



## A COMPARATIVE STUDY BETWEEN TWO DOSE FRACTIONATION SCHEDULES; 8 GY IN SINGLE FRACTION VERSUS 30 GY IN 10 FRACTIONS IN PALLIATIVE MANAGEMENT OF BONE METASTASES.

### Oncology

**Dr Jyotiman Nath** Registrar, Department of Radiation Oncology, Cancer Hospital, Gauhati medical College

**Dr Gautam Sarma\*** Assistant Professor, Department of Radiation Oncology, Cancer Hospital, Gauhati medical College. \* Corresponding Author

### ABSTRACT

Bone is the third most common site affected by metastatic disease, after the lung and the liver. Since pain is the major cause of morbidity in these patients, pain control significantly improves quality of life. The aim of the study is to compare the single fraction radiotherapy (8Gy) with multiple fraction radiotherapy (30Gy in 10 fractions) in management of painful bone metastases in terms of pain palliation and analgesic requirement. This is a hospital based prospective study where 44 patients of painful bone metastases were enrolled. Arm A (n=21) and Arm B (n=23) received 8 Gy in single fraction and 30 Gy/10 fractions respectively. Pain palliation was compared between the groups and there was no significant difference in pain palliation at the end of 3 months (p=0.66). Regarding analgesic requirement at 3 months by the two groups, both the fraction schedules are statistically similar (p=0.67)

### KEYWORDS

Radiotherapy, Metastases, Fractionation, Palliation, Analgesic

#### Background

Bones are one of the most common sites of distant metastases in patients with advanced malignancy. It is the third most common site affected by metastatic disease, after the lung and the liver. The most common primaries are from breast and prostate which collectively constitutes approximately 80% of total cases.<sup>1</sup>

Bone mets can involve any part of the skeletal system. In axial skeleton spine being the most common site followed by pelvis and the ribs.<sup>2</sup>

Metastatic deposits to the bone from any primary cause significant and debilitating pain and complications such as pathological fracture, spinal cord compression, hypercalcaemia etc. Since pain is the major cause of morbidity in these patients, pain control significantly improves quality of life.<sup>3</sup>

Treatment is primarily palliative in nature with the intention to relieve pain, prevent fractures, maintain activity mobility, and if possible to prolong survival. EBRT is a well recognized and effective palliative treatment modality bone metastases, with up to 80% of patients experiencing some improvement in pain.<sup>4</sup>

There is continued debate over the appropriate fractionation scheme for the most effective regimen of palliative radiation therapy to treat bone metastases. Numerous prospective randomized and retrospective trials have been done so far to evaluate the effectiveness of single fraction and multiple fraction longer duration courses in the palliative treatment of painful bone metastases.

The aim of the study is to compare the single fraction radiotherapy (8Gy) with multiple fraction radiotherapy (30Gy in 10 fractions) in management of painful bone metastases in terms of:

- q Pain palliation
- q Analgesic requirement

#### Method and Material

This is a hospital based prospective study, conducted in the department of Radiotherapy, Assam Medical College Hospital, Dibrugarh, Assam after approval of the institutional ethics committee Study period:- 1 year (July 2014 to June 2015)

#### Inclusion Criteria:

1. Biopsy or cytology proven malignant disease with symptomatic skeletal metastasis verified by either X-ray or CT-scan or MRI and by clinical examination.
2. Either solitary or multiple bone metastases, which can be encompassed in a single radiotherapy portal.
3. Karnofsky performance status of  $\geq 40$ , age  $\geq 18$  years of either sex.
4. Patients with an initial pain score of at least 5 or above as per visual analogue scale (VAS).

#### Exclusion criteria:

1. Karnofsky performance status of  $< 40$ , age  $< 18$  yrs.
2. Patients who were irradiated previously at the same region.
3. Patients with existing pathological fracture and features of spinal cord compression.
4. Patients receiving chemotherapy or hormone therapy or within the last 4 week period.

**Sample size:** - 44 (arm A=21 and arm B=23). The cases in each group were randomized.

The patients were explained about the study and written informed consents were obtained. Patient's pain score was evaluated just before starting of treatment using visual analogue scale for assessment of pain intensity with score 10 being the worst pain and score 0 being no pain. Pre-treatment analgesic use was also recorded using WHO analgesic step ladder.

Painful bony sites were identified with the help of clinical history, physical examination (locating the points of maximum tenderness), and imaging (X-ray/ CT/MRI).

The patients in arm A received 8 Gy in a single fraction and the patients in arm B received 30Gy in 10 fractions over 2 weeks.

The patients were treated in a telecobalt machine (Theratron 780 C) with single direct posterior portal for vertebral metastases and parallel opposed portals for the pelvis and long bones. Dose was prescribed to the mid vertebral body in patients with vertebral metastasis. For long bone and pelvis; mid plane prescribed dose was delivered by two opposing portals. Analgesics were administered according to WHO cancer pain ladder for adults and WHO principles. The patients were followed up at 1 month, 2 month and 3 month post-radiotherapy. The follow-up was done either in the outpatient department or by telephonic interviews. The patients were assessed for pain palliation in terms of complete response, partial response, intermediate response and pain progression. Patients were also assessed about analgesic requirement in each follow up.

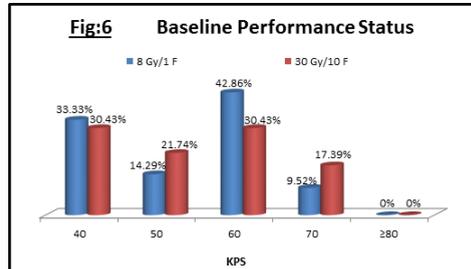
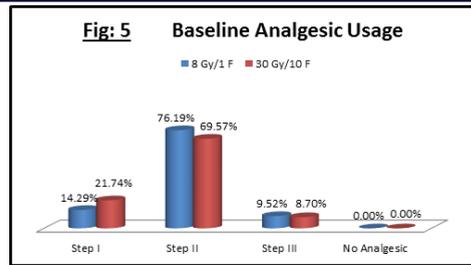
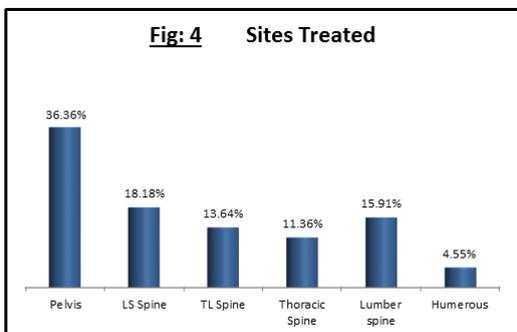
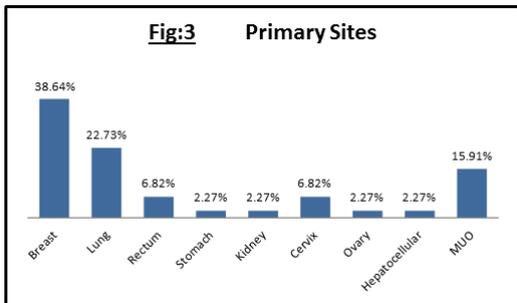
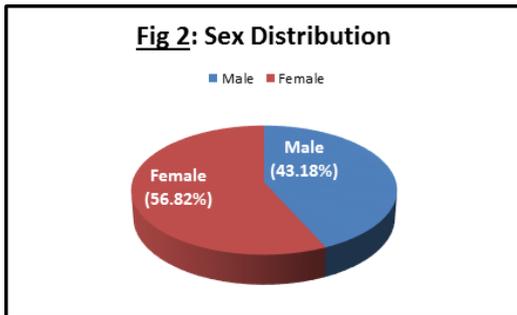
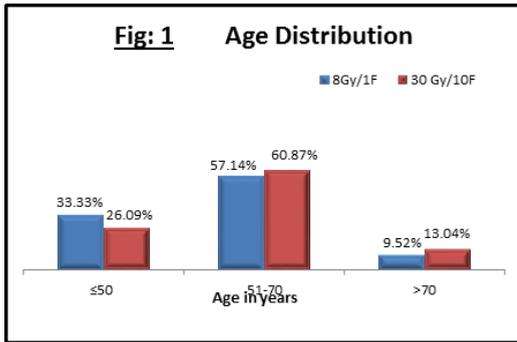
The response criterias were followed according to the updated international consensus on palliative radiotherapy endpoints 2012, according to which, complete response is defined as a pain score of 0 at treated site with no concomitant increase in analgesic intake. Partial response is defined as pain reduction of 2 or more at the treated site on a scale of 0 to 10 without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain. Pain progression is defined as increase in pain score of 2 or more above baseline at the treated site with stable analgesic use, or an increase of 25% or more analgesic use compared with baseline with the pain score stable or 1 point above baseline. Indeterminate response is defined as any response that is not captured by the complete response, partial response, or pain progression definitions.<sup>5</sup>

**Statistical Methods:**

Fisher's exact test has been used to find the significance of type of responses between the two doses of fractionation schedules and to compare the analgesic use by the two groups at baseline and last follow-up. Student t- test and chi-square test have been used to compare the baseline patient characteristics and to find out significance of pain score and performance status of the two study groups at the last follow-up, respectively.

**Results**

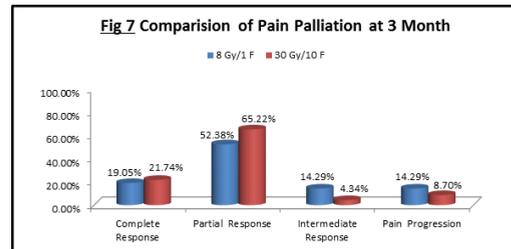
Baseline patient characteristics were compared. Fig. 1 depicts the age distribution of the patients between the two groups. The mean ages of the groups were 56.43±9.35 years (8 Gy/1F) and 59.30±10.22 years (30 Gy/10 F) respectively. The two study groups were homogeneous with respect to age (p=0.34). Females were more common in the study than males (56.82% vs. 43.18%, p=0.97, Fig 2). Breast cancer was most common primary (38.64%) followed by lung (22.73%, Fig 3). Pelvis was the most common treated site of bone metastases (36.36%, Fig 4). Baseline analgesic usage by the patients and baseline performance status of the patients were also compared and the groups were statistically homogeneous, p=0.85 and p=0.88 respectively (Fig 5, Fig 6 respectively)



Patients were assessed for pain relief at 1 month, 2 month, and 3 month post-radiotherapy. At the end of 3rd month, single fraction arm showed slightly less complete and partial responders in comparison to the multiple fraction arm (CR 19.05% vs. 21.74% and PR 52.38% vs.65.22%, respectively). On the other hand pain progression was more in the single fraction arm (14.29% vs. 8.70%). But statistically the arms did not show any significant difference in terms of pain relief and hence both fractionation schedules are equally effective in pain palliation (p=0.66) [Table 1 & Fig 7]

**Table 1:-Comparison of responses of the two arms in third follow-up at 3 month**

3 <sup>rd</sup> month Follow-up	8 Gy/1F (n=21)	30 Gy/10 F (n=23)
CR	4 (19.05%)	5 (21.74%)
PR	11 (52.38%)	15 (65.22%)
IR	3 (14.29%)	1 (4.34%)
PP	3 (14.29%)	2 (8.70%)
Inference	p=0.66	



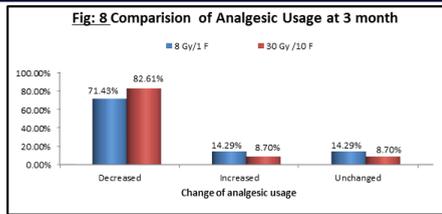
Regarding analgesic requirement, majority of the patients in both the arm used WHO step I analgesic at the end of 3 month. 4 patients in 8 Gy/1F arm (19.05%) and 5 patients in 30 Gy/10F arm (21.74%) claimed no use of analgesics at last follow-up. Overall 15 patients in 8 Gy/1F arm (71.43%) and 19 patients in 30 Gy/10F arm (82.61%) had experienced decrease in analgesic requirement. There was no statistically significant difference between the two arms with respect to analgesic requirement (p=0.67). [Table 2,3 & Fig 8]

**Table 2:-Use of analgesics by the two groups at the end of 3 months**

Analgesic	8 Gy/1F (n=21)	30 Gy/10 F (n=23)
Step I	11 (52.38%)	16 (69.56%)
Step II	4 (19.04%)	1 (4.35%)
Step III	2 (9.52%)	1 (4.35%)
No Analgesic	4 (19.05%)	5 (21.74%)
Inference	p=0.42	

**Table 3:-Change of Analgesic requirement by the two groups at the end of 3 months**

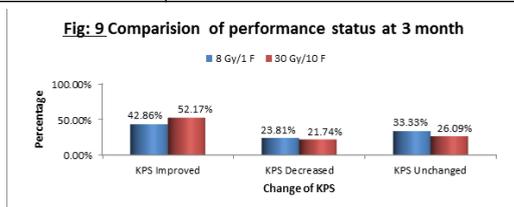
Analgesic Use	8 Gy/1F (n=21)	30 Gy/10 F (n=23)
Decreased	15 (71.43%)	19 (82.61%)
Increased	3 (14.29%)	2 (8.70%)
Unchanged	3 (14.29%)	2 (8.70%)
Inference	p= 0.67	



9 patients in 8 Gy/1 F arm (42.86%) and 12 patients in 30 Gy/10 F arm (52.17%) showed improvement in performance score. Decreased in performance score was noted in 5 patients in each group (23.81% and 21.74% in 8 Gy/1 F and 30Gy/10 F arm, respectively). 7 patients in 8Gy/1F arm (33.33%) and 6 patients in 30 Gy/10 F arm (26.09%) showed no any change in performance status. There was no significant difference between the two groups in terms of change of performance score (p=0.81). [Table 4, Fig 9]

**Table 4:-Change of Performance score of the two groups at the end of 3 months**

KPS	8 Gy/1F (n=21)	30 Gy/10 F (n=23)
Number Improved	9 (42.86%)	12 (52.17%)
Number Decreased	5 (23.81%)	5 (21.74%)
Number Unchanged	7 (33.33%)	6 (26.09%)
Significance	p= 0.81	



**Review of Literature**

The effects of radiation on painful bone metastasis has been recognized for many years with early reports found from the beginning of the 20<sup>th</sup> century, not long after the discovery of X rays. Radiotherapy is an enduring, established means of achieving analgesia for bone metastases that dates back to 1930.<sup>9,10</sup>

Numerous randomized trials have been conducted on dose fractionation schedules of palliative radiotherapy. Despite that, there is still no uniform consensus on the optimal dose fractionation scheme.<sup>8</sup>

The first large randomized study evaluating different dose and fractionation schemes was the Radiation Therapy Oncology Group (RTOG) 74-02 trial. The major goal was to determine the optimal palliative fractionation schedule. In this trial, the patients with solitary bone metastases were randomized to 40.5 Gy in 15 fractions versus 20 Gy in 5 fractions. Patients with multiple painful metastases were allocated to one of four treatment schedules: 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions. The initial analysis of this trial by Tong et al in 1982 showed no statistically significant difference in response rates between any of the treatment arms, with complete responses in 49% to 61% of patients.<sup>6,7</sup> However, many aspects of this randomized effort were criticized; including the inclusion of a heterogeneous group of primary cancer sites, the use of physician assessment of pain, and the fact that narcotic relief and the incidence of radiation therapy re-treatment were not taken into consideration.

The first randomized study comparing the two dose fractionations; 8 Gy single fraction versus 30 Gy in 10 fractions was published in 1986 by Price et al. The complete response rate was found to be 9% in both the groups.<sup>11</sup>

In a randomized clinical trial by Foro Amalot et al., a total of 160 patients from July 1999 to December 2001 were enrolled with an intention-to-treat; 82 patients received 30 Gy in 10 fractions and 78 patients received a single fraction of 8-Gy. The overall response was 75% in 8 Gy arm and 86% in 30Gy arm (p=0.134). At 3 weeks; complete and partial response rates were 15% and 60% in the 8Gy arm, 13% and 73% in the 30 Gy arm. Pain progression was observed in 43% of the patients in the 30-Gy arm and in 28% in the 8 Gy arm. Although the retreatment rate was higher for the single fraction arm than the

multiple fraction arm (28% vs. 2%, respectively); the single fraction of 8 Gy was found to be safe and effective in terms of pain relief.<sup>12</sup>

Kassa et al conducted a randomised multicenter trial comparing 8 Gy single fraction vs. 30 Gy in 10 fractions in the treatment of painful bone metastases. From April 1998 to July 2000 six centers were included. In conclusion overall there was no significant difference in survival between the two groups and the study endorses the adoption of single-fraction radiotherapy as standard.<sup>13</sup>

Kapoor et al published the results of a single centre prospective study of single fraction (8 Gy) vs. multiple fraction radiotherapy (30 Gy in 10 fractions) for bone metastases. Complete response was 22% and 17%; and partial response was 36% and 43% in single fraction and multiple fraction, respectively.<sup>14</sup>

Numerous randomized controlled trials done so far have demonstrated that both single fraction and multiple fraction dose schedules are equally efficacious for palliative treatment of bone metastases. Multiple fraction schedules may be indicated in the treatment of complicated bone metastases, such as those causing neuropathic pain, pathologic fractures or spinal cord compression. As such, guidelines from the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) recommend single fraction radiotherapy as the preferred treatment for uncomplicated bone metastases. Despite of such evidence based guidelines it has been seen that, in last twenty years, there was an overall global reluctance to practice evidence-based medicine by employing single fractions for uncomplicated bone metastases.<sup>15,16</sup>

**Conclusion**

Control of pain is the major goal in patients with bone metastases. Use of appropriate dose fractionation of EBRT is of paramount importance in palliative management. High dose shorter course treatment schedules have been found to be equally efficacious as low dose multiple fraction schedules in various randomised trials so far in terms of pain palliation and analgesic requirement.

Due to shorter treatment duration, less hospital stay and low cost; the short course of 8 Gy in a single fraction is more convenient for both patient and care giver and hence can be considered as standard of care for this group of patients. However unbiased selection of cases and study in a larger population need to be done to re-affirm this statement keeping in mind about the treatment duration, cost and the treatment related toxicities.

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