A RETROSPECTIVE STUDY OF THE IMPACT OF RADIATION FRACTIONATION ON PAINFUL BONE METASTASIS

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ABSTRACT

BACKGROUND

Bone metastasis and bone pain are most detrimental to the life of cancer patients. There is a significant discrepancy between the physician estimate of pain and the pain level reported by the patient. We wanted to evaluate the effectiveness of radiotherapy in reducing the bone pain and identify the suitable dose fractionation schedule.

METHODS

This is a retrospective cohort study analysis carried out in patients with bone metastasis who presented to radiotherapy department, MCH Kottayam from August 2010 to January 2015 and were treated with radiotherapy. Data collected from the case records to assess the response to radiotherapy in patients who were treated with either 20GY/5# or 8GY/1#, response was assessed periodically with the universal pain assessment tool.

RESULTS

Even though there was difference in the type of pain controlled by the two radiation fractions, the overall pain score showed no statistically significant difference in the overall pain control between the two arms.

CONCLUSIONS

20 Gy/5 fractions and 8 Gy/single fraction schedules of radiotherapy were found to be similar in terms of rates of pain relief, narcotic use, and pathologic fracture. In terms of acute control of patient symptoms of bone pain, either of the two schedules may be used without compromising outcome.

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BACKGROUND

Bone metastasis and bone pain are most detrimental to quality of life of cancer patients. The incidence of bone metastases varies significantly depending on the primary site, with breast and prostate cancer accounting for up to 70% of patients with metastatic disease¹. Other primary sites with a propensity for bone metastases include thyroid, melanoma, and kidney. Some hematologic malignancies including myeloma and lymphoma can also cause significant pain and bone destruction. Solitary bone metastases occur in <10% of patients.

Metastases can occur in any bone, though they are more common in sites containing red bone marrow. Approximately 70% of bone metastases occur in the axial skeleton, with metastasis most frequently occurring in the spine, pelvis, and ribs. The lumbar spine is the single most frequent site of bone metastasis.²

In the appendicular skeleton, the proximal femurs are the most common site of metastatic disease. Overall survival of bone metastasis depends on the primary site and the presence or absence of visceral metastases.³

The most common symptom of bone metastases is slowly progressive, fairly well localized insidious pain may radiate to other areas. The pain may be worse at night. Approximately 1% of bone metastases lead to pathologic fracture, with annual fracture rates of 5–20%.⁴

The mechanism of pain from bone metastases is not clearly understood. Possible mechanisms include mechanical instability, irritation of periosteal stretch receptors, tumour-directed osteoclast-mediated osteolysis, and tumour cells themselves, or tumour-induced nerve injury, production of nerve growth factor or stimulation of other cytokine receptors.⁵

Prognostic Factors

1. Histology: median survival of patients with Bone metastases in breast, prostate, and lung cancer are 69, 40, and 13 weeks, respectively.
2. Presence of only a limited number of bone metastases and absence of visceral metastases is a favourable factor.
3. Good performance status.
4. Absence of co morbidities.
5. Response to treatment especially hormone or chemotherapy.

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Evaluation

The physical examination is an important step in evaluating a patient with bone metastases. Firm palpation will often elicit the specific area of pain, with point tenderness often pointing directly to the affected area in the bone. It is important to carefully evaluate the entire skeletal system with examination, as intense pain at one site often masks subjective reports of pain at other sites. A thorough neurologic examination is also important, especially in patients with spinal metastases, to carefully evaluate for the possibility of spinal cord, cauda equina, or nerve root compression.

Imaging

Plain radiographs are typically the most appropriate first imaging study. The primary disadvantage of plain radiographs is that small lesions are rarely seen. Approximately 30% to 50% of the bone mineral content must be lost before the lesion will be apparent on x-rays.⁶

Comparative studies have shown PET scans to be more sensitive than Tc-99 m scintigraphy or whole-body MRI scans in detecting bone metastases.⁷

Pain Management

There is a significant discrepancy between the physician estimate of pain and the pain level reported by the patient.⁸ The use of a validated pain scale, such as the Brief Pain Inventory or universal pain assessment tool, gives the patient an opportunity to describe the severity of pain and the interference of pain with function in a manner that can be understood both by the patient and the physician.⁹ This also allows for comparisons of pain levels over time, to better assess the effectiveness of treatments.

Pain control can be achieved in the majority of patients using the World Health Organization analgesic ladder. The WHO three-step analgesic ladder provides the most straightforward and universally accepted approach to analgesia. The ladder describes a process for combining non-opioid, opioid, and adjuvant drugs, titrated to meet the individual needs of the patient according to the severity of pain. A randomized controlled trial of an algorithm based upon the WHO ladder demonstrated that a standardized approach to cancer pain management using the algorithm provided more effective analgesia than routine oncology care.¹⁰

There are multiple treatment options for patients with painful bone metastases which include, surgical management, external beam radiation therapy, systemic therapy and radionuclide therapy.¹¹ Bone metastases are the most common indication for palliative radiotherapy.¹² There are multiple randomized trials which have compared between single and multiple fraction radiotherapy, in order to assess the pain relief. It has been found that most of the response in terms of pain relief occurs 4-6 weeks after radiation. A sustained pain relief is seen in approximately 55-65% of patients.¹²

The response to treatment depends on a large number of factors¹³ like

1. Sex.
2. Primary site.
3. Histology.
4. Performance status.

5. Type of lesion (Osteolytic vs. Osteoblastic).
6. Location of the metastases (weight-bearing vs. non-weight-bearing).
7. Extent of disease.
8. Number of painful sites.
9. Level of pain prior to treatment.

The effectiveness of the treatment also depends on the goal: palliation of pain, prevention of pathologic fracture, avoidance of future treatments, or local control of the disease.

Local-field external-beam radiation therapy is typically used for palliation of a few discrete areas of painful metastases.¹² Various doses and fractionations have been tested in randomized trials, and results from most trials demonstrated that a large single dose and more fractionated radiation provided similar symptomatic control. There have been various studies in the past comparing different fractionation schedules which varying from 40 Gy to 8GY. However, the most commonly used fractionation are 30 GY/10#, 20GY/5#, and 8GY/1 #. There are no level one evidence favouring any of the above-mentioned regimen. Nevertheless, in a high volume centers long fractionation schedules will increase the machine time and there by more patient waiting. It will not only affect the palliative treatments but also influence the starting time in radical cases. In this scenario many high volume centers invariably opts for the shorter versions of radiotherapy in palliative cases, our study is to retrospectively analyse the case sheets to assess the effectiveness of shorter versions of radiotherapy in palliative scenarios.

Aim of The Study

This study is to evaluate the efficacy of external beam radiation therapy in achieving pain relief for patients with painful bony metastases. The two radiation fractionation schedules compared in this study are multiple fraction (20 Gy/ 5 fractions) and single fraction treatment (800 cGy single fraction).

In addition, the change in analgesic requirement between the two arms has also been assessed in this study.

METHODS

This study is a retrospective cohort study of Case records of all patients who are reported to MCH Kottayam with diagnosis of Bone metastasis between the duration of August 2010 to January 2015 and are treated with radiotherapy dose of either 20 GY/5# or 8 gy/1# were collected and data about the response to treatment was retrieved. Data of 150 patients were eligible for the study and was segregated into two groups based on the dose fractionation regimen. Patients were excluded if no retrievable data was available from the case records.

Dose of Radiotherapy	20 GY/5#	8GY/1#
Total number of patients	96	84
Total number of patients included in the analysis	75	75

Inclusion Criteria

1. Age 18 years or older.
2. Patients must have signed an approved informed consent.

3. Patients with a proven primary (solid tumour) malignancy presenting with painful bony metastases and treated with palliative radiation with either 20 Gy/5# OR 8 Gy/1#

Exclusion Criteria

1. Patients with a diagnosis of multiple myeloma, lymphoma or haematological malignancies.
2. Patients with painful bony metastases in more than 5 sites.
3. Patients with pathological fracture, spinal cord compression.
4. Patients treated with other dose fractionation schedules.

Duration of Study

Patient's data were analysed over a period of 4 months after obtaining ethical clearance.

Sample Size

Retrospective Cohort Study.

Statistical Analysis

Data was entered in Microsoft Excel & analysis was done. SPSS software version 15 was used for analysis. The pain score data in two group (20 Gy/5# and 8 Gy/1#) per week is compared with student t test. Qualitative variables are expressed in percentage or proportion and association of reduction in pain from baseline to observational period of 12 weeks analysed using chi-square test.

RESULTS

The patients were evaluated. Patients who were irregularly followed up or with missing data from case sheets were also excluded from the study. After careful evaluation, 75 patients each were chosen in the two groups and each patient compared with the other group to evaluate results. In this study 150 patients satisfied the criteria of patient selection from January 2012 to December 2015.

Study Procedure

- Patients meeting the inclusion and exclusion criteria will be included in the study.
- The patients who received the above mentioned 2 different fractionations will be compared and analysed.
- The baseline pain score and the patient reported pain score which has been recorded according to the institutional protocol in the master case sheet was retrieved and analysed.
- The data on prescription of analgesic according to the WHO pain ladder which was recorded in the Master case sheet will be evaluated.
- Retrospective comparison of these factors between the two arms will be used to determine the better treatment protocol for pain control.

All patients accrued in this study will be planned for external beam radiation using the conventional simulator housed in the Department of Radiotherapy at our center. The treatment fields were defined following x-ray imaging of the involved region on the x-ray simulator. For vertebral metastases, one vertebra above and below the involved vertebra would be included in the radiation portal, the lateral

extent of the field would encompass the transverse process of the vertebra bilaterally. For bone metastases at other sites, a minimum of 2cm margin would be given around the radiologically visible lesion.

The number of treatment fields were decided by the depth of the region of interest. Vertebral lesions were treated using a single on field technique, whereas other sites would be treated with opposing anterior and posterior beams. All patients in this study will be treated with the Theratron 780C Telecobalt therapy unit housed in the Department of Radiotherapy, at our institute.

As per institutional protocol all patients will be given bisphosphonate therapy after ensuring that the renal function and the serum calcium levels were within normal limits. All patients were sent to physical medicine department so as to devise braces/ support measures so as to enable early rehabilitation and ambulation. All patients were started on analgesics based on their pain score keeping in tune with the WHO analgesic ladder.

Assessment Tools

To assess the pain, Universal pain assessment tool was adopted.

Step	Drugs
1	Paracetamol, NSAIDS (and adjuvants if needed)
2	Mild Acting Opioids + Step 1 Non-Opioids (and adjuvants if needed) Mild Acting Opioids: Codeine, Dihydrocodeine, Dextropropoxyphene
3	Stronger Opioids + Step 1 Non-Opioids (and adjuvants if needed) Stronger Opioids; Morphine, Diamorphine, Fentanyl, Hydromorphone

Table 1. WHO Analgesic Ladder

Adjuvant Drugs

Tricyclic Antidepressants, anti convulsants, Steroids.

Definitions

Case

Patients with a proven primary (Solid tumour) malignancy presenting with painful bony metastases.

Response

Decrease in pain score by at least 2 points.

No Response

If the pain score remains at the pre-treatment level.

Progression

Worsening of pain score after completion of treatment.

Analgesic Response	% Decrease in Analgesic Requirement (Dose in mg)
Mild	At Least 25%
Moderate	25% - 50%
Good	50% - 75%
Excellent	75%-100%

Table 2. Analgesic Response

Primary Site

Lung cancer cases accounted for 50% of the patients in this study 20% of the patients in this study had breast as the primary site of disease.

Site of Bone Metastases

In this study bone metastases were recorded in the pelvis, vertebra, rib & femur. 74% of bone metastases in this study occurred in the vertebra.

As vertebral metastases were found to account for majority of the cases, a subset analysis showed that lumbar vertebra accounted for 48.6% of all vertebral metastases. Sites of bone metastases were further subdivided into weight-bearing sites Include vertebra in weight bearing site. (i.e., pelvis, femur, tibia, sacrum, and/or sacroiliac joints) or non-weight-bearing sites.

76% of patients presented with bone metastases to non-weight bearing sites. No new bone metastases were recorded in any of the patients during the period of this study.

Pain Score

Pain was assessed using the universal pain assessment tool. Patients graded pain from zero (No pain) to ten (Worst possible pain).

Pain was graded according to the Pain Score as follows

Pain Grade	Pain Score
Mild	1-2
Moderate	3-6
Severe	7-10

Table 3. Pain Grade

Pain score was assessed at presentation. The mean pain score at presentation was 6.82. The pain score at presentation ranged from five to nine.

Arm 1 had 30 patients with moderate pain and 45 patients with severe pain. Arm 2 had 36 patients with moderate pain and 39 patients with severe pain.

Pain Score at First Follow Up (2nd Week)

The mean pain score at first follow up was 6.78. The pain score at first follow up ranged from four to nine. There was no statistically significant difference in pain scores at first follow up between the two arms. p value = 0.438

From the figure depicted above it is clear that the distribution of patients with moderate and severe pain remains the same as at presentation.

Pain Score at Second Follow Up (3rd Week)

The mean pain score at second follow up was 6.62. The pain score at second follow up ranged from four to nine. There was no statistically significant difference in pain scores at second follow up between the two arms. p value= 0.15. The number of patients with moderate and severe pain remain the same in Arm 1. In Arm 2 the number of patients with moderate pain has increased from 36 to 42, thereby decreasing the number of patients with severe pain from 39 to 33.

The mean pain score at third follow up was 5.88. The pain score at third follow up ranged from one to nine. There was no statistically significant difference in pain scores at third follow up between the two arms. p value = 0.738. In each arm 3 patient reported mild pain. Compared to the second follow up the number of patients reporting severe pain has decreased in both the arms. A greater proportion of patients report moderate pain in both the arm.

The mean pain score at fourth follow up was 4.48. The pain score at fourth follow up ranged from one to one to eight. There was no statistically significant difference in pain scores at fourth follow up between the two arms. p value = 0.738. At fourth follow up, it can be noted that the number of patients reporting severe pain has further decreased in both arms. At the same time the number of patients reporting mild pain has increased in both arms. The number of patients reporting moderate pain has remained more or less the same in both the arms.

The mean pain score at fifth follow up was 3.69. The pain score at fifth follow up ranged from one to one to nine. There was no statistically significant difference in pain scores at fifth follow up between the two arms. p value not significant. 3 patient in arm 2 reports no pain. A steady decrease in number of patients reporting severe pain is noted in both arms. The proportion of patients reporting mild pain is increasing in both arms, whereas number of patients reporting moderate pain has remained more or less constant in both arms.

The mean pain score at sixth follow up was 3.08. The pain score at sixth follow up ranged from one to one to nine. There was no statistically significant difference in pain scores at sixth follow up between the two arms. p value =NS. Both the arms have 4 patient each reporting no pain. The trend observed previously is continued here, with decreasing number of patients reporting severe pain in both arms. The proportion of patients reporting mild pain has been consistently increasing in both arms, with a more profound increase in arm 2. The mean pain score at seventh follow up was 3.22. The pain score at seventh follow up ranged from one to one to nine. There was no statistically significant difference in pain scores at seventh follow up between the two arms.

The number of patients in arm 1 reporting no pain has increased from 3 to 12, whereas no such increase has been noted in arm 2. The number of patients reporting mild pain has remained fairly the same in both arms. No further decrease in the number of patients reporting severe pain was noticed.

Follow Up No. of Weeks	Mean Pain Score (20 Gy/5#)	Mean Pain Score (8Gy/1#)	Mean pain Score (All Patients)	Pain Score (range)	Pain Score (Std. Deviation)	p Value
At Presentation (baseline)	6.92	6.72	6.82	5-9	1.224	
2 nd Week	6.92	6.64	6.78	4-9	1.282	0.438
3 rd Week	6.88	6.36	6.62	4-9	1.260	0.155
4 th Week	5.96	5.8	5.88	1-9	1.814	0.738
6 th Week	4.92	4.04	4.48	1-8	2.150	0.117
8 th Week	3.76	3.63	3.69	1-9	2.153	0.683
10 th Week	3.83	2.85	3.08	1-9	2.211	0.429
12 th Week	3.71	2.79	3.22	1-9	2.344	0.141

Table 4. Summary of Pain Scores

The difference in mean pain score at 12 weeks from baseline mean pain score (At week 0) has been evaluated by Chi Square test. There is a statistically significant reduction in pain with radiation from baseline (wk. 0) during the period of study (wk 12) with chi square statistics 7.9093 and a significant p value, $p= 0.004918$. But the reduction in mean pain scores between the 20Gy/5# and 8 Gy/1# are did not show any statistical difference across each week throughout this study. The variables between the 2 groups in each week were analysed by Chi-square test with $p= 0.5678$ shows that the reduction in pain with radiation is observed similar between the 2 groups of radiation fractionation used in this study of 20 Gy/5# and 8 Gy/1# and the difference is statistically not significant.

The graph above shows that a steep decrease in mean pain score is noted from the 4th week onwards i.e. from 5.88 to 4.48 at the 6th week. This decrease in mean pain score is noted up to the 10th week, after which a non-significant increase in mean pain score is noted at the 12th week.

Figure 6. Mean Pain Score Across 2 Arms

Figure 7. Arm 1 Grade of Pain Profile During Study Period

The line graph in figure 7 shows that initially all patients in Arm 1 reported severe and moderate pain. There was a sharp decline in patients reporting severe pain from week 3 onwards, this decrease continued up to week 8. The number of patients reporting moderate pain increased from week 3 and stabilized from week 6-8, thereafter a steady decrease is noted. Patients reporting mild pain increased from week 3 onwards, reaching a maximum at week 10. The number of patients reporting mild pain started increasing from week 8 onwards, peaking at week 12.

Figure 8. Arm 2 Grade of Pain Profile During Study Period

Pain Response

The p value for pain response was 0.695, there by proving that there was no statistically significant difference in pain response between both the arms.

Figure 9. Comparison of Pain Response

The bar graph shows an equitable distribution between the 2 arms with respect to number of patients achieving a pain response, no pain response & progression of pain.

Analgesic Step

At presentation all patients were started on Step 1 of the WHO analgesic ladder. At presentation all patients were on either step 2 or 3. By week 12 it is observed that more than 50% of patients were on No or step 1 analgesics. This observation was not statistically different between 2 arms.

Figure 10. Analgesic Step Used Arm 1

Figure 11. Analgesic Step Used Arm 2

DISCUSSION

Various randomized trials were conducted for comparing Radiation fractionation and pain relief. In RTOG 9714¹⁴ study it is found that external beam radiation therapy was effective at palliating pain from bone metastases, with complete or partial improvement in pain observed at 3 months after randomization in 66% (375 patients) of the 573 patients. At 3 months of follow-up. Similar to the results of our study, this study found no difference between the response of patients in the arm receiving 30 GY in 10 treatment fractions and in the arm receiving 8 GY in a single treatment fraction, in terms of pain relief, narcotic relief, or pathologic fracture incidence, regardless of stratification used in the analysis. Treatment was well tolerated with few adverse effects.

The complete response rate in the RTOG 9714 trial was 16%, substantially lower than the previous RTOG 7402¹⁵ study. The reasons for this difference may include the assessment method used and the severity of pain or extent of disease. For the RTOG 7402 trial, physicians scored pain with a four-point scale, whereas patients in our study scored pain by use of a more sensitive 10-point scale in the Brief Pain Inventory. In addition, the patients treated in this study is different from that treated 25 or more years ago. Although there were few systemic therapy options during the RTOG

7402 trial, second-, third-, and fourth line chemotherapy options are currently available for breast cancer. In addition, multiple hormonal manipulations are available for the treatment of both breast and prostate cancer, and bisphosphonates are used in many of these patients.

Pain control is better understood, with much more emphasis on adequate pain management now than 25 years ago. Thus, the patients who are referred for palliative radiation therapy now may have more widespread disease that has become resistant to other therapies, as reflected in this study by the severity of pain scores (72% of the patients in this study had severe pain at study entry) and the Karnofsky performance status scores (nearly 25% of the patients in this study had Karnofsky performance status scores of 60 or lower, and more than 75% had Karnofsky performance status scores of 80 or lower). The quality-of-life assessments also show that the patients in this study have many symptoms. Although this group of patients was ill with moderate-to-severe pain before treatment with radiation therapy, a substantial proportion had improvement in pain 3 months after treatment, and nearly one-third no longer required narcotic pain medication. The results may have been better if patients were treated earlier in the course of their disease, since previous studies have shown that patients with moderate pain are more likely to respond to treatment than those with severe pain ¹.

The only difference in outcomes between the two arms was the rate of re-treatment, with substantially more patients in the 8-Gy arm receiving retreatment than in the 30 Gy arm. This observation may be an indication that the 8-Gy treatment is less effective than the longer course of 30 Gy in 10 treatment fractions. However, rates of pain relief, narcotic use, and pathologic fracture incidence were equivalent in the two treatment arms. There may be other factors involved in the decision to re-treat a patient, such as potential physician bias. There may be more willingness to give another treatment after a single-dose treatment than after a higher-dose treatment, especially retreating areas adjacent to sensitive critical normal structures (such as spinal cord, bowels, or lungs). There may be less willingness to give another treatment after a treatment of 30 Gy in 10 fractions because of the higher acute toxicity associated with that regimen. Even if there is a real increase in the need for retreatment among patients receiving a single-dose treatment, this problem may be counter balanced by the reduced rate of acute toxicity in these patients.

A consensus statement from the Second Workshop on Palliative Radiotherapy and Symptom Control in 2000 ¹⁶ confirmed the efficacy of radiation therapy, even with a single treatment, in palliating painful bone metastases. There is increasing evidence that a single 8-Gy dose provides pain relief equivalent to longer courses of palliative treatment, although the short course of treatment is associated with a higher rate of retreatment.

This study has several limitations. This study included only patients with metastases from primary breast or prostate cancers to allow an adequate follow-up period to assess response and toxicity, because these patients tend to survive longer than patients with bone metastases from other primary sites. However, the outcomes may be different for patients with bone metastases from another primary site. A second limitation of the study involves completion of the

assessment tool. The Brief Pain Inventory was completed by only 573 (67.8%) of the 845 patients at the 3-month assessment point. As would be expected in this group of patients, 160 of the 845 patients had died or were too ill to complete the form at 3 months. Thus, the Brief Pain Inventory was completed by 573 (83.6%) of the 685 patients who were alive and able to complete the form.

CONCLUSIONS

20 Gy/5 fractions and 8 Gy/ single fraction schedules of radiotherapy were found to be similar in terms of rates of pain relief, narcotic use, and pathologic fracture. In terms of acute control of patient symptoms of bone pain, either of the two schedules may be used without compromising outcome.

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