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RESEARCH ARTICLE

PALLIATION OF BONE METASTASIS USING DIFFERENT FRACTIONATION OF RADIOTHERAPY

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ABSTRACT

Background: Bone metastases occur in almost all tumors and it is the third most common site involved by metastasis. Breast and prostate cancer are the most common primary sites metastasising to bone, accounting for up to 70% of total cases. The problems associated with bone metastasis are pain, pathologic fractures, spinal cord compression and hypercalcemia. The prognosis of patients with bone metastases is poor, with median survival ranging from months to few years depending upon site and the presence or absence of visceral metastases. Optimal management of bone metastases requires a multidisciplinary team. Radiotherapy is an integral part of palliation of bone metastasis. Patients who have improvement in pain after radiotherapy may also have improvement in quality-of-life scores.

Purpose: To know the pain relief using Visual Analogue Scale in bone metastasis patients for different fractionation and also to assess the quality of life by EORTC QLQ-C30 module questionnaire

Methods and Materials: A prospective study done on patients with bone metastasis from any primary, whose malignancy was histologically proven and the bone metastasis was confirmed by histology and/ or imaging. Patients who previously received radiation therapy to the region concerned and the presence of any co-morbid conditions to which the patient's symptoms could be attributed to were excluded from the study. It was conducted from September 2013 to April 2015 on sixty patients for pain management and to improve the quality of life in patients receiving palliative radiotherapy. A total of sixty patients were divided in four groups with fifteen patients in each group. Different fractionation of radiotherapy, 8 Gy in single fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions and 30 Gy in 10 fractions were delivered using Linear accelerator of 6MV photons. Following radiotherapy pain was assessed within the patients of one group and the results were compared with each of the other groups. Pain scale for pre radiotherapy was compared with post radiotherapy at 1 week, 1month and 3 months follow up respectively. By using visual analogue scale and quality of life questonnaire (EORTC QLQ-C30 module) data was analyzed by ANOVA test.

Observations and Results: ANOVA test was used for comparision between each group and the results were considered statistically significant only if p value was < 0.05. Pain relief using visual analogue scale was almost same in all the four groups when compared with each other but there was a significant pain relief in each group when compared to the pre radiotherapy pain scale. P value of performance status was statistically significant in Group B- 0.005 when compared to the other groups. Quality of life, using questonnaire (EORTC QLQ-C30 module), symptomatic scale showed improvement in Group A-0.002, Group C- <0.001 and Group D-<0.001 whereas p value of functional scale was <0.001 in all four groups.

Conclusion: All four fractionation treatment schedules provided significant pain relief and improvement in Quality of life for both symptomatic and functional scale. Therefore consideration of choice of treatment schedule should be based on mean survival and patient convenience.

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INTRODUCTION

Bone is the third most common site involved by metastasis, behind lung and liver.

The incidence of bone metastases varies significantly, depending on the primary site, Breast and prostate cancer are the most common primary metastatising to bone, accounting for up to 70% of bone metastasis. Other primary sites include lung, thyroid, melanoma, and kidney which constitutes approximately 30% to 40% of cases and gastrointestinal sites constitutes 3% to 15% of patients with metastatic disease.[1] Myeloma and lymphoma also causes significant pain and bone destruction.

Mean survival in carcinoma lung with bone metastasis is low, 6 months but carcinoma breast or prostate with bone only metastatic site is 2 to 4 years.[2]

The axial skeleton with lumbar spine is the most common site of bone metastasis. The common sites of bone metastasis from primaries are Scapula from renal primaries, skull from breast, distal appendicular skeleton (tibia, fibula) and acral sites (especially the hands) are more common with lung primaries. Involvement of the toes is seen more commonly with genitourinary primaries.[3]

The problems associated with bone metastasis are pain which is the most common symptom, pathologic fractures, spinal cord compression and hypercalcemia are also seen these are referred as skeletal-related events (SRE). Pathologic fractures may be the first sign of metastatic bone disease. In breast carcinoma, as many as 35% of patients with bone disease experience a fracture.[4]

Bone metastases are often described as either osteolytic or osteoblastic. The destruction of bone by osteolytic metastases is not by the tumor cells directly, but the factors that activate the osteoclasts for bone resorption are RANKL, interleukin-1, interleukin-6, and macrophage inflammatory protein 1α, are produced by the tumor cells. The exact pathophysiology of osteoblastic activation are unknown. [5]

Metastases to the bone most often occur in the red marrow and most common route of spread is hematogenous and to lesser extent by direct extension. Osteolytic and osteoblastic lesions are seen in all cancers metastatising to bone. Breast and lung cancers more commonly cause an osteolytic-appearing lesions, prostate and thyroid cancers causes an osteoblastic appearance. In myeloma purely osteolytic lesions are seen.[6]

The exact mechanism of pain in bone metastasis is unknown, but Possible mechanisms are mechanical instability, irritation of periosteal stretch receptors, tumor-directed osteoclast-mediated osteolysis, tumor cells themselves, or tumor-induced nerve injury, production of nerve growth factor, or stimulation of other cytokine receptors. Combination of therapies is be superior to single therapy to control pain occurring by different mechanisms.[7] Confirming the pain due to metastasis in cancer patient is done by examination, “point tenderness”, imaging and/ or histological confirmation. Radiographs are the first imaging study done during evaluation as these are easy to obtain and inexpensive but approximately 30% to 50% of the bone mineral content must be lost before the lesion will be apparent on x-rays. Nuclear medicine bone scan (Technetium-99m) is the best method for screening and to evaluate the extent of metastatic disease in the bone. Computed tomography (CT) scans are more sensitive to detect cortical destruction and to assess the risk of a pathologic fracture. Magnetic resonance imaging (MRI) is better than plain radiography or nuclear medicine bone scintigraphy at assessing the involvement of trabecular bone of vertebral bodies. Comparative studies have shown PET scans to be more sensitive than Tc-99m scintigraphy or whole-body MRI scans in detecting bone metastases.[8,9]

Pain control can be achieved in the majority of patients using the World Health Organization analgesic ladder.

Who Analgesia Ladder For Pain Management

Step	Analgesia
Step I	Non opioids - acetaminophen or nonsteroidal anti-inflammatory drugs
Step II	weak opioids - codeine
Step III	Strong opioids - morphine

Medications are given round the clock and as and when required additionally.70% to 76% of patients will have good pain relief.[10] Adjuvant medications such as gabapentin, pregabalin, or amitriptyline may be added for neuropathic pain. Antianxiety or antidepressant medications may also be of benefit in selected patients.

The goals of surgical intervention are to prevent or relieve pain, improve motor function, and improve overall quality of life, by preventing or treating the pathologic fractures. Pathological fractures to femur very common and 65% of pathological fractures are required surgical treatment.[11]

The risk of pathologic fracture of the femur begins to significantly increase when there is destruction of >50% of the cortex; the risk of fracture is 80% when >75% of the cortex is destroyed. Greatest reduction in strength of the femur occurs with lesions in the inferior and medial aspect of the femoral neck, and posterior lesions have the least impact.

Mirel’s Scoring System Of Prediction Of Pathological Fracture Risk

Score	Pain	Location	Cortical destruction	Radiographic appearence
1	mild	Upper limb	<1/3	Blastic
2	moderate	Lower limb	1/3-2/3	Mixed
3	severe	Peritrochanteric	>2/3	Lytic

A scoring system proposed by Mirels, has a 12-point scale based on the location of the lesion, pain, extent of cortical destruction, and radiographic appearance. The risk of fracture is 15% for a score of 8 and 33% for a score of 9. He proposed that prophylactic fixation is indicated for a score of ≥9.[12]

Following procedures are also used to relieve pain and complications associated with the bone metastasis. Vertebroplasty is an effective method of palliating pain from vertebral body metastases. Kyphoplasty may be a better option than vertebroplasty in patients with vertebral wall deficiency.

Radiofrequency ablation (RFA) may be used to ablate the tumor but is most effective for tumors that are osteolytic or mixed osteolytic and blastic. [13]

External-beam radiotherapy may be an appropriate option for palliation of localized bone pain. For diffuse or constitutional and widespread disease systemic chemotherapy is better option. Because of the potential for increased toxicity when both modalities are delivered concurrently, it is never adviced to combine chemotherapy with concurrent radiation therapy.

Response is assessed in bone metastasis and defined based on imaging, pain response and quality of life parameters. Complete response is achieved if there is a disappearance of all lesions on radiographs for at least 4 weeks, whereas for partial response requires some recalcification of lytic lesions, which may not be evident for 6 months or more.[14]

Hormonal therapy has the potential for providing excellent palliation of metastatic disease with limited morbidity. Serious complications of bone metastasis like pathologic fracture, spinal cord compression and development of extraskeletal metastases, and also ureteral obstruction were two fold less frequent in patients who received immediate hormone ablation therapy in carcinoma prostate compared to cohort who did not receive hormonal therapy.[15]

Denosumab is a human monoclonal antibody specific for the RANK ligand. The mechanism of action is it binds to RANKL and thus inhibits the formation, activation, maturation, and survival of osteoclasts. Patients with metastatic breast or prostate cancer showed superior resultsin in delaying or preventing the time to skeletalrelated events for denosumab when compared with zoledronic acid in a prospective randomized study.[16]

Radiation Therapy

Radiation therapy has been reported to be effective treatment in palliating localized painful bone metastases. Partial and complete pain relief was seen in 80% and 50% respectively when physician response for pain was used and the data from patient evaluation of pain was slightly lower than physicians response for pain it was 70% and 25% for partial and complete response for pain relief respectively.[17]

Patients who have improvement in pain after radiotherapy showed improvement in quality-of-life scores. Radiation therapy should be an integral part of palliative treatment for bone metastases.[18]

METHOD AND MATERIALS

A prospective study done on patients with bone metastasis, whose malignancy was histologically proven and the bone metastasis was confirmed by histology and/ or imaging. Patients who previously received radiation therapy to the region concerned and the presence of any co-morbid conditions to which the patient's symptoms could be attributed to were excluded from the study. It was conducted from September 2013 to April 2015 on sixty patients for pain management and to improve the quality of life in patients receiving palliative radiotherapy.

Inclusion Criteria: Patients with bone metastasis from any primary

Exclusion criteria*:* Previous radiation therapy to the region concerned and Presence of any co-morbid condition to which the patient's symptoms could be attributed

A total of sixty patients were recruited based on above criteria and divided in four groups with fifteen patients in each group. Different fractionation of radiotherapy Group A- 8 Gy in single fraction, Group B- 20 Gy in 5 fractions, Group C- 24 Gy in 6 fractions and Group D- 30 Gy in 10 fractions were delivered using Linear accelerator of 6MV photons. Pain was evaluated using Visual Analogue Scale. It consists of numbers from 0 to 10 where 0 represents no pain at all and 10 represents the worst pain one could imagine. The score of 1-9 represents variable severity of pain between the two extremes and performance status by ECOG scale. [19]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities.Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Statistical Analysis

Following radiotherapy pain was assessed within the patients of one group by using repeated measure ANOVA test variation for time period one to last time period and the results were compared with each of the other groups using one way ANOVA test for visual analogue scale and performance scale, for quality of life life questonnaire (EORTC QLQ-C30 module) POSTHOC test was used. Pain scale for pre radiotherapy was compared with post radiotherapy at 1 week, 1month and 3 months follow up respectively. Results were considered statistically significant if p value was < 0.05.

RESULTS

The sixty patients were divided in four groups, according different fractionation. Patient charactestics are as shown in Table 1. Radiotherapy Group A- 8 Gy in single fraction, Group B- 20 Gy in 5 fractions, Group C- 24 Gy in 6 fractions and Group D- 30 Gy in 10 fractions. Pain relief using visual analogue scale was almost same in all the four groups when compared with each other but there was a significant pain relief in each group when compared to the pre radiotherapy pain scale. P value of performance status was statistically significant in Group B- 0.005 when compared to the other groups. Quality of life, using questonnaire (EORTC QLQ-C30 module), symptomatic scale showed improvement in Group A-0.002, Group C- <0.001 and Group D-<0.001 whereas p value of functional scale was <0.001 in all four groups.

Table 1 Patient and Tumor Characteristics

		GROUP							
		GROUP A		GROUP B		GROUP C		GROUP D	
		Count	Column N %	Count	Column N %	Count	Column N %	Count	Column N %
SEX	MALE	7	46.7%	8	53.3%	10	66.7%	10	66.7%
	FEMALE	8	53.3%	7	46.7%	5	33.3%	5	33.3%
DIAGNOSIS	PROSTATE	3	20.0%	2	13.3%	1	6.7%	3	20.0%
	BREAST	7	46.7%	3	20.0%	2	13.3%	4	26.7%
	HEAD AND NECK	3	20.0%	3	20.0%	2	13.3%	3	20.0%
	LUNG	1	6.7%	4	26.7%	8	53.3%	3	20.0%
	GYNAE	0	0.0%	2	13.3%	1	6.7%	0	0.0%
	GIT	0	0.0%	1	6.7%	1	6.7%	1	6.7%
	MUO NECK	1	6.7%	0	0.0%	0	0.0%	1	6.7%
SITE OF METASTASIS	LUMBAR	3	20.0%	4	26.7%	6	40.0%	2	13.3%
	THORASIC	2	13.3%	6	40.0%	4	26.7%	4	26.7%
	PELVIS	2	13.3%	3	20.0%	3	20.0%	6	40.0%
	FEMUR	3	20.0%	0	0.0%	2	13.3%	0	0.0%
	CERVICAL	1	6.7%	1	6.7%	0	0.0%	0	0.0%
	STERNUM	4	26.7%	1	6.7%	0	0.0%	2	13.3%
	RIBS	0	0.0%	0	0.0%	0	0.0%	1	6.7%
ANALGESICS WHO	0	0	0.0%	1	6.7%	0	0.0%	1	6.7%
	1	4	26.7%	4	26.7%	2	13.3%	4	26.7%
	2	4	26.7%	5	33.3%	9	60.0%	6	40.0%
	3	7	46.7%	5	33.3%	4	26.7%	4	26.7%

Comparision between groups **Table 2**

Visual Analogue Scale Score							
GROUP		**Source**	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**P VALUE**
GROUP A	TIME	Greenhouse-Geisser	115.080	1.562	73.677	28.360	**<0.001**
GROUP B	TIME	Greenhouse-Geisser	180.073	2.031	88.681	88.587	**<0.001**
GROUP C	TIME	Greenhouse-Geisser	185.480	2.511	73.862	152.868	**<0.001**
GROUP D	TIME	Greenhouse-Geisser	121.680	2.507	48.532	70.562	**<0.001**

Table 3

Performance Ecog Score							
GROUP		**Source**	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**P VALUE**
GROUP A	TIME	Greenhouse-Geisser	.680	1.267	.537	.718	.447
GROUP B	TIME	Greenhouse-Geisser	7.745	2.358	3.285	6.121	.005
GROUP C	TIME	Greenhouse-Geisser	3.680	1.374	2.678	3.090	.095
GROUP D	TIME	Greenhouse-Geisser	3.000	1.000	3.000	5.000	.052

Quality of life eortc qlq-30 **Table 4**

Functional Scale							
GROUP		**Source**	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**P VALUE**
GROUP A	TIME	Greenhouse-Geisser	6652.520	1.455	4570.764	30.993	**<0.001**
GROUP B	TIME	Greenhouse-Geisser	9249.105	1.317	7024.490	38.726	**<0.001**
GROUP C	TIME	Greenhouse-Geisser	11191.300	2.397	4669.206	69.801	**<0.001**
GROUP D	TIME	Greenhouse-Geisser	6916.843	1.390	4975.791	36.416	**<0.001**

Table 5

SYMPTOMATIC SCALE							
GROUP		**Source**	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**P VALUE**
GROUP A	TIME	Greenhouse-Geisser	4012.732	1.353	2966.867	19.245	**.002**
GROUP B	TIME	Greenhouse-Geisser	2862.701	1.403	2041.056	11.212	**.009**
GROUP C	TIME	Greenhouse-Geisser	1125.513	1.820	618.371	97.217	**<0.001**
GROUP D	TIME	Greenhouse-Geisser	2929.753	1.408	2080.139	41.394	**<0.001**

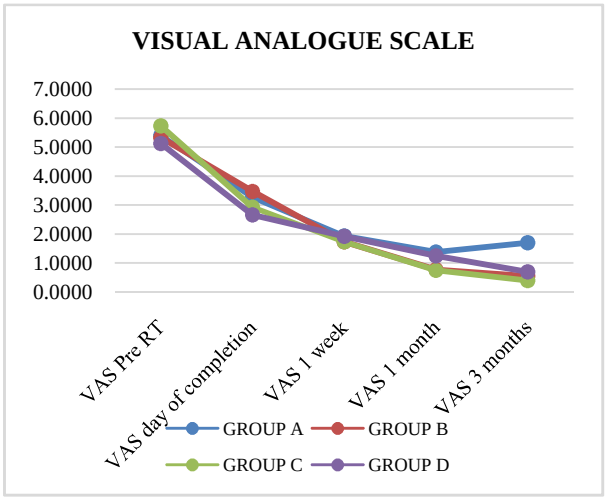

Figure 1

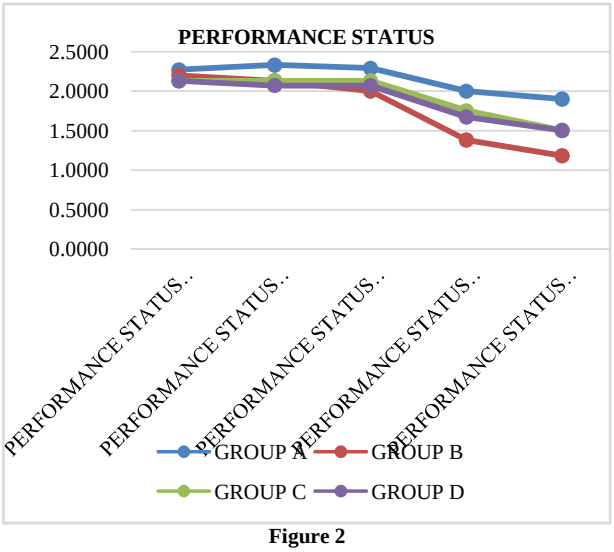

Figure 2

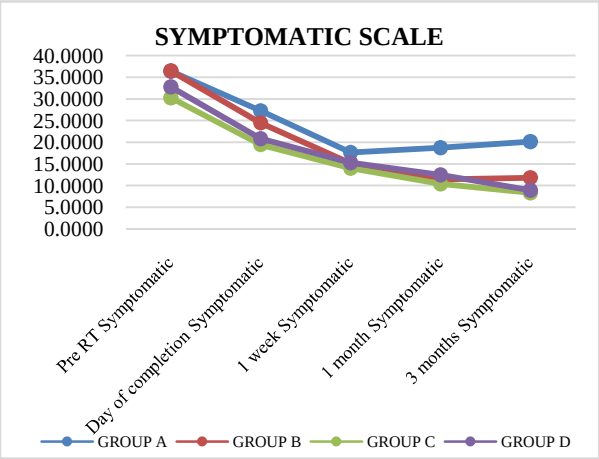

Figure 3

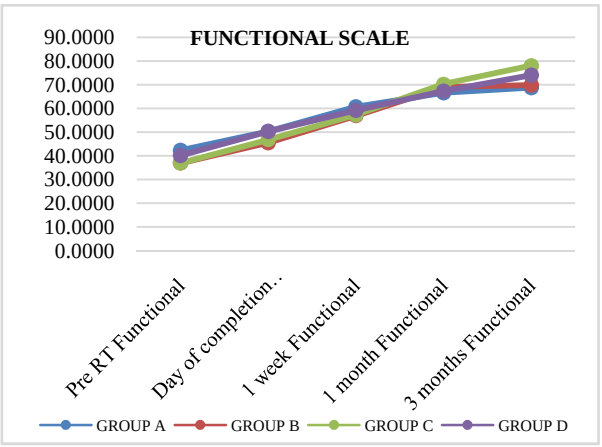

Figure 4

Repeated Measures Anova Test for Comparison Of The Time Periods Within Group

Table 6A pain scale visual analogue scale

Group		Mean	Std. Deviation	N
GROUP A	VAS Pre RT	5.40	1.955	10
	VAS day of completion	2.90	1.524	10
	VAS 1 week	1.70	1.160	10
	VAS 1 month	1.20	1.317	10
	VAS 3 months	1.70	2.263	10
GROUP B	VAS Pre RT	5.27	1.679	11
	VAS day of completion	3.55	1.214	11
	VAS 1 week	1.64	1.206	11
	VAS 1 month	.73	.905	11
	VAS 3 months	.55	.820	11
GROUP C	VAS Pre RT	5.60	1.265	10
	VAS day of completion	2.70	.949	10
	VAS 1 week	1.40	.843	10
	VAS 1 month	.50	.707	10
	VAS 3 months	.40	.699	10
GROUP D	VAS Pre RT	4.90	1.370	10
	VAS day of completion	2.50	.850	10
	VAS 1 week	1.60	.843	10
	VAS 1 month	.70	.823	10
	VAS 3 months	.70	.823	10

Table 7A Performance Status

GROUP		Mean	Std. Deviation	N
GROUP A	PERFORMANCE STATUS Pre RT	2.00	.943	10
	PERFORMANCE STATUS day of completion	2.10	.994	10
	PERFORMANCE STATUS 1 week	2.10	.994	10
	PERFORMANCE STATUS 1 month	1.80	1.033	10
	PERFORMANCE STATUS 3 months	1.90	1.101	10
GROUP B	PERFORMANCE STATUS Pre RT	2.09	.831	11
	PERFORMANCE STATUS day of completion	2.00	.894	11
	PERFORMANCE STATUS 1 week	1.82	1.079	11
	PERFORMANCE STATUS 1 month	1.27	1.191	11
	PERFORMANCE STATUS 3 months	1.18	1.328	11
GROUP C	PERFORMANCE STATUS Pre RT	2.10	.316	10
	PERFORMANCE STATUS day of completion	2.10	.568	10
	PERFORMANCE STATUS 1 week	2.10	.568	10
	PERFORMANCE STATUS 1 month	1.60	1.075	10
	PERFORMANCE STATUS 3 months	1.50	1.179	10
GROUP D	PERFORMANCE STATUS Pre RT	2.00	.943	10
	PERFORMANCE STATUS day of completion	2.00	.943	10
	PERFORMANCE STATUS 1 week	2.00	.943	10
	PERFORMANCE STATUS 1 month	1.50	.972	10
	PERFORMANCE STATUS 3 months	1.50	.972	10

Table 7 B

Group		Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Group a	time	Greenhouse-Geisser	.680	1.267	.537	.718	.447
Group b	time	Greenhouse-Geisser	7.745	2.358	3.285	6.121	**.005**
Group c	time	Greenhouse-Geisser	3.680	1.374	2.678	3.090	.095
Group d	time	Greenhouse-Geisser	3.000	1.000	3.000	5.000	.052

Table 8A Symptomatic Scale (Eortc Qlq-30)

GROUP		Mean	Std. Deviation	N
GROUP A	Pre RT Symptomatic	47.223333	15.2908230	6
	Day of completion Symptomatic	36.803333	13.0203190	6
	1 week Symptomatic	22.223333	10.4287711	6
	1 month Symptomatic	16.666667	8.3320002	6
	3 months Symptomatic	20.138333	13.0199991	6
GROUP B	Pre RT Symptomatic	36.111667	15.2897330	6
	Day of completion Symptomatic	30.555000	11.3865583	6
	1 week Symptomatic	18.751667	5.1022874	6
	1 month Symptomatic	12.498333	5.2715175	6
	3 months Symptomatic	11.803333	5.5393381	6
GROUP C	Pre RT Symptomatic	27.085000	2.4075506	4
	Day of completion Symptomatic	20.832500	3.4007095	4
	1 week Symptomatic	11.457500	2.0850000	4
	1 month Symptomatic	8.330000	0E-7	4
	3 months Symptomatic	8.330000	0E-7	4
GROUP D	Pre RT Symptomatic	33.331429	8.6741425	7
	Day of completion Symptomatic	20.238571	5.0615921	7
	1 week Symptomatic	13.691429	2.0347517	7
	1 month Symptomatic	8.925714	1.5761119	7
	3 months Symptomatic	8.925714	1.5761119	7

Table 6 b

GROUP		Source	Type III Sum of Squares	df	Mean Square	F	Sig.
GROUP A	time	Greenhouse-Geisser	115.080	1.562	73.677	28.360	<0.001
GROUP B	time	Greenhouse-Geisser	180.073	2.031	88.681	88.587	<0.001
GROUP C	time	Greenhouse-Geisser	185.480	2.511	73.862	152.868	<0.001
GROUP D	time	Greenhouse-Geisser	121.680	2.507	48.532	70.562	<0.001

Table 8 B

GROUP	Source		Type III Sum of Squares	df	Mean Square	F	Sig.
GROUP A	time	Greenhouse-Geisser	4012.732	1.353	2966.867	19.245	.002
GROUP B	time	Greenhouse-Geisser	2862.701	1.403	2041.056	11.212	.009
GROUP C	time	Greenhouse-Geisser	1125.513	1.820	618.371	97.217	<0.001
GROUP D	time	Greenhouse-Geisser	2929.753	1.408	2080.139	41.394	<0.001

Table 9A Functional Scale (Eortc Qlq-30)

Descriptive Statistics				
	GROUP	Mean	Std. Deviation	N
GROUP A	Pre RT Functional	40.239000	22.5167160	10
	Day of completion Functional	49.285000	22.2513501	10
	1 week Functional	60.715000	20.5211426	10
	1 month Functional	70.237000	19.6737598	10
	3 months Functional	68.809000	21.8061268	10
GROUP B	Pre RT Functional	37.230909	15.1814574	11
	Day of completion Functional	45.237273	11.6654911	11
	1 week Functional	57.792727	13.1304921	11
	1 month Functional	69.263545	16.9199274	11
	3 months Functional	69.915455	17.0143636	11
GROUP C	Pre RT Functional	38.812000	8.1751491	10
	Day of completion Functional	48.333000	6.1525316	10
	1 week Functional	61.668000	9.2867837	10
	1 month Functional	74.287000	14.5811225	10
	3 months Functional	78.096000	14.8383094	10
GROUP D	Pre RT Functional	42.857000	17.2070522	10
	Day of completion Functional	51.668000	13.5179065	10
	1 week Functional	62.618000	14.4619346	10
	1 month Functional	71.192000	14.1282883	10
	3 months Functional	74.050000	13.6755223	10

Acute toxicity was significantly high in 30/10 fraction than 8/1 fraction arm: 17% versus 10%. Retreatment was higher in single fraction arm 18% versus 9%.[24] Meta-analysis of 12 randomized trials also have confirmed those findings.[25] Dutch Bone Metastasis Study in 2010 has shown that pain responded in ~50% of patients with short survival, regardless of fractional schema. Single fraction should be preferred, and additional palliative measure remain essential.[26]

Our results were similar to the results of RTOG 74-02 first largest randomized study, Tong *et al*. North American multicenter trial (RTOG 97-14), Hartsell *et al*. Meta analysis of 12 randomized trials there was no significant difference in the probability of achieving pain relief with different fractionation schedules of localized RT in painful uncomplicated bone metastases. It was against the result of Roose *et.al*. Single fraction 8Gy may be considered for short mean survival patients.

Table 9B

GROUP	Source		Type III Sum of Squares	df	Mean Square	F	Sig.
GROUP A	time	Greenhouse-Geisser	6652.520	1.455	4570.764	30.993	<0.001
GROUP B	time	Greenhouse-Geisser	9249.105	1.317	7024.490	38.726	<0.001
GROUP C	time	Greenhouse-Geisser	11191.300	2.397	4669.206	69.801	<0.001
GROUP D	time	Greenhouse-Geisser	6916.843	1.390	4975.791	36.416	<0.001

DISCUSSION

The first large randomised study evaluating different dose and fractionation schemes was Radiation Therapy Oncology Group (RTOG) 74-02 trial.[20] The initial study by Tong *et al*. showed no statistically significant difference in response rates between any arms. Two large contemporary multicentric randomized trials and a meta-analysis have found no significant difference in the probability of achieving pain relief with different fractionation schedules of localized RT in painful uncomplicated bone metastases.[21,22] One study differs slightly in results. Roos *et al*. found better outcome in multiple fraction arm when 20 Gy/5 fractions was used. 8/1 was not shown to be as effective as 20/5, nor was it statistically significantly worse. Outcomes were generally poorer for 8/1, although the quantitative differences were relatively small.[23]A meta-analysis have found no significant difference in the probability of achieving pain relief with different fractionation schedules of localized RT in painful uncomplicated bone metastases. Published results of a North American multicenter trial (RTOG 97-14), Hartsell *et al*. found the results between single versus multiple fractionation comparable in terms of toxicity. They reported 3-month complete pain relief in 8/1 fraction 15% versus 18% in multiple fraction (statistically non-significant [NS]); partial 50% versus 48% (NS); stable 26% versus 24%; progressive 9% versus 10%.

CONCLUSION

All four fractionation treatment schedules provided significant pain relief and improvement in Quality of life for both symptomatic and functional scale. Therefore consideration of choice of treatment schedule should be based on mean survival and patient convenience.

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