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Palliative Radiotherapy for Bone Metastases – A Prospective Study Comparing Different Fractionation Schedules

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Abstract: *Bone metastasis is a common manifestation of malignancy, causing various morbidities. The mainstay of treatment of uncomplicated painful bone metastases is palliative radiotherapy. The purpose of this study is to assess and compare the efficacy of different radiotherapy fractionation schedules in terms of pain relief. 80 patients were randomised to 4 different radiotherapy fractionation schedules of8Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions and 30 Gy in 10 fractions. Pain was assessed by Visual Analog Scale (VAS), performance status and analgesic usage. Significant pain reduction was seen in all the arms. Mean VAS score prior to radiotherapy was 5.23, and this reduced to 2.88 on treatment completion.Post radiotherapy, the scores reduced to 0.79 and 0.81, at 1 month and 3 months respectively. Complete pain relief was seen in 40% of the patients. 25% of the patients in 8 Gy in 1 fraction had complete pain relief, whereas in the remaining 3 arms this was 45% each. It was concluded that the different fractionation schedules of radiotherapy used in the treatment of painful bone metastases have been found to be effective in reducing pain, with no significant difference seen between the groups.*

Keywords: *Fractionation, Metastases, Pain, Radiotherapy, VAS*

I. Introduction

Bone is the third most common organ affected by metastasis from a malignancy.[1]The common primary sites for bone metastases are from the breast and prostate which account for upto 70%.Commonly, the axial skeleton is involved, with the lumbar spine being the most frequent site.[2]Bone metastases can cause various morbidities like pain, pathological fractures, spinal cord compression, hypercalcemia and can affect the quality of life.[1,2] The treatment for bone metastases is mainly palliative, and includes medical treatment, radiation therapy, surgery, and bone targeted treatment.[3] The mainstay of treatment of uncomplicated painful bone metastases is external beam radiotherapy.[4] Improvement in pain is seen in 60% to 80% of the patients following radiotherapy.[2] There are different radiotherapy fractionation schedules for the palliation of bone metastases, and they have found that 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]

This study assessed and compared the efficacy of four different radiotherapy fractionation schedules in terms of pain relief in patients with painful bone metastases treated at our institution.

II. Materials And Methods

All the patients with histologically or radiologically provenbone metastases at the Department of Radiotherapy in Father Muller Medical College, Mangalore, from September 2014 to January 2016, were taken up for the study.Patients with bone metastasis from any primary cancer were included. Patients with prior radiotherapy to the region concerned were excluded from the study. 80 patients, with 20 patients in each group, satisfying the inclusion and exclusion criteria were prospectively randomized to four groups: Arm A - 8 Gy in 1 fraction, Arm B - 20 Gy in 5 fractions, Arm C - 24 Gy in 6 fractions, Arm D - 30 Gy in 10 fractions. In all patients, the primary malignancy was histopathologically confirmed and the metastases were histologically or radiologically verified. Informed consent was obtained from all the patients. Each patient underwent clinical evaluation which included detailed history, physical examination, laboratory investigations, and imaging studies. Baseline pain, analgesic usage, and any other significant symptom were recorded prior to starting treatment. 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 monthly after completion of treatment, and patient's general condition, pain reduction, and analgesic usage was recorded at 1 and 3 months post radiotherapy.

Data Analysis – the collected data was analyzed by analysis of variance, Friedman test, Wilcoxon signed rank test and Kruskal-Wallis test.

III. Results

The study comprised of 80 patients with 20 patients each in the four arms. The mean age was 53.66 years. 52.5% of the patients were males and 47.5% females.In the entire study population, 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.In the 8 Gy in single fraction arm, 45% of the metastases were from breast. Head and neck comprised of 25%, prostate 20%, lung 5%, and unknown primary 5%.In the 20 Gy in 5 fractions arm breast contributed to 35% of the metastases. Liver, head and neck, prostate, cervix, stomach comprised of 25%, 15%, 10%, 10%, 5% respectively.50% of the metastases in the 24 Gy in 6 fractions arm were from the lung; head and neck comprised of 20%, breast 15%, and prostate, esophagus, ovary contributed to 5% each.In the 30 Gy in 10 fractions arm 40% of the metastases were from the breast, 20% from the lung, 15% from prostate, 15% from head and neck, 5% from the liver and 5% from unknown primary.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, constituting 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) - Pain reduction was significant in all the arms (Table 1). The mean VAS score was 5.23 prior to start of treatment. This score reduced to 2.88 at the completion of treatment and further dropped to 0.79, and 0.81 at 1 month and 3 months post completion of radiotherapy.The mean VAS score prior to start of treatment in the each of the arms were 5.31, 5.21, 5.54 and 4.87 in Arm A, Arm B, Arm C and Arm D, respectively. On completion of radiotherapy, 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 mean VAS scores at 1 month post radiation therapy was 1.15, 0.71, 0.62 and 0.67 in each arm respectively. Pain reduction at 3 months post radiation therapy was significant with VAS scores of 1.54, 0.57, 0.54, 0.60in each arm respectively. But the reduction was not significant when compared to the scores at 1 month after treatment. There was also no significant difference in the pain relief when the various fractionation schedules were compared.

Table 1: Pain assessment by Visual Analog Scale)

Groups		Mean	Std. Deviation	Median(IQR)	Friedman test value	p value
8 Gy	Pre RT	5.31	1.843	5(4-7)	41.111	p<0.001
	day of completion	3.00	1.414	4(2-4)		HS
	1 week	1.69	1.032	2(1-2)		
	1 month	1.15	1.214	1(0-2)		
	3 months	1.54	2.025	1(0-2)		
20 Gy	Pre RT	5.21	1.528	5.5(4-6)	51.245	p<0.001
	day of completion	3.29	1.204	3.5(2-4)		HS
	1 week	1.64	1.082	2(1-2)		
	1 month	.71	.914	0(0-2)		
	3 months	.57	.852	0(0-1.25)		
24 Gy	Pre RT	5.54	1.198	6(4-6)	49.299	p<0.001
	day of completion	2.77	.927	2(2-4)		HS
	1 week	1.46	.776	2(1-2)		
	1 month	.62	.768	0(0-1)		
	3 months	.54	.776	0(0-1)		
30 Gy	Pre RT	4.87	1.302	5(4-6)	54.533	p<0.001
	day of completion	2.47	.834	2(2-3)		HS
	1 week	1.47	.743	2(1-2)		
	1 month	.67	.816	0(0-1)		
	3 months	.60	.828	0(0-1)		

Complete pain relief was seen in 40% of the entire study population. 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.

The reduction in usage of analgesics 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). (Table 2)

Table 2 : Analgesic usage

Groups		Mean	Std. Deviation	Median(IQR)	Friedman test value	p value
8 Gy	Pre RT	2.08	.862	2(2-3)	4.000	.406
	day of completion	2.15	.899	2(2-3)		NS
	1 week	2.15	.899	2(2-3)		
	1 month	1.77	1.092	2(1-2.5)		
	3 months	1.85	1.144	2(1-3)		
20 Gy	Pre RT	2.14	.770	2(2-3)	25.333	p<0.001
	day of completion	2.07	.829	2(2-3)		HS
	1 week	1.93	.997	2(1.75-3)		
	1 month	1.29	1.139	1.5(0-2)		
	3 months	1.21	1.251	1(0-2.25)		
24 Gy	Pre RT	2.08	.277	2(2-2)	12.791	.012
	day of completion	2.00	.577	2(2-2)		sig
	1 week	2.00	.577	2(2-2)		
	1 month	1.46	1.050	2(0.5-2)		
	3 months	1.38	1.121	2(0-2)		
30 Gy	Pre RT	2.07	.799	2(2-3)	22.667	p<0.001
	day of completion	2.07	.799	2(2-3)		HS
	1 week	2.07	.799	2(2-3)		
	1 month	1.73	.884	2(1-2)		
	3 months	1.33	1.113	2(0-2)		

IV. Discussion

The primary goal in the treatment of bone metastases is pain relief. In our study external beam radiation therapy was found to be effective in palliating 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 other arms had complete pain relief. The results were comparable with that of the other studies.

In the RTOG 9714 trial complete pain relief was achieved in 17% of the patients whereas 49% of the patients had partial relief. 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.[8]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]

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 8 Gy single fraction arm. However, when the analgesic usage in the four arms were compared with each other no significant changes were observed.

Among the patients recruited in our study 8 patients required reirradiation for recurrence of pain after response to initial radiation therapy. Of these patients 2 patients had received 8 Gy in single fraction, 4 patients had received 20 Gy in 5 fractions and 2 patients had received 30 Gy in 10 fractions. Reirradiationwas found to be more in the multi-fraction arm than in the single fraction. Whereas most of the other studies have observed higher reirradiation rates in the single fraction arm. In RTOG 9714 trial the reirradiation was twice more common in the 8 Gy in single fraction arm (18%) than in the 30 Gy in 10 fraction arm (9%).[8] Nielson et al. in their study found 21% of the patients in the 8 Gy in single fraction arm to be irradiated whereas 13% of the patients in the 20 Gy in 5 fractions arm were reirradiated.[7]

Our study showed that different radiotherapy fractionation schedules used in the treatment of painful bone metastases have been effective in reducing pain. This reduction was found to be similar between the groups with no significant difference between the four groups.

V. Conclusion

Different radiotherapy fractionation schedules used in the palliation of painful bony metastases have been found to be effective in reducing pain, with no significant difference between the various groups, andreirradiation rates were not found to be higher in the 8 Gy in single fraction arm.

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