

Single Fraction Compared with Multiple Fraction Re-Irradiations in Patients with Painful Bone Metastases

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Abstract

Objectives: Patients with painful bone metastasis treated with palliative radiation therapy (RTH) may require re-irradiation. This work aims at assessing the efficacy and safety of re-irradiation for painful bone metastases using single 8 Gy fractions versus (4 Gy × 5 fractions).

Methods: From June 2011 to December 2012, previously irradiated bone metastases were re-irradiated with single 8 Gy fractions (group I) or, 4 Gy × 5 fractions (group II). Pain management index (PMI) was determined. Pearson's r correlation coefficient was calculated between negative PMI at presentation and age, ECOG Performance Status, sex, and primary cancer site.

Results: Two months after RTH, about one fifth of patients achieved no pain, mild pain in 75.5% of the remaining patients and no patient suffered from severe pain. There was no significant difference ($p>0.05$) between groups (I and II) regarding pain relief. Negative PMI score, was reduced to from 37% at presentation to 25%, at 2 months follow up. A strong negative association between PMI and performance status ($p=0.0057$, 95% confidence interval between 0.109 and 0.557) was found.

Conclusion: Palliative re-irradiation with either single 8 Gy fraction or with, 4 Gy × 5 fractions was effective and safe in pain relief.

Keywords: Efficacy; Bone metastasis; Re-irradiation

Introduction

More than 60% of patients with cancer develop bone metastasis, and autopsy studies of patients who die of breast, prostate, or lung cancer have shown that as many as 85% have bone metastases at the time of death [1]. Bone metastases are a common cause of skeletal complications, including severe bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy [2]. Patients with painful bone metastasis are frequently treated with external beam radiation therapy that can provide significant palliation in 50–80% of patients, with up to one-third of patients achieving complete pain relief at the treated site [3]. However, a proportion of patients experience pain relapse. These patients may be re-irradiated with either single or multifraction regimens, depending on the initial RT characteristics [4]. Patients receiving a single fraction were more likely to receive re-irradiation to the same site as compared to patients receiving multiple fractions. However, an increased analgesic consumption was seen in the latter group as compared to the single-fraction group [5]. The primary objective was to determine the efficacy and safety of re-irradiation for painful bone metastases using two fractionation schemes (single 8 Gy fractions versus 5 fractions of 4 Gy). Secondary objectives included evaluation of pain control, and analgesic use.

Patients and Methods

This prospective study was conducted on patients with previously irradiated bone metastases who attended radiation oncology department from June 2011 till end of December 2012. Informed consent was obtained for all patients, and the protocol was approved by an institutional review board of South Egypt Cancer Institute, Assiut University. These patients were selected according the following inclusion criteria; 18 years and over, ECOG performance status of ≤2, histologically or cytologically confirmed malignancy, bone Metastases at clinically painful areas confirmed by imaging (bone scan, and MRI), no radiological evidence of high-risk lesions for pathological fractures

in the extremities (lytic lesions > 3 cm or >50% cortical erosion of bone diameter), no clinical or radiological evidence of spinal cord compression. All patients received systemic therapy such as salvage chemotherapy (and/or salvage hormonal therapy for patients with metastatic prostate and hormone receptor positive breast cancer), bisphosphonates, and palliative re-irradiation. Radiation doses to spinal bones were prescribed to the mid-vertebral body, with inclusion of one vertebral body above and below the painful vertebral body level. A mid-plane dose was prescribed for opposed fields, taking into account the normal tissue tolerance of those structures included in the treated volume. Long bone lesions were treated with at least a 2 cm margin proximal and distal to the radiographically evident abnormality. Patients were treated with either anterior/posterior fields or a single direct field. The patients were irradiated according to one of the following schedules:

Group I: Patients receive single-fraction radiotherapy (8 Gy) on day 1.

Group II: Patients receive multiple-fraction radiotherapy (to a total of 20 Gy) over 5 days or over 8 days if re-irradiation of the spine and/or whole pelvis is involved. Patients were assessed at presentation and 2 months after re-irradiation regarding pain and analgesic scores. A pain score of "0" defined an absence of pain, (1) was for mild pain, (2) for

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moderate pain, and (3) for severe pain. These pain scores corresponded to the ESAS and BPI worst pain score categorization of (0) as an absence of pain, (1-4) for mild pain, (5-6) for moderate pain, and (7-10) for severe pain [6]. A patient's analgesic score was calculated based on the analgesic prescribed by the physician. No prescribed analgesic was scored as (0), a nonopiod (i.e., NSAIDs) was (1), a weak opioid (e.g., codeine) was (2), and a strong opioid (e.g., morphine, fentanyl) was scored as (3) [7].

Response to different radiation regimens was assessed according to update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases [8]. Table 1 describes the response categories. The PMI was then determined by subtracting the worst pain score from the analgesic score [9]. Table 2 describes the scoring system.

Patients with negative PMI scores were classified as receiving inadequate analgesic treatment for their pain. Pearson's r correlation coefficient was calculated between negative PMI at presentation and age, ECOG Performance Status, sex, and primary cancer site.

Results

Median follow up was 7 months (range from 2 to 14 months). Median age of patients was 55 years (range 26- 74). The ratio of males to females was approximately equal, with 29 (48.3%) males and 31 (51.7%) females. The most common primary cancer sites were breast, bladder, multiple myeloma, and lung, affecting 36.7%, 18.3%, 13.3% and 10% of patients, respectively.

Performance status of patients, as measured by the ECOG score, was 1 in 11 patients (18.3%), and 2 in 49 patients (91.7%). At presentation, 48.3% (n=29) of patients suffered from moderate pain, and 51.7% (n=31) suffered from severe pain. Furthermore, 10% (n=6) of patients were prescribed, nonopiods (NSAIDs), 40% of patients (n=24) were prescribed weak opioids, and 50% (n=30) strong opioids on presentation. Most patients received first palliative irradiation with total dose of 2000 cGy in 5 fractions (n=44; 73%), and only 16 patients (27%) received a total dose of 3000 cGy in 10 fractions. Median interval between first palliative irradiation and re-irradiation was 18 months (range of 6-54 months). Patients' characteristics are found in Table 3.

Description	Item
A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent [OMED])	Complete response (CR)
Pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or Analgesic reduction of 25% or more from baseline without an increase in pain.	Partial response (PR)
Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or An increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline.	Pain progression

Table 1: Response categories according to the international consensus on palliative radiotherapy of bone metastases [8].

Analgesic score	Pain intensity			
	NO Pain (0)	Mild Pain (1)	Moderate Pain (2)	Severe Pain (3)
No analgesics (0)	0	- 1	- 2	-3
Non opioid (1)	1	0	- 1	- 2
Weak opioid (2)	2	1	0	- 1
Strong opioid (3)	3	2	1	0

Table 2: Pain Management Index (PMI) [9].

Characteristics	NO (%)
Age (years)	
Range	26-74
Median	55
Sex	
Male	29 (48.3)
Female	31 (51.7)
Performance status (ECOG)	
1	11 (18.3)
2	49 (91.7)
Primary tumor	
Breast	22 (36.7)
Bladder	11 (18.3)
Multiple myeloma	8 (13.3)
Lung	6 (10)
Prostate	2 (3.4)
Others	11 (18.3)
Metastatic site	
Spines	33 (55)
Pelvis	15 (25)
Spines / Pelvis	7 (11.7)
Extremities	5 (8.3)
Pain Score	
2 (Moderate pain; 5-6 on pain scale)	29 (48.3)
3 (Severe pain; 7-10 on pain scale)	31 (51.7)
Analgesic Score	
1 (NSAI drugs)	6 (10)
2 (weak opiods)	24 (40)
3 (strong opiods)	30 (50)
Dose and fractionation of first RTH	
2000cGy / 5 fractions	44 (73.3)
3000 cGy / 10 fractions	16 (26.7)
Interval between first RTH and re-irradiation	
Range (months)	6 – 54
Median (months)	18
Re-irradiation Group	
Group I (single RTH dose of 8 Gy)	28 (46.7)
Group II (5 RTH doses; 4 Gy each)	32 (53.3)
Total	60 (100)

Table 3: Patients' characteristics.

The proportions of patients—at presentation—with moderate and severe pain were 32% and 68% respectively in group I and were 62.5% and 37.5% respectively in group II. At 2 months follow up, 22% achieved no pain, 64% experienced mild pain, and only 14% moderate pain in group I, and 16% achieved no pain, 59% experienced mild pain, and only 25% moderate pain in group II (Figure 1).

Regarding analgesic consumption, the proportions of patients—at presentation—with non, weak, and strong opioid prescription were 11%, 46% and 43% respectively in group I patients, and 13%, 50% and 37% respectively in group II. At 2 months follow up, 32% of group I (n=9) and 19% of group II (n=6) patients showed no analgesic prescription, increased percentage of patients with non opioid prescription (16 patients, 57% in group I & 24 patients, 75% in group II), decreased percentages of patients with weak (2 patients in group I and one patient in group II) and strong (one patient in each group) opioid prescription (ranged between 3% and 7%) (Figure 2).

Response to single fraction and multiple fractions radiation regimens is shown in Table 4. Rates of overall pain relief were 96.4% and 87.5% with CR rates were 21% and 16% in group I and II respectively. There was no significant difference ($p>0.05$) between both groups.

Inadequate analgesic pain management, which was represented by a negative pain management index (PMI) score, was found in 37% (n=22) of all patients at presentation, and was reduced to 25% (n=15),

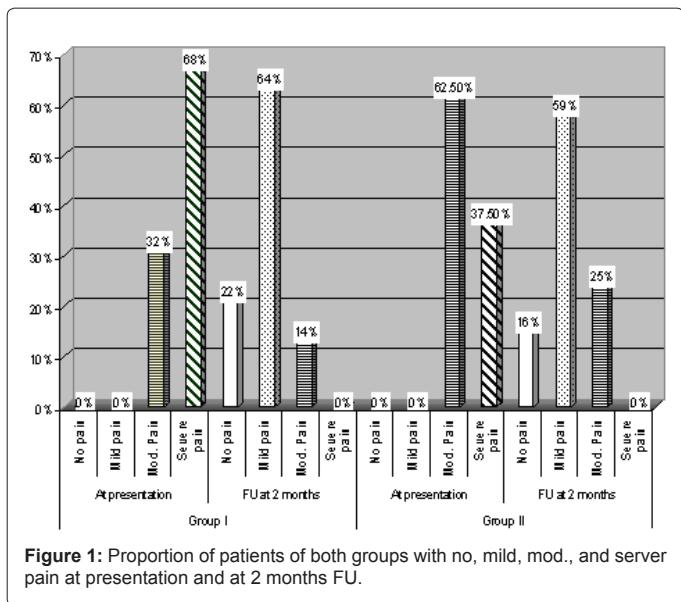


Figure 1: Proportion of patients of both groups with no, mild, mod., and server pain at presentation and at 2 months FU.

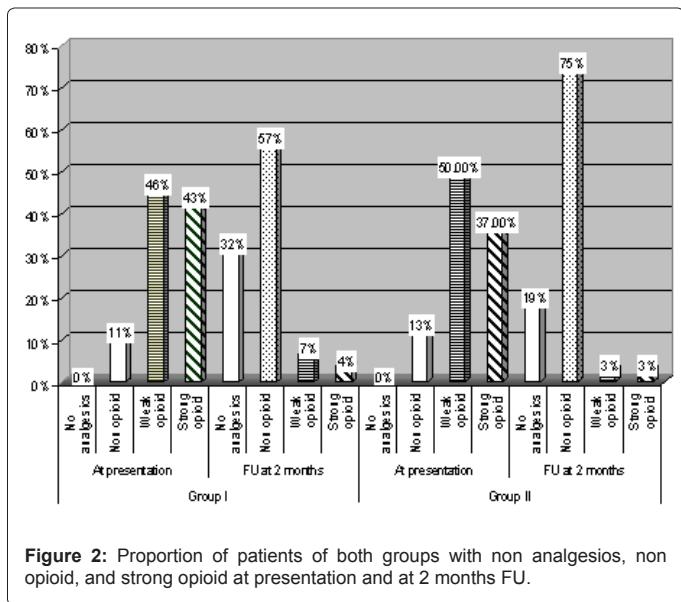


Figure 2: Proportion of patients of both groups with non analgesics, non opioid, and strong opioid at presentation and at 2 months FU.

Response	Group I (n=28)	Group II (n=32)	P value
CR (n=11)	6 (21.4)	5 (15.6)	
PR (n=44)	21 (75)	23 (71.9)	
NR (n=5)	1 (3.6)	4 (12.5)	0.423

Table 4: Response rate in group I&II patients.

at 2 months follow up. In group I patients, negative PMIs were reduced from 46% at presentation to 29% at 2 months follow up, and in group II, from 28% to 22% (Figure 3).

Patients tolerated the treatment well. No acute or late toxicity of re-irradiation were observed and no pathological fractures or spinal cord compressions were seen in any of these patients during the follow up.

PMI and patients' characteristics

The relation of negative PMI at presentation and age, ECOG performance status, sex, and primary cancer site was done using

Pearson's r correlation coefficient. A strong negative association between PMI and performance status ($p=0.0057$, 95% confidence interval between 0.109 and 0.557) was found. Other variables were not significant ($p>0.05$) in the analysis.

Discussion

Eight Gy was by far the most commonly administered single fraction dose within 24 randomised trials of radiation therapy for the palliation of bone metastases (84% of all patients received 8 Gy). In trials that directly compared different single fraction doses, doses of 8 Gy produced superior pain response rates compared to doses less than 8 Gy [10].

Randomized trials have demonstrated also, that single-fraction radiation therapy is sufficient to achieve palliation of painful bone metastases with optimized convenience for both patients and caregivers. Moreover, patients receiving single radiotherapy dose of 8 Gy may receive more re-irradiations [11].

The present study and many other trials compared single 8 Gy fraction and multiple fraction re-irradiation for palliation of patients with bone metastases [5,12-18]. The main goal of the present study was to determine the efficacy and safety of re-irradiation for painful bone metastases using either single 8 Gy fraction or 5 fractions of 4 Gy. At presentation, all patients suffered from pain (from moderate to severe intensity), in spite of analgesic consumption in both groups. Two months after palliative radiation therapy, no patient suffered from severe pain, and about one fifth of patients (11 out of 60 patients; 18.3%) achieved no pain. Pain in the vast majority of remaining patients (37 out of 49 patients; 75.5%) was of mild intensity. Our results are confirmed by Van der Linden et al. [17] 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 two 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 single 8 Gy 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 [5,12-17]. Furthermore, pending results of the NCIC CTG SC.20 trial in Canada [18], suggested that re-treatment with a single 8Gy fraction or 20Gy/5 fractions are reasonable alternatives.

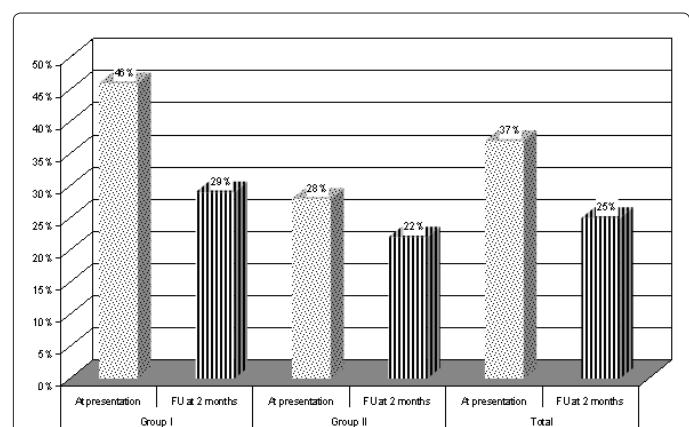


Figure 3: Proportion of patients of both groups with negative PMI presentation and at 2 months FU.

Regarding analgesic consumption, palliative radiation resulted in a dramatic decrease in analgesic consumption at 2 months. There was no evidence to suggest that a single 8 Gy fraction provides inferior pain relief to a more prolonged course of treatment in painful bone metastases, though single fractionation is associated with a 20% incidence of re-treatment versus 8% with fractionated therapy [5,19-21].

At 2 months postradiation follow up, one fourth of patients (n=15) achieved no analgesic prescription, and two thirds (n=40) non opioid prescription. The proportion of patients with opioid (weak and strong opioids) prescription decreased from 88% (n=53) to 8% (n=5). This is consistent with Mitera et al. [9], who found the increased percentage of no analgesic use and decreased percentage of strong opioid prescription.

Inadequate analgesic pain management, which was represented by a negative pain management index (PMI) score, was found in 37% (n=22) of all patients at presentation, and was reduced to 25% (n=15), at 2 months postradiation follow up. In group I patients, negative PMIs were reduced from 46% at presentation to 29% at 2 months follow up, and in group II, from 28% to 22%. Mitera et al. [9] confirmed our results and showed a reduction of negative PMI from 26% at presentation to 16% at 2 months postradiation.

The relation of negative PMI at presentation and age, ECOG performance status, sex, and primary cancer site was done using Pearson's r correlation coefficient. A strong negative association between PMI and performance status ($p=0.0057$, 95% confidence interval between 0.109 and 0.557) was found. Other variables were not significant ($p>0.05$) in the analysis. This finding is consistent with the published literature [9,22-25].

The present study showed that inadequate analgesic pain management was relatively low (37%) when compared with other countries. In the United States, Cleeland et al. [26] found that 42% of patients were undermedicated. In France, Larue et al. [27] found that 57.5% of patients were undermedicated. In Germany, the proportion was 44%; and in the Netherlands, it was 42% [28]. The prevalence of inadequate analgesic pain management may be highest in Asian countries. In China, 67% of patients were undermedicated, [29] whereas in India, the proportion was 79% [30]. There may be socioeconomic reasons why pain medications may not have been used for patients. In developed countries, socioeconomic status of the population is relatively high, with good access to doctors and prescription drugs, and social programs to provide drugs for underprivileged patients are better than in developing countries [31]. Furthermore, in developing countries, morphine and other analgesics are not available, or might be very expensive [9].

Conclusion

Palliative re-irradiation either by using single fraction or multiple fractions was effective and safe in pain relief. Inadequate analgesic pain management, represented by a negative PMI is still a problem for patients with painful bone metastases referred for re-irradiation.

Authors' Contributions

MMS and MEA carried out the patient diagnosis, management and follow up. MIE carried out the patient diagnosis, management, follow up, statistical analysis, drafting of the manuscript, and writing the final manuscript. All authors have read and approved the final manuscript.

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