

Multifraction radiotherapy for palliation of painful bone metastases: 20 Gy versus 30 Gy

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ABSTRACT

Aims and Background: To compare 2 multifraction radiotherapy schedules in the palliation of painful bone metastases.

Methods and Study design: We retrospectively analyzed clinical data of 105 patients with a total of 140 painful bone metastases who were treated with 20 Gy in 5 fractions or 30 Gy in 10 fractions. The primary tumors were breast (30%), lung (28%), and prostate (14%). The main sites of irradiation were spine (n = 79) and sacrum or pelvis (n = 39). Pain was graded by patients according to the pain numeric rating scale just before and 1 month after radiotherapy. Pain progression was defined as an increase ≥ 2 on pain scale after an initial response.

Results: The overall response rate at 1 month was 88.6%. Overall response rate was 89.6% in the 20-Gy arm and 87.3% in the 30-Gy arm ($p = 0.669$). The rate of complete response was statistically better in patients treated with 30 Gy ($p = 0.019$). The mean reduction in pain was 3.2 in the 20-Gy group and 3.6 in the 30-Gy group. Pain progression was 6.5% and 1.6%, respectively. The incidence of acute toxicity was statistically significantly higher in the 30-Gy arm (23.8%) than in the 20-Gy arm (2.6%) ($p = 0.001$). One pathologic fracture of the irradiated bone was observed in the 30-Gy arm. Two lesions, one in each group, were re-irradiated for pain recurrence. Pain progression was found in 6.5% of the irradiated lesions in the 20-Gy arm and in 1.6% in the 30-Gy arm.

Conclusions: In our series, both regimens achieved high rate of pain relief, although the group treated with higher total dose reported better complete response rate. The 30-Gy arm had a significantly higher rate of acute toxicity.

Keywords: Bone metastases, Multifraction radiotherapy, Palliation

Introduction

Bone metastases are one of the most common manifestations of metastatic disease in patients with cancer and are the third most common site of distant metastases after liver and lung (1). Autopsy series report evidence of bone metastases in up to 85% of patients with cancer, depending on the primary tumor (2). The incidence and prognosis of bone metastases varies with primary sites. Metastases to the bone occur in up to 70% of prostate and breast cancer cases and in up to 40% of lung, renal cell carcinoma, and thyroid cancer cases (3).

On the basis of associated symptoms, bone metastases are classified as complicated and uncomplicated. The main

symptom of uncomplicated bone metastases is severe pain, which causes a substantial burden in morbidity and contributes to the decreased quality of life experienced by these patients. In case of uncomplicated bone metastases, the aim of treatment is palliation of pain. Control of symptoms can be achieved with the use of radiotherapy (RT) and analgesic drugs, while bisphosphonates can be administered to prevent and reduce the incidence of skeletal-related events. Improvement of pain with RT is obtained in 50%-80% of patients and complete pain relief is obtained in 20%-50% of patients (4, 5). In the presence of pathologic fractures and spinal cord compression, bone metastases are defined as complicated (6). Treatment of pathologic fracture consists of surgical stabilization, with adjuvant RT to improve recalcification of the osteolytic bone. Spinal cord compression represents a complication that requires urgent treatment to avoid irreversible neurologic deficits. The management of spinal cord compression includes decompressive surgery or RT delivered in single or multiple fractions (4).

Different RT schedules are used for uncomplicated bone metastases treatment: 40 Gy in 20 fractions, 30 Gy in 10 fractions, 20 Gy in 5 fractions, and single fractions of 10 Gy, 8 Gy, 6 Gy, or 4 Gy (7-9). The most appropriate fractionation schedule is a matter of debate, but several randomized trials

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have compared short versus long course treatments, finding no difference in terms of pain relief (10-13). However, it was observed that patients receiving a single fraction of RT experienced recurrence of pain and required re-irradiation to the same site more often compared to patients receiving multiple fractions (14).

In this report, we review our experience in patients with painful uncomplicated bone metastases treated with 20 Gy in 5 fractions or 30 Gy in 10 fractions with the aim to compare the palliative effect of these 2 types of fractionation.

Patients and Methods

Between February 2010 and January 2014, 105 patients with a total of 140 painful bone metastases from different solid tumors were treated with 2 different RT schedules at our institution. Of the 140 lesions, 77 were treated with a radiation dose of 20 Gy delivered in 5 fractions over 1 week and 63 received a radiation dose of 30 Gy delivered in 10 fractions over 2 weeks.

Patients and tumor characteristics are shown in Table I. There were 59 men and 46 women. Sixty-eight (65%) patients were treated for a single bone metastasis and 37 (35%) patients for 2-4 metastases. The median patient age was 64 years (range 32-86). The primary tumors included breast carcinoma (30%), lung carcinoma (28%), prostate adenocarcinoma (14%), and other histologies (28%). The most common site of bone metastases was the spine (n = 79) followed by sacrum or pelvis (n = 39) and other sites (n = 22). Ninety-three (88%) patients were taking analgesic drugs at the time of RT. Patients received 3D conformal RT delivered with 6/15 megavoltage photons from a linear accelerator. Target volumes were identified on planning computed tomography images and simulation of treatment fields was performed before treatment. All patients completed the planned RT schedule.

The primary objective of our study was to compare the effectiveness in pain relief of the 2 different RT schedules. The secondary endpoint was to compare acute toxicity, pathologic fracture, spinal cord compression, and retreatment rates between the 2 groups. Pain was graded according to the pain numeric rating scale (NRS) (15). The NRS is a single 11-point numeric scale that assesses pain severity, ranging from 0 to 10, with 0 indicating absence of pain and 10 indicating maximum pain intensity. The severity of pain was assessed prior to and 1 month after the end of RT. The clinical response to irradiation was classified as complete response (CR), resolution of pain; partial response (PR), improvement ≥ 2 on the NRS; and no response, no change in pain symptoms or deterioration. Pain progression was defined as an increase in pain ≥ 2 after an initial response. Toxicity was measured by use of Radiation Therapy Oncology Group criteria (16).

Chi-square test and logistic regression model were used to identify factors that influence the pain response. Pain relief was stratified by RT schedule, site of treatment, age (≤ 50 years or > 50 years), sex, histology, and use of analgesic drugs. Limit for statistical significance was $p < 0.05$. Chi-square test was used to compare the acute toxicity with dose. Statistical evaluation was performed using Statistical Package for the Social Sciences version 20 (SPSS Inc., SAS, Chicago, IL).

TABLE I - Patients and tumor characteristics

	20 Gy, n (%)	30 Gy, n (%)
Number of patients	58	47
Number of lesions	77	63
F/M	28/30	25/22
Age, y, median (range)	68 (35-86)	65 (32-82)
Histology		
Breast carcinoma	18 (31)	14 (30)
Lung cancer	20 (35)	9 (19)
Prostate adenocarcinoma	6 (10)	9 (19)
Others	14 (24)	15 (32)
Number of metastases per patient		
Single	45 (77)	31 (66)
Multiple (2-4)	13 (23)	16 (34)
Site of metastases		
Spine	47 (61)	32 (51)
Sacrum or pelvis	19 (25)	20 (32)
Others	11 (14)	11 (17)

TABLE II - Outcomes of 140 irradiated lesions

	20 Gy, %	30 Gy, %
Overall response	89.6	87.3
Complete response	6.5	19
Partial response	83.1	68.3
No response	10	13
Pain progression	6.5	1.6
Acute toxicity	2.6	23.8

Results

Outcomes of treatment are shown in Table II. The overall response rate at 1 month was 88.6%. The overall response rate was 89.6% (CR and PR rates 6.5% and 83.1%, respectively) in the 20-Gy arm compared with 87.3% (CR and PR rates 19% and 68.3%, respectively) in the 30-Gy arm ($p = 0.669$). The rate of CR was statistically better in patients treated with 30 Gy ($p = 0.019$). The mean reduction in pain was 3.2 in the 20-Gy group and 3.6 in the 30-Gy group. Pain progression was found in 6.5% of the irradiated lesions in the 20-Gy arm and in 1.6% in the 30-Gy arm. This difference was not statistically significant.

The incidence of acute toxicity was statistically significantly higher in the 30-Gy arm (23.8%) than in the 20-Gy arm (2.6%) ($p = 0.001$). Adverse events were mainly represented by gastrointestinal toxicity, with nausea, vomiting, and diarrhea being the most common acute side effects experienced by patients. Only one patient, in the 30-Gy arm, had grade 4 acute toxicity (diarrhea). Two patients, in the 30-Gy arm, reported mild dysphagia. There was no grade 3-4 toxicity in the 20-Gy group, while grade 1-2 toxicities were represented

by nausea and vomiting. One patient in the 30-Gy arm experienced pathologic fracture of the irradiated bone 4 months after treatment. Two lesions, one in each group, were re-irradiated for pain recurrence 5 and 18 months after initial treatment, respectively.

By logistic regression, no difference in response rate at 1 month was found between the 2 treatment arms when stratified by RT schedule, site of treatment, age (≤ 50 years or > 50 years), sex, histology, and use of analgesic drugs.

Discussion

The optimal doses and fractionation for the treatment of symptomatic bone metastases are not well-defined and several randomized trials have compared different schedules concluding that single-fraction RT is as effective for pain relief as multifraction regimens such as 20 Gy in 5 fractions or 30 Gy in 10 fractions, although re-irradiation for recurrent pain is required more often after single-fraction treatment (10-13). Results from a meta-analysis by Wu et al (10) including data from 8 randomized trials comparing single-fraction RT with 8-10 Gy to multifraction regimens with doses of 20-30 Gy delivered in 5-10 fractions showed similar response rates between groups. The overall and CR rates were 72.7% and 39.2% for patients treated with single-fraction RT and 72.5% and 40% for those treated with multifraction regimens. In the meta-analysis by Sze et al (11), which included 3508 patients from 12 randomized trials, overall response (OR) rates were 60% after single-fraction and 59% after multifraction RT and respective CR rates were 34% and 32%. More recently, in a systematic review of 25 randomized trials comparing single-fraction versus different multifraction regimens, Chow et al (13) found similar response rates between treatment arms. Overall response rates were 72% in patients treated with single-fraction RT and 74% in those receiving multifraction regimens. Respective CR rates were 28% and 30%. Taken together, these results support the use of single-fraction RT as an alternative to fractionated treatment and, on this basis, a recent guideline by the American Society for Therapeutic Radiology and Oncology recommended single fractions for uncomplicated bone metastases, as patient convenience is optimized (17). However, the authors suggested that multifraction RT could also be considered, as patients are less likely to require retreatment. In clinical practice, many physicians prefer to prescribe multifraction regimens (18). However, a careful selection of patients should be made and single-fraction or short-course multifraction schedules should be considered preferable in patients with poor performance status and/or limited life expectancy. Nevertheless, when possible, patient preference should also be considered in treatment decisions. Shakespeare et al (19) used a decision board instrument based on the Dutch Bone Metastasis Study to determine which fractionation schedule patients would choose between single-fraction or multifraction RT. The authors reported that 85% of patients chose the multifraction schedule because of lower retreatment and fracture rates compared to single-fraction RT, while the reasons for choosing the single-fraction treatment were cost or convenience. In contrast, Szumacher et al (20) found that 76% of patients preferred single-fraction RT because of convenience.

In the current study, we compared 2 multifraction RT schedules of 20 Gy in 5 fractions and 30 Gy in 10 fractions in patients with painful bone metastases. We found similar rates of pain relief between groups, suggesting that an abbreviated course of RT is as effective as long-course treatment for palliation of symptomatic bone metastases. The overall response rate at 1 month was 88.6%. The overall response rate was 89.6% (CR and PR rates 6.5% and 83.1%, respectively) in the 20-Gy arm compared with 87.3% (CR and PR rates 19% and 68.3%, respectively) in the 30-Gy arm ($p = 0.669$). The rate of CR was statistically better in patients treated with 30 Gy ($p = 0.019$). The mean reduction in pain was 3.2 in the 20-Gy group and 3.6 in the 30-Gy group. Pain progression was found in 6.5% of the irradiated lesions in the 20-Gy arm and in 1.6% in the 30-Gy arm. Our results compare favorably with previously reported series. Niewald et al (21) found no significant difference in pain relief in 100 patients randomly assigned to receive 20 Gy in 5 fractions or 30 Gy in 15 fractions. Complete response rates were 14% for the 20-Gy arm and 22% for the 30-Gy arm. However, despite a small trend favoring the 30-Gy treatment, the authors concluded that the 20-Gy schedule is preferable because of the limited life expectancy of patients with bone metastases. In a randomized trial of 150 patients treated with a single fraction of 8 Gy or multifractions of 20 Gy or 30 Gy, El-Shenshawy et al (22) reported similar response rates among the 3 groups. The OR and CR rates were 78% and 32% in patients who received 20 Gy and 80% and 32% in those who received 30 Gy, respectively. In a similar 3-arm randomized trial of 60 patients with bone metastases, Safwat et al (23) reported OR rates of 65% and 45% for patients treated with 20 Gy and 30 Gy, respectively.

The main reason for using single-fraction or short-course RT in patients with bone metastases is that high radiation total doses may be associated with an increased risk of acute and late toxicity and this is of concern in patients with a worsened quality of life and a limited life expectancy. In our study, acute toxicity occurred in 2.6% of patients who received 20 Gy and in 23.8% of patients receiving 30 Gy ($p = 0.001$). In 272 patients randomly assigned to receive 8 Gy in single fraction or 20 Gy in 5 fractions, Roos et al (24) reported 2% of grade 3 toxicity in patients treated with 20 Gy. No grade 4 toxicity was observed. In another randomized trial, by Hartsell et al (25), comparing single-fraction (8 Gy) versus multifraction (30 Gy) RT in patients with breast or prostate cancer, grade 2-4 toxicities occurred in 17% of 433 patients who received 30 Gy. In the randomized trial by El-Shenshawy et al (22), no significant difference in acute toxicity rate was observed between the 20-Gy and 30-Gy arm. More recently, in 160 patients randomly assigned to receive single-fraction RT of 8 Gy or multifraction treatment of 30 Gy in 10 fractions, Foro Arnalot et al (26) reported grade 1-2 toxicity in 18% of patients treated with 30 Gy. No grade 3-4 toxicity was observed.

The main long-term side effect of RT to the bone is the potential risk of pathologic fracture in the irradiated region. However, as suggested by Rades (27), it may sometimes be difficult to distinguish between fractures due to progression/recurrence of osteolytic bone metastases and radiation-induced fractures. In our series, one case of pathologic fracture was

observed in the 30-Gy arm. In a randomized trial of 239 patients treated with 8 Gy in single fraction or 20 Gy in 4 fractions, Nielsen et al (28) observed pathologic fractures in 5% of patients who received 20 Gy. Roos et al (24) reported a pathologic fracture rate of 4% for the 20-Gy arm. Similar results were reported by Hartsell et al (25). In another randomized trial of 376 patients treated with 8 Gy or 30 Gy, 11% of patients who received 30 Gy experienced pathologic fracture of the irradiated bone (29).

Although single-fraction or short-course RT offer an effective treatment for palliation of bone metastases, re-irradiation is often required for pain recurrence and a second course of RT may be associated with an increased risk of toxicity. Niewald et al (21) reported a re-irradiation rate of 2% for both 20-Gy and 30-Gy arms. In the study by Nielsen et al (28), 12% of patients treated with 20 Gy required re-irradiation. El-Shenshawy et al (22) reported re-irradiation rates of 10% in the 20-Gy group and 4% in the 30-Gy group. In the trial by Foro Arnalot et al (26), 2% of patients receiving 30 Gy were re-irradiated. Higher retreatment rates of 24%-25% for patients treated with 20 Gy and 9%-15% for patients who received 30 Gy have been reported in few other studies (23-25). In the current study, the re-irradiation rates were equivalent in both groups, but not statistically significant.

In conclusion, with the limitation of a retrospective study, our findings indicate that both 20 Gy in 5 fractions or 30 Gy in 10 fractions provide similar favorable symptomatic palliation of bone metastases. Complete response rate was higher in the 30-Gy group. Nevertheless, more intense RT is associated with higher toxicity, suggesting that an abbreviated course of 20 Gy could be preferred with the aim to reduce the risk of treatment-related complications while maintaining similar pain control. More randomized trials comparing different fractionation schedules of RT and including assessment of quality of life and cost-effectiveness are warranted to better determine the overall impact of these regimens and to guide physicians in the choice of the best treatment option.

Disclosures

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