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## RESEARCH ARTICLE

### Evaluation of four fractionation schedules of radiation therapy in re-irradiation of painful bone metastases.

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#### Abstract

**Background:-** Palliative radiotherapy has proven to be successful in treating pain caused by metastatic lesions in any bone. In most prospective randomized trials on radiotherapy for bone pain, responses up to 70% were reported. However, when survival was prolonged, recurrent pain was reported in up to 50% of patients. It is to be expected for the future, since patients are living longer with disseminated disease, that symptoms may recur & therefore retreatment of bone metastases for palliative reasons will increase.

**The aim of the study:-** Is to evaluate the efficacy and safety of re-irradiation for painful bone metastasis comparing different fractionation regimens with an assessment of subjective response & toxicity.

**Patient and methods:-** one hundred and twenty patients with bone metastasis or bone pain with previous irradiation were included in this prospective randomized study comparing 8 and 6 Gy single fraction with multiple fractions 3 Gy in 10 fractions and 4 Gy in 5 fractions. The primary end point of treatment was the relief of pain, improvement of quality of life. However, the secondary end point was comparing the short term side effects of these treatment regimens.

**The results:-** pain response: after 2 weeks, complete response was observed in 23.3% in group I, 13.3% in group II, III & 20% in group IV and partial response in 66.7% in group I, 73.3% in group II, 76.7% in group III & 70% in group IV. After 4 weeks, complete response was observed in 23.3%, in group I, III & IV while 16.7% only in group II and partial response in 70% in group I, IV & 73.3% in group II, III. After 8 weeks as shown in table 4, complete response was observed in 26.7% in group I, 23.3% in group II, 33.3% in group III & 30% in group IV and partial response in 70% in the group I&II, 63.3% in group III & 66.7% in group IV. no significant difference in pain response was observed between the four groups. Analgesic requirement after 8 weeks of radiotherapy: patients that complained of pain that required strong narcotic decreased in group I: from 10 to 5, group II: from 13 to 6, group III: from 13 to 5, group IV: from 12 to 6. Patients with karnofsky p.s. 90-100 increased from 0 to 1 in all groups while patients of karnofsky p.s. 70-80 increased from 8 to 23 and from 10 to 22, from 12 to 25 and from 9 to 22 in group I, II, III and IV respectively. Evaluation of acute toxicity: treatment was tolerated in all groups, as, grade I diarrhea occur only in 1 patient in group I and II & dermatitis occur in 3 patients, 1 in each group I, II, and III.

**Conclusion:-** the results of our study seem to confirm that there no significant difference between the four regimens of dose fractionation of external beam radiotherapy (8 Gy single fraction, 6 Gy single fraction, 30 Gy in ten fractions and 20 Gy in five fractions) in palliative treatment of bone metastasis as regard pain relief so the use of 8 Gy single fraction of radiotherapy may be of benefit for the patient by reducing treatment time and cost also reducing the treatment burden for hospital, staff and equipment.

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## Introduction:-

Treatment of bone metastases comprises a large part of the radiotherapy daily practice. Palliative radiotherapy has proven to be successful in treating pain caused by metastatic lesions in any bone, and in treating neurological complaints caused by compression of the spinal cord due to lesions in the vertebral column<sup>(1)</sup>. In most prospective randomized trials of radiotherapy for bone pain, responses up to 70% were reported. However, when survival was prolonged, recurrent pain was reported in up to 50% of patients. It is to be expected for the future, since patients are living longer with disseminated disease, that symptoms may recur & therefore re-treatment of bone metastases for palliative reasons will increase<sup>(2)</sup>. In this study, the evidence-based outcomes for response and duration of response to initial and subsequent radiotherapy were presented. Guidelines were formulated to re-treatment of bone metastases, with a focus on timing, expected complications and preferred radiotherapy techniques<sup>(3)</sup>. Bone is the third most frequent site of tumor metastasis, after lung & liver. The malignant tumors that frequently metastasize to the skeleton are from common primary sites, in particular breast, prostate, and lung. The incidence and prevalence of bone metastases in cancer patients are difficult to determine with accuracy and the clinical incidence is lower than the true pathological rate. Studies report a frequency of 10–47% of all patients with breast cancer developing metastases to the bone detected during their illness, but in autopsy studies, more than 70% of breast cancer patients had tumor deposits in the bone<sup>(4)</sup>. Duration of survival after the clinical manifestation of bone metastases depends on whether the metastasis is a solitary lesion or multiple metastases exist throughout the skeleton. When the patient also has visceral metastases the prognosis is generally worse<sup>(5)</sup>. In addition, the type of primary tumor affects the disease outcome. Patients with breast cancer or prostate cancer may have a prolonged survival, sometimes stretching over several years. Improvements in systemic therapy and the relatively long clinical course of these primary tumors underline this observation. When considering treatment options the probability of occult metastasis is a major factor for physicians when deciding which treatment to apply so when there is a high risk, adjuvant systemic therapy or, in the case of bone metastases, Bisphosphonates may be of great benefit<sup>(5)</sup>. Several trials are now on assessment of effect of re-irradiation, single fraction versus multiple fractions. There is promising effects of bone re-irradiation for treatment of bone pain & neurological manifestations with little toxicity<sup>(6-8)</sup>. We here report on the results of re-treatment with a single fraction of 8 Gy and 6 Gy after initial RT, which were also compared with other multi-fractions

Re-irradiation regimens as (3 Gy in 10 fractions and 4 Gy in 5 fractions).

## Patients and methods:-

This prospective randomized study was conducted in Clinical Oncology and Nuclear Medicine Department, Zagazig University Hospitals and included, one hundred and twenty patients with bone metastasis or bone pain with previous irradiation who were admitted to hospital from July 2013 to September 2015. Patients were eligible if they had bone metastases resulting in clinically important pain, judged by the physician and the patient. The inclusion criteria were biopsy or cytology-proven malignant disease, bone metastasis (at any site) verified by bone X-ray, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI), and Karnofsky Performance Status (PS)  $\geq 50$ <sup>(9)</sup>, and recurrent bone pain in a patient with previous history of bone metastasis & irradiation on the same lesion. Patients who had a history of pathological fractures were excluded. Patients were randomly classified into 4 groups:-group I: Single fraction = 8 Gy, group II: Single fraction 6 Gy, group III: 3 Gy in 10 fractions and group IV: 4 Gy in 5 fractions. All patients were subjected to the following: Clinical evaluation: Complete history taking with the full history of presenting symptoms & history of previous bone mass or pain & previous irradiation including (dose, site & fractionation schedule). Clinical examination including: general examination, assessment of P.S & Local examination, including sites of bone lesions. Laboratory investigations include: Complete blood picture, kidney, liver function tests, serum alkaline phosphatase, and serum calcium. Radiological investigations include: X-Ray of site of interest, bone scan, MRI (if needed), and C.T. (if needed). For all patients, pain intensity was assessed using simplified VAS (visual analog scale) (none, mild, moderate and severe). Visual analogue scale (VAS) which graduated on a horizontal line (10 cm), from 0 (no pain) at one end to 10 (severe pain) at the other end, the patient asked to mark on this line where the intensity of the pain lies and the distance from no pain to the patient's mark numerically indicates the severity of pain, where, less than 3 considered no pain, mild 3-5, moderate 5-7 and 7-10 severe pain<sup>(10)</sup>. Analgesic required was assessed for all patients by using 4-point categorical scale (no analgesic, no narcotic, mild narcotic and strong narcotic analgesic), the doses of these analgesics were recorded for all the patients before treatment. Patients' performance status was also evaluated according to performance status scales of Karnofsky<sup>(9)</sup>.

### Treatment:-

Before the start of therapy, all patients received detailed information about the radiotherapy and written consent to treatment was obtained. Briefly, all patients was treated with Cobalt - 60 unit or 6-15 Mv photons from Linear accelerator (Linac, Elekta 151204, precise plan, release 2.12, 477.08). For spinal lesions, the fields included at least one vertebral body above and below the painful vertebrae., all doses were prescribed to appropriate depth of the posterior edge of the vertebral corpora by using direct fields. Parallel-opposed fields were used to treat pelvis, hip, and long bones. Fields were planned to include known skeletal manifestations with an additional 2–3 cm margin. Treatment doses: group I: Single fraction : 8 Gy , group II: 6 Gy , group III : 3 Gy in 10 fractions , and group IV: 4 Gy in 5 fractions . Treatment evaluation and follow up all patients was assessed weekly during treatment to monitor toxicity. After treatment, the patients were followed up monthly with clinical examination. X-ray, bone scan & C.T or MRI (If needed) were used 2 months after treatment for assessment of tumor response and then at 3-6 month interval. Evaluation of treatment response was done by: pain response , analgesic requirement, and performance status . The response was assessed according to WHO criteria <sup>(11)</sup> with the definition of subjective response as complete response (CR) defined as a complete disappearance of pain with no need for analgesics. Partial response (PR) defined as an improvement in pain score by at least one category, with the pain still existing. No response (NR) defined as the pain remained the same or increased. Evaluation of radiation toxicity: by WHO toxicity criteria of skin toxicity, gastrointestinal toxicity Hematological toxicity <sup>(12)</sup>. The study was conducted with the approval of the institutional research board (IRB).

### Statistical methods:-

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel Software. Data were then imported into the Statistical Package for the (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data, qualitative represent as number and percentage, quantitative continues group represent by mean  $\pm$  SD , the following tests were used to test differences for significance; Differences between frequencies (qualitative variables) and percentages in groups were compared by Chi-square test (X<sup>2</sup>) /Fisher's Exact test. Differences between parametric multiple groups by ANOVA (F). P value was set at <0.05 for significant results and <0.001 for the highly significant result. Data were collected and submitted to statistical analysis.

### Results:-

One hundred and twenty patients were included in this study ,randomly distributed into four groups: group I treated with 8 Gy single fraction , group II : 6 Gy single fraction , group III :3 Gy in 10 fractions ,and the fourth one received 4 Gy in 5 fractions . Their age ranged from 28 to 69 years old. All of them had painful bony metastases from breast cancer (71 patients), bladder cancer (15 patients) , prostate cancer( 18 patients), , multiple myeloma (5 patients) , and 11 patients with other different primaries. .Seventy seven patients were females, while males were forty three. The four groups of the study, each of 30 patients, were balanced in age, sex, type of malignancy and number of bone metastatic sites and have shown no significant difference regarding any of these clinical features. Performance status of patients, as measured by Karnofsky scale was 50-60% in 81(67.5%) patients and 39(32.5%) patients had 70-80%. At presentation, 50.8 % (n=61) of patients suffered from severe pain, and 35% (n=42) suffered from moderate pain. Furthermore, 17.5% (n=21) of patients were prescribed nonopioids (NSAIDs), 42.5% of patients (n=51) were prescribed weak opioids, and 40% (n=48) were prescribed strong opioids on presentation Table (1) . The majority of patients received first palliative irradiation with total dose of 30 Gy in 10 fractions (n=65 , 64.2%), 36 patients (30%) received a total dose of 20 Gy in 5 fractions, and 19 patients (15.8%) received 8 Gy single fraction . Median interval between first palliative irradiation and re-irradiation was 18 months (range of 6–54 months). Two weeks after radiotherapy, 23.3%, 13.3%,13.3%,and 20% of patients were achieved complete response(CR) in group I,II,III ,and group IV respectively. After 4 weeks of treatment, complete response was observed in 7(23.3%) patients in each of group I,III,VI, and only 5 (16.7%) patients in group II. After 8 weeks of RT ,number of patients had complete response increased to 8 (26.7%) patients ,7 (23.3%) patients 10(33.3%) ,and 9 (30%)patients in group I, II ,III ,and IV, respectively with no statistical significance Table (2). Analysis of patients achieved complete response according to site of metastasis shown statistically insignificant (Table 3) . As regards the analgesic requirement, the number of patients was required strong narcotic reduced from 10 to 5 in group I, from 13 to 6 in group II, from 13 to 5 in group III ,and from 12 to 6 in the fourth group as shown in Table (4). PS was improved 8 weeks after radiotherapy as shown in Table (4) .Patients had PS 70-80% Karnofsky score increased to 23(76.7%) in group I ,22 (73.3%) in group II ,25 (83.3%) in group III, and 22 (73.3%) in group IV without a statistically significant difference. Treatment was tolerated in all groups, as shown in table ( 4 ), grade I diarrhea

occur only in 1 patient in group I & group II while dermatitis occur in 3 patients, 1 in group I, 1 in group II & 1 in group III.

**Table (1): Patients' characteristics**

	<b>Group I S F:8Gy</b>	<b>Group II S F:6Gy</b>	<b>Group III 3Gy /10 fx</b>	<b>Group IV 4Gy/5 fx</b>	<b>F/<sup>2</sup></b>	<b>P</b>
<b>Age</b> Mean $\pm$ S D Median( Range)	48.5 $\pm$ 9.9 49.5(29-69)	47.5 $\pm$ 10.1 45.5(30-68)	47.6 $\pm$ 11.5 47.5(28-69)	46.9 $\pm$ 11.5 43(29-69)	<b>0.15</b>	0.92
<b>Sex</b> Male Female	10(33.3%) 20(66.7%)	12(40%) 18(60%)	11(36.7%) 19(63.3%)	10(33.3%) 20(66.7%)	0.39	0.94
<b>Primary tumor</b> Breast cancer Bladder cancer Prostate cancer Myeloma Others	18(66.7%) 4(13.3%) 4(13.3%) 1(3.3%) 3(10%)	18(66.7%) 4(13.3%) 4(13.3%) 2(6.7%) 2(6.7%)	17(63.3%) 3(10%) 5(16.7%) 1(3.3%) 4(63.7%)	18(66.7%) 4(13.3%) 5(16.7%) 1(3.3%) 2(6.7%)	2.06	0.99
<b>Radiological types of metastases</b> Osteolytic Osteosclerotic Mixed	6(20%) 10(33.3%) 14(46.7%)	7(23.3%) 5(16.7%) 18(60%)	7(23.3%) 6(20%) 17(56.6%)	5(16.7%) 10(33.3%) 15(50%)	3.74	0.71
<b>Site of metastases</b> Spine Pelvis Extremities	16(53.3%) 7(23.3%) 7(23.3%)	15(50%) 8(26.7%) 7(23.3%)	17(56.6%) 7(23.3%) 6(20%)	15(50%) 9(30%) 6(20%)	0.68	0.99
<b>P S</b> 50-60% 70-80%	22(73.3%) 8(26.7%)	20(66.7%) 10(33.3%)	18(60%) 12(40%)	21(70%) 9(30%)	1.3	0.7

**Table (1): Patients' characteristics cont.**

	<b>Group I S F:8Gy</b>	<b>Group II S F:6Gy</b>	<b>Group III 3Gy /10 fx</b>	<b>Group IV 4Gy/5 fx</b>	<b>F/<sup>2</sup></b>	<b>P</b>
<b>Pain score</b> Mild Moderate Severe	4(13.3%) 8(26.7%) 18(13.3%)	5(16.7%) 10(33.3%) 15(50%)	3(10%) 15(50%) 12(40%)	5(16.7%) 9(30%) 16(53.3%)	4.6	0.59
<b>Analgesic requirement</b> Non-narcotic Mild narcotic Strong narcotic	6(20%) 14(46.7%) 10(33.3%)	5(16.7%) 12(40%) 13(43.3%)	6(20%) 11(36.7%) 13(43.3%)	4(13.3%) 14(46.7%) 12(40%)	1.5	0.95
<b>Time from 1ry RT(months)</b> 6 18 $\geq$ 24	2 7 21	2 8 20	1 11 18	2 9 19	1.6	0.94

**Table (2): Pain response after 2, 4, and 8 weeks of RT**

		Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	$\chi^2$	P
2weeks	NR	3 (10 %)	4 (13.3%)	3 (10 %)	3 (10 %)	1.74	0.94
	PR	20 (66.7 %)	22(73.3%)	23 (76.7 %)	21 (70 %)		
	CR	7 (23.3 %)	4(13.3%)	4 (13.3 %)	6 (20 %)		
4 weeks	NR	2 (6.7 %)	3(10%)	1 (3.3 %)	2 (6.7 %)	1.5	0.95
	PR	21 (70 %)	22(73.3 %)	22 (73.3 %)	21 (70 %)		
	CR	7 (23.3 %)	5(16.7%)	7 (23.3 %)	7 (23.3 %)		
8 weeks	NR	1 (3.3 %)	2(6.7%)	1 (3.3 %)	1 (3.3 %)	1.3	0.97
	PR	21 (70 %)	21(70%)	19 (63.3%)	20 (66.7%)		
	CR	8 (26.7 %)	7(23.3%)	10 (33.3%)	9 (30 %)		

**Table (3) Complete responder after 8 w in studying groups as a regard site of bone metastasis**

	Group I (n=8)	Group II (n=7)	Group III (n=10)	Group IV (n=9)	$2\chi$	P
Spine	5 (62.5 %)	4(57 %)	6 (60 %)	5 (55.6 %)	0.48	0.99
Pelvis	1 (12.5 %)	1(14.3 %)	2 (20 %)	2 (22.2 %)		
Extremities	2 (25 %)	2(28.5 %)	2 (20 %)	2 (22.2 %)		

**Table (4) studied groups as a regard analgesics requirement , PS ,and complications after 8 weeks of RT**

		Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	2χ	P
No analgesics		14 (46.7%)	12(40 %)	14 (46.7 %)	15 (50 %)	1.73	0.99
Non-narcotic		7 (23.3 %)	7(23.3%)	8 (26.7 %)	5 (16.7 %)		
Mild narcotic		4 (13.3 %)	5(16.7%)	3 (10 %)	4 (13.3 %)		
Strong narcotic		5 (16.7 %)	6(20%)	5 (16.7 %)	6 (20 %)		
Comparison between studying groups as regard PS after RT							
50-60 %		6 (20 %)	7(23.3%)	4 (13.3 %)	7 (23.3 %)	1.26	0.97
70-80 %		23 (76.7 %)	22(73.3%)	25 (83.3 %)	22 (73.3 %)		
90-100 %		1 (3.3 %)	1(3.3%)	1 (3.3 %)	1 (3.3 %)		
Comparison between studied groups as regard RT complications (diarrhea,dermatitis)							
Diarrhea	G0	29 (96.7 %)	29(96.7%)	30 (100 %)	30 (100 %)	2.03	0.56
	G1	1 (3.3 %)	1(3.3%)	0	0		
Dermatitis	G0	29 (96.7 %)	29(96.7%)	29 (96.7 %)	30 (100 %)	1.02	0.79
	G1	1 (3.3 %)	1(3.3%)	1 (3.3 %)	0		

## Discussion:-

The goals in treatment of bone metastasis include pain relief, preservation of mobility and function, optimized quality of life and minimizing of hospitalization. Radiation therapy is considered as the treatment of choice for palliation of painful bone metastasis. A wide range of single and multifractions dose regimens have been used. Also data from retrospective studies and prospective trials showed that single fraction may be as effective as multifraction regimens<sup>(13)</sup> The need for re -irradiation in the metastatic disease appears when other modalities of treatment lose their efficacy. The aim of re-irradiation in the metastatic disease is mainly palliative to control a particular symptom. However, this theoretical benefit must be confronted against the risk of an undesirable toxicity.<sup>(2)</sup> The results of this study support the hypothesis that single fraction 8 Gy compared to multiple-fraction radiotherapy provides the same degree of pain relief, and that the impact of fatigue and overall quality of life is equivalent. These findings are the same as in Alhosainy et al<sup>(8)</sup> and in accordance with several studies<sup>(6,14-17)</sup>, several systematic reviews<sup>(18-22)</sup>. In the present study 120 patients with recurrent bone metastasis in different sites were allocated into four treatment groups. Group I treated with 8 Gy in single fractions, group II treated with 6 Gy single fraction, group III treated with 30 Gy in ten fractions and group IV treated with 20 Gy in five fractions to compare the effect of these four regimens of radiation therapy for pain relief. At presentation, all patients suffered from pain (from moderate to severe intensity), in spite of analgesic consumption in four groups. Eight weeks after palliative radiation therapy, no patient suffered from severe pain, and about one fourth of patients (34out of 120 patients; 28.3 %) achieved no pain. Pain in the vast



majority of remaining patients (81 out of 86 patients; 94 %) was of mild intensity. Our results are confirmed by Van der Linden et al. <sup>(23)</sup> who stated that, re-irradiation of bone metastases is effective in providing pain relief. In the current study, there was no significant difference ( $p>0.05$ ) between the four radiotherapy groups regarding pain relief. Our study showed also that patients tolerated the treatment well. This is in agreement with many studies which confirmed that 8 Gy single fraction and multiple-fraction radiotherapy provides comparable degrees of pain relief varying from 50% to 85% for peripheral and vertebral bone metastases, and that the impact on quality of life is equivalent. In both groups, there was a clinically and statistically significant reduction in pain score <sup>(14,15,24-27)</sup>. Furthermore, the results of the NCIC CTG SC.20 trial in Canada <sup>(17)</sup>, suggested that re-treatment with a single 8Gy fraction or 20Gy/5 fractions are reasonable alternatives in pain relief of patients with painful bone metastases previously treated with radiotherapy ( overall response 28% versus 32% in single fraction and multiple fractions respectively ). As regards analgesic requirement, palliative radiation resulted in a dramatic decrease in analgesic consumption at 8 weeks. There was no evidence to suggest that 8 & 6 Gy single fraction provide inferior pain relief to a more prolonged course of treatment in painful bone metastases <sup>(14,28-30)</sup>. At 8 weeks post radiation follow up, one half of patients in group IV (n=15), fourteen patients in group I, III, while only 12 patients in group II achieved no analgesic prescription, and 73% of patients in group III, 70% in group I, 67% in group IV, and 63% of patients in group II need non opioid prescription. The proportion of patients with opioid (weak and strong opioids) prescription decreased from 82.5% (n=99) to 31.7% (n=38). This is consistent with Mitera et al. <sup>(31)</sup>, who found the increased percentage of no analgesic use and decreased percentage of strong opioid prescription. that pain response and analgesic consumption improved in more than 70% of patients treated with single fraction RT (8Gy) as well as with both other fractionation regimens. A significantly improved score of pain and analgesia, was observed in all patients treated with 8 Gy, 6 Gy single fraction, 30Gy/10 fr. regimen, and in patients receiving 20Gy/5fr. regimen

### Conclusion:-

The results of our study seem to confirm that there no significant difference between the four regimens of dose fractionation of external beam radiotherapy (8 Gy single fraction, 6 Gy single fraction, 30 Gy in ten fractions and 20 Gy in five fractions) in palliative treatment of bone metastasis as regard pain relief so the use of 8 Gy single fraction of radiotherapy may be of benefit for the patient by reducing treatment time and cost also reducing the treatment burden for hospital, staff and equipment.

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