Original Article:

Study of three different fractionation regimens in palliative radiotherapy for painful bone metastases

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ABSTRACT

Background: To assess the efficacy of single fraction with two different multi-fractionated radiotherapy regimens in treatment of painful bone metastases.

Methods: Patients with painful bone metastases were randomly assigned to receive: Arm A: 8 Gray (Gy) in single fraction (n=15), Arm B: 20 Gy in 5 fractions at the rate of 4 Gy per fraction (n=15) and Arm C: 30 Gy in 10 fractions at the rate of 3 Gy per fraction (n=15). The arms were compared in terms of pain relief, performance improvement, analgesic requirement and duration of overall response at 1week, 1month, and 3 months after treatment.

Results: Pain relief in Arms A, B and C at 1 week were 60%, 53.3% and 60%; at 1 month were 71.4%, 73.3%, 73.3%, at 3 months were 78.5%, 80% and 80% respectively. Performance improvement in Arm A, B and C at 1 week 60%, at 1 month 65%, 66% and 66%, at 3 months 78.5% ,80% and 80% respectively. Duration of overall response in all the patients who improved after therapy is 3 months

There was no statistically significant difference between three arms with respect to pain relief, performance improvement, analgesic requirement and duration of overall response.

Conclusions: The 8 Gy Single fraction is as efficacious as multi-fractionated regimens. Moreover, it is less expensive, decreases duration of hospital stay so single fraction can be used as an effective palliation method.

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INTRODUCTION

Bones are the third most common site of distant metastases after lung and liver in advanced cancer.[1] About 50% of all cancer patients develop metastases in their life time and approximately half of them develop skeletal metastases.[2] Lung, breast and prostate malignancies are the common causes of bone metastases. Other primaries include urinary bladder, kidney, uterus, thyroid malignancies and melanoma.[3] Most of the bone metastases are mixed variety but pure lytic lesions are seen in multiple myeloma and pure osteoblastic lesions are seen in prostate malignancy.[3] Skeletal metastases are usually multiple, solitary metastases are seen only in less than 10% of cases.[4] Metastatic bone disease is associated with skeletal complications that can cause considerable morbidity and mortality, including bone pain, impaired mobility, hypercalcemia, pathological fractures and spinal cord compression.[5] Proper care of bone metastasis requires interdisciplinary care among radiologists, radiation and medical oncologists, surgeons, pain medical specialists and palliative care professionals.[6] Current management of bone metastases includes radiotherapy, chemotherapy, hormone therapy, surgery, radionuclide and supportive therapy

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either alone or in combination.[7] 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.[4] Radiotherapy is the most effective treatment for bone metastases.[8] At least 75% of patients achieve pain relief following radiotherapy and half of them stay free from pain.[1]

Different fractionation radiotherapy regimens are in practice for palliation of painful bone metastases. The purpose of this study was to assess the efficacy of single fraction radiotherapy 8 Gray and two different multi-fractionated radiotherapy regimens 20 Gray in 5 fractions and 30 Gray in 10 fractions in the palliative treatment of painful bone metastases. In Indian patients where metastatic disease constitute a significant proportion of our total cancer workload in radiotherapy departments, as greater than 50% of the patients present in advanced stage and ultimately develop metastases**,** this study addresses a therapeutic question of considerable clinical significance.

MATERIAL AND METHODS

Prospective randomized study conducted in department of Radiotherapy, Nizam's Institute of Medical Sciences (NIMS), Hyderabad during the period of 2009-2011. The study included 45 patients with painful bone metastases from any primary site, localized to a single region that could be encompassed in a single radiation field. Patients with previous radiotherapy to the region concerned or presence of any co-morbid conditions to which the patient's symptoms can be attributed were excluded from the study. The study protocol was approved by the ethics committee of the NIMS, Hyderabad. The patients were randomly assigned to receive Arm A: 8 Gray (Gy) in single fraction (n=15); Arm B: 20 Gy in five fractions (n=15); and Arm C: 30 Gy in ten fractions (n=15).

Follow-up

Patients were followed for 3 months. Reviews were done at 1 week, 1 month and 3 months after completion of radiotherapy. Patients who met the inclusion criteria were recruited in to the study and informed consent was taken.

Positioning and technique

For spinal metastases treatment was prescribed in prone position. For long bone and pelvic bone metastases treatment was prescribed in supine position. The target volumes were delineated based on clinical and radiological judgment. Fields were planned to include known skeletal manifestation with an additional 4-5 cm margin. For spinal lesion the field included two vertebral bodies above and below the painful vertebrae. A single direct field for spinal metastases and two parallel opposed fields for pelvic and long bones were delivered. High energy linear accelerator and cobalt 60 (Theratron-780C) machine was used to deliver the treatment.

Patient evaluation criteria

Pain score, Eastern Co-operative Oncology Group (ECOG) performance scale[9] and analgesic requirement were recorded at baseline 1 week, 1 month and 3 months after completion of treatment. Pain relief was evaluated by verbal rating scale,[10] a 5 point pain scale from 0-4, where 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; and 4 = extremely severe pain. Pain relief was defined as decrease in pain score by at least one point with respect to the pretreatment value.

The ECOG grading system is shown in Table 1. Improvement in performance status was defined as a decrease in ECOG functional outcome score[9] by at least one grade with respect to pre-treatment value.

Analgesic requirement was graded according to type of analgesic needed for pain relief, as: 0 = not requiring any analgesics; 1 = simple

Table 1: The Eastern Co-operative Oncology Group grading system of functional status[9]

Grade 0 = Fully active, able to carry on all pre-disease performance without any restriction
Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
Grade 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Grade 4 = Completely disabled, cannot carry on any self-care totally confined to bed or chair.
Grade 5 = Dead

analgesics such as non-steroidal anti-inflammatory drugs (NSAIDS); 2 = mild narcotics (codeine, tramadol); 3 = strong narcotics (morphine, fentanyl); and 4 = high dose narcotics inadequate. The extent of pain relief was the main indicator for effective palliation.

Overall response was defined as decrease in pain score by at least one point with respect to the pretreatment value. Complete response was defined as achieving a pain score of 0 at any point during follow-up. Duration of overall response was defined as the time from initial response till return of pain to its baseline value.

Statistical analysis

Vertical and horizontal comparisons (detailed below) were carried out by Chi-square test. The three arms of treatment were compared at the end of 1 week, 1 month and 3 months in terms of percentage patients in each arm showing decrease in pain relief, improvement in performance status and decrease in analgesic requirement to know whether single fraction or multiple fraction radiation treatments has same effect or not (vertical comparison). Horizontal comparison was done to know whether the response achieved by either single fraction or multiple fractions was persisting for the same duration of period or not. Statistical software SPSS version 11.5 was used for statistical analysis.

RESULTS

In Arm A, the mean age of the patients was 56.7 (range 29-75) years. In Arm B, the mean age of the patients was 54.4 (range 30-78) years. In Arm C, mean age of the patients was 55.2 (range 40-75 years). Age distribution of patients in the three treatment arms is depicted in Table 2.

Of the 45 patients with skeletal metastases included in the study the primary was lung in 17 (37.7%), breast in 11 (20%), prostate in 4 (8.8%), cervix and thyroid each in 2, liposarcoma, endometrium, renal cell carcinoma, submandibular gland and stomach in 1 patient each. In 4 (8.8%) cases, primary was not found. In majority of cases, pelvis and spine were the most common sites of involvement followed by femur, radius and humerus. Pelvis was involved in 17 (37.7%) and spine involvement was seen in 17 (37.7%) patients. Remaining 11 patients had metastases in the appendicular skeleton.

Response to treatment

Overall response rates in terms of pain relief in Arm A, Arm B and in Arm C at the end of 1 week, 1 month and 3 months are depicted in Table 3. In all the three arms mean pain scores improved from week 0-12, which was suggestive of adequate palliation as defined for the purpose of this study (Table 3). Improvement in performance status at the end of 1 week, 1 month and at 3 months depicted in Table 4.

Analgesic usage

Number of patients with decrease in analgesic usage at the end of 1 week, 1 month and 3 months are depicted in Table 5. There was a shift of analgesic usage from strong narcotics

Table 2: Age distribution in the 3 treatment arms

Age (years)	Arm A (No.)	Arm B (No.)	Arm C (No.)	Total (No.)
<30	1	0	0	1
30-39	0	2	0	2
40-49	3	3	5	11
50-59	4	5	6	15
60-69	4	2	2	8
>70	3	3	2	8

Arm A = 8 Gy in single fraction; Arm B = 20 Gy in 5 fractions at the rate of 4 Gy per fraction and Arm C = 30 Gy in 10 fractions at the rate of 3 Gy per fraction

Gy=Gray

Table 3: Pain relief with treatment

Variable	At 1 week (No.)	At 1 month (No.)	At 3 months (No.)	p-value
Arm A	9/15	10/14	11/14	0.54
Arm B	8/15	11/15	12/15	0.26
Arm C	9/15	11/15	12/15	0.46
p-value	0.91	0.99	0.99	

Arm A = 8 Gy in single fraction; Arm B = 20 Gy in 5 fractions at the rate of 4 Gy per fraction and Arm C = 30 Gy in 10 fractions at the rate of 3 Gy per fraction

Gy=Gray

Table 4: Improvement in performance status

Variable	At 1 week (No.)	At 1 month (No.)	At 3 months (No.)	p-value
Arm A	9/15	9/14	11/14	0.54
Arm B	9/15	10/15	12/15	0.48
Arm C	9/15	10/15	12/15	0.48
p-value	1.00	0.98	0.99	

Arm A = 8 Gy in single fraction; Arm B = 20 Gy in 5 fractions at the rate of 4 Gy per fraction and Arm C = 30 Gy in 10 fractions at the rate of 3 Gy per fraction

Gy=Gray

Table 5: Decrease in analgesic requirement

Variable	At 1 week (No.)	At 1 month (No.)	At 3 months (No.)	p-value
Arm A	11/15	12/14	12/14	0.60
Arm B	11/15	13/15	13/15	0.55
Arm C	10/15	12/15	12/15	0.61
p-value	0.89	0.86	0.86	

Arm A = 8 Gy in single fraction; Arm B = 20 Gy in 5 fractions at the rate of 4 Gy per fraction and Arm C = 30 Gy in 10 fractions at the rate of 3 Gy per fraction

Gy=Gray

to mild narcotics or NSAIDS. Fifteen patients did not use any analgesic at the end of 3 months.

Duration of response to treatment

All the patients who improved after therapy showed sustained response till the end of 3 months.

Out of 9 complete responders 2 sustained the response for less than 4 weeks, 4 patients up to 8 weeks and remaining 3 maintained till the end of follow-up. There was no statistically significant difference in between the three arms among all the variables compared.

DISCUSSION

Metastatic bone disease is the most common malignant bone lesion seen in adults. The management of these patients is nearly always palliative, but as such it requires no less judgmental skill and inter-disciplinary co-operation than doe's curative treatment, the orthopedic surgeon and medical oncologist along with the radiation oncologist must be aware of the most appropriate measures and their timing during management. In the present study 80% of patients obtained overall pain relief whereas the remaining 20% of patients did not obtain any pain relief. These responses were almost in accordance with the findings of published trials.[11-14] The rate of complete pain relief in our study (20%) was slightly different from those reported in literature.[11-14] This can be attributed to difference in questionnaires used, timing of pain evaluation after radiotherapy or the small number of patients and shorter duration of follow-up in our study. There are several difficulties involved in these kinds of trials, like patient selection, type of primary, site and extent of metastases, choice of end points, definition of precise contribution from radiotherapy and other co-interventions like analgesics, systemic treatment, and psychosocial support. Investigations involving measurement of pain relief are difficult to analyze because some patients do not survive long enough to complete full assessment.

Other major problem is measurement of pain. Several scales like the visual analogue scale (VAS), 101-point scale, 6-point behavioural scale, 5-point verbal rating scale, amongst others have been documented in the literature. In our study, we selected a 5-point verbal rating scale which is a subjective scale and easily understandable to the patient. Compliance of the patient has always been a problem in studies involving palliative treatment because patients usually have advanced disease and poor life expectancy. Moreover, the care givers often lacked the motivation to assist with follow-up. The compliance of the patients was better than expected in our study as the numbers of hospital visits were kept to a minimum and all the patients were followed up via telephone to update their score forms in the first week. All patients completed their forms in time. There was no loss to follow-up.

Another subject that generates interest is the issue regarding re-irradiation of the index site. Few trials have reported higher rates of re-irradiation in the single fraction arms.[14,15] In our study, no patient came for re-treatment of the index site during 3 months of follow-up. According to the present study, all the three treatment schedules are equally effective with respect to the evaluated variables and no regimen is superior to other. When pain relief is the primary goal, as it is in most cases of painful bone metastases, treatment with single fraction regimen may be more appropriate. When treatment objectives other than pain relief are equally important, the choice of schedule requires further consideration. There may be sub-group of patients who requires fractionated treatment at a higher dose. Patients with pathological fractures or those at high risk for pathological fracture and patients with extensive soft-tissue involvement may also

benefit from higher dose, if the intent of treatment is the reduction of tumor bulk in addition to pain relief. We are of the opinion that all the three fractionation regimens are equally efficacious in terms of pain reduction but single fraction schedules may be preferred for patient convenience without compromising the palliative effect. The use of a single fraction could be of benefit to hospital staff and treating institutions especially in the Indian scenario where the radiotherapy departments are already overburdened. It also allows for more chances of re-treatment as the maximum tolerated dose of the adjacent structures is not crossed.

Comparison of our results with other studies[11-14] revealed that, in terms of overall response our results are almost in accordance with those trials.[11-14] We observed a complete response in 20% patients with single fraction and multiple fraction treatment. This figure is some what lower to the complete response observed with single fraction (33.4% to 35%) and multiple fractions (72.5% to 78%) observed in other studies.[12,13] This could have been due to difference in questionnaires used, definition of complete response and small number of patients in our study.

External beam radiotherapy has been, and continues to be, the mainstay for the treatment of painful bone metastases. All the three groups showed equal efficacy or no statistically significant difference in terms of pain palliation, decrease in analgesic requirement, improvement in performance status and duration of overall response. Among all the three arms 8 Gray single fraction has greater convenience, lower cost and less duration of hospital stay with same efficacy. This makes 8 Gray single fraction as the treatment of choice for majority of cases of bone metastases. Among reported trials,[11-14] patients in the lower dose group are more frequently associated with re-irradiation of the index site, so in patients with very advanced disease and short life expectancy, where the treatment goal is to decrease the pain then 8 Gray single fraction is the treatment of choice.

The 8 Gray single fraction has greater convenience, lower cost and less duration of hospital stay with same efficacy for palliation of painful bone metastases. Our observations suggest that 8 Gray single fraction could be the treatment of choice for majority of cases of uncomplicated bone metastases. However, these but as our study observations need to be confirmed in studies with a large sample size. Patients in the lower dose group are more frequently associated with re irradiation of the index site, so in patients with very advanced disease and short life expectancy, where the treatment goal is decrease in pain then 8 Gray single fraction is the treatment of choice

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