Comparison of 8Gy Single Fraction versus 20Gy in Five Fractions or 30Gy in 10 Fractions Radiotherapy for the Treatment of Metastatic Bone Pain

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ABSTRACT

Objectives: The aim of this study was to compare the effectiveness of pain control of most common fractionation used in oncology to treat bone metastases which are 8Gy single fraction, 20Gy in five fractions and 30Gy in 10 fractions.

Method: A total sample of 120 patients who were known to have stage IV cancer with bone metastasis were allocated to receive either 8Gy single fraction, 20Gy in five fractions or 30Gy in 10 fractions for the treatment of their pain between January 2007 and December 2009 at King Hussein Medical Center. Pain severity and analgesic requirements were recorded by the investigator on a questionnaire before treatment, at two weeks and at one, two, three, four, five, six, eight, 10 and 12 months after radiotherapy. Pain relief was the primary endpoint of treatment benefit.

Results: There was no difference in the time to first improvement in pain, time to complete pain relief, or in time to first increase in pain at any time up to 12 months after randomization, nor in the class of analgesics used. Retreatment was twice as common after 8Gy as after multifraction radiotherapy, although retreatment for residual or recurrent pain did not reflect a difference between the three groups in the probability of pain relief.

Conclusion: A single fraction of 8Gy when used for the treatment of bone metastasis is as safe and effective as a multifraction regimen for the palliation of metastatic bone pain for at least 12 months. This may make it suitable alternative to the multifraction radiotherapy regimens.

Key words: Bone metastases; Radiotherapy; Pain relief; Palliation

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Introduction

Bone metastases are a major complication of many solid tumors such as prostate, lung and thyroid cancers. Although bone metastases often start clinically silent, yet they may lead to serious complications such as pain, fractures, and hypercalcemia. These complications usually impact on the performance status (PS) and quality of life (QoL) of the patient. Most patients experiencing bone pain eventually require opiates which can significantly alter the patient QoL .[1-3]

As many as 80 percent of patients with solid cancers develop painful bone metastases to the spine, pelvis, and extremities during the course of their disease .[4] When bone pain is limited to a single or a limited number of sites, External Beam Radiation Therapy (EBRT) to a local field can provide pain relief in 80 to 90 percent of cases, with complete pain response obtained in 50 to 60 percent of cases.[4-6]Although treatment can be effective for patients with mild, moderate, or severe pain, early intervention may be useful in maintaining quality of life and minimizing side effects of analgesic medications.[7] Consensus statements from the

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National Comprehensive Cancer Network on Cancer Pain, the Second Workshop on Palliative Radiotherapy and Symptom Control, and the Ontario Guidelines for Palliative Pain all advocate the use of EBRT in palliating painful bone metastases[8-10] The mechanism by which radiotherapy (RT) achieves relief of bone pain is poorly understood, but it might be expected that higher doses would be needed for neuropathic pain if pressure on nerve(s) entrapped by soft tissue extension from osseous metastases is primarily responsible for the pain. On the other hand, if neuropathic pain is instead mainly due to 'chemical' irritation of nerves or nociceptors by pain mediators elaborated in the region of the tumor (the mechanism essentially proposed for uncomplicated bone pain),[11] then lower 'anti-inflammatory' radiation doses may suffice as for localized pain. Limited survey data suggest that clinicians are more reluctant to use single fraction RT when neuropathic pain is present[12,13] presumably reflecting the former view and also possible concerns about threatened cord compression in the case of spinal metastases.[14]

There is very limited data on the efficacy of radiotherapy for palliating pain from bone metastases among patients nearing the end of life,[15] and no data on the impact of treatment on the functional abilities of patients in this setting.[16] For more than two decades an ongoing discussion on the optimal radiotherapy regimen has taken place. The first randomized study assessing the effect of one fraction of 8Gy versus multiple fractions (3Gy x 10) was published in 1986.[17] No difference was found between the regimens with regard to onset and/or duration of pain.[18] In 1974 the Radiation Therapy Oncology Group (RTOG) initiated a randomized clinical trial comparing various dose-fractionation schedules in the palliation of cancer metastatic to bone. The trial was closed in February of 1980 and results have been published in 1982,[19] with the conclusion that "low-dose short schedules are as effective as more aggressive protracted programs".[20] Since that time, different radiotherapy schedules have been employed for palliation of bone metastasis: 40Gy in 20 fractions, 30Gy in 10 fractions and single fractions of 8Gy, 6Gy or 4Gy. Several randomized prospective trials and meta-analyses have been reported showing the same results in pain relief when comparing single doses *vs*. protracted treatments. Despite clinical evidence supporting single-fraction regimens, fractionated treatments remain the choice for pain treatment in many institutions worldwide.[21]

Methods

This study is a hospital-based study which was conducted between January 2007 and December 2009 at King Hussein Medical Center involving 120 patients who were divided into three equal groups. Eligibility criteria consisted of a histological diagnosis of malignant disease, a radiological diagnosis of skeletal metastasis, a clinical diagnosis of skeletal pain due to malignant disease (symptomatic patient), adult (more than 15 years old), the use of photon beam and gamma rays, and acceptance to complete regular pain questionnaires at regular follow up for 12 months. Exclusion criteria were pathological fracture of a long bone, previous radiotherapy to the index site and metastasis to the ribs or sternum as this needs an electron beam or orthovoltage X-ray.

The aim of the study was to compare the clinical and biological palliative effect of single fraction RT 8Gy for painful bone metastases of solid malignant tumors with other two common types of fractionation schedules: 20Gy, five fractions over one week and another one of 30Gy, 10 fractions over two weeks and to see if lower dose of radiation is as effective as higher doses of radiation. Treatment took place under the supervision of the main author at Al Bashir hospital, Ministry Of Heath in Jordan – radiotherapy department.

Evaluation included complete history taking, clinical examination including performance status, pain scale, mobility, previous or current medication, the type and dose of analgesia. Routine blood investigations, radiological examination and bone scanning were mandatory.

Pre-treatment pain was scored by patients before the start of treatment, usually one or two days prior to the time of radiotherapy planning. A question relating to pain severity over the previous 24 hour period was scored on a 4-point graded scale (none, a little, quite a bit, very much). The questionnaire was identical to that used in two previous trials.[17, 22]

Post-treatment assessments of pain and analgesic usage were collected at two weeks and at one, two, three, four, five, six, eight, 10 and 12 months after the start of treatment. Questionnaires were filled by the investigator during these visits. Patients went off the study at death or after 12 months of follow-up. Recruitment to the trial was continued until the target of 120 patients had been reached.

Patients were divided into three equal groups of 40 patients. According to the fractionation radiotherapy regimen, the first group received 30Gy in 10

fractions over two weeks (30Gy/10fr), the second group received 20Gy in five fractions (20Gy/5fr) over one week, and the third group received a single fraction of 8Gy. Radiotherapy regimen specified the use of photons from LA 6 or 10MV. Bone metastases in thoracic, lumbar spine, or sacrum were treated with single field at depth 4-6cm according to the depth of the vertebrae. Other sites including cervical spine were treated with parallel opposing fields to mid plane. The prescribed dose was the maximum absorbed dose at depth in single fields and the central dose for opposing fields. Pain assessment was based on questioning the patient by the investigator during the interview. Any patient who accepts to complete regular pain questionnaires during the face-to-face interview by the investigator for 12 months was deemed eligible for analysis.

Mean and standard deviation were used as descriptive values of quantitative data and ANOVA for comparison of the three study variables.

Pain relief was defined as a decrease of 25% of the initial score before starting treatment reflecting an improvement in pain, mobility, performance status and decrease of analgesia. Time to first pain relief was measured as the time between randomization and the first assessment recording an improvement in pain score.

Time to first increase in pain was measured as the time between randomization and the first assessment recording an increase in pain score compared to the pre-treatment level. A complete pain response was defined as no pain. Retreatments to the index site were identified and recorded in the patients file. P value of 0.05 was considered as statistically significant. T test was used for the pre and post treatment comparison. The study was approved by the ethical committee of Royal Medical Services.

Results

The age of the patients ranged from 32 to 73 years. Subjects had painful bony metastases from breast cancer (64 patients), prostate cancer (36 patients), bronchogenic cancer (11 patients) and renal cell carcinoma (9 patients). Eighty three percent of patients had either primary breast or prostate tumors. Sites of pain treated with RT were most often centered on the pelvis or hip or lumbar spine. The three groups of the study were balanced in age, gender, type of malignancy and number of bone metastatic sites and did not show any significant differences regarding any of these clinical features as shown in Table I.

All patients received appropriate treatment delivered by LA 6MV and 10MV photons. The number of fields ranged from one to three in most of the patients using single or two parallel opposing fields and sometimes up to five fields. Pre and post treatment pain severity and analgesic/coanalgesic use are summarized in Table II which shows that three patients out of 120 (2.5%) recorded no pain on the day of their pre-treatment assessment. The majority (72%) recorded taking either mild or strong narcotics.

Only one patient was lost to follow up. Ninety eight (82%) of 120 of patients originally randomized remained in the study for the complete 12 months of follow-up and completed the questionnaire at their regular interviews. Among the 98 patients with follow-up, compliance with the pain questionnaires was ≥95% at every time point. These 98 eligible patients who have been analyzed during the study period represent 49% of the patients treated at Al Bashir hospital who has been treated palliatively (i.e. not all patients treated at Al Bashir Hospital are treated palliatively). Six patients (15%) of the group receiving single fraction 8Gy had pain recurrence at the irradiated sites and needed repeated irradiation at week seven. Five patients in the 20Gy/5fr group and three patients in the 30Gy/10fr group needed to be reirradiated at weeks 11 and 12 respectively.

After treatment, (see Tables III to VI) there were variable significant degrees of improvement in patients belonging to each of the three treatment groups regarding pain score (p=.002, .002 & .008), frequency and dose of analgesia (p=.003, .008 & .01), mobility (p=.16, .03 & .001), and performance status (p=.08, .16 & .01). The total score of all clinical parameters showed a similar significant response in all groups receiving single or fractionated palliative irradiation (p=. 04, .04 & .001) (Table VII).

Time to first pain relief and time to first complete pain relief was analyzed and showed no statistically significant differences between the three groups (logrank test). Overall 75% of evaluated patients experienced pain relief at some time during follow-up and the difference was not statistically significant between the three groups as the pain relief was 75%, 76%, and 74% for the 30Gy, 20Gy, and 8Gy respectively. Time to first retreatment of the index site, based on 98 patients, was significantly higher in patients who received the single fraction at week 7 compared with 11 and 12 weeks in the 20Gy and 30Gy respectively. This was the only statistically significant difference between the three groups. One patient suffered a pathological fracture of a long bone index site over the follow-up period.

Table I: Patient characteristics and radiotherapy details

Group	30Gy	20Gy	8Gy
Gender			
Male	19	22	20
Female	21	18	20
Type of Cancer			
Breast	23	22	19
Prostate	11	12	13
Lung	4	3	4
Kidney	2	3	4
RT Machine			
L.A. 6MV	39	38	40
L.A 10MV	1	2	0
Number of Field			
Single field	29	28	29
Two opposed	11	12	11

Table II: Pre-treatment assessment

Group	30Gy	20Gy	8Gy	Total
Pain severity				120
Severe	9(23%)	10(24%)	9(23%)	
Moderate	17(43%)	17(42%)	17(42%)	
Mild	12(29%)	13(34%)	13(29%)	
None	2 (5%)	0	1(6%)	
Analgesics at baseline				120
Severe	15(36%)	14(37%)	15(36%)	
Mild	13(34%)	13(32%)	13(35%)	
Non narcotic	8(20%)	10(20%)	8(19%)	
None	4(10%)	3(11%)	4(10%)	
Analgesics at 6 months				110
Severe	13(35%)	12(32%)	11(30%)	
Mild	7(20%)	8(22%)	9(25%)	
Non narcotic	5(15%)	5(15%)	5(15%)	
None	12 (30%)	12(31%)	11(30%)	
Analgesics at 12 months				98
Severe	11(32%)	13(38%)	12(36%)	
Mild	8(25%)	8(26%)	8(24%)	
Non narcotic	6(18%)	3(12%)	4(14%)	
None	8(25%)	8(24%)	9(26%)	

Table III: Pain status in response to the different RT fractionation schedules

	Pain status			Significance
	GP 30Gy/10fr	GP 20Gy/10fr	GP 8Gy/1fr	
Number of respondents	28/40	30/40	28/40	NS
Pain score (±SD) before RT	1.65(±0.21)	2.0(±0.26)	2.15(±0.44)	NS
Pain score (±SD) week 6 after RT	0.75(±0.08)	1.1(±0.05)	1.35(±0.1)	NS
Pain score decrease after 6 weeks RT within each group	P=.002	P=.002	P=.008	

NS: Not significant

Table IV: Analgesia status in response to the different RT fractionation schedules

	Analgesia status			Significance
	GP 30Gy/10fr	**GP 20Gy/10fr**	**GP 8Gy/1fr**	
Number of respondents	22/40	32/40	24/40	NS
Analgesia score (±SD) before RT	1.9 (±0.17)	1.15 (±0.27)	1.15 (±0.3)	NS
Analgesia score (±SD) at week 6 after RT	0.75 (±0.11)	0.45 (±0.05)	0.65 (±0.1)	NS
Analgesia score decrease after 6 weeks of RT within each group	P=.003	P=0.008	P=0.01	

NS: Not significant

Table V: Mobility status in response to the different RT fractionation schedules

	Mobility status			Significance
	GP 30Gy/10fr	**GP 20Gy/10fr**	**GP 8Gy/1fr**	
Number of respondents	22/40	20/40	24/40	NS
Mobility score (±SD) before RT	1.65 (±0.3)	2.11 (±0.08)	2.75 (±0.7)	NS
Mobility score (±SD) at week 6 after RT	1.05 (±0.4)	1.1 (±0.08)	1.05 (±0.05)	NS
Mobility score decrease after 6 weeks of RT	P=.16	P=.03	P=.001	

NS: Not significant

Table VI: Performance status in response to the different RT fractionation schedules

	Mobility status			Significance
	GP 30Gy/10fr	**GP 20Gy/10fr**	**GP 8Gy/1fr**	
Number of respondents	18/40	12/40	26/40	NS
Performance status—ECOG scale score (±SD) before RT	1.7 (±0.15)	1.7 (±0.3)	2.3 (±0.5)	NS
Performance status—ECOG scale score (±SD) at week 6 after RT	1.25 (±0.2)	1.3 (±0.4)	1.65 (±0.4)	NS
Performance status—ECOG scale score decrease after 6 weeks of RT	P=.08	P=.16	P=.01	

NS: Not significant

Table VII: Total clinical score variation in response to the different RT fractionation schedules

	Total score			Significance
	GP 30Gy/10fr	**GP 20Gy/10fr**	**GP 8Gy/1fr**	
Number of respondents	34/40	30/40	38/40	NS
Total clinical score (±SD) before RT	6.8 (±0.35)	6.96 (±0.56)	8.4 (±01.1)	NS
Total clinical score (±SD) 6 weeks after RT	3.8 (±0.41)	3.95 (±0.71)	4.4 (±0.7)	NS
Total clinical score decrease after 6 week of RT	P=.004	P=.04	P=.001	

NS: Not significant

Discussion

Despite the availability of strong opioids, the existence of various other treatment options for bone pain, and the publication of pain management guidelines, most patients with bone metastases have traditionally received inadequate treatment of their pain.[23] Recently, a new treatment involving bisphosphonates for bone metastasis has been developed. Bisphosphonates have evident place in therapy for bone metastasis by reducing bone-related events,[24] however, radiotherapy remains the main effective treatment of pain from bone metastasis.[25] Appropriate fractionation regimens have been studied by numerous randomized trials over the last two decades. Many of them have shown that there are no differences between the regimens for the end point of pain response rates.[1,14] More than 40 different EBRT fractionation schedules have been reported in the literature, with 30Gy in 10 fractions being most common in the United States, 20Gy in five fractions in Canada, and single-fractions of 8Gy in some European countries (such as United Kingdom).[26,27] Frequent low-dose treatments (e.g. 30Gy in 10 daily fractions) permit a greater total RT dose and may decrease late toxicity. Multiple clinical trials, a systematic review of the literature, and this trial suggest that single fraction treatments and shorter fractionation schedules appear to provide equal palliation with improved patient convenience and cost effectiveness, although the need for retreatment may be higher.[20,28-32] The evidence of the advantages of a single fraction of 8Gy compared with longer fractionated courses are illustrated by three large randomized trials with similar results:

- In a Dutch multicenter trial, in which 1171 patients with painful bone metastases were randomly assigned to 8Gy in a single dose or 24Gy in six fractions, the palliative benefit was similar in both groups, as was treatment-related toxicity. However, retreatment was required by significantly more patients treated with a single fraction (25 *vs.* 7 percent).[28, 29]
- A British trial randomly assigned 765 patients with painful bone metastases to 8Gy as a single fraction, 20Gy in five fractions, or 30Gy in 10 fractions with median 12 month follow-up. There were no differences in any of the pain end points among the three groups. Patients treated with a single fraction were twice as likely to require reirradiation of the same site, but the majority could be successfully retreated with a single fraction [11].
- In the 'Radiation Therapy Oncology Group (RTOG) trial 9714', 949 patients with prostate or breast cancer and painful bone metastases were randomly assigned to 8Gy in a single fraction or 30Gy in 10 fractions. Patients with evidence of cauda equina syndrome or epidural spinal cord compression were excluded. There were no significant differences in the rates for complete and partial pain relief, the use of narcotics, or the incidence of subsequent pathologic fractures. However, patients treated with a single fraction were twice as likely to require retreatment (18 *vs*. 9 percent). [31]

Based upon these results, and the result of this study, a single fraction of 8Gy for the management of painful bone metastases should be strongly considered. Although the incidence of recurrent symptoms may be higher, this can be effectively managed with retreatment.[32,33] The findings that single fraction RT has been associated with higher re-treatment is usually due to clinicians' reluctance to reirradiate patients after higher dose fractionated RT (20Gy in 5 fractions over one week and 30Gy in 10 fractions over 2 weeks) compared with lower dose fractionated RT (8Gy in a single fraction).[11] A further analysis by the Bone Pain Trial Working Party, investigating associations between retreatment and subsequent experience of pain, showed no statistically significant differences in pain outcome between retreated patients and those not retreated. Absolute pain scores at the follow-up point immediately prior to retreatment did not differ significantly between the randomized groups, and neither was there any evidence of differences in response, whether considering pain increase or pain relief, following retreatment between the two groups. The data therefore gave no suggestion that retreatment following a single fraction of radiotherapy is more necessary than after a multifraction regimen.[11]

Data in the present study indicate that pain response and analgesic consumption improved in more than 75% 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 single fraction, 20Gy in five fractions regimen, and in patients receiving 30Gy in ten fractions regimen and this data is supported by previous studies[9,11,34] and by one study from the middle east (Egypt) where pain response and analgesic consumption improved in more than 70% of patients treated by the three regimens.[1]

Conclusion

Taking into account all outcomes of response in terms of pain relief, and analgesic use, we found no statistically significant difference between the three treatment schedules under test. Neither was there any suggestion of an increased level of short-term adverse effects associated with a single fraction of 8Gy radiotherapy. A single fraction of 8Gy radiotherapy thus appears as safe and effective as a multifraction regimen for the palliation of metastatic bone pain for at least 12 months. Its greater convenience and lower cost therefore make 8Gy single fraction radiotherapy the treatment of choice for the majority of patients.

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