

Original Article

Single fraction radiotherapy is more acceptable than multi-fraction radiotherapy to palliate the metastatic bone pain

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Abstract

One of the main goals of palliative radiation treatment is the relief of pain or dysfunction caused by the bone metastasis. Most patients achieve pain relief after irradiation. The striking clinical observation is that some patients experience symptom relief within 24hrs after the irradiation. This quasi experimental study was carried out in the department of Oncology, BSMMU from January 2014 to June 2014 with the intention to compare the role of single fraction and multiple fraction radiotherapy in the management of bone secondaries as regard as potency for pain relief. A total of 100 patients with age up to 70 years and of any sex having cytologically or histologically proven malignant diseases with the painful bone metastases in single or multiple sites without pathological fracture were selected for the study. They had no history of previous radiotherapy on the treatment site. Patients were divided in to two Arm A and Arm B with 50 patients in each arm. Arm A was treated with single (8 Gy) fraction radiotherapy and Arm B was treated with multiple fraction (30 Gy) radiotherapy i.e. 300 cGy per fraction in 10 fractions, 5 days a week for two weeks by telecobalt or orthovoltage machine. 44 patients in Arm A & 46 patients in Arm B completed the study. Onset of pain relief after completion of 4th week radiation were 68% in Arm A and 67.4% in Arm B. It was observed that, after 8th week of radiation 81.8% in Arm A and 86% in Arm B were relieved from pain. According to histological typing, 45% in Arm A & 52% patients in Arm B

had complete response; 40% in Arm A & 37% patients in Arm B had partial response and overall distribution of no response of patient in Arm A was 18% and in Arm B was 7%. Metastatic bone pain represents one of the major indications in the external beam radiation therapy today. The disease can be efficiently treated by the use of either single fraction or multifraction radiotherapy without any significant difference in response to rate and early toxicities.

Key words: Single fraction radiotherapy, multi-fraction radiotherapy, metastatic bone pain

Introduction

Metastatic bone disease is a painful condition that can develop in conjunction with cancers of the breast, prostate, lung or other organs. It occurs when cancer cells at an original site metastasize (travel) to the bone. Metastatic cancer is the most common neoplasm that involves the skeletal system.¹

Pain due to cancer is feared by every patient who is diagnosed with cancer because pain is associated with advanced disease specially end stage disease. About three quarters of patient with end stage disease will eventually need pain management.²

Palliative treatment is a significant part of cancer care in a radiotherapy department. Radiation is very effective in providing pain relief. Almost two thirds of patient will experience improvement in their pain with complete and long lasting pain relief in about half of the patients.³

Breast cancer that has only metastasized to the bone has a better prognosis than when breast cancer has spread to visceral organs. The most primary tumors commonly associated with these distal bone metastases are lung, breast, prostate, kidney and thyroid.⁴

The time interval from the initial diagnosis of primary tumor to the first evidence of bone involvement can vary greatly. Metastatic lesion of bone may be the first evidence of tumor or latent period may be greater than 10 years at presentation⁵, secondary deposits may be single or may be multiple which aids their recognition.⁶

Individual deposits may come to attention because of pain and swelling or a pathological fracture. If the patient is

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known to have a primary tumor, secondary deposits in bone don't usually present a diagnostic problem. Difficulties can occur when a secondary deposit is the first indication that a particular patient is suffering from a malignancy.

The prognosis of bone metastasis is generally poor; though the course of the disease may be relatively slow over a period of years.⁷ The usual presentation of bony metastasis is pain. Possible local mechanisms of inducing bone pain are - 1) release of chemical mediators, 2) increased pressure within the bone, 3) micro fracture, 4) stretching of the periosteum, 5) reactive muscle spasm, 6) nerve root infiltration, 7) compression of the nerves due to collapse of bone.⁸

Management of painful localized bone metastasis typically utilizes radiation therapy and graduated use of opiate analgesics.⁹ The aim of treatment is relieving pain as simply and quickly as possible. Analgesic can only increase the pain threshold level for time being but cannot destroy the malignant cells which is responsible for proliferation and elevation of periosteum from which pain occurs. Radiotherapy kills the cells as well as decreases the tumor mass and relieves pain without loss of tissue.

Methods

This quasi experimental study was carried out in the department of Oncology, BSMMU from January 2014 to June 2014 with the intention to compare the role of single fraction and multiple fraction radiotherapy in the management of bone secondaries as regard as potency for pain relief.

A total of 100 patients with age up to 70 years and of any sex having cytologically or histologically proven malignant diseases with the painful bone metastases in single or multiple sites without pathological fracture were selected for the study. They had no history of previous radiotherapy on the treatment site. Patients were divided in to two Arm A and Arm B with 50 patients in each arm.

Sampling technique was simple random sampling; every odd number of patients was taken in Arm A & every even number patient was taken in Arm B. Arm A was treated with single (8 Gy) fraction radiotherapy and Arm B was treated with multiple fraction (30 Gy) radiotherapy i.e. 300 cGy per fraction in 10 fractions, 5 days a week for two weeks by telecobalt or orthovoltage machine.

Complete history and physical findings, location and size of lesions were recorded prior to treatment. Laboratory studies i.e. complete blood count, kidney function test, liver function test were done in each patient. Radiologic studies - X-ray of affected part, radio isotope bone scan were also

done. Registration of analgesic consumption was done. Pain assessment was done by visual analog scale. Patients were managed symptomatically with antibiotics, oral mouth wash, steroids, antiemetic, vitamins, blood transfusion and nasogastric tube feeding according to their needs throughout the treatment period. All patients were advised to take proper skin care during treatment.

The radiation was given by a telecobalt or orthovoltage machine. Arm A (Single fraction group) received a single fraction of 8Gy whereas Arm B (Multi fraction group) received 30 Gy in 10 daily fractions over two weeks. The prescribed dose was the maximum absorbed dose in single field and the central dose for opposed fields. The treated fields included, if possible, a 2 cm margin on each side of the metastasis and one unaffected vertebral body on each side for spine metastasis.

Evaluation after treatment included patient's complete history and physical examination, toxicity of the treatment, pain response evaluation by visual analog scale, laboratory studies - CBC with differential and platelet count, kidney function test, Liver function test, radiological studies- X-ray of affected part. Follow up was performed weekly i.e. 1st, 2nd, 3rd, 4th and 8th weeks after completion of radiation.

The responses were classified by several parameters - 1) Complete response: absence of pain in treatment site, 2) Partial response: a decrease in the pain score by at least two points on visual analog scale, 3) No response: no relief of pain, 4) Progression: pain does not relief but there is increase in pain score.

The following outcome variables were studied - age, sex, smoking habit, clinical features, primary sites, affected sites, histological variety, radiological variety & response to therapy. Written informed consent was taken from each patient. Study protocol was approved by the institutional review board of BSMMU.

Results

Hundred (100) patients with metastatic bone disease were included in two arms with 50 patients in each arm. Among the 100 patients, 3 patients had withdrawn from the study for personal reason & 7 patients were lost to follow up. Finally Arm A consisted of 44 patients & received a single fraction of 8 Gy tumor dose and Arm B included 46 patients who received 30 Gy tumor dose in 10 fractions over two weeks.

Regarding the age of the patients, highest number of patients belonged to 50-59 years age group in both the Arms (50% and 43.5% in ArmA & ArmB respectively). (Table-I)

Table-I : Distribution of Patients according to age.

Age in Year	Arm A		Arm B	
	No of Patient	Percentage	No of Patient	Percentage
30-39	2	4.5	2	4.3
40-49	11	25	12	26
50-59	22	50	20	43.5
60-69	9	20.5	12	26
Total	44	100	46	100

Among 90 patients studied, the most common symptom was localized pain; 72.7% in arm A and 74% in arm B. Other symptoms were paraplegia, severe backache, and weakness of lower limb. (Table-II)

Table-II: Distribution of patients according to clinical presentation.

Symptoms/ Signs	Arm A		Arm B	
	No. of Patient	Percentage	No. of Patient	Percentage
Localized pain	32	72.7	34	74
Paraplegia	6	13.6	4	8.7
Weakness of the lower limb	2	4.5	1	2
Severe backache	4	9	7	15
Total	44	100	46	100

Lung was the most common primary site of tumour in both the Arms (31.8% & 32.6%) followed by breast, prostate & thyroid. primary site was unknown in 13.6% in Arm A & 8.7% patients in Arm B. ((Table-III)

Table-III: Distribution of patients by primary sites.

Primary site	Arm A		Arm B	
	No of Patient	Percentage	No of Patient	Percentage
Lung	14	31.8	16	32.6
Prostate	10	22.7	12	26
Breast	11	25	8	17.3
Thyroid	2	4.5	4	8.7
Unknown	6	13.6	4	8.7
Kidney	1	2.3	2	6.5
Total	44	100	46	100

Among 90 patients, vertebrae were the most common site of metastasis (72% in Arm A, and 71.7% in Arm B). Other sites are pelvis, limbs, and ribs. Distribution of patients according to sites of bony metastasis. (Table - IV)

Table -IV: Distribution of patients according to sites of bony metastasis.

Primary site	Arm A		Arm B	
	No. of Patient	Percentage	No. of Patient	Percentage
Vertebrae	32	72.7	33	71.7
Pelvis	5	11.4	5	10.9
Limbs	5	11.4	7	15.2
Ribs	2	4.5	1	2.2
Total	44	100	46	100

According to histological variety of metastasis/primary lesion, 45.5% & 39% had adenocarcinoma in Arm A and Arm B patients respectively. (Table-V)

Table-V: Distribution of patients according to histological variety.

Types of Tissue	Arm A		Arm B	
	No. of Patient	Percentage	No. of Patient	Percentage
Adeno carcinoma	20	45.5	18	39
Squamous cell carcinoma	12	27.3	12	26
Follicular	1	2.3	3	6.5
Papillary	1	2.3	1	2.2
Sarcoma	4	9	3	6.5
Small cell Ca	2	4.5	3	6.5
Undifferentiated	4	9	6	13
Total	44	100	46	100

Osteolytic bone lesions were more prevalent (54.5% & 56.5% in armA & arm B respectively) among the study subjects followed by osteosclerotic & mixed lesions. (Table-VI)

Table -VI: Distribution of patients according to radiological appearance of bone.

Types of Lesion	Arm A		Arm B	
	No. of Patient	Percentage	No. of Patient	Percentage
Osteolytic	24	54.5	26	56.5
Osteo sclerotic	10	22.7	12	26
Mixed (both lytic and sclerotic)	10	22.7	8	17.4
Total	44	100	46	100

Onset of pain relief for the two treatment arms was 68% in Arm A and 67.4% in Arm B after completion of 4th week radiation. It was observed that, after 8th week of radiation 81.8% in Arm A and 86% in Arm B were relieved from pain. Onset of pain relief is shown in (Table-VII).

Table -VII: Distribution of Patients according to onset of pain relief.

Week	Pain relief (Complete & Partial)			
	Arm A		Arm B	
	No. of Patient	Percentage (%)	No. of Patient	Percentage (%)
1st Week	14	31.8	12	26
2nd Week	21	47.7	22	47.8
3rd Week	25	56.8	27	58.7
4th Week	30	68	31	67.4
8th Week	36	81.8	40	86

20 patients of Arm A and 24 patients of Arm B were completely responded. Overall distribution of complete response of pain is shown in (Table -VIII).

Table -VIII: Overall distribution of complete response of patients.

Group	No of patient	Complete Response	Percentage
Arm A	44	20	45
Arm B	46	24	52

Discussion

The study was carried out with an aim to compare the effect of single fraction radiotherapy & multiple fraction radiotherapy in metastatic bone pain. Metastatic bone disease is common particularly in older age people.¹⁰ The present study showed that the patient with metastatic bone cancer were mostly at advanced age. Peak age was between 50-59 years. This study coincides with the study.¹¹

The most commonly involved primary site was lung, which was 31.8% in Arm A and 32.6% in Arm B. Next common sites were prostate, breast & unknown primary in 22.7%, 25% & 14% in Arm A and 26%, 17.3% & 8.7% in Arm B respectively. This study corresponds with the study of the effect of single fraction compared to multiple fractions on painful bone metastasis: a global analysis of the Dutch bone metastasis study.¹²

In this study, vertebrae were most common sites of involvement, which were 72.7% in arm A & 71.7% in arm B respectively. This study correlates with the study of multiple and single fraction palliative radiotherapy in bone secondaries -A prospective study.¹³ Next common sites are pelvis, limb & ribs which are 11.4%, 11.4% & 4.5% in Arm A and 10.9%, 15.2% & 2.2% in Arm B respectively. This findings also correlates with the above mentioned study.¹³

Radiological study revealed lytic nature of the involved site in 54.5% of cases; 22.7% being sclerotic, and 22.7% mixed in Arm A. In Arm B 56% were of lytic nature with , 26% being sclerotic, & 18% mixed. It corresponds with multiple & single fraction palliative study-a prospective study.¹³

According to histological typing, in Arm A, adenocarcinoma was found in 45.5%, squamous cell carcinoma 27.3% & undifferentiated 9%. In Arm B they were 39%, 26% & 13% respectively.

The most common presenting symptom irrespective of histology is localized pain which was 72.7% in arm A and 74% in arm B. Many metastatic lesions are not painful and are detected by radiography and bone scintigraphy. Other symptoms are paraplegia 13.6%, severe backache 9%, and weakness of lower limb 4.5%. In the arm B group they were 8.7%, 15%, 2% respectively. Similar observations regarding the clinical presentation were also made by.¹⁴

In response to radiotherapy in Arm A, complete response was achieved in 35% of adenocarcinoma, 75% of squamous cell carcinoma, 100% of papillary cinoma, 50% of small cell cinoma & 25% of undifferentiated ca. In Arm B they were 38%, 83%, 100%, 50% and 33% respectively.

Complete response was observed 45% in Arm A & 52% in Arm B. Partial response in Arm A was 40% & Arm B it was 37% at 8th weeks after completion of treatment. Onset of pain relief for the two treatment arms which was 68% in Arm A and 67.4% in Arm B after completion of 4 weeks radiation.

It is observed that, after 8 weeks of radiation 81.8% in Arm A and 86% in Arm B were relieved from pain. Reports of various studies and results of the present prospective study indicate that there is no significant difference between speed of onset and overall incidence of pain relief following single and multiple fractions of radiation in metastatic bone pain.

It is to be noted that in spite of large treatment fields in some patients no significant early toxicity was observed in both groups and side effects were generally mild in nature and tolerated. Adverse effects are mainly skin reaction, nausea & vomiting. Rate of toxicities occurring in both arm were

almost same. This observation correlates with the above mentioned study.¹³

Metastatic bone pain represents one of the major indications in the external beam radiation therapy today. The disease is efficiently treated by the use of either single fraction or multifraction radiotherapy without any significant difference in response to rate and early toxicities.

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