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Original Article

Comparison between Single Fraction versus Multiple Fraction Radiotherapy in Terms of Pain Control and Prevention of Skeletal Related Events in Patients with Bone Metastasis Candidates for Radiotherapy

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ABSTRACT

Background: Metastasis are the most common type of malignant tumor which involve bone, according to OSCER (Oncology Services Comprehensive Electronic Record) among 382,733 study patients, breast cancer (36 %), lunge cancer (60%), and colorectal cancer (12%) were the most common, incidence of bone metastasis was 2.9% at 30 days, 4.9% at 1 year, 5.6% at 2 years, 6.9% at 5 years, 8.4 % at 10 years. Incidence varied by tumor type with prostate cancer patients were at highest risk (18%-29%) followed by lunge, renal and breast cancer.

Aim of the Work: This study aim to prove the equivalency and the efficacy of single fraction radiotherapy (800cGY) and multiple fraction radiotherapy (10 fractions, 300 cGY / fraction, 1 fraction / day, 5 days per week over 2 weeks to a total of 3000cGy) in terms of pain relief and prevention of skeletal related events.

Results: In this study we collected data of 60 patients, 5 patients died and 55 patients received active treatment who were divided into 2 arms, Arm I represented 28 patients received single fraction radiotherapy on sites of bone metastasis (800cGY) and Arm II represented 27 patients received multiple fraction radiotherapy on sites of bone metastasis (total of 3000cGY in 10 fractions). Regarding to pain response, it was evaluated at zero, 2,4 weeks and 2,4 months using Visual Analogue Scale and Numeric Rating Scale or telephone interviews. Complete response was defined as no pain for 4 months, partial response was defined as at least 2 points lower than initial response, stable response was defined as 1 point change in pain score and progressive response was defined as pain score that's at least 2 points higher than initial response. In our study, in Arm I patient achieving complete response represented 50% and in Arm II 40.7% which is non significant of P value 0.490, while partial response in Arm I represented 39.3% and 18.5 % in Arm II which is non significant of P value 0.090, stable response in Arm I represented 3.6% and 33.3% in Arm II which is highly significant of P value 0.004 and progressive response in Arm I represented 7.1% and in Arm II 7.4% which is non significant of P value 0.974.

Conclusion: Single fraction radiotherapy is equivalent to multiple fraction radiotherapy in terms of palliating pain of bone metastasis and prevention of skeletal related events.

Keywords
Single Fraction,
Multiple Fraction,
Bone Metastasis.

INTRODUCTION

Bone metastases occur in up to 70% of prostate cancer patients and breast cancer patients during the course of their disease. Up to 40% of patients with lung cancer, renal-cell carcinoma and thyroid cancer develop bone metastases [1]. Bone metastases may be osteoblastic, osteolytic, or mixed. Quality of life may be significantly impaired as a consequence of painful bone metastases. If pathological fractures or spinal-cord compression occur typically referred to as skeletal-related events (SREs), the metastases are defined as 'complicated'. Without such complications, the metastases are defined as 'uncomplicated' [2].

The primary tumour releases cells that pass through the extracellular matrix, penetrate the and are then transported to distant or-

gans via the circulatory system. Circulating breast and prostate cancer cells have a particular affinity for bone. Most disseminated tumour cells die, but the bone marrow micro-environment may act as a reservoir for malignant cells [3]. Treatments vary depending on the underlying disease. External beam radiotherapy, endocrine treatments, chemotherapy, targeted therapies and radioisotopes are all important. In addition, orthopaedic intervention may be necessary for the structural complications of bone destruction or nerve compression [4].

Complementing these treatments is the role of bone-targeted agents. Treatment decisions depend on whether the bone disease is localised or widespread, the presence or absence of extraskeletal metastases and the nature of the underlying malignancy. Radiotherapy is relevant throughout the clinical course of the disease [5]. Radiotherapy is a safe and effective therapy and is well established for such a situation. A fractionation regimen with a short overall treatment time (≤1 week) would be preferred if it was as effective as longer courses (2–4 weeks).

Randomized clinical trials and meta-analyses have demonstrated that single-fraction radiotherapy with 1 × 8 Gy is as effective for pain relief as multi-fraction regimens such as 5 × 4 Gy in 1 week or 10 × 3 Gy in 2 weeks. Re-irradiation for recurrent pain in the irradiated region is required more often after single-fraction radiotherapy than multi-fraction radiotherapy; however, re-irradiation following single-fraction radiotherapy is safe and effective. Thus, 1 × 8 Gy is considered the standard regimen for uncomplicated painful bone metastases without pathological fractures or spinal cord compression. Multi-fraction long-course radiotherapy results in fewer recurrences of spinal-cord compression within the irradiated spinal region. Thus, long-course multi-fraction radiotherapy should be reserved for patients with a relatively favorable survival prognosis. Pain assessment in bony metastasis by different tools such as The Numeric Pain Rating Scale, Visual Analog Scale, Adult Non-Verbal Pain Scale [6].

AIM OF THE WORK

To prove efficacy and equivalency of single fraction radiotherapy (800 cGy) and multiple fraction radiotherapy (10 fractions, 300 cGy/ fraction, 1 fraction/day, 5days per week over 2 weeks to a total of 3000 cGy) in terms of pain relief and prevention of skeletal related events.

PATIENTS AND METHODS

Type of study is a prospective cross sectional study**,** all available data (including patient, tumor, and treatment characteristics), will be extracted from patient files. **Study setting** in Department of clinical oncology and nuclear medicine, Ain shams university hospitals, Cairo, Egypt. **Study population** included patient with bony metastasis treated with single fraction or multiple fractions radiotherapy in the period from June 2017 till June 2018.

Inclusion Criteria

Patients included in this study aged 18 years or more, with histological diagnosis of malignancy, with radiological evidence of painful bone metastasis and life expectancy of 12 weeks or more.

Exclusion Criteria

Patients excluded who were primarily diagnosed with multiple myeloma
Patients with bone metastasis in sites previously irradiated, previously received radioisotope treatment.
Patients with medical conditions or circumstances that may impede treatment or follow up.

Randomization

60 Patients were randomized to 1 of 2 treatment arms:
Arm I: 30 Patients receiving single-fraction radiotherapy (8Gy) on one day.
Arm II: 30 Patients receiving multiple-fractions radiotherapy (to a total of 30Gy) 10 fractions total, delivered as single fraction per day (300cGy), 5days per week over 2 weeks.

Evaluation of Response

Response was assessed at 0, 2, 4 weeks then 2, 4 months by Visual Analogue Scale and Numeric Rating Scale or telephone interviews.

Complete response was defined as no pain for 4 months, partial response was defined as at least two points lower than intial response, stable response was defined as one point change in pain score and progressive response was defined as pain score that is at least two points higher than initial response.

Statistical analysis

Data was analyzed using SPSS 16. Mean + standard deviation was computed for age, weight and height. Chi square test was applied to compare cardiovascular side effects. Repeated measures analysis of variance (ANOVA) was used to compare effects like heart rate, systolic and diastolic blood pressures of the two groups. P-value of 0.05 or less was considered statistically significant.

RESULTS

Table 1. Patient characteristics in two groups

		Single Fraction	Multiple Fraction	Test value	P-value	Sig
		No.= 30	No.= 30			
Age	Mean ± SD	57.13 ± 11.04	52.77 ± 13.14	1.394•	0.169	NS
	Range	30 – 78	23 – 81			
	Median	59.50	52.50			
Sex	Male	14 (46.7%)	15 (50.0%)	0.067*	0.796	NS
	Female	16 (53.3%)	15 (50.0%)			
DM	Negative	20 (66.7%)	19 (63.3%)	0.073*	0.787	NS
	Positive	10 (33.3%)	11 (36.7%)			
HTN	Negative	24 (80.0%)	21 (70.0%)	0.800*	0.371	NS
	Positive	6 (20.0%)	9 (30.0%)			

Table 2. Primary diagnosis, site of metastasis and percentage of SRE in both arms

		Single Fraction		Multiple Fraction		Test value*	P-value	Sig.
		No.= 30		No.= 30				
Diagnoses	Breast	11	36.7%	16	53.3%	1.684	0.194	NS
	HCC	2	6.7%	3	10.0%	0.218	0.640	NS
	Lung	8	26.7%	4	13.3%	1.667	0.197	NS
	MUO	2	6.7%	2	6.7%	0.000	1.000	NS
	Prostate	5	16.7%	3	10.0%	0.577	0.447	NS
	Rectum	0	0.0%	1	3.3%	1.017	0.313	NS
	Thyroid	1	3.3%	0	0.0%	1.017	0.313	NS
	U.B	1	3.3%	1	3.3%	0.000	1.000	NS
Sites of secondary bone Metastasis	Hip Joint	5	16.7%	1	3.3%	2.963	0.085	NS
	Lower Half	2	6.7%	0	0.0%	2.069	0.150	NS
	Lt Femur	2	6.7%	0	0.0%	2.069	0.150	NS
	Pelvic	5	16.7%	3	10.0%	0.577	0.447	NS
	Ribs	4	13.3%	2	6.7%	0.741	0.389	NS
	Rt Femur	3	10.0%	1	3.3%	1.071	0.300	NS
	Rt humerus	0	0.0%	1	3.3%	1.017	0.313	NS
	Rt Shoulder	0	0.0%	1	3.3%	1.017	0.313	NS
	Shoulder	1	3.3%	1	3.3%	0.000	1.000	NS
	Vertebrae	8	26.7%	20	66.7%	9.643	0.001	HS
SRE	Negative	27	90.0%	28	93.3%	0.218	0.640	NS
	Positive	3	10.0%	2	6.7%			

Table 3. Analgesics used in both groups

Pain medication	Single Fraction	Multiple Fraction	Test value	P-value	Sig.
	No.= 30	No.= 30			
Fentanyle patch	1 (3.3%)	2 (6.7%)			
Profenid	12 (40.0%)	5 (16.7%)	4.116*	0.128	NS
Tramadol HCL	17 (56.7%)	23 (76.7%)			

Table 4. Pain response in single fraction group and multiple fraction group through 4 months follow up

		Single Fraction	Multiple Fraction	Test value	P-value	Sig.
1st Week	Median	8 (6 – 10)	8.5 (8 – 10)	-1.302	0.193	NS
	Range	3 – 10	4 – 10			
2nd week	Median	6 (5 – 8)	7 (5 – 9)	-0.785	0.433	NS
	Range	3 – 10	4 – 10			
2 month	Median	4 (3 – 8)	7 (3 – 9)	-1.190	0.234	NS
	Range	3 – 10	2 – 10			
4 month	Median (IQR)	3 (0 – 8)	7 (0 – 9)	-1.366	0.172	NS
	Range	0 – 10	0 – 10			

Table 5. Response rate in both arm according to numerical analogue scale

		Single Fraction		Multiple Fraction		Test value	P-value	Sig.
		No.	%	No.	%			
Response	Responder	25	89.3%	16	59.3%	6.531	0.011	S
	Non responder	3	10.7%	11	40.7%			

Table 6. Table showing percentage of responders and non responders in both arms

		Single Fraction		Multiple Fraction		Test value	P-value	Sig.
		No.	%	No.	%			
Response	Complete response	14	50.0%	11	40.7%	0.475	0.490	NS
	Partial response	11	39.3%	5	18.5%	2.874	0.090	NS
	Progression	2	7.1%	2	7.4%	0.001	0.974	NS
	Stable disease	1	3.6%	9	33.3%	8.185	0.004	HS

DISCUSSION

Metastases are the most common type of malignant tumor which involve bone; the skeleton is the third common site for metastasis after the lung and liver [7].

As a palliative intervention, radiotherapy is effective at treating painful bone metastases, and the side effects associated with its use are manageable. Between 50% and 80% of cancer patients have at least partial relief of their pain following external beam radiotherapy (EBRT), and complete relief may be seen in up to one-third [8].

From a health systems perspective, single fraction EBRT is convenient for patients and cost-effective in comparison to multi-fraction RT [9].

A single 8 Gy fraction provides non inferior pain relief compared with a more prolonged RT course in painful spinal sites and may therefore be particularly convenient and sensible for patients with limited life expectancy [10].

Despite overwhelming evidence that equivalent pain relief from painful bone metastases could be achieved from a single radiation treatment, practice patterns among US radiation oncologists still favor a multi fraction course of radiation [11].

In our present study we compared single fraction radiotherapy and multiple fraction radiotherapy and we found that single fraction radiotherapy was equivalent to multiple fraction regimens and more convenient to most of our patients for many factors such as old age, severe pain, and poor performance.

As regard patient characteristics in our present study mean age in both groups was almost 57 to 59 years old, as for gender patients were equally distributed between both arms.

In a similar study by Bayard and colleagues published in 2014, included 90 patients, the mean age was 62.6, in this study there was a male predominance (62.8 % in Arm I and 57.7% in Arm II) which is different from our study and that affect this study in the ratio of primary diagnoses whereas prostate cancer patients represented (31.1%) [12].

In another study conducted by **Majumder and his colleague** which included 53 patients from July 2010 to May 2011 and were divided between two arms, as regard baseline patient characteristics similarly to our study Median age was 58 years and 60 years in arm A and arm B, respectively however Unlike our study Male patients were predominant in both the arms (84.8% in arm A, 80.6% in arm B) and that explained why the most common primary diagnosis in Majumder study was prostatic cancer represented (81.8% in arm A and 77.4% in arm B).

As regard Nature and site of Metastases in our present study in Arm I there was a predominance of patients with metastatic breast cancer representing 36.7% followed by metastatic lung cancer represents 26.7% then metastatic prostate cancer represents 16.7% and others types represented 20% (HCC, MUO, thyroid and U.B), while in Arm II there was also a predominance of metastatic breast cancer patients represented 53.3% followed by lung 13.3% followed by HCC and Prostatic cancer each 10% then other cancers represented 13.3% (MUO, rectum and U.B). **Similarly In** a study conducted by **Gutierrez and his colleagues** published in 2014 regarding primary diagnosis in Arm I breast cancer patients represented (40%) which is nearly equal to ratio in our study, lung cancer patients represented (11.1%), prostate cancer patients represented (31.1%) which was higher than our study and that was explained by predominance in male ratio in both arms, other types of cancers represented (17.8%) but in Arm II breast cancer patients represented 37.8 %, prostate and lung cancer patients represented 20 % each and other types

of cancer represented 22.2% [12].

About sites of secondary bone metastasis in our study in Arm I vertebral metastasis represented the majority 26.7%, pelvic and hip joints represented 16.7% each, ribs represented 13.3%, right femur and left femur represented 10% and 6.7% respectively, lower half represented 6.7% and left shoulder represented 3.3 %, in Arm II vertebral metastasis also represented the majority 66.7%, pelvic represented 10%, ribs 6.7%, hip joint, right shoulder, left shoulder, right humerus and right femur all represented 3.3% each. Similarly In IAEA phase III study comparing patients receiving 4 GY and patients receiving 8 GY for palliating bone metastasis these were the results of comparing both arms as regard site of irradiation and primary tumors, As regard site of metastasis majority of patients were vertebrae 41% in arm I receiving 8 cGY and 40% in arm II receiving 4 cGY, pelvis and femurs together represented 22% in each arms, femurs with hip represented 49% in arm I and 52 % in arm II and humerus represented 15 % in both arms. Also In another study conducted on a subset of patients with painful vertebral metastases only in the Radiation Therapy Oncology Group 97-14 trial (RTOG 97-14) divided also into two arms those patients receiving single fraction radiotherapy 8 GY and patients receiving 30 GY/10 fractions, as regard treatment sites were to the lumbar (51%) or thoracic (36%) spine, to the cervical spine or to multiple spine sites [14].

As regard pain response in our study we found that external beam radiation therapy was effective at palliating pain from bone metastases, with complete or partial improvement in pain observed through 4 months after randomization was of total 68% (41 patients) out of the 60 patients. At 4 months of follow -up, we found no difference between the response of patients in the arm I receiving 8 Gy in a single treatment fraction and in the arm II receiving 30 Gy in 10 treatment fractions, 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.

Patients in both arms were divided into patients achieving complete response, partial response, stable response, or progressive response.

As for complete response, it is defined as pain score zero at 4 months, this represented 50% in Arm I compared to 40.7% in Arm II (p=0.490) which is non-significant.

As for partial response, it is defined as at least two points lower than initial response, this group of patients represented 39.3% in Arm I compared to 18.5% in Arm II which is also non-significant (p=0.090).

As for Stable response is defined as one point change in pain score which represented 3.6% in Arm I compared to 33.3% in Arm II which is highly significant (p=0.004) and that might be explained by non-compliance of patients who received 10 fractions due to pain, old age and poor performance and Lastly progressive response which is defined as pain score that is at least two points higher than initial response represented 7.1% in Arm I in comparison to 7.4% in Arm II which was non-significant (p= 0.974).

As regard pain response in **Majumder and his colleagues** study grade of pain was significantly reduced in both arms after treatment, According to visual analogue scale (VAS) pain score progressive pain were seen in 15.4% (n = 4) in arm A and 23.1% (n = 6) in arm B, Other patients reported to have partial pain response (84.6% in arm A and 76.9% in arm B). Those having partial pain response were reported to have decreased need for analgesics [13].

In another study conducted by Howell and his colleagues and published in 2013 as regard pain response patients with partial or complete pain response in 70% versus 62% for single fraction (SF) versus multiple fractions (MF) arms which was not significant (P value 0. 59) [15].

Similarly, Lutz et al. [10] in his review of high-quality data showed that pain relief was equal following a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions for patients with previously unirradiated painful bone metastases [10].

A meta-analyses confirmed these results using combined data from 5617 patients in 25 RCTs with overall response rates of 60% versus 61% for SF and multiple fraction (MF) regimens [16].

Similarly, in a phase III RCT including 5617 patients. The overall response rate was similar in patients receiving single fractions (1696 of 2818; 60%) and multiple fractions (1711 of 2799; 61%). Complete response rates were 620 of 2641 (23%) in the single fraction arm and 634 of 2622 (24%) in the multiple fraction arm. Similar to our study, No significant difference was seen in overall or complete response rates; however the likelihood of requiring re-irradiation was 2.6-fold greater in the single fraction arm (P < 0.00001) [8].

CONCLUSION

Single fraction radiotherapy is equivalent to multiple fraction radiotherapy in terms of palliating pain of bone metastasis and prevention of skeletal related events.

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