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Palliative Radiotherapy in the Management of Bone Metastasis: A Retrospective Analysis

Jain AK[1], Rajpurohit V S[2], Sharma R[3], Jain K[4], Tanwar S[5], Meena R[6]

[1]Assistant Professor, Department of Radiation Oncology, SMS Medical College, Jaipur
Corresponding author Email: *drabhayalwar[at]gmail.com*

[2]Senior Medical Officer, Department of Radiation Oncology, RNT Medical College, Udaipur

[3]Senior Professor, Department of Radiation Oncology, SMS Medical College, Jaipur

[4]Research Officer, Ministry of Ayush, New Delhi

[5]Senior Resident, Department of Radiation Oncology, SMS Medical College, Jaipur

[6]Senior Resident, Department of Radiation Oncology, SMS Medical College, Jaipur

Abstract: ***Introduction: Bone is a frequent site of metastasis and typically indicates a short term prognosis in cancer patients. Prognosis of cancer becomes worse once the cancer metastasize to the bones. The treatment of bone metastasis is primarily palliative which requires multidisciplinary approach. Radiotherapy is the mainstay treatment in bone metastasis. The aim of this retrospective study is to analyze the effectiveness of radiotherapy in the symptoms of bone metastasis. Method: Total 168 patients diagnosed with bone metastasis were included in the study from Jan 2020 to May 2021 at the department of Radiation Oncology, SMS Medical College, Jaipur. Patients were treated with Co - 60 teletherapy in fractionation schedule ranging from 30 Gy in 10 daily fraction, 20 Gy in 5 daily fraction, 6.25 Gy per weekly fractionfor one month and 8 Gy in single fraction. Result: The median age of the cohort was 54.81 yrs. The most common site of primary tumor was the lung (30.35%) followed by breast (13.09%) and prostate (11.90%). The most common bone involved was spine (69.04%) followed by pelvis (10.71%).6.25Gy/ fraction schedule was most effective in the symptomatic relief in pain and 3 Gy/fraction schedule was most effective in stability/ movement. Conclusion: The current preferred institutional protocol of hypo - fractionated palliativeRTof6.25Gyperfractionweekly upto a maximum of four fractions given usually on Saturday showed better outcome to alleviate the symptoms of bone metastasis as compared with other palliative schedules of Radiotherapy.***

Keywords: Bone metastasis, radiotherapy, fractionation schedule

1. Introduction

Metastasis is a process that involves loss of intercellular cohesion, cell migration, angiogenesis, access to systemic circulation, survival in circulation, evasion of local immune responses and growth atdistantorgans.[1, 2]Bone is the third most frequent site of metastasis, after the lung and liver.3Prostate and breast cancer are responsible for the about 70% of the skeletal metastases.[4]

The other common sites of primary tumors leading to bone metastasis are thyroid, lung and kidney. Bone metastasis affects the patient's quality of life by causing pain, increased risk of pathologic fracture, spinal cord compression, neurological deficit, and/ or reduced mobility. Pathophysiology of bone metastasis is a complex phenomenon.[5] 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).[6] Bone pain is the most common complication of metastatic bone disease, and bone metastasis is the most common cause of cancer relatedpain.[7] Severity of pain depends on entrapment of nerves, release of chemical mediators, structural damage caused by fractures, and reactive muscle spasm irrespective of the size or degree of bone involvement.[8] Pathologic fractures are a relatively late complication occurring after 3 - 6 months. 9 Contrast enhanced MRI is the investigation of choice to detect spinal metastasis.

Treatment of bone metastasis is primarily palliative which requires multidisciplinary approach such as local treatment i.e. radiotherapy and surgery, systemic treatment i.e. chemotherapy, endocrine therapy, use of radioisotopes and supportive care i. e. analgesics, anti - inflammatory drugs and bisphosphonates with an objective to relieve pain, prevent fractures and maintain mobility.[10, 11]

The use of analgesics according to the WHO ladder is recommended. Opioids remain the corner stone for cance rpain; some adjuvant analgesics that may be used are antidepressants, corticosteroids, anticonvulsants and muscle relaxants.[12 - 14]Intravenous use of bisphosphonates are more effective to prevent bone loss by decreasing the activity of mature osteoclasts than oral administration but there are some adverse events like skeletal pain, nausea, vomiting, headache, renal dysfunction, and osteonecrosis of the jaw.[15 - 18]

Denosumab is a human monoclonal antibody binds 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.[19]

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.

Spinal cord compression should be treated with corticosteroids, and definitive treatment either in the form of RT or surgical decompression should be initiated within 24 hours. Surgery is preferred in case of fracture. Single - fraction RT is the preferred option unless there is a contraindication; it reduces distress and inconvenience associated with repeated session.[20] The prognosis of bone metastasis 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 and response to treatment.[9, 21]

2. Materials and Methods

The present study was a retrospective study wherein the data were collected from case papers of patients who received RT with cobalt-60 tele therapy unit with two dimensional radiation planning for bone metastasis from Jan 2020 to May 2021 in the Department of Radiotherapy, SMS Medical College, Jaipur.

Patients diagnosed with malignancy on HPE (either through Fine Needle Aspiration Cytology or Biopsy from the primary site of the tumor) and bone metastasis (either through contrast enhanced MRI, Computed Tomography, PET Scan or Bone Scan) were included for the study. Patients with primary bone tumors and multiple myeloma and who did not complete the prescribed RT schedule within prescribed time frame were excluded.

Total 168 patients were included in the study. The data were analyzed for various socio- demographic and clinic - pathological factors. Effectiveness of RT was assessed in terms of symptomatic relief in pain and insomnia, improvement in stability/ movement and decrease in the requirement of analgesics by patients.

Symptomatic relief of pain was measured using the Hundred Paisa Pain Scale (HPPS) after one month 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.[22] HPPS was used for assessing all the end points including pain relief, stability, insomnia relief. Result was assessed in percentage and proportion for statistical analysis.

For RT planning, the involved area was marked with appropriate margin as per the guideline depending on site. Marker X - rays were done before delivering radiation to confirm the adequacy of the marked fields. Selection of fractionation schedule depends on patient characteristics (compliance to treatment, life expectancy), tumor related factors (histology of primary tumor, interval time from primary diagnosis to bone metastasis) and the clinical judgment of radiation oncologists. However, in all cases, the intent was palliative and hypo - fractionated schedules were preferred over conventional one. The dose perfraction and number of fractions ranged from 30Gy in 10 fractions with 3Gy per fraction for 5 fractions per week, 20Gy in 5 fractions with 4Gy per fraction for 5 fractions per week, 12.5Gy in 2 fractions with 6.25Gy 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 8Gy in single fraction. The biologically equivalent dose (BED) is $25.78Gy_2$ and 40 Gy_2 for 6.25Gy and 8Gy 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.

3. Results

The baseline information of the patient, tumor, site of bone metastasis and treatment characteristics of the entire cohort are shown in Table - 1. The median age was54.81 (range 29–84) years. Males out weighed females by a ratio of 2: 1. The most common site of primary tumor giving rise to bone metastasis was lung (30.35%), followed by breast (13.09%) and prostate (11.9%); however, primary tumor remained unknown in 19.64% of the patients. More than one bone was involved in three – fourth of the cases. The most common bone involved was vertebrae (69.07%), followed by pelvis (10.71%). Among vertebrae, thoracic vertebrae were most commonly involved (62.93% i. e.73patients) either alone or in conjunction with cervical/ lumbosacral vertebrae or with pelvis. Similarly, lumbar vertebrae were involved in 57.75% (67/116) of the cases, whereas cervical vertebrae in 12.06% (14/116) of the cases. The most common RT schedule was 25 Gy in 4 weekly fractions (70.8%), followed by 30Gy 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, 76.27% of patients receiving this regimen reported more than 50% pain relief; whereas the maximum improvement in stability/movement was noted with 3Gy/fraction schedule, 75%ofpatientsreceiving this regimen reported >50% improvement. The 8 Gy single - fraction schedule was associated with maximum relief in insomnia (63.63% of the patients had >50% relief) and decrease in analgesic requirement (54.54% of the patients had >50% decrease in requirement). The 4 Gy/ fraction schedule was associated with least outcome in all symptom palliation.

Table 1: Observation of patients diagnosed with bone metastasis

Parameters	n (%)
Total number of patients	168 (100)
Gender	
Male	110 (65.47)
Female	58 (34.52)
Age (years)	
<40	25 (14.88)

41 - 50	37 (22.02)
51 - 60	46 (27.38)
61 - 70	41 (24.40)
>70	19 (11.30)
Site of primary tumor	
Lung	51 (30.35)
Breast	22 (13.09)
Prostate	20 (11.90)
Gastro – intestinal tract	13 (7.73)
Kidney	9 (5.35)
Female genital tract	8 (4.76)
Head and neck	7 (4.16)
Urinary bladder	5 (2.97)
Unknown	33 (19.64)
Number of bones involved	
Single	39 (23.21)
Multiple	129 (76.78)
Site of bone metastasis	
Spine	116 (69.04)
Pelvis	18 (10.71)
Spine and pelvis	8 (4.76)
Femur	5 (2.97)
Humerus	5 (2.97)
Skull	4 (2.38)
Scapula	4 (2.38)
Below knee	3 (1.78)
Below elbow	3 (1.78)
Sternum	2 (1.19)
Radiotherapy details (Gy/fraction)	
6.25	118 (70.23)
3	20 (11.90)
4	19 (11.30)
8	11 (6.54)

Table 2: Relief in the symptoms of bone metastasis

Symptoms	3 Gy/fraction *n* (%)	4Gy/ fraction *n* (%)	6.25 Gy/fraction *n* (%)	8 Gy/fraction *n* (%)
Total No. of patients	20	19	118	11
Pain relief (%)				
< 50	6 (30.00)	13 (68.42)	28 (23.72)	3 (27.27)
>=50	14 (70.00)	6 (31.57)	90 (76.27)	8 (72.72)
Relief in insomnia (%)				
< 50	8 (40.00)	12 (63.15)	46 (38.98)	4 (36.36)
>=50	12 (60.00)	7 (36.84)	72 (61.01)	7 (63.63)
Improvement in stability/movement (%)				
< 50	1/4 (25.00)	3/6 (50)	11/20 (55.0)	0
>=50	3/4 (75.00)	3/6 (50)	9/20 (45.0)	0
Decrease in analgesic requirement (%)				
< 50	14 (70.00)	18 (94.73)	77 (66.25)	5 (45.45)
>=50	6 (30.00)	1 (5, 26)	41 (34.74)	6 (54.54)

4. Discussion

Cancer pain may be somatic, neuropathic, 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 pain is moderate or severe in more than one - third of cases.[23] Spinal metastases are the most common tumors of the spine, comprising approximately 90% of the spinal masses.[24] 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.[25] In case of bone metastases, the primary aim of palliative RT is to relieve pain and prevent collapse or impending fracture. Hypo - fractionated 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.[26] Kapoor et al. have compared the pain relieving efficacy of 8Gy administered in a single fraction (62%) versus 30Gy 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 follow – up rate of 60%, 23%, 9% and 9%, respectively, in10 fraction group and 58%, 27%, 7%, and 6%, respectively, in single fraction group.[27] The present study has utilized HPPS, which is a valid, reliable, and responsive scale to assess musculoskeletal pain.[22, 28 - 30]

A number of dose fraction at ion regimens have been cited in the literature ranging from 2 to 8Gy perfraction, like 30Gy in 10 fractions, 27Gy in 8 fractions, 24Gy in 6 fractions, 20Gy in 5 fractions, 20Gy in 4 fractions, and 8Gy in single fraction.[31, 32] 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 multifraction 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.[32] The risk of radiation – induced 6.25Gy 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 Spartacusetal., the hypo – fractionated palliative RT schedule of 25Gy in 4 weekly fractions of 6.25Gy was found effective not only in providing symptomatic relief but also in terms of tolerance by 98 patients of loco regionally advanced head and neck cancer.3[3] Similar results have also been found in case of bone metastasis in the present study.

5. Conclusion

The present study illustrates a cohort of patients with bone metastasis treated at a tertiary care center with hypo - fractionated 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 hypo - fractionated palliative RT of 6.25Gy per fraction weekly upto a maximum of four fractions given usually on Saturday showed better outcome to alleviate the symptoms of bone metastasis as compared with other palliative schedules of Radiotherapy. This is the most convenient schedule for the patients who came from distant areas and also for 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.

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