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Original Article

Symptom Palliation in Patients with Bone Metastases Treated with Radiotherapy

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Abstract

Context: Skeleton is the most common organ affected by metastases. Bone pain is the most common symptom of metastatic bone disease. The treatment of bone metastasis is primarily palliative requiring multidisciplinary therapies; radiotherapy (RT), however, remains the cornerstone of the treatment. **Aims:** The aim of this study is to measure the effectiveness of RT in terms of symptomatic relief in pain and insomnia, improvement in stability/movement, and decrease in the requirement of analgesics by patients using the Hundred Paisa Pain Scale. **Subjects and Methods:** The RT records of 226 patients with bone metastasis treated at the department of Radiotherapy, SMS Medical College, Jaipur; from July 2015 to December 2016 over cobalt-60 teletherapy unit were analyzed. The RT dose fractionation ranged from 30 Gy in 10 daily fractions, 20 Gy in 5 daily fractions, 12.5 Gy in 2 weekly fractions, and 8 Gy in single fraction. **Results:** The median age of the cohort was 54 (range, 29–84) years. The most common site of primary tumor was lung (30.1%), followed by breast (12.4%) and prostate (11.9%). The most common bone involved was vertebrae (71.2%), followed by pelvis (14.6%); among vertebrae, thoracic vertebrae were most commonly involved (63.9%), followed by lumbar vertebrae (57.8%). The maximum relief in pain was seen with 6.25 Gy/fraction schedule, whereas the maximum improvement in stability/movement was noted with 3 Gy/fraction schedule. The 8 Gy single-fraction schedule was associated with maximum relief in insomnia and decrease in analgesic requirement. **Conclusion:** The current institutional protocol of weekly hypofractionated palliative RT of 6.25 Gy per fraction up to a maximum of four fractions given on Saturday has shown results comparable with other schedules with well tolerance and achievement of acceptable symptom palliation. This weekly schedule is practically convenient to both the patients who mostly came from far-flung areas and the institute as it spares the already overburdened machine to carry on conventional RT from Monday to Friday.

Keywords: *Bone metastases, palliation, radiotherapy*

Introduction

The skeleton is the most common organ to be affected by metastatic cancer.[1] The most common sites of primary tumors leading to bone metastasis are breast, prostate, thyroid, lung, and kidney, with breast carcinoma causing the greatest morbidity. Metastasis to bones results in an overall compromise in patients' quality of life (QoL) by causing pain, increased risk of pathologic fracture, spinal cord compression, neurological deficit, and/or reduced mobility. The pathophysiology of bone metastasis is a complex phenomenon not fully understood.[2] The presence of metastatic cancer cells in the bone hampers the normal process of bone turnover, activating osteoclasts. This forms the basis of differential radiological appearance (lytic, sclerotic, or mixed).[3] Bone pain is the most common complication of metastatic bone disease, and bone metastasis is the most common cause of cancer-related pain.[4] Pain is usually disproportionate to the size or degree of bone involvement and is caused by entrapment of nerves, release of chemical mediators, structural damage caused by fractures, and reactive muscle spasm.[5] Pathologic fractures are a relatively late complication, occurring after an average of 3–6 months.[6] Contrast-enhanced magnetic resonance imaging (MRI) is the investigation of choice to detect spinal metastasis.

The treatment of bone metastasis is primarily palliative, with an intention to relieve pain, prevent fractures, and maintain mobility, requiring multidisciplinary therapies such as local treatment in the form of radiotherapy (RT) and surgery;

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systemic treatment in the form of chemotherapy, endocrine therapy, and radioisotopes; and supportive care in the form of analgesic and anti-inflammatory drugs and bisphosphonates.[7,8] The treatment should be individualized according to patients' clinical condition and life expectancy. The use of analgesics according to the WHO ladder is recommended. Opioids remain the cornerstone for cancer pain; some adjuvant analgesics that may be used are antidepressants, corticosteroids, anticonvulsants, and muscle relaxants.[9-11] Bisphosphonates are safe and effective in treatment for the prevention of bone loss, which act by decreasing the activity of mature osteoclasts.[12,13] Oral bisphosphonates do not appear to be as effective as intravenous administration.[14,15] Their potential adverse events include skeletal pain, fatigue, nausea, vomiting, headache, renal dysfunction, and bisphosphonate-associated osteonecrosis of the jaw. Denosumab is a human monoclonal antibody binding to human receptor activator of nuclear factor kappa-B ligand, which reduces risk of developing skeletal-related events in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumors.[16] Chemotherapy and endocrine therapy are given as per the guidelines to treat the primary tumor; however, they are difficult to measure in terms of pain relief. Radioisotopes have less toxicity, easy administration, and effectiveness in subclinical sites of metastases but have their peculiar problems pertaining to storage, dispensing, and administration.

In case of spinal cord compression, patients should be treated with corticosteroids, and definitive treatment either in the form of RT or surgical decompression should be initiated within 24 h. Surgery is preferred when fracture occurs; however, careful selection of patients is required. RT is the cornerstone of treatment. Single-fraction RT is the preferred option unless there is a contraindication; it reduces distress and inconvenience associated with repeated session.[17] The prognosis of metastatic bone disease depends on various factors, such as performance status of patients, site of primary disease, time interval between diagnosis of primary and bony metastasis, extent of the bone disease, presence of extraosseous disease, treatment taken, and response to treatment.[1,6]

Subjects and Methods

The present study is a retrospective study, wherein the data from the RT records were extracted for patients who received RT for bone metastasis from July 2015 to December 2016 in the department of Radiotherapy, SMS Medical College, Jaipur; over cobalt-60 teletherapy unit with two-dimensional radiation planning. The inclusion criteria included both histopathological proof of malignancy (either a fine-needle aspiration cytology or biopsy from the primary site of the tumor) and radiological proof of bone metastasis (either contrast-enhanced MRI, computed tomography, or bone scan). Patients with primary bone tumors and multiple myeloma, who did not complete the prescribed RT schedule within prescribed time frame, and who did not consent were excluded. A total of 226 patients were found eligible. The data were analyzed for various sociodemographic and clinic-pathological factors. The primary end point of the study was to measure the effectiveness of RT in terms of symptomatic relief in pain and insomnia, improvement in stability/movement, and decrease in the requirement of analgesics by patients. The percentage of symptom relief was measured using the Hundred Paisa Pain Scale (HPPS) at 1 month post-RT. The HPPS consists of an 11-point horizontal scale on a sequence of paisa in multiples of ten, with 0 paisa indicating no pain at all and 100 paisa indicating worst pain.[18] HPPS was used for assessing all the end points including pain relief, stability, insomnia relief, since the patients we got were usually of lower socioeconomic status, and they were better able to understand the HPPS. Howsoever illiterate a person is, he or she somehow manages to count the paisa easily and adequately. Hence, the use of HPPS is simpler compared to its counterparts, even in illiterate persons, which contributed most our patient bulk. Decrease in requirement of analgesics is indirectly related to relief in pain; hence, the use of HPPS to quantify decrease in analgesics is justified. For statistical analysis, the results were reported in percentage and proportion.

For RT planning, the area of interest was marked with appropriate margin as per the guidelines depending on site, and marker X-rays were done before delivering radiation to confirm the adequacy of the fields marked. The fractionation schedules varied from patient to patient based on the clinical judgment of treating radiation oncologists and performance status and life expectancy of patients, as per the institutional protocol. However, in all cases, the intent was palliative and hypofractionated schedules were preferred over conventional one. The dose per fraction and number of fractions ranged from 30 Gy in 10 fractions with 3 Gy per fraction for 5 fractions per week, 20 Gy in 5 fractions with 4 Gy per fraction for 5 fractions per week, 12.5 Gy in 2 fractions with 6.25 Gy per fraction for one fraction per week (the number of fractions was increased to a maximum of four in some patients depending on severity of pain, site of lesion, and life expectancy), and 8 Gy in single fraction. The biologically equivalent dose (BED) is 25.78 Gy_2 and 40 Gy_2 for 6.25 Gy and 8 Gy single fractions, for α/β ratio 2, i.e., spinal cord, respectively.

Besides RT, patients also received primary -tumor-directed chemotherapy/hormonal therapy, supportive treatment in the form of analgesics, and bisphosphonates as per the requirement. The bisphosphonate of choice was zoledronic acid, given as 4 mg intravenous infusion over 10 min, provided that blood urea and serum creatinine were within normal limits.

Results

The baseline patient, tumor, and treatment characteristics of the entire cohort are shown in Table 1. The median age was 54 (range, 29–84) years. Males outweighed females by a ratio of 2:1. The most common site of primary tumor giving rise to bone metastasis was lung (30.1%), followed by breast (12.4%) and prostate (11.9%); however, primary tumor remained unknown in 19.9% of the patients. More than one bone was involved in three-forth of the cases. The most common bone involved was vertebrae (71.2%), followed by pelvis (14.6%); among vertebrae, thoracic vertebrae were most commonly involved (63.9%, i.e., 103 patients), either alone or in conjunction with cervical/lumbosacral vertebrae or with pelvis. Similarly, lumbar vertebrae were involved in 57.8% (93/226) of the cases, whereas cervical vertebrae in 11.2% (18/226) of the cases. The most common RT schedule was 25 Gy in 4 weekly fractions (70.8%), followed by 30 Gy in 10 fractions delivered over 2 weeks (11.9%) and 20 Gy in 5 daily fractions (11.5%); a single shot of 8 Gy was delivered in 5.8% of the cases only. The response to treatment is shown in Table 2. The maximum relief in pain was seen with 6.25 Gy/fraction schedule, 76.2% of patients receiving this regimen reported more than 50% pain relief; whereas the maximum improvement in stability/movement was noted with 3 Gy/fraction schedule, 80% of patients receiving this regimen reported >50% improvement. The 8 Gy single-fraction schedule was associated with maximum relief in insomnia (69.2% of the patients had >50% relief) and decrease in analgesic requirement (53.8% of the patients had >50% decrease in requirement). The 4 Gy/fraction schedule was associated with least outcome in all symptom palliation.

Table 1: Baseline characteristics of the entire cohort

Parameters	*n* (%)
Total number of patients	226 (100)
Gender	
Male	151 (66.8)
Female	75 (33.2)
Age (years)	
<40	34 (15)
41-50	48 (21.2)
51-60	61 (27)
61-70	53 (23.5)
>70	30 (13.3)
Site of primary tumor	
Lung	68 (30.1)
Breast	28 (12.4)
Prostate	27 (11.9)
Gastro-intestinal tract	17 (7.5)
Kidney	13 (5.8)
Female genital tract	11 (4.9)
Head and neck	10 (4.4)
Urinary bladder	7 (3.1)
Unknown	45 (19.9)
Number of bones involved	
Single	52 (23)
Multiple	174 (77)
Site of bone metastasis	
Spine	161 (71.2)
Pelvis	33 (14.6)
Spine and pelvis	7 (3.1)
Femur	6 (2.7)
Humerus	6 (2.7)
Skull	4 (1.7)
Scapula	3 (1.3)
Below knee	2 (0.9)
Below elbow	2 (0.9)
Sternum	2 (0.9)
Radiotherapy details (Gy/fraction)	
6.25	160 (70.8)
3	27 (11.9)
4	26 (11.5)
8	13 (5.8)

Discussion

Cancer pain is often experienced in several different ways. It may be somatic, neuropathic, or psychogenic; acute or chronic; tumor induced or treatment (surgery/chemotherapy/RT) induced; and due to infection, obstruction, occlusion, or destruction of tissue or organ. In a meta-analysis based on 52 studies, the pooled prevalence of pain was >50% in all cancer types, and more than one-third graded their pain as moderate or severe.[19] Spinal metastases are the most common tumors of the spine, compromising approximately 90% of the spinal masses.[20] Within the spinal column, metastasis is more commonly found in the thoracic region, followed by the lumbar region; the cervical region is the least likely site of metastasis. This is consistent with the findings of the present study.

Palliative RT is required in 30%–50% of all cancer patients.[21] In case of bone metastases, the primary aim of palliative RT is to relieve pain and prevent collapse or impending fracture. Good clinical judgment and expertise is required in prescribing correct fractionation schedule. Hypofractionated palliative RT is a feasible option. Many randomized trials in the treatment of bone metastases have reported that RT reduces bone pain and decreases analgesic consumption. A number of tools have been cited in the literature to measure palliation of pain. Li *et al*. have used Brief Pain Inventory and reported a complete, partial, and overall response rate of 21%, 45%, and 66%, respectively, at 2 months following palliative RT for painful bone metastases in 101 patients.[22] Kapoor *et al*. have compared the pain-relieving efficacy of 8 Gy administered in a single fraction (62%) versus 30 Gy administered in 10 fractions (38%) as per the Visual Analog Scale in 250 patients of bone metastasis and have reported an overall response, stable pain, progressive pain, and lost to

Table 2: Symptom relief at 1 month post-radiotherapy

Symptoms	3 Gy/fraction, *n* (%)	4 Gy/fraction, *n* (%)	6.25 Gy/fraction, *n* (%)	8 Gy/fraction, *n* (%)
Total number of patients	27	26	160	13
Pain relief (%)				
<50	8 (29.6)	14 (53.8)	38 (23.8)	4 (30.8)
≥50	19 (70.4)	12 (46.2)	122 (76.2)	9 (69.2)
Relief in insomnia (%)				
<50	11 (40.7)	11 (42.3)	64 (40)	4 (30.8)
≥50	16 (59.3)	15 (57.7)	96 (60)	9 (69.2)
Improvement in stability/movement (%)				
<50	1/5 (20)	3/6 (50)	11/19 (57.9)	0
≥50	4/5 (80)	3/6 (50)	8/19 (42.1)	0
Decrease in analgesic requirement (%)				
<50	23 (85.2)	26 (100)	106 (66.2)	6 (46.2)
≥50	4 (14.8)	0	54 (33.8)	7 (53.8)

follow-up rate of 60%, 23%, 9%, and 9%, respectively, in 10-fraction group and 58%, 27%, 7%, and 6%, respectively, in single-fraction group.[23] The present study has utilized HPPS, which is a valid, reliable, and responsive scale to assess musculoskeletal pain.[18,24-26]

A number of dose fractionation regimens have been cited in the literature ranging from 2 to 8 Gy per fraction, like 30 Gy in 10 fractions, 27 Gy in 8 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, 20 Gy in 4 fractions, and 8 Gy in single fraction.[27,28] The American Society for Radiation Oncology evidence-based guidelines regarding palliative RT for bone metastasis based on 25 randomized clinical trials, 20 prospective single-arm studies, and 4 meta-analyses/systemic reviews has concluded that external beam RT is the mainstay of treatment of painful, uncomplicated bone metastases, and the multi-fraction regimen has the advantage of a lower incidence of retreatment to the same site, whereas the single-fraction regimen has proven more convenient for both patients and caregivers.[28] The risk of radiation-induced myelopathy was 3% when the combined BED of two courses was <135.5 Gy_2, the interval between the courses was not <6 months, and neither single course delivered a BED of >98 Gy_2. In contrast, the Swedish Council on Technology Assessment in Health Care based on a total of 63 scientific articles involving 8051 patients has concluded that although palliative RT gives an overall pain relief in more than 80% of the patients, lasting for at least 6 months in approximately 50% of the patients, pain relief does not depend on the fractionation schedules used.[29] Irradiation of skeletal metastases remains a palliative treatment. RT significantly reduces the number of late complications such as spinal cord compression or pathological fractures. Berg *et al.* evaluated the effect of single-fraction half-body irradiation of 8 Gy for the lower body and 7 Gy for the upper body on pain and QoL in patients having multiple bony metastases using EORTC QLQ-C30 and found it a safe and effective tool in providing long-lasting pain relief in 76% of the patients.[30] As far as dose fractionation of 6.25 Gy per fraction is considered for palliation of bone metastases, the present study is the only study to the best of our knowledge. In a study by Spartacus *et al.*, the hypofractionated palliative RT schedule of 25 Gy in 4 weekly fractions of 6.25 Gy was found effective not only in providing symptomatic relief but also in terms of tolerance by 98 patients of locoregionally advanced head-and-neck cancer.[31] Similar results have also been found in case of bone metastasis in the present study.

Conclusion

The present study represents a cohort of patients with bone metastasis treated at a single center with hypofractionated palliative RT with different fractionation schedules based on clinical judgment of treating radiation oncologists and performance status of patients. The current preferred institutional protocol of once-weekly hypofractionated palliative RT of 6.25 Gy per fraction up to a maximum of four fractions given usually on Saturday showed results comparable with other palliative schedules with well tolerance and achievement of acceptable symptom palliation in the majority of patients. This weekly schedule is practically convenient to both the patients who mostly came from far-flung areas and the institute as it spares the already overburdened machine to carry on conventional RT of other patients treated with curative intent from Monday to Friday. Moreover, in telecobalt machines without the facility of treatment planning system, which is the actual scenario in most of the centers, a single shot of dose as high as 8 Gy may not be precisely delivered to the region of interest, leading to both tumor miss and normal tissue damage. Retrospective nature and short follow-up remain major limitations of the present study.

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Conflicts of interest

There are no conflicts of interest.

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