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ROLE OF VARIOUS FRACTIONATION SCHEDULES OF RADIATION THERAPY IN TREATMENT OF BONE METASTASES

Oncology

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ABSTRACT

BACKGROUND: Bone metastasis is a common manifestation of malignancy and is the third most common organ affected by metastasis. Bone metastases can cause various morbidities and affect the quality of life. The treatment intent in bone metastases is palliative. External beam radiotherapy is the mainstay of treatment of uncomplicated painful bone metastases. Different radiotherapy fractionation schedules are in practice for palliation of painful bone metastases.

OBJECTIVES: To report the outcomes of various fractionation schedules of radiation therapy in terms of pain relief and improvement of quality of life in patients with painful bone metastases.

METHODS: A prospective randomised study performed on 80 patients were randomised to 4 treatment arms with different radiation therapy fractionation schedules at the Dept. of Radiation Oncology, Father Muller Medical College Hospital. The fractionation radiation doses used in the study were 8 Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions and 30 Gy in 10 fractions. Patients were assessed for pain by Visual Analog Scale (VAS) and Rupee scale, performance status, analgesic usage, quality of life before initiating the treatment, on the day of completion of treatment, 1 week, 1 month and 3 months post completion of treatment.

RESULTS: In our study majority of the metastases were from the breast of 33.75%, 25% from the lungs, 18.75% from the head and neck, and 12.5% from prostate. Cervix (2.5%), esophagus (1.25%), stomach (1.25%), liver (1.25%), ovary (1.25%) comprised the other primary sites. 2.5% of the metastases were from unknown primary. In total 27.5% of the patients had metastases to the thoracic vertebra, 26.25% to the lumbar vertebra, 22.5% to the pelvis, 8.75% to the sternum, 6.25% each to cervical vertebra and femur and 1.25% each to humerus and ribs. The pain reduction was significant in all the 4 arms. The mean VAS score was 5.23 prior to start of treatment. The score reduced to 2.88 at the completion of treatment and further dropped to 1.57, 0.79, and 0.81 at 1 week, 1 month and 3 months post completion of radiation therapy. Similar results were obtained using the Rupee scale for assessment of pain. The mean score prior to treatment was 54.23 in the entire study group. It is reduced to 33.81, 25.87, 12.78 and 12.84 on the day of treatment completion, 1 week, 1 month and 3 months post completion of radiation therapy. Complete pain relief occured in 40% of the patients. 25% of the patients in 8 Gy in 1 fraction had complete relief of pain whereas the complete relief in the remaining 3 arms was 45% each. Improvement in the quality of life was observed in all the arms, both in terms of symptoms and function.

CONCLUSION: This prospective study demonstrated that various radiation fractionation schedules used in the treatment of painful bone metastases have been effective in reducing the pain. The pain reduction by various fractionation schedules are similar and no statistically significant difference was noted. Quality of life improved in all the four treatment arms post radiation therapy. 8 Gy in single fraction may be considered for treatment of painful bone metastases.

KEYWORDS

Bone metastases; VAS; Rupee scale; Pain; Quality of Life

INTRODUCTION

Bone metastases is a common manifestation of malignancy that can cause severe and debilitating effects. It is the third most common organ affected by metastasis.[1] Bone metastases can present as pain, pathological fractures, hypercalcemia, spinal cord compression and affect the quality of life.[1,2] Breast, prostate are common primary sites for bone metastases, accounting for up to 70%. Other primary sites include lung, thyroid, melanoma, kidney. Bone metastases commonly involves axial skeleton with lumbar spine being the most frequent site. Primary site of malignancy and presence of any other site of metastasis determine the overall survival. Patients with bone metastases from prostate or breast have longer median survival of 2 to 4 years, when compared with bone metastases from lung cancer with median survival of 6 months.[2] With prolongation in survival, improving quality of life is necessary. The treatment intent in bone metastases is palliative with management comprising of radiation therapy, medical treatment, surgery, bone targeted therapy depending on biology of disease, extent of skeletal involvement, life expectancy of the patient.[3]

External beam radiotherapy (RT) provides successful palliation of painful bone metastasis and is the mainstay of treatment of uncomplicated painful bone metastases. External beam RT (EBRT) can provide significant palliation of painful bone metastases in 50–80% of patients, with up to one-third of patients achieving complete pain relief.[4] Different radiation fractionation schedules are in practice for palliation of symptomaticbone metastases. Pain relief with 30 Gy in 10 fractions is 78%, 79 % with 24 Gy in 6 fractions, 76% with 20 Gy in 5 fractions and 75% with 8 Gy single fraction.[5,6,7]

The purpose of this study is to report the outcomes of various fractionation schedules of radiation therapy in terms of pain relief and improvement of quality oflife in patients with painful bone metastases treated at our institution.

MATERIALS AND METHODS

Source of Data:

All the patients with metastases to bone which were histologically or radiologically proven at the Department of Radiation Oncology in Father Muller Medical College, Mangalore, were taken up for the study.

Patients with bone metastasis from any primary cancer were included in the study.

Exclusion criteria included those patients who previously received radiation therapy to the region concerned and presence of any co-morbid condition to which the patient's symptoms could be attributed.

METHOD OF COLLECTION OF DATA:

A total of 80 patients, with 20 patients in each group, satisfying inclusion and exclusion criteria were prospectively randomized to the four treatment groups by the lottery method. 4 fractionation schedules

used were Arm A received 8 Gy in 1 fraction, Arm B received 20 Gy in 5 fractions, Arm C received 24 Gy in 6 fractions and Arm D received 30 Gy in 10 fractions.

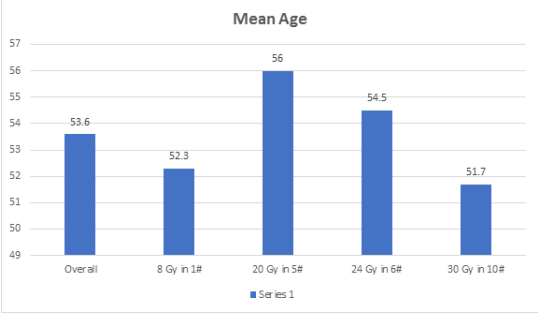
In all patients, the primary malignancy was histopathologically proven and the metastases were histologically or radiologically confirmed. Informed consent was obtained from all the patients before they underwent clinical evaluation including a detailed history, physical examination, laboratory and radiological investigations. Histological diagnosis was established when feasible or was established radiologically. Evaluation of baseline pain, analgesic usage, performance status, quality of life was done and recorded on the first day of treatment. At the same time, the scoring system was explained to the patient.

All patients were planned using ECLIPSE 8.6 treatment planning system and photons were delivered from a 6 MV VARIAN linear accelerator. Patients were followed up prospectively for 3 months after completion of treatment or till death whichever was earlier. Follow up was done at 1 week, 1 month and 3 months. At each follow-up, assessment of patient's general condition, performance status, analgesic usage, quality of life, pain intensity and side effects were done.

Statistical Analysis:
Collected data was analyzed by analysis of variance, Friedman test, Wilcoxon signed rank test and Kruskal-Wallis test.

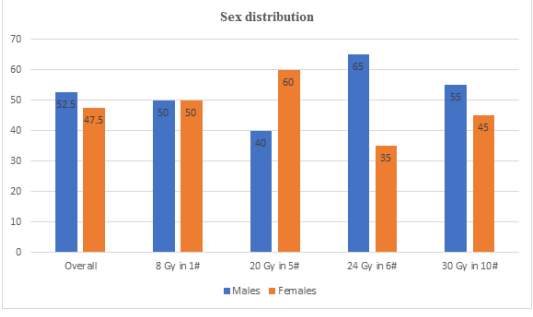
RESULTS
The study comprised of 80 patients with 20 patients each in the 4 arms.

Age
The mean age was 53.66 years. There was no significant difference in the outcome based on age.



Graph 1: Mean Age

Sex distribution
52.5% of the patients were males and 47.5% females.



Graph 2: Sex distribution

Primary tumor site
Overall 33.75% of the metastases were from the breast, 25% were from the lungs, 18.75% from the head and neck, and 12.5% from prostate. Cervix (2.5%), stomach (1.25%), esophagus (1.25%), ovary (1.25%), liver (1.25%) comprised the other primary sites. 2.5% of the metastases were from unknown primary.

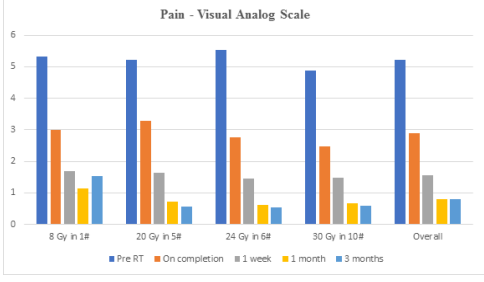
Site of metastases
In total 27.5% of the metastases were to the thoracic vertebra, 26.25% to the lumbar vertebra, 22.5% to the pelvis, 8.75% to the sternum, 6.25% each to cervical vertebra and femur and 1.25% each to humerus and ribs.

Lumbar spine was the most common site of metastases in the 8 Gy in single fraction arm and 24 Gy in 6 fraction arm comprising 30% and 35% respectively. Thoracic spine (40%) was most commonly involved in the 20 Gy in 5 fraction arm and pelvis (40%) was most common in 30 Gy in 10 fraction arm.

Pain relief : Visual analog scale
The pain reduction was significant in all the 4 arms. The mean VAS score was 5.23 prior to start of treatment. The score reduced to 2.88 at the completion of treatment and further dropped to 1.57, 0.79, and 0.81 at 1 week, 1 month and 3 months post completion of radiation therapy.

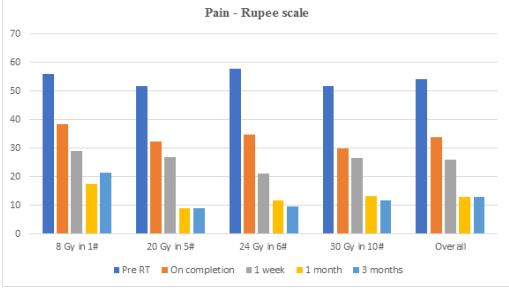
The mean VAS score prior to start of treatment in the various arms were 5.31, 5.21, 5.54 and 4.87 in Arm A, Arm B, Arm C and Arm D respectively. On the day of completion of radiation therapy there was significant relief of pain with scores 3, 3.29, 2.77 and 2.47 in the 4 arms respectively ($p < 0.001$). The pain relief continued at 1 week, 1 month and 3 months post radiation therapy. The mean VAS scores at 1 week post treatment being 1.69, 1.64, 1.46 and 1.57 respectively and 1 month post radiation therapy being 1.15, 0.71, 0.62 and 0.67 respectively.

The reduction in pain at 3 months post radiation therapy was significant with score 1.54, 0.57, 0.54, 0.60 respectively. But the reduction was not significant when compared to the scores at 1 month post treatment. In the 8 Gy in single fraction arm there was a slight increase in the score at the end of 3 months (1.54) when compared to that at 1 month post radiation therapy. Also the reduction in pain from 1 week to 3 months post treatment was not significant (p 0.615).



Graph 3: Visual Analog Scale

Rupee scale
Similar results were obtained using the Rupee scale for assessment of pain. The mean score prior to treatment was 54.23 in the entire study group. It reduced to 33.81, 25.87, 12.78 and 12.84 on the day of completion, 1 week, 1 month and 3 months post completion of radiation therapy. The pain reduction was significant in all the 4 groups. But as with the VAS, the pain reduction at 3 months post radiation therapy in 8 Gy in 1 fraction arm was not significant when compared to 1 week and 1month post radiation therapy (p 0.157).



Graph 4 : Rupee scale

Complete pain relief
Complete pain relief was seen in 40% of the patients. 25% of the patients in 8Gy in 1 fraction had complete relief of pain whereas the complete relief in the remaining 3 arms was 45% each.

Performance status
ECOG performance status before the commencement of radiation therapy was 3.04 (mean) in the entire study population. There was no

significant change in the performance status on the day of completion of treatment. The improvement in the performance status at 1 week post radiation therapy was significant in all the arms except 24 Gy in 6 fractions arm (p 0.157). The improvement in performance status continued till 3 months in all the 4 groups. But the improvement was not significant from 1 month to 3 months post radiation therapy. In the 8 Gy in single fraction arm the performance status failed to improve at 3 months when compared to that at 1 week post radiation therapy, but the improvement was significant in the remaining 3 arms.

Quality of life

There was improvement in the quality of life in all the arms, both in terms of function and symptoms. The mean score of symptomatic quality of life based on the EORTC BM22 module prior to start of radiation therapy was 32.77. It was reduced to 21.7, 13.08, 6.77 and 6.35 on day of completion, 1 week, 1 month and 3 months after radiation therapy (p <0.001). The score prior to radiation therapy in Arm A, Arm B, Arm C and Arm D were 38.14, 34.91, 28.85, and 29.17 respectively. There was a significant drop to 27.88, 22.92, 17.95 and 18.06 respectively in the 4 arms on the day of completion of treatment. It further improved to 15.71, 13.09, 11.86, and 11.67 at 1week post treatment and 9.29, 6.55, 5.13, and 6.11 at 1 month post treatment in the 4 arms respectively. The improvement from 1 month to 3 months was not significant but was significant from 1 week to 3 months post treatment except in the 8 Gy in 1 fraction arm (p 0.082).

Table 1: Quality of life - Symptomatic

Groups		Mean	Std. Deviation	Median(IQR)	Friedman test value	p value
8 Gy	Pre RT	38.14	14.815	33.33(27.085-50)	47.720	p<0.001
	day of completion	27.88	13.542	25(18.75-33.33)		HS
	1 week	15.71	10.086	16.67(8.33-16.67)		
	1 month	9.29	9.645	12.5(0-12.5)		
	3 months	10.90	12.790	12.5(0-14.585)		
20 Gy	Pre RT	34.91	21.468	27.085(22.9175-43.7525)	49.717	p<0.001
	day of completion	22.92	10.433	20.83(15.6275-26.0425)		HS
	1 week	13.09	6.086	10.415(8.33-16.67)		
	1 month	6.55	6.878	8.33(0-9.3725)		
	3 months	5.65	6.857	4.165(0-8.33)		
24 Gy	Pre RT	28.95	4.647	29.17(25-29.17)	50.727	p<0.001
	day of completion	17.95	4.622	16.67(12.5-20.83)		HS
	1 week	11.80	3.740	12.5(8.33-12.5)		
	1 month	5.13	4.218	8.33(0-8.33)		
	3 months	3.84	4.322	0(0-8.33)		
30 Gy	Pre RT	29.17	10.447	25(20.83-33.33)	57.021	p<0.001
	day of completion	18.06	6.804	16.67(12.5-25)		HS
	1 week	11.67	3.230	12.5(8.33-12.5)		
	1 month	6.11	4.689	8.33(0-8.33)		
	3 months	5.00	5.029	8.33(0-8.33)		

Table 2: Quality of life – Symptomatic – Wilcoxon signed rank test

		wilcoxon signed rank test p value	
8 Gy	day of completion - Pre RT	.000	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.002	.
	1 month - 1 week	.001	.
	3 months - 1 week	.082	.
	3 months - 1 month	.180	.
20 Gy	day of completion - Pre RT	.002	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.001	.
	1 month - 1 week	.002	.
	3 months - 1 week	.002	.
	3 months - 1 month	.180	.
24 Gy	day of completion - Pre RT	.000	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.001	.
	1 month - 1 week	.001	.
	3 months - 1 week	.002	.
	3 months - 1 month	.157	.
30 Gy	day of completion - Pre RT	.000	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.001	.
	1 month - 1 week	.001	.
	3 months - 1 week	.001	.
	3 months - 1 month	.157	.

The outcomes in terms of functional quality of life were similar. The scores prior to treatment in the entire study population was 40.25 and improved significantly to 48.90, 61.33, 72.17, and 73.47 on the day of completion, 1 week, 1 month and 3 months post radiation therapy respectively (p <0.001). The mean scores were39.01, 42.18, 39.01, and 40.79 respectively in Arm A, Arm B, Arm C, and Arm D. It improved to 43.96, 51.19, 48.53 and 51.91 in the respective arms on the day of completion of radiation therapy. It further improved to 58.61, 62.93, 60.44, and 63.33 at 1 week post treatment and 69.96, 73.64, 72.71, and 72.38 at 1 month post treatment. As with the symptomatic quality of life the improvement at 3 months post treatment in 8 Gy in 1 fraction arm failed to be significant when compared to that at 1 week and 1 month post radiation therapy. The improvement in functional quality of life at 3 months when compared to 1 month was significant only in the 30 Gy in 10 fractions arm (p 0.018).

Table 3 : Quality of life – Functional

Groups		Mean	Std. Deviation	Median(IQR)	Friedman test value	p value
8 Gy	Pre RT	39.01	20.262	30.95(22.62-54.765)	45.463	p<0.001
	day of completion	43.90	23.782	38.1(30.95-65.475)		HS
	1 week	58.61	18.636	54.76(42.86-73.81)		
	1 month	69.96	18.559	66.67(52.38-86.905)		
	3 months	69.80	20.261	66.67(52.38-86.905)		
20 Gy	Pre RT	42.18	17.507	42.86(27.975-51.785)	50.450	p<0.001
	day of completion	51.19	15.025	48.81(35.71-64.29)		HS
	1 week	62.93	15.505	60.715(50-76.19)		
	1 month	73.64	17.259	79.76(54.165-90.48)		
	3 months	74.15	17.192	80.95(54.76-90.48)		
24 Gy	Pre RT	39.01	7.749	40.48(38.095-42.86)	51.057	p<0.001
	day of completion	48.53	5.371	50(47.62-51.19)		HS
	1 week	60.44	9.147	64.29(52.38-67.86)		
	1 month	72.71	14.566	76.19(61.91-85.71)		
	3 months	75.64	15.187	85.71(61.91-85.906)		
30 Gy	Pre RT	43.79	16.468	40.48(28.57-52.38)	57.917	p<0.001
	day of completion	51.91	12.797	52.38(42.86-64.29)		HS
	1 week	63.33	14.643	59.52(52.38-76.19)		
	1 month	72.38	14.337	69.05(64.29-88.1)		
	3 months	75.24	14.224	73.81(64.29-88.1)		

Table 4 : Quality of life – Functional – Wilcoxon signed rank test

		wilcoxon signed rank test p value	
8 Gy	day of completion - Pre RT	.007	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.002	.
	1 month - 1 week	.001	.
	3 months - 1 week	.014	.
	3 months - 1 month	.593	.
20 Gy	day of completion - Pre RT	.002	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.001	.
	1 month - 1 week	.001	.
	3 months - 1 week	.002	.
	3 months - 1 month	.066	.
24 Gy	day of completion - Pre RT	.000	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.001	.
	1 month - 1 week	.001	.
	3 months - 1 week	.002	.
	3 months - 1 month	.180	.
30 Gy	day of completion - Pre RT	.000	.
	1 week - Pre RT	.000	.
	1 month - Pre RT	.000	.
	3 months - Pre RT	.001	.
	1 week - day of completion	.000	.
	1 month - day of completion	.000	.
	3 months - day of completion	.001	.
	1 month - 1 week	.001	.
	3 months - 1 week	.001	.
	3 months - 1 month	.018	.

Analgesic scale

The reduction in usage of analgesic was not significant in the 8 Gy in single fraction arm (p 0.406). Significant reduction was seen in the 24 Gy in 6 fraction arm (p 0.012) with reduction in score from 2.08 to 1.38 at the end of 3 months. The analgesic usage reduction was significant in 20 Gy in 5 fractions arm and 30 Gy in 10 fractions arm with reductions 2.14 to 1.21 and 2.07 to 1.33 respectively ($p<0.001$).

DISCUSSION

The primary goal in the treatment of bone metastases is pain relief and improvement in quality of life of the patient.

In our study palliative radiation therapy was found to be effective in relieving pain. Pain relief was significant in all the four arms. There was no significant difference in the pain relief when the various fractionation schedules were compared. Overall 40% of the patients had complete pain relief at the end of 3 months. The complete pain relief was 25% in the 8 Gy in single fraction arm whereas 45% of the patients in each of the multi-fraction arms had complete pain relief. The results were comparable with that of the other studies. RTOG 9714 trial showed complete response in 17% of the patients whereas 49% of the patients had partial response.8 There was no difference in response between the 8 Gy in 1 fraction and 30 Gy in 10 fractions arms at the end of 3 months. Nielson et al found that at the end of 3 months post radiation therapy 73% of patients in 8 Gy arm had pain relief whereas 76% had pain relief in the 20 Gy arm.[7]

Dutch Bone Metastases Study analysed the complete pain relief at the end of 1year post radiation therapy and found 33% of patients in 24 Gy arm versus 37% of patients in 8 Gy arm had complete pain response.[6]

RTOG 7402 study showed that 54% of the patients achieved a complete pain relief and 83% of the patients had experienced partial pain relief.[5]

Table 5: Complete pain relief

Fractionation schedule	Our study	RTOG 9714	Dutch Bone Metastases Study	RTOG 7402
8Gy in 1#	25%	15%	37%	-
20Gy in 5#	45%	-	-	54%
24Gy in 6#	45%	-	33%	-
30Gy in 10#	45%	18%	-	54%

The Rupee scale has also been used in this study for comparison of pain response among the various arms. The results have been similar to that with VAS. There are no trials comparing the effectiveness of fractionation schedules in the treatment of bone metastases using the Rupee scale. As the Rupee scale has only 5 scores when compared to 11 scores in VAS it may be a less effective tool. However, it may be more useful in the Indian scenario as it is easily understood by all.

Improvement in the performance status was seen in all the four treatment arms. The improvement was more in the multi-fraction arms when compared to the single fraction arm but was not statistically significant.

There has been improvement in the quality of life following radiation therapy.

The improvement has been significant in all the four arms but no statistically significant difference has been found among the 4 arms of the study. Nielson et al found no change in the quality of life post radiation therapy between the 8 Gy in single fraction and 20 Gy in 5 fractions arms.[7]

Dutch Bone Metastases Study compared the quality of life in the patients treated with 8 Gy in 1 fraction and 24 Gy in 6 fraction for bone metastases. They concluded that there was no significant difference in the overall quality of life between the two treatment groups.[6]

The scales used for assessment of quality of life in each of the studies were different. EORTC QLQ-BM22 module was used in our study. The reliability and validity of this module has been tested and has been recommended for usage in assessment of quality of life in painful bone metastases.[9]

In our study 33.75% of the primary site comprised of breast, 25% from lung, 18.75% from head and neck, 12.5% from prostate. The primary site has an impact on effect of radiation therapy in treatment of bone metastases.2 The RTOG 9714 study included patients with metastases either from breast or prostate only as these subset of patients tend to have a longer survival and thus allowing adequate follow up and assessment response and toxicity of the treatment.[8]

The usage of analgesics during and after radiation therapy was assessed. A significant reduction in usage of analgesics was seen in the multi-fraction arms, whereas the reduction was not significant in the single arm. However, when the analgesic usage in the four arms were compared with each other no significant changes were observed.

CONCLUSION

Various radiation fractionation schedules used in the treatment of painful bone metastases have been effective in reducing the pain.

The reduction in pain by various fractionation schedules are similar and no statistically significant difference was noted.

Quality of life improved in all the four treatment arms post radiation therapy.

8 Gy in single fraction may be considered for treatment of painful bone metastases.

The assessment of pain by Rupee scale may be used in the Indian scenario.

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