on physician also.[2,3] Breast, prostate, lung, urinary bladder, kidney, uterus, thyroid malignancies, hematologic malignancies and melanoma malignancies are the causes of bone metastases. Among them, lung, breast and prostate are the common causes.[4] Skeletal metastases can be multiple as well as solitary metastases which are seen only in less than 10% of cases.[5] The axial skeleton is the most common site of bone metastases and frequently

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involve spine, pelvis and ribs. The lumbar spine is the most frequent site of bone metastases.[6,7,8,9] In the appendicular skeleton, the proximal femora is the most common site of metastatic bone disease followed by humerus. Bone metastases in prostate cancer are usually osteoblastic and sclerotic in nature. In metastatic breast cancer, osteolytic lesions are found in 80% of patients. In lung carcinomas, osteolytic lesions are more frequent than an osteoblastic one, although a mixed lesions are common.[15] In hepatocellular carcinoma, bone metastases are osteolytic, destructive and expansible lesions with large, bulky, soft-tissue masses.[22] The skeletal related events(SRE) includes spinal cord or nerve root compression, severe bone pain, pathologic fractures, and hypercalcemia of malignancy which significantly compromise quality of life and may negatively affect survival.[30] Various management options for bone metastases includes radiotherapy, chemotherapy, hormone therapy, surgery, radionuclide and supportive therapy either alone or in combination.[46] In most cases the treatment intent is palliative. Treatment goals are pain relief, preservation of mobility, function and quality of life and if possible, prolongation of survival.[5] Radiotherapy is the most effective treatment used for painful bone metastases.[56] The role of palliative radiotherapy is well established. Radiotherapy is a modality frequently used for bone metastases, usually as an outpatient treatment for pain palliation and prevention of impending fracture. Numerous trials have demonstrated the efficacy of PRT for the relief of bone pain.[58-61] In our study, we have addressed the clinical effects of various fractionation schedules in palliative RT to bone metastases in a tertiary care hospital and have been initiative to evaluate the efficacy of long arm versus short arm of radiotherapy in terms of clinical outcome and improvement in quality of life.

MATERIALS AND METHODS

This prospective study was conducted from March 2016 to October 2017 in the Department of Radiotherapy, Guru Gobind Singh Medical College and Hospital, Faridkot. This study compared the pain relieving efficacy and improvement in quality of life index by using two frequently administered radiation treatment plans: 8 Gy administered in a single fraction in one day versus 20 Gy in five fractions in five days with painful bone metastases.

INCLUSION CRITERIA:

1) Histologically proven primary malignancy
2) Age less than 70 yrs.
3) Radiological evidence of bone metastases.
4) ECOG performance status equal or less than 3.
5) Signed written consent as per institutional regulation.

EXCLUSION CRITERIA:

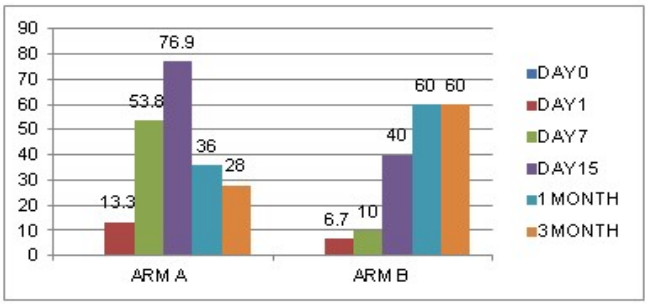
1) Pathological or impending fracture of the treatment site.
2) Painful area that had received prior radiation therapy.
3) Patients not fulfilling the inclusion criteria are excluded from the study.

The total number of patients were 60, which were clinically and radiologically proven bone metastases as well, by using either modalities like Radiographs, CT scan, MRI, Bone Scan or PET Scan. Patients were randomized as per presentation consecutively. They were alternatively selected in each arm, labelled as following: Arm A: 8 Gy in a single fraction/ one day and Arm B: 20 Gy in five fractions/ five days. All patients were planned on Simulator-CT (Simulix – Nucleotron) according to involved sites and after written consent, treated on cobalt 60 machine. Both arms were compared in terms of pain relief, performance improvement, analgesic requirement and duration of overall response at day1, day7, day15, 1month and 3 months after treatment. Pain relief was evaluated by VAS numeric pain scale as 0= no pain; 1-3 = mild, 4-6 = moderate and 7-10 = severe pain. The quality of life assessed by ECOG performance status. In ECOG grading system, the improvement in performance status was defined as a decrease in ECOG functional outcome score by at least one grade with respect to pre-treatment value. The response categories were: 1) Complete response: a pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily. 2) Partial response: pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain. 3) Pain progression: increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in comparison with baseline with the pain score stable or 1 point above baseline. 4) Intermediate response: any response that is not captured by the complete response, partial response, or pain progression definitions. All patients received appropriate pain medications as per the World Health Organization stratified three-step analgesic ladder. 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. Patients evaluated just before starting the treatment and followed up immediately after completion of RT, after 7 days, after 15 days, at 1 month and then 3 months of completion of RT. Statistical analysis was conducted using the statistical package for Social Sciences(SPSS) version 20.

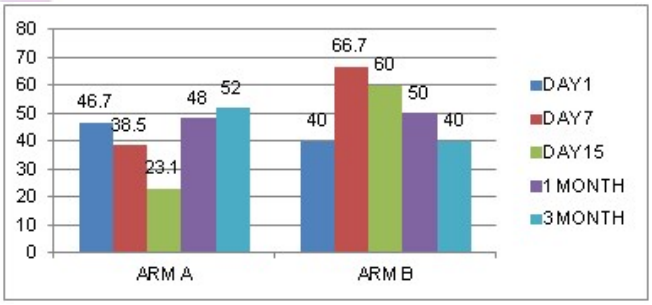
RESULTS

Median age in Arm A and Arm B was 58 yrs and 55 yrs respectively. Majority of patients were of carcinoma breast (45%) followed by carcinoma prostate (38%). Majority of patients were diagnosed by bone scan (43.3%) followed by radiographs (33.3%) and followed by PET CT Scan (15%). Majority of metastatic bone lesions were found in spine(68.3%) followed by pelvis(25%) followed by long bones(5%).

	8Gy/single fraction/one day NO(%)	20Gy/5 fractions/ 5days NO(%)
Median Age	58yrs	55yrs
Sex		
Male	56.7	43.3
female	43.3	56.7
Primary diagnosis		
Breast	36.7	53.3
Prostate	50	26.7
Multiple myeloma	3.3	10
Gastrointestinal	0	3.3
Head and Neck	6.7	0
Lung	0	3.3
Unknown primary	3.3	3.3
Mode of diagnosis		
Radiographs	20	46.7
CT Scans	0	3.3
MRI	13.3	0
Bone Scan	53.3	33.3
PET CT Scan	13.3	16.7
Site distribution	66.7	
Spine	26.7	70
Pelvis		23.3
Long Bones	3.3	6.7
Scapula		0
	3.3	



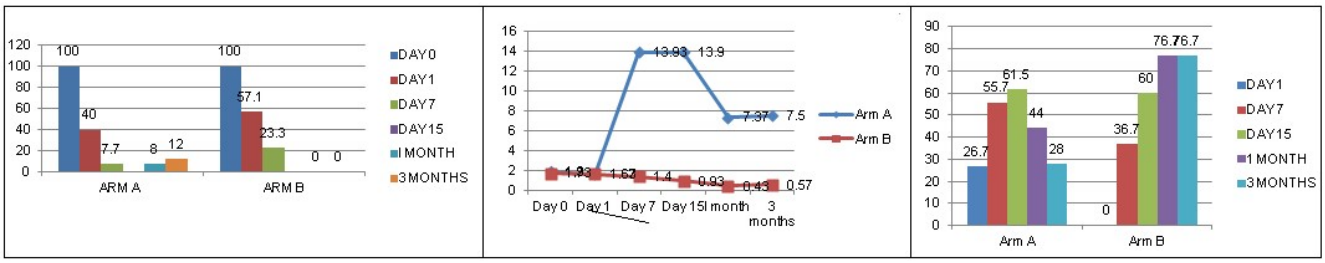
Graph 1



Graph 2

After 3 months of follow up, in Arm A, out of 25 patients, 7 patients (28%) had no pain and in Arm B, out of 30 patients, 18 patients (60%) had no pain[Graph 1]. In Arm A, out of 25 patients, mild pain was seen in 13 patients (52%) and in Arm B, out of 30 patients, mild pain was seen in 12 patients (40%) after 3 months of follow up[Graph 2].

Moderate pain was seen only in 3 patients (12%) in Arm A. Upto day 15 of follow up, pain relief was better in Arm A as compared to Arm B, but after 3 months of follow up, we observed that Arm B was better[Graph 3].



Graph 3 Graph 4 Graph 5

The requirement of analgesics dropped in both the arms in comparison to pretreatment analgesics requirement, but after 3 months of follow up it was observed that Arm B required less analgesics as compare to Arm A[Graph 4]. After follow up of 3 months, complete response in terms of pain relief was seen in 36% of patients in Arm A and 63.3% of patients in Arm B. After 3 months of follow up, Partial response was seen in 0% of patients in Arm A and 26.7% of patients in Arm B. After 3 months of follow up, pain progression was seen in 64% of patients in Arm A and 10% of patients in Arm B. In our study, at day 1of follow up, improvement in performance status in comparison to pretreatment baseline performance status in Arm A and Arm B were 26.7% and 0% respectively (p=0.002) which was statistically significant. After 1 month of follow up, improvement in performance status by comparing baseline performance status in Arm A and Arm B were 44% and 76.7% respectively (p=0.002) which was statistically significant. After 3 months of follow up, improvement in performance status by comparing baseline performance status in Arm A and Arm B were 28% and 76.7% respectively (p=0.002). Thus, we found in our study that there were improvement in performance status of the patients in both arms but Arm B was better than Arm A in terms of performance status[Graph 5].

DISCUSSION

Metastatic bone disease is the most common malignant bony lesion seen in adults. About 50% of all cancer patients develop metastases in their life time and approximately more than half of patients develop skeletal metastases.[1] We enrolled 60 patients of proven bone metastases. Our study compared the single fraction of 8Gy versus multiple fraction i.e 20Gy in five fractions radiotherapy for palliation of painful bone metastases. The baseline characteristics of patients in both arms were comparable. We observed that age was negatively associated with the use of Palliative RT for bone metastases, which is consistent with the findings of similar studies.[94] Median age in Arm A and Arm B was 58 yrs and 55 yrs respectively. In our study, in Arm A, majority of the patients were of carcinoma prostate(50%), followed by carcinoma breast(36.7%). In Arm B, majority of the patients were of carcinoma breast(53.3%), followed by carcinoma prostate(26.7%). Similar results were seen in a study conducted by Hartsell WF *et al*[4] in which Lung, breast and prostate malignancies were the common causes of bone metastases. Spine (45%) and pelvis (38.3%) were the most common sites of bone metastases followed by long bones (5%). Similar results were seen in study by Kakhki VRD *et al*.[9] Modalities like radiographs, CT Scan, MRI, Bone scan and PET Scan were used for the diagnosis of bone metastases and majority of our patients were diagnosed as bone metastases by bone scintigraphy i.e. bone scan(43.3%) followed by radiographs (33.3%) and followed by PET CT Scan (15%). Similar modalities were used in study conducted by Ripamonti C *et al* for diagnostic workup. In our study, we found that after palliative RT and adequate analgesic use after 3 months of follow up, the results between Arm A and Arm B in pain relief that at day 1, day 7 and day 15 was slightly better in the Arm A as compared to Arm B. However, at the end of follow up, in Arm A, no pain in 28% of patients (n=7), mild pain in 52% of patients (n=13), moderate pain in 12% of patients (n=3) and in Arm B, no pain in 60% of patients (n=18) and mild pain in 40% of patients (n=12) which showed that at the end of follow up pain reduction occurred in both arms but Arm B was better. But there is still a controversy regarding the optimal fractionation schedule of RT in bone metastases. Ratanatharathorn *et al* reviewed many of these studies and concluded that higher-dose, longer-course regimens provided better pain outcomes than low-dose regimens. Sze *et al* found that both regimens resulted in equivalent levels of pain relief but in different rates of re-treatment and pathologic fractures between arms. The study conducted by Howell DD[10] *et al* showed 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. The requirement of analgesics dropped in both the arms in comparison to pretreatment analgesics requirement, but after 3 months of follow up it was observed that Arm B required less analgesics as compare to Arm A. These results were consistent with the study conducted by Negi

P et al where the requirement of opioid analgesia dropped from 4.5% to 1.8% following palliative RT. After follow up of 3 months in our study, complete response in terms of pain relief was seen in 36% of patients in Arm A and 63.3% of patients in Arm B. After 3 months of follow up, Partial response was seen in 0% of patients in Arm A and 26.7% of patients in Arm B. After 3 months of follow up, pain progression was seen in 64% of patients in Arm A and 10% of patients in Arm B. Similar results were showed by Majumder D in which they found that 8 Gy in single fraction vs 30 Gy in 10 fraction for palliative vertebral metastases were equally effective. In contrast, Wu *et al* performed a meta-analysis of studies comparing single versus multiple fractions of radiotherapy for palliation of painful bone metastases. They found a complete response rate of 32% – 33%, an overall response rate of 72% – 73%, and no difference in response rates comparing a single treatment with multiple treatments. In our study, at day 1of follow up, improvement in performance status in comparison to pretreatment baseline performance status in Arm A and Arm B were 26.7% and 0% respectively (p=0.002) which was statistically significant. After 1 month of follow up, improvement in performance status by comparing baseline performance status in Arm A and Arm B were 44% and 76.7% respectively (p=0.002) which was statistically significant. After 3 months of follow up, improvement in performance status by comparing baseline performance status in Arm A and Arm B were 28% and 76.7% respectively (p=0.002). Thus, we found in our study that there were improvement in performance status of the patients in both arms but Arm B was better than Arm A in terms of performance status. Similarly study conducted by Jilla S *et al* in which they compared three arms: 8 Gy in single fraction, 20 Gy in 5 fractions and 30 Gy in 10 fractions. They concluded that there was improvement in performance status of patients in all arms but no statistically significant difference between three arms with respect to performance improvement.

CONCLUSION

8 Gy in single fraction in one day is as efficacious as multi-fractionated regimen but 8 Gy in single fraction in one day has greater convenience, lower cost and less duration of hospital stay with same efficacy for palliation of painful bone metastases. Short course regimens can be used for patients with short life expectancy, while higher dose per fraction schedules (i.e. 20 Gy in 5 fractions in 5 days) should be reserved for patients with longer life expectancy.

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