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Comparison of twice weekly palliative RT versus continuous hypofractionated palliative RT for painful bone metastases

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ABSTRACT

Background: Palliative hypofractionated radiotherapy (RT) is an effective mode of treating painful bone metastasis. While 8 Gy single fraction radiation is often effective for the same, for complicated bone metastases a protracted fractionated regimen is preferred, of which 30 Gy/10#/2weeks or 20 Gy/5#/1 week are the most common worldwide. However such schedules add to the burden of already overburdened radiation treatment facilities in a busy center, wherein alternative logistic favourable schedules with treatment on weekends are preferred. Here we compare the efficacy of a twice weekly schedule to that of standard continuous 20 Gy/5 #/1 week schedule in terms of pain relief, response and quality of life.

Materials and methods: A prospective non randomized study was undertaken from Jan 2018 to May 2019, wherein eligible patients of complicated bone metastases received palliative radiotherapy of 20 Gy/5#, either continuously for 5 fractions from Monday to Saturday or twice weekly, Saturday and Wednesday, starting on a Saturday over about 2 weeks. Pain relief was assessed by the Visual Analogue Scale (VAS) and FACES pain scale recorded prior to starting palliative RT and at 4 weeks, 3 months and 6 months.

Results: Thirteen patients received continuous Hypofractionated RT while 16 received it in a twice weekly schedule. Spine was the most common site receiving palliative Radiation (27/29), while breast cancer was the most common primary (16/29). The demographic and the baseline characteristics were comparable. The mean pain score decline at 4 weeks was 2.56 ± 1.1 and 2.71 ± 0.52 in the 5-day and the two-week schedule, respectively (p = 0.67).

Conclusion: A twice weekly schedule over about two weeks was found to be equivalent in pain control and response to the standard fractionated palliative radiation and, thus, can be safely employed in resource constrained, busy radiotherapy centers.

Key words: bone metastases; palliative care; radiation oncology department

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Introduction

Bone metastasis is a common complication in case of advanced cancers [1]. Skeleton is the third most common site of metastatic disease after lung and liver. Eighty percent of bone metastases originate from prostate, breast and lung [1, 2]. Bladder, kidneys, thyroid, lymphomas, and sarcomas are other malignancies which often metastasise to bone [3]. Axial skeleton is affected most commonly due to bone metastasis, with the lumbar spine being most frequently affected. Among

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the regions of the appendicular skeleton, it is the proximal femur that is most frequently affected [2]. Bone metastases usually involve pain, spinal cord compression, hypercalcemia and pathological fracture [4]. All of these singularly or cumulatively hamper Quality of Life, sleep and mobility of the patient [5]. Effectiveness of treatment of such painful bony metastases depends on the goal of treatment — palliation of pain, prevention of pathological fracture, avoidance of re-treatment and local control of disease.

Pain is the most commonly associated symptom, though the mechanism of pain is not fully understood. Mechanical instability, irritation of periosteal stretch receptors, tumour directed osteoclast mediated osteolysis, tumour cells themselves, tumour induced nerve injury, production of nerve growth factors, stimulation of other cytokine receptors are possible mechanisms [2, 6, 7]. Radiotherapy has been an effective mode of treating painful bone metastasis [2, 8–10]. Overall, 70-80% of patients respond to therapy and 1/3 achieve complete response. Response to treatment depends on multiple factors. Optimal dose and fractionation appropriate for treating painful bone metastasis has been a matter of extensive research since last two decades. Though hypofractionated palliative radiotherapy has been the mainstay of treatment, there have been many trials which have proposed various regimes [11–13]. There is also debate between single fraction *vs* multiple fraction regimes; however, recent metaanalyses have proven the equivalence of single fraction over protracted ones in pain relief for uncomplicated bone metastases [14].

Many dose fractionation options exist in the palliation of symptomatic bone metastases, with a single 8 Gy in one fraction, 20 Gy in five fractions, and 30 Gy in ten fractions [14–16] being the most common fractionation schedules. An Italian survey has reported doses ranging from 8 Gy to 45 Gy for palliative radiotherapy in bone metastases for both 2D and 3D techniques [17]. Various regimes are employed in our institution, with protracted fractionation schedule preferred for patients with complicated bone metastases and for the weight bearing bone. However, continuous protracted palliative regimes demand more manpower, logistics and machine occupancy time which are already overburdened by patients receiving definitive radiotherapy. In this scenario we tried a novel regime of 20 Gy/5#, twice a week (on Wednesday and Saturday). Treating on Saturday shifted a portion of the machine occupancy away from routine definitive care patients; also it gave a bit of a relief to ambulatory patients as well as their caregivers, as they need not come on weekdays throughout a week, reducing indirect cost incurred. Whether this increase of overall treatment time by treating twice weekly over a period of 15 days affects the pain control efficacy or pain relief as compared to standard 5 days needed to be tested. Hence, we undertook this prospective study to compare this novel regimen of protracted treatment of radiotherapy (20 Gy/5# over 15 days) with standard palliative radiation 20 Gy/5# over 5 days in terms of overall pain relief and retreatment rates.

Materials and methods

A prospective non-randomized study was done in the Department of Radiotherapy, from Jan 2018 to May 2019 among the total of 30 patients who had painful bone metastasis requiring fractionated palliative radiotherapy. Palliative radiotherapy was given to all of them using Co^{60} (Theratron 780C), employing clinical or CT based planning. Patients were given the option of being treated according to their convenience, one group of patients were treated with conventional regime of 20 Gy/5# for continuous 5 days and the other group of patients were given 20 Gy/5# in a twice a week regime. In the twice a week arm, treatment was delivered on Saturdays and on Wednesdays/Thursdays. The inclusion criteria consisted of any painful bone metastases requiring fractionated radiotherapy in the axial or appendicular skeleton. The radiotherapy planning was mostly done clinically by direct skin marking using an anatomical landmark, which was verified by plain X-ray using lead markers for center and margins. Single direct posterior field was used for spinal metastases, while parallel opposed field arrangements were used for the hemipelvis and for other appendicular skeletal involvement. Presence of widespread metastases needing systemic management, hemibody irradiation or synchronous symptomatic brain metastases led to the exclusion from the study. Use of bisphosphonates was allowed in both arms.

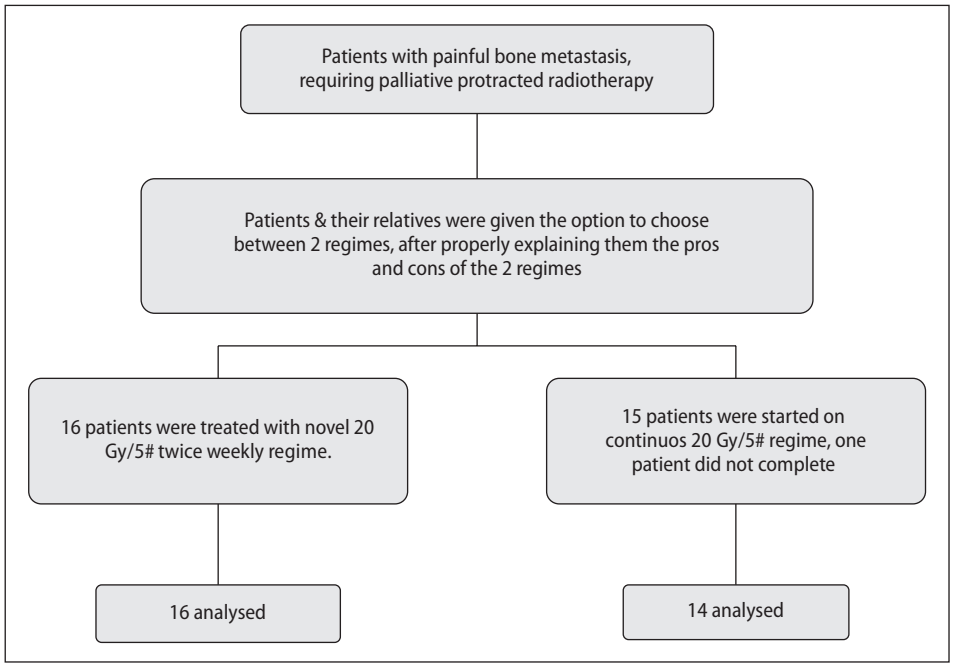

Figure 1. Selection and distribution of patients between the two arms

Pain control

The primary outcome measured was reduction in pain or pain control, while secondary objectives were quality of life, duration of pain control, need for re-irradiation, and development of skeletal related events. Pain control was assessed by Visual Analogue Scale (VAS) and FACES pain score before and about 4 weeks after completion of radiotherapy [18, 19]. Initially, before treatment, the patients are asked to mark on a FACES Scale the worst pain they have experienced within last 3 days. The Faces pain scales consist of a series of line diagrams of faces with expressions of increasing distress. The FACES pain score was chosen for its ease of use and simplicity, and due to the fact that it obviates of effect of literacy and language in assessing pain. The Visual Analogue scale was also used similarly. The visual analogue scale is a continuous scale consisting of a horizontal line of 10 cm, with 11 equidistant marking from 0 to 10. The pain VAS requires little training to administer and score and has been found to be acceptable to patients. Post treatment pain assessment was done at follow up visits at 4 weeks, 3 months and 6 months after completion of the palliative radiotherapy. A complete response to palliative radiotherapy was ascertained if the patient marked zero on the VAS scale or the "no hurt" FACE as the worst pain experienced within last 3 days. A partial response meant the pain persisted after radiotherapy but reduced in intensity by at least two points as compared to the pre-RT score without increase in the intake of opioid analgesics. A progressive disease meant the pain score of two units more than the initial score or the same score with increased uptake of morphine.

Data analyses

Data was analysed using IBM SPSS software Version 20. Pain control duration was defined by time interval between the first reduction of pain score to the return of pain score to the baseline or above. The baseline characteristics were compared between the two groups. The χ^2 test was used to test the difference in the proportions of responses between the two groups. Tests were considered significant if the P value was less than or equal to 0.05, and all tests were two-sided.

Results

A total of thirty patients were accrued, including 14 in the conventional treatment arm. Breast was the main primary followed by prostate in both arms. 14 patients (metastatic breast cancer –8, metastatic prostate cancer –4, other –2) were treated in the conventional treatment arm and 16 patients

Table 1. Comparison of baseline characteristics of the two fractionation arms

Patient characteristics	Arm		p-value
	Five-day schedule N (%)	Two-week schedule N (%)	
Age (median in years)	57	55	0.37
Sex			
Male	6 (46)	7 (44)	0.59
Female	8 (54)	9 (56)	
Primary site			
Breast	7 (54)	9 (56)	0.79
Prostate	4 (31)	5 (31)	
Others	3 (13)	2 (13)	
Site of mets			
Lumbo sacral spine	7 (54)	4 (25)	0.42
Thoracic spine	3 (23)	6 (38)	
Pelvis	2 (15)	5 (31)	
Appendicular skeleton	1 (8)	1 (6)	
ECOG Performance Status			
1	8 (57)	7 (44)	0.16
2	4 (28)	6 (37)	
3 or more	2 (14)	3 (19)	
Number of osseous mets			
Single	9 (69)	11 (68)	0.65
Multiple	4 (31)	5 (32)	
Pain score before RT			
5–6	3 (23)	5 (31)	0.6
7–10	11 (87)	11 (67)	
Pain medications before RT			
Non opiod	10 (77)	9 (56)	0.22
Opiods	3 (23)	7 (44)	

ECOG — Eastern Cooperative Oncology Group; RT — radiotherapy

(metastatic breast cancer — 9, metastatic prostate cancer — 4, other — 3) were treated in the 20 Gy/5# twice weekly arm. Spine was the most common site for palliative RT followed by pelvis in both arms. The demographic and baseline characteristics of both arms were comparable (Tab. 1). There are treatment interruptions in one patient in the continuous fraction arm due to acute upper toxicity. In the continuous RT arm, the mean pain score before and after radiation using Visual Analogue Score was 7.71 and 2.5 respectively ($p < 0.001$, paired samples t test) for FACES Pain Score it was 4.07 and 1.36 ($p < 0.001$, paired samples T test). Similar values were obtained from the twice weekly arm VAS — 7.68 and 1.98, FACES Pain Score — 3.8 and 1.27 (before and after RT) ($p < 0.001$, paired samples t test). In both arms no retreatments were required in the same field during 6 months of follow up. The pain scores regressed drastically in both arms at 4 weeks after palliative radiotherapy but thereafter stabilized at 3 and 6 months.

Discussion

Painful metastases to bone is one of the most common sequel of several cancers and demands multimodality management for symptom control and palliation [1, 3]. Among various other measures of palliation, radiotherapy to painful bone metastases is the most common intervention employed worldwide [21, 22]. Adequate management of skeletal metastases and palliation of

Table 2. Comparison of response in terms of pain control as assessed by Visual Analogue Scale (VAS) score change after 4 weeks of completion of radiation therapy (RT) (p = 0.48, Chi square test)

Pain Response(VAS score) to RT	Arm		Total
	Two weeks schedule	Five day schedule	
Complete response	8 (50)	5 (38)	13 (45)
Partial response	4 (25)	6 (46)	10 (34)
Overall response	12 (75)	11 (84)	23 (79)
Stable disease	4 (25)	2 (16)	6 (21)

Table 3. Comparison of FACES score before radiation therapy (RT) and 4 weeks after completion of RT among the two groups

FACES score	Five day schedule	Two weeks schedule	Total	p-value
Pre RT	3.86 ± 1.3	4.07 ± 0.73	3.97 ± 1.05	0.609
4 weeks after completion of RT	1.27 ± 0.79	1.36 ± 0.84	1.31 ± 0.81	0.769
3 months after completion of RT	1.23 ± 0.56	1.34 ± 0.48	1.27 ± 0.52	0.465
6 months after completion of RT	1.34 ± 0.48	1.41 ± 0.39	1.38 ± 0.45	0.556

pain is of paramount importance in these groups of patients to improve quality of life [10, 23, 24]. Radiation therapy is a simple, non-interventional, cheap and effective method for pain palliation and achieves complete pain response to 25–30% of patients and some response in about 50–60% of patients [25]. Though various dose fractionations have been used for pain relief, ample literature and recent systematic review has shown that the efficacy of single fraction palliative RT (8 Gy/single fraction) is similar to that of protracted courses (30 Gy/10#, 20 Gy/5#, 22.5 Gy/5#, 20 Gy/2#, etc.) for uncomplicated bone metastases, in achieving pain relief [14, 16, 26, 27]. However, worldwide single fraction RT is not practiced universally and use of multi-fractionated RT is quite common. This is more so for complicated bone metastases, where multi-fractionated regimen are the preferred regimen [14]. Among the multi-fractionated regimen, 30 Gy/10# or 20 Gy/5#, randomized control trials comparing the two regimens came up with different results (28,29). Hence, optimal dose fractionation is not known and these two fractionation schedules are used most commonly across the globe with the highest objective response of 76% and 67%, respectively [26]. In our institution also these are the most common schedules in practice for complicated bone metastases.

The present study was undertaken to evaluate the clinical effect, in terms of pain control and quality of life between the standard continuous hypofractionated palliative radiotherapy and twice weekly schedule of hypofractionated radiotherapy for painful bone metastases with the same dose per fraction and total dose (20 Gy/5#). The protracted schedule was opted as per choice of the patient and their caregivers and for logistic reason. Caregivers of palliative care patients often suffer from emotional distress and life restrictions. Continuous protracted radiation means daily engagement of caregivers leading to loss of work hours and at times livelihood or wages. A twice weekly schedule, on the other hand, allows for greater flexibility for caregivers. Moreover, the biologic rationale for comparability of the two regimes derives from the fact that the total dose and dose per fraction remain the same in both the arms. The total treatment duration in the protracted arm was within 3 weeks so dose correction for repopulation was deemed unnecessary. Thus, this trial tested the hypothesis that such protraction does not lead to statistically significant difference in oncological and palliative outcomes.

Re-treatment for recurrence is usually required in about half of the patients who live more than one year, though the Dutch study revealed the median time to progression was about 20–24 weeks [30]. In the current study there were no cases of re-treatment within the first 24 weeks of follow up suggesting that a more favourable group of patients was included in this cohort. About 16/29 patients had breast cancer primary, which could possibly explain

the same. Similarly, skeletal related events like fracture or spinal cord compression, which is generally observed in a small proportion (2% in the Dutch study), was not observed in the present trail since both the sample size and follow up duration were not enough to detect any difference of such events between the two groups.

One possible disadvantage of protracted twice weekly schedule could be slower response, leading to slower pain relief compared to the continuous RT course. This may lead to poor to poorer quality of life among these patients. However this study found that quality of life in none of the domains was significantly different among the two treatment arms. The reason could be that since time to response after a continuous fractionated course of radiotherapy is usually 2 to 4 weeks, protracting the course to about 2 weeks might not affect the time to response. The Pain scores were evaluated 4 weeks after completion of RT and, thus, might not have been able to detect any small difference in quality of life scores during the course of the protracted RT schedule. There may have been earlier response to continuous RT course, which, however could have been missed since post radiotherapy evaluation was assessed after 4 weeks [30]. Nonetheless, this study shows that protracting the RT schedule for logistic and other reasons does not affect the quality of life adversely. Also there wasn't any difference in response to pain after 4 weeks; this response was sustained similarly in both arms on follow up, up to 6 months of completion of radiotherapy.

Conclusion

From this study it can be concluded that a twice weekly schedule over about two weeks, utilising weekend treatments, was found to be equivalent in pain control and response to the standard fractionated palliative radiation for complicated bone metastases and, thus, can be safely employed in those resource-constrained, busy radiotherapy centres where palliative radiation puts pressure on already overburdened radiation facilities. Also, since such protracted schedules also did not have any significant impact on quality of life domains they can be utilised routinely. However a well-planned randomized control trial with a larger sample size and longer follow up is needed for proper validation of that finding.

Conflict of interest

None declared.

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