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Original Research Article

The Comparative Study between 20 Gy in 5 Fractions versus 8 Gy in Single Fraction in Bony Metastasis with Zoledronic Acid

Vikas Pal[1], Ashar Iqbal Lodi[2], Saurabh Karnawat[3], Ramesh Arya[4]

[1]Consultant, Department of Radiation Oncology, Jhansi Cancer Centre and Multispeciality Hospital, Jhansi, UP

[2]Assistant Professor, Department of Radiation Oncology, Sri Aurobindo Medical College & Post Graduate Institute, Indore, MP

[3]Assistant Professor, Department of Radiation Oncology, Ruxmaniben Deepchand Gardi Medical College, Ujjain, MP

[4]Professor and Head, Department of Radiation Oncology, Mahatma Gandhi Memorial Medical College, Indore, MP

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Corresponding author: Dr. Saurabh Karnawat

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Abstract

Background: Metastasis is the characteristic feature of primary cancer. Bony metastasis is more commonly seen in breast and prostate carcinomas. The incidence is very high and varies from 65-70%. 40% of patients with bony metastasis experience pain. External beam radiotherapy provides pain relief in 80-90%, with complete pain relief in 50-60% patients. Palliative therapy with zoledronic acid can be given as a single-dose treatment (8 Gy in 1 fraction) and multiple fractions (20 Gy in 5 fractions) for pain relief. Single-fraction treatment has been found advantageous. Hence, the present study was undertaken to compare single and multiple-fraction doses with regard to the response and quality of life in patients with bony metastasis.

Methodology: The prospective, randomized, comparative study was conducted during a 1-year study period. 100 patients with primary malignancy were included and randomized to Arm-A (8 Gy in 1 fraction) or Arm-B (20 Gy in 5 fractions). Pain assessment, Quality of Life and functional outcome were assessed. Independent means compared using Unpaired 't' test and proportional comparison done using Fisher's Exact test. A p value of <0.05 was taken as statistically significant.

Results: Pain score in both the groups decreased, but was significantly lower in Arm-A ($P < 0.05$). Recurrence rate was 8% in Arm-A and 18% in Arm-B, but it was not significant ($P > 0.05$). Global Health Status showed improvement in both arms, but difference was not significant ($P > 0.05$). Improvements in physical, role functioning, emotional functioning, social functioning were seen in both arms, but was better in Arm-A. Symptoms scales/items, nausea/vomiting and diarrhea scores also showed improvement in both the arms, but again was better in Arm-A.

Conclusion: Palliative radiotherapy with single-fraction treatment was much better as compared to multiple-fraction treatments. It was cost effective, required lesser hospital stay and had lower recurrence rate. Pain was better controlled in single-fraction treatment compared to multiple-fraction treatment.

Keywords: Palliative radiotherapy, Single-fraction treatment, Multiple-fraction treatment, Zoledronic acid, Recurrence of carcinoma, Pain relief.

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Introduction

A characteristic feature of primary cancer is metastasis, which mostly metastasizes to the lung, liver, and bone. Bony metastasis is commonly seen in breast and prostate carcinomas. The incidence of bone metastasis depends on the primary site of the cancer. In breast and prostate cancer, the incidence of metastasis varies from 65-70% to 30-40% in lung, thyroid, and renal carcinomas. Overall, among patients who died due to breast, prostate, and lung carcinoma, metastasis was seen in up to 85% and between 3–15% in gastrointestinal malignancies. Bone metastasis is seen in the axial skeleton (spine, pelvis, and ribs) and appendicular skeleton, with the lumbar spine being the most common site. The proximal femur is the most common bone affected in the appendicular skeleton. Toes' involvement is seen in genitourinary primaries. Breast cancer and prostate

cancer is commonest primary which leads to death in bone metastasis patients. 40% of patients with bony metastasis experience pain. Almost every patient with a bone metastasis from a primary malignancy requires palliative care and pain management. Usually, multidisciplinary treatments are required for management, which may include radiotherapy, surgery, chemotherapy, bisphosphonates, hormonal treatment, radioisotopes, analgesics, etc.

After radiation therapy, nearly 80-90% of patients with bony metastasis experience partial pain relief, and nearly 50% experience complete pain relief. Around 2/3rds of the patients experience pain improvement, with complete and long-lasting pain relief in about 50% of the patients.[1] External beam radiotherapy to a local field provides pain relief in 80-90% of cases, with complete pain relief in 50-60% of cases.[1,2]

Palliative therapy with zoledronic acid can be given as a single fraction (SF) of 8 Gy or as multiple fractions (MF) of 20 Gy in 5 fractions. Arcangeli et al.[3] reported that single-dose treatments of 8 Gy provided similar pain-relief as multi-dose treatments of 20 Gy in 5 fractions or 30 to 24 Gy in 10 to 8 treatment fractions. After a single-fraction treatment, the duration of treatment is reduced, and retreatment is possible. In patients with initial low pain scores, the treatment response rates were better, although there was no consistent dose-response relationship for palliation of bone metastasis.

Two treatment schedules of zoledronic acid radiotherapy were compared to assess response and quality of life in patients with bony metastasis. We also assessed the occurrence and survival time in these patients after the treatment.

Material and Methods

The present prospective, randomized, comparative study was conducted in Government Cancer Hospital, Mahatma Gandhi Memorial Medical College, and Indore during the study period of 1 year. One hundred patients with primary malignancy presenting with radiologically proven painful bony metastasis or patients with known / unknown primary malignancy with radiologically proven bone metastases were included in the patients. The study was approved by the Institutional Ethics Committee of the institution.

The inclusion criteria for the study were: age more than 18 years; painful bony metastasis in a proven case of primary malignancy and a proven case of multiple myeloma; Serum creatinine level less than 2.0 mg/dl; Leucocyte count more then 3500/cubic mm; Haemoglobin more than 10 gram/dl; Platelets more then 100000/cubic mm and Total bilirubin less than 2.5 mg /dl; while Pregnant and lactating women; Laboratory evidence of renal disease; Previous radiotherapy to the region of bone metastasis which will be treated in the study; Previously received or currently receiving oral or iv bisphosphonate therapy; Cord compression case; Karnofsky performance status < 40; Pathological fracture or impending fracture at the site of treatment or there to be planned surgical excision; and Patient and/or his/her legally acceptable representative not willing to provide voluntary written informed consent to participate in the study were excluded from the study.

The patients were randomised into two groups using computer generated numbers: Arm-A and Arm-B. Arm-A patients received 8 Gy single fraction and zoledronic acid 4 mg. Arm-B patients received 20 Gy in 5 fractions 4 Gy per fraction and zoledronic acid 4 mg.

Patients of both arms received zoledronic acid in a dosage of 4 mg at an interval of 28 days as a 15 minutes infusion from day-1 of radiotherapy till the last follow-up visit. Only when the complete hemogram and renal function were found to be within normal limits was a zoledronic infusion administered.

After completion of radiotherapy, pain assessment was done using a visual analogue pain scale and quality of life by EORTC QLQ-30 questionnaires version 3.0, at 0 weeks, 8 weeks, and 16 weeks from the start of radiation. The functional outcome was assessed using Karnofsky Performance Status.[4]

The comparison of means between the groups was done using Unpaired ‘t’ test, proportional comparison was done using Fisher’s Exact test. A p value of <0.05 was taken as statistically significant. All the patients underwent treatment free of cost, as it is a state government run hospital. The present study was not funded by any pharmaceutical company or any institution. All patients were enrolled in the study after obtaining voluntary written informed consent. All the rights of the patients were held. All personal information were kept confidential.

Results

We included 50 patients each in Arm-A and Arm-B after randomization. In Arm-A, the majority of the patients were in the age group 61-80, while in Group-B, the majority of them were in the age group 41-60 years. (Table 1) Males were more numerous in both arms than females.

Table 1: Distribution according to age

Age	Arm-A		Arm-B		Total	
	No.	%	No.	%	No.	%
<=20 years	2	4.0	2	4.0	4	4.0
21-40 years	9	18.0	9	18.0	18	18.0
41-60 years	18	36.0	29	58.0	47	47.0
61-80 years	21	42.0	10	20.0	31	31.0
Total	50	100.0	50	100.0	100	100.0

In Arm-A, 4% of patients had a Karnofsky Performance Status score of 70, 26% had a score of 60, 28% had a score of 50, 24% had a score of 40, and 18% had a score of 30. In Arm-B, 14% of patients had a Karnofsky Performance Status score of 70, 30% had a score of 60, 32% had a score of 50, 20% had a score of 40, and 4% had a score of 30. In Arm-A, 30.0% of patients had a primary in the lung, 18.0% in the breast, and 8.0% had Ewing Sarcoma as the primary. In Arm-B, 14 (28.0%) patients had primary in the prostate, 11 (22.0%) had primary in the breast, and 5 (10.0%) had primary in the lung. The rest of the primaries are mentioned in the given table. (Table 2)

Table 2: Distribution according to primary

Primary	Arm-A		Arm-B		Total	
	No.	%	No.	%	No.	%
Anal canal	0	0.0	2	4.0	2	2.0
Brain	2	4.0	0	0.0	2	2.0
Breast	9	18.0	11	22.0	20	20.0
Ewing Sarcoma	4	8.0	0	0.0	4	4.0
Gall bladder	1	2.0	0	0.0	1	1.0
HCC	1	2.0	0	0.0	1	1.0
Lung	15	30.0	5	10.0	20	20.0
Multiple Myeloma	2	4.0	0	0.0	2	2.0
Pancreas	2	4.0	0	0.0	2	2.0
Penis	0	0.0	4	8.0	4	4.0
Prostate	3	6.0	14	28.0	17	17.0
RCC	2	4.0	2	4.0	4	4.0
Rectum	0	0.0	2	4.0	2	2.0
STS	1	2.0	0	0.0	1	1.0
Suprarenal mass	2	4.0	0	0.0	2	2.0
Thyroid	0	0.0	2	4.0	2	2.0
Unknown	5	10.0	6	12.0	11	11.0
Urinary bladder	1	2.0	0	0.0	1	1.0
Wilms Tumor	0	0.0	2	4.0	2	2.0
Total	50	100.0	50	100.0	100	100.0

In Arm-A, 70% of patients had metastasis in the spine, 16% in the hip, 6% in the femur, and 2% each in the elbow, gluteal, and sacrum, respectively. In Arm-B, all patients had metastasis in the spine. Metastasis in the spine was seen in the majority of the patients in both groups. (Table 3)

Table 3: Distribution according to metastasis

Metastasis	Arm-A		Arm-B		Total	
	No.	%	No.	%	No.	%
Elbow	2	4.0	0	0.0	2	2.0
Femur	3	6.0	0	0.0	3	3.0
Hip	8	16.0	0	0.0	8	8.0
Ribs	1	2.0	0	0.0	1	1.0
Spine	35	70.0	50	100.0	85	85.0
Tibia	1	2.0	0	0.0	1	1.0
Total	50	100.0	50	100.0	100	100.0

Complete response was seen in 38% in Arm-A and 24% in Arm-B, partial response in 44% in Arm-A and 44% in Arm-B, progression in 4% in Arm-A and 8% in Arm-B and no response in 14% in Arm-A and 14% in Arm-B. The mean pain score (as assessed using the Visual Analogue Scale) was comparable between the two arms at Week-0 and at Week-8 ($P > 0.05$), while it was significantly lower in Arm-A compared to Arm-B at Week-16 ($P = 0.018$). In both groups, there was a decrease in the mean pain score from Week-0 to Week-16. In Arm-A, the recurrence rate was 8%, while in Arm-B, it was 18%. There was no statistically significant difference in recurrence rate between the two arms ($P = 0.234$).

Improvement in the Global Health Status was seen in both arms from Week-0 to Week-16, but the improvement was not statistically significant at each follow-up between the two arms ($P > 0.05$). The physical and role functioning scores showed improvement from Week-0 to Week-16 in both the arms, but the difference was statistically not significant at each follow-up between the two arms ($P > 0.05$). (Table 4) The emotional functioning score showed improvement in both arms from Week-0 to Week-16. The mean emotional functioning score was better in Arm-A at Week-0 and Week-8 compared to Arm-B ($P < 0.05$), while at Week-16, the mean emotional functioning score was comparable between the two arms ($P > 0.05$). (Table 4)

The social functioning score showed improvement in both arms from Week-0 to Week-16. The mean social functioning score was comparable between the two arms at Week-0 and Week-16 ($P > 0.05$); while the mean social functioning score was significantly higher in Arm-A compared to Arm-B at Week-8 ($P < 0.05$). (Table 4)

Table 4: Comparison of functional scales

Functional Scales	Follow-up	Arm-A	Arm-B	t value	P value
Physical Functioning Score	Week-0	47.73 ± 23.33	40.79 ± 17.34	1.687, df=98	0.095, NS
	Week-8	59.64 ± 25.65	52.47 ± 22.02	1.480, df=95	0.142, NS
	Week-16	70.04 ± 27.78	63.06 ± 28.79	1.183, df=90	0.240, NS
Role Functioning Score	Week 0	30.99 ± 19.64	31.00 ± 22.59	-0.002, df=98	0.998, NS
	Week 8	46.18 ± 23.96	40.07 ± 27.44	1.165, df=95	0.247, NS
	Week 16	73.25 ± 35.17	65.31 ± 39.88	1.011, df=90	0.315, NS
Emotional Functioning Score	Week 0	46.51 ± 31.54	32.33 ± 22.19	2.600, df=98	0.011*
	Week 8	56.03 ± 30.78	43.68 ± 29.35	2.022, df=95	0.046*
	Week 16	71.27 ± 32.07	65.12 ± 34.74	0.873, df=88	0.385, NS
Social Functioning Score	Week 0	37.06 ± 22.51	32.01 ± 24.71	1.069, df=98	0.288, NS
	Week 8	52.84 ± 28.31	38.94 ± 31.15	2.295, df=95	0.024*
	Week 16	73.47 ± 34.41	62.62 ± 42.15	1.349, df=90	0.181, NS

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

A comparison of symptoms scales/items was performed between the two arms. The mean fatigue score, pain score, dyspnea score, insomnia scores, and appetite loss scores showed improvement in both the groups from Week-0 to Week-16, but there was no statistically significant difference between the two arms at all the follow-ups ($P > 0.05$). (Table 5) Nausea/vomiting scores and constipation scores were comparable between the two arms at Week-0 and Week-16 ($P > 0.05$), while the mean nausea/vomiting scores were significantly lower in Arm-A at Week-8 compared to Arm-B ($P < 0.05$). A diarrhoea score could be assessed at Week-0 and Week-8 only; while a financial difficulty score was assessed at Week-8 and Week-16, and there was no statistically significant difference between the two arms ($P > 0.05$). (Table 5)

Table 5: Comparison of Symptoms Scales / items

Symptoms Scales / Items	Follow-up	Arm-A	Arm-B	t value	P value
Fatigue score	Week 0	56.21 ± 27.09	60.88 ± 28.61	-0.839, df=98	0.404, NS
	Week 8	31.91 ± 23.94	38.66 ± 32.01	-1.172, df=95	0.244, NS
	Week 16	19.25 ± 22.02	22.68 ± 24.84	-0.701, df=90	0.485, NS
Nausea / Vomiting score	Week 0	17.00 ± 31.68	26.46 ± 32.91	-1.465, df=98	0.146, NS
	Week 8	4.96 ± 11.47	12.99 ± 17.91	-2.613, df=95	0.010*
	Week 16	4.08 ± 8.82	6.04 ± 9.48	-1.025, df=90	0.308, NS
Pain Score	Week 0	68.67 ± 26.65	76.67 ± 24.03	-1.576, df=98	0.118, NS
	Week 8	41.13 ± 19.63	44.00 ± 18.06	-0.749, df=95	0.455, NS
	Week 16	23.72 ± 18.62	22.35 ± 18.47	0.354, df=90	0.724, NS
Dyspnea Score	Week 0	0.00 ± 0.00	6.00 ± 22.02	-1.927, df=98	0.057, NS

	Week 8	23.70 ± 37.35	23.49 ± 33.40	0.029, df=87	0.977, NS
	Week 16	17.02 ± 32.51	19.33 ± 30.19	-0.363, df=95	0.717, NS
Insomnia Score	Week 0	22.92 ± 30.10	34.75 ± 71.54	-1.055, df=93	0.294, NS
	Week 8	18.44 ± 26.76	19.33 ± 26.17	-0.166, df=95	0.869, NS
	Week 16	14.81 ± 25.19	19.56 ± 27.73	-0.853, df=89	0.396, NS
Appetite Loss Score	Week 0	5.99 ± 16.06	14.89 ± 27.64	-1.952, df=95	0.054, NS
	Week 8	9.93 ± 20.76	14.67 ± 27.90	-0.944, df=95	0.347, NS
	Week 16	12.59 ± 21.66	18.43 ± 25.82	-1.173, df=90	0.244, NS
Constipation Score	Week 0	12.59 ± 25.91	21.98 ± 33.53	-1.499, df=90	0.137, NS
	Week 8	4.67 ± 15.08	15.33 ± 27.11	-2.431, df=98	0.017*
	Week 16	6.38 ± 13.24	13.99 ± 27.02	-1.746, df=95	0.084, NS
Diarrhea Score	Week 0	0.00 ± 0.00	6.00 ± 23.99	-1.769, df=98	0.080, NS
	Week 8	9.63 ± 24.23	6.00 ± 23.99	0.733, df=93	0.465, NS
	Week 16	0.00 ± 0.00	0.00 ± 0.00	-	-
Financial Difficulties Score	Week 0	0.00 ± 0.00	0.00 ± 0.00	-	-
	Week 8	7.09 ± 16.93	14.66 ± 31.70	-1.454, df=95	0.149, NS
	Week 16	5.92 ± 12.88	15.59 ± 31.74	-1.901, df=90	0.060, NS

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant

Discussion

Pain at the site of metastasis is the most common symptom in patients with bony metastasis. The main goals of treatment are maximum pain relief, with minimum morbidity and a shorter hospital stay. Treatment of bony metastasis with traditional methods necessitates a longer hospital stay in patients in poor general condition and has significant financial implications.

The present study was a comparison of a single fraction of 8 Gy and 5 fractions of 4 Gy each (total 20 Gy) in patients with bony metastasis in terms of pain relief and quality of life assessment.

The prevalence of metastatic bone disease is highest in breast and prostate cancer, together accounting for 80% of all cases.[5] In our study most common primary cancer which leads to bone metastasis is Breast (20.0%), Lungs (18.0%), Prostate (17.0%), Cancer from unknown origin (11.0%), renal cell carcinoma (4.0%), carcinoma of penis (4.0%), Ewing sarcoma (4.0%), Carcinoma of pancreas (2.0%), Rectum (2.0%), Anal canal (2.0%), Brain(2.0%), suprarenal mass (2.0%), Multiple myeloma (2.0%), Wilms tumor (2.0%), Soft tissue sarcoma (1%), Hepatocellular carcinoma(1%), carcinoma of gall bladder(1%), Ca urinary bladder (1%).

Body et al.[6] in their study reported an incidence of bony metastasis from 47 to 85% in breast cancer, 33 to 85% in prostate cancer and 32 to 60% in lung cancer patients. The incidence of bony metastasis in breast, lung and prostate cancer was lower in the present study as compared to Body. The reason for lower incidence could be due to smaller sample size.

The most common sites of bone metastasis in our study were the vertebral (85.0%) and non-vertebral (15.0%). In non-vertebral site includes elbow, femur, tibia, hip, ribs. In Roos et al.[7] study, the index sites were spine (89%), ribs (9%) and others (2%). In our study, the overall response (complete plus partial) rate to palliative radiotherapy was 70%, which is similar in both Arm-A and Arm-B. Our findings are very similar to the overall response of 45–61% in a single fraction (8 Gy) and 53–70% in multiple fractions (20 Gy in 5 fractions).[7]

A complete response was seen in 36% and a partial response was seen in 44% of the patients, which was equivalent to the Roos et al. [7] study, which reported a complete response of 18–34%. The Dutch Bone Metastases Study [8] showed a complete response rate of 35% and a systematic review done by Sze et al.[9] showed a complete response rate of 32–34%.

In Arm-A, 28% of patients showed complete response, 44% showed partial response, 4% showed progression of the disease, and 14% showed no response. In Arm-B, 34% patients showed complete response, 44% showed partial response, 8% showed progression of the disease and 14% showed no response. In Badzio et al.[10] study, complete pain relief was achieved in 36% of patients in the single fraction group and 39% of patients in the multiple fraction group. 33% of patients in the single fraction group and 29% of patients in the multiple fraction group experienced remarkable pain relief; and 14% of patients in the single fraction group and 16% of patients in the multiple fraction group experienced moderate pain relief.

The mean pain score was comparable between Arm-A and Arm-B at Week-0 and Week-8, while it was significantly lower in Arm-A compared to Arm-B at Week-16 ($P < 0.05$).

The Global Health Status showed better improvement in Arm-A from Week-0 to Week-16. Similarly, the physical functioning score, role functioning score, and cognitive functioning score showed better improvement in Arm-A from Week-0 to Week-16, but there was no significant difference in these parameters between Arm-A and Arm-B at all follow-ups ($P > 0.05$).

The emotional functioning score showed improvement in both arms from Week-0 to Week-16. The mean emotional functioning score was better in Arm-A at Week-0 and Week-8 compared to Arm-B ($P < 0.05$), while at Week-16, the mean emotional functioning score was comparable between the two arms ($P > 0.05$).

The social functioning score showed improvement in both arms from Week-0 to Week-16. The mean social functioning score was comparable between the two arms at Week-0 and Week-16 ($P > 0.05$); while the mean social functioning score was significantly higher in Arm-A compared to Arm-B at Week-8 ($P < 0.05$).

Comparison of symptomatic scales in both arms of symptoms like fatigue score, pain score, insomnia score, diarrhoea score, loss of appetite score, constipation score, and fatigue score decreased from Week 0 to Week 16 in both the groups, with a slightly better improvement seen in Arm-A in comparison to Arm-B, but there was no statistically significant difference seen between the two groups at all the time intervals ($p > 0.05$).

Nausea/vomiting scores and constipation scores were comparable between the two arms at Week-0 and Week-16 ($P > 0.05$), while the mean nausea/vomiting scores were significantly lower in Arm-A at Week-8 compared to Arm-B ($P < 0.05$). A diarrhoea score could be assessed at Week-0 and Week-8 only; while a financial difficulty score was assessed at Week-8 and Week-16, and there was no statistically significant difference between the two arms ($P > 0.05$).

The limitations of the study were smaller sample size, which did not allow for detailed statistical analysis of performance status, side effects, duration of treatment steroid use. Also due to shorter duration of study, late complications and compliance of treatment could not be evaluated.

Conclusion

Single fraction (8 Gy in 1 fraction) compared to multiple fractions (20 Gy in 5 fractions) provided slightly better results in terms of overall response rate. The Global Health Status, Functional Health Scale including its subscales was better in the single fraction group compared to the multiple fraction group, though statistically it was not significant. Other assessment tools like the symptom scale, constipation score, and loss of appetite scores were found to be better in the single fraction group. The financial difficulties score was also lower in the single fraction group, as the duration of hospital stay was shorter and required optimal symptom management, while the multiple fraction group required a longer hospital stay and additional care with symptoms management.

No additional benefit in pain due to bone metastasis was seen in single fraction group compared to multiple fraction group, but quality of life was much better in patients who received single fraction of 8 Gy.

For more significant and more reliable result we recommend a study with larger sample size and longer follow-ups.

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