ABSTRACT

Background

Despite high-level evidence in the literature, the use of single-fraction radiotherapy (RT) for management of painful bone metastases is not widely practiced in the world, as highlighted in several practice-pattern surveys. Fractionation of palliative RT for bone metastases has not been addressed in Iran, where the most common clinical practice is the use of 30 Gy in 10 fractions. Thus, we decided to perform a randomized clinical trial to compare responses in our patients with those reported in the international literature.

Patients and Methods

Adult patients with multiple painful uncomplicated bone metastases were randomized to 8 Gy in a single fraction or 30 Gy in 10 fractions. Pain was graded by the patients on a scale of 1 to 4 just before and again 1 month after the end of RT. Palliative response was defined as “complete” (pain reduction of 2 grades or more), “partial” (pain reduction of 1 grade or more, but less than 2 grades), and “no response” (pain reduction of less than 1 grade).

Results

We randomized 70 patients in this trial (63% women; mean age: 51.6 years). Sites of treatment included spine (n = 27), sacrum or pelvis (n = 25), extremities (n = 14), ribs (n = 3), and sternum (n = 1). Patients graded their pain before RT in a range from 1.8 to 4.0 (mean: 3.2). All patients finished their scheduled course of RT without incident.

Unfortunately, 5 patients died less than 1 month after the end of RT, and 7 did not return for any follow-up and could not be contacted. As a result, only 58 patients (31 who received multiple fractions, and 27 who received a single fraction) were available for evaluation of pain 1 month after treatment. At that time, pain was graded in a range from 1.0 to 4.0 (mean: 2.0).

The reduction in pain grade ranged from –0.8 to 2.6 (mean: 1.1). We observed 8 (14%) complete responses, 33 (57%) partial responses, and 17 (29%) no responses, for an overall response rate of 71%.

The number of responders was 21 (78%) among those who received a single fraction and 20 (65%) among those who received multiple fractions (p > 0.1). The mean reduction in pain was 1.1 in both groups. The 10-fraction group contained a higher number of complete responders (11 of 31 as compared with 6 of 27 in the 1-fraction group)—a result that was not statistically significant. The mean reduction in pain was 1.4 in patients 50 years of age or younger and 0.9 in patients more than 50 years of age (p = 0.01). Of the 8 complete responses, 7 (87.5%) were seen in the patients 50 years of age or younger, and the mean age of patients with a complete response (38.7 years) was significantly lower than that of patients with a partial response or no response (53.7 years, p = 0.017).

By logistic regression, patient sex, primary tumour, RT site, and type of treatment (single-fraction vs. multifraction) did not have any significant effect on pain reduction. The only factor with a significant effect was age (p = 0.002).

Conclusions

Our trial showed no significant difference in pain relief after palliative radiotherapy with 1 or 10 fractions in Iranian patients. The overall response rate was 71%, similar to results in the international literature. Younger patients responded better.

KEY WORDS

Bone metastases, fractionation, palliative, radiotherapy

1. INTRODUCTION

Bone metastasis is a common occurrence in advanced malignancy, frequently causing significant and
debilitating pain and complications such as pathologic fracture and spinal cord compression. Radiotherapy (RT) is a modality frequently used for bone metastasis, usually as an outpatient treatment. However, RT requires daily hospital attendance at a specialized centre that may be some distance from the patient’s home. A protracted course of RT may cause considerable problems for patients, especially those with poor performance status and limited life expectancy. It may also increase the workload of the treatment centre.

In uncomplicated bone metastases, high-level evidence in the literature has demonstrated pain relief that is equal for single and multiple fractions of RT. Despite that evidence, the use of single fractions for the management of painful bone metastases is not as widely practiced in the world as the evidence may suggest. This discordance between the results of randomized trials and patterns of practice has been highlighted in several practice-pattern surveys.

The fractionation of palliative RT for bone metastases has not been addressed and no clinical trial has evaluated the fractionation issue in Iran, where the most common clinical practice is the use of 30 Gy in 10 fractions. Thus, we decided to perform a randomized clinical trial of single versus multiple fractions of radiation for palliation of bone metastases in Iranian patients. We then compared responses in our patients with those mentioned in the international literature.

2. PATIENTS AND METHODS

Adult patients with painful uncomplicated bone metastases requiring palliative RT were eligible for the trial; patients with cord compression or existing or impending pathologic fracture were not accrued into the study. This trial was ethically approved, supported, and monitored by the Research Services Office of the Research Vice Chancellor, Tehran University of Medical Sciences, Tehran, Iran (trial 911).

After written informed consent, patients were randomized to palliative RT with either 8 Gy in a single fraction or 30 Gy in 10 fractions over 2 weeks. Patient pain was evaluated just before treatment using a questionnaire of 5 questions about pain severity, the highest degree of pain in the preceding 24 hours, the effect of the pain on the patient’s daily activities and sleep, and the analgesics used. Answers were recorded by the patient or by a caregiver if the patient was unable to do so. Pain was graded on a scale of 1 (mild pain) to 4 (very severe pain) by the average of the patient’s responses to the 5 questions. Palliative RT was started immediately afterward. Hematologic and gastrointestinal side effects of RT were recorded.

Pain and analgesic use were evaluated again using the same questionnaire 1 month after the end of RT. Telephone follow-up was attempted for patients who did not come back to the clinic after treatment.

We compared the patients’ grade of pain before and after RT and the mean values of reduction in pain grade between the single-fraction and multi-fraction groups. Palliative response was defined as “complete” (pain reduction of at least 2 grades), “partial” (pain reduction of 1 grade or more, but less than 2 grades), and “no response” (pain reduction of less than 1 grade), and mean response was also compared between the two groups of patients.

We used the SPSS statistical software package, version 11.5.0, for data entry and statistical analysis. Chi-square and independent samples t-tests were used for comparison between the patient groups; logistic regression was used to evaluate the various associated factors. Correlation of reduction in pain grade and narcotic use was also sought. Statistical significance was considered at $p < 0.05$.

3. RESULTS

From 2001 to 2003, 70 patients with multiple painful uncomplicated bone metastases were randomized for the trial, 36 to a single fraction and 34 to 10 fractions of palliative RT. Of these patients, 63% were women, age range was 20–77 years (mean: 51.6 years), and 36% (51%) were more than 50 years of age. Primary tumours included breast ($n = 32$), gastrointestinal ($n = 12$), prostate ($n = 10$), kidney and bladder ($n = 6$), head and neck ($n = 4$), unknown ($n = 3$), lung ($n = 1$), cervix ($n = 1$), and lymphoma ($n = 1$). Sites of treatment included spine ($n = 27$), sacrum or pelvis ($n = 25$), extremities ($n = 14$), ribs ($n = 3$), and sternum ($n = 1$).

The pain grade before RT ranged from 1.8 to 4.0, with a mean of 3.2 ± 0.5 (standard deviation). Four patients (6%) claimed no use of analgesics, 30 (43%) used non-narcotic analgesics, 22 (31%) used weak narcotics, and 14 (20%) used strong narcotics.

All patients finished their scheduled course of RT without incident. Side effects included only mild gastrointestinal disturbances (nausea and, to a lesser extent, diarrhea) in 5 of the multi-fraction patients and in 3 of the single-fraction patients; no interruption of treatment was required because of side effects.

Unfortunately, 5 patients died within 1 month after the end of RT, and 7 did not return for follow-up and could not be contacted (5 single-fraction and 2 multi-fraction patients, $p > 0.1$). Only 58 patients (31 multi-fraction, 27 single-fraction) were therefore available for evaluation of pain 1 month after treatment. The grade of pain and use of analgesics in the evaluable patients before RT were similar to those of the entire patient population (pain grade range: 1.8–4.0; mean: 3.2 ± 0.5; 7% no use of analgesics, 43% non-narcotic analgesics, 28% weak narcotics, and 22% strong narcotics).

In the evaluation using the same questionnaire 1 month after RT, the pain grade ranged from 1.0 to 4.0 (mean: 2.0 ± 0.8). The reduction in pain grade ranged from −0.8 to 2.6 (mean: 1.1 ± 0.8). Of the evaluable patients, 21 (36%) claimed no use of analgesics, 19 (33%) used non-narcotic analgesics, 12 (21%) used weak narcotics, and 6 (10%) used strong narcotics.
The reductions in pain and in analgesic use (strong to weak narcotics, non-narcotics, or no analgesics) were positively correlated \( (p = 0.01) \). We observed 8 (14%) complete responses, 33 (57%) partial responses, and 17 (29%) no responses by the definitions outlined in “Patients and Methods,” for an overall response rate of 71% in patients evaluated 1 month after RT.

Between the patients receiving single and multiple fractions of RT, there were no significant differences in terms of sex, mean age, and grade of pain before and after treatment \( (p > 0.1) \). The mean reduction in pain was 1.1 in both groups, and the number of responders was 21 (78%) in the single-fraction group and 20 (65%) in the multi-fraction group, a difference that was not statistically significant \( (p > 0.1) \). The number of complete responders was higher in the multi-fraction group \( (11 \text{ of } 31) \) than in the single-fraction group \( (6 \text{ of } 27) \), but that difference was not statistically significant.

The mean reduction of pain was 1.4 in patients 50 years of age or younger and 0.9 in patients more than 50 years of age \( (p = 0.01, \text{Figure 1}) \). Of the 8 complete responses, 7 \( (87.5\%) \) were seen in patients 50 years of age or younger, and the mean age of patients with a complete response \( (38.7 \text{ years}) \) was significantly lower than that of patients with partial or no responses \( (53.7 \text{ years}, p = 0.017) \).

By logistic regression analysis, no significant effect on reduction of pain was seen for sex, primary tumour, RT site, or type of treatment (single-fraction vs. multi-fraction). The only factor with a significant effect was age \( (p = 0.002) \).

![Figure 1](https://example.com/fig1.jpg)

**Figure 1** Reduction in pain grade after palliative radiotherapy, by age. Closed squares = 50 years of age or younger; open circles = more than 50 years of age.

4. **DISCUSSION**

As yet, no consensus has developed regarding the most appropriate fractionation for RT in metastatic bone pain. Two large contemporary multicentre randomized trials \( ^2-^3 \) and a meta-analysis of 16 randomized trials \( ^4 \) have found no significant difference in the probability of achieving pain relief with different fractionation schedules of localized RT in painful uncomplicated bone metastases. More recently, published results of a North American multicentre trial [Radiation Therapy Oncology Group (RTOG) 97-14] \( ^8 \) and a meta-analysis of 12 randomized trials \( ^9 \) have confirmed those findings. Our findings are also in agreement, showing no significant difference in the degree of pain relief or in the response rate with treatment using either 8 Gy in 1 fraction or 30 Gy in 10 fractions in Iranian patients. In contrast, a Canadian trial reported in abstract form \( ^{10} \) indicated that 20 Gy given in 5 fractions was superior to 8 Gy in 1 fraction for painful bone metastases, although significant pain relief in that trial \( (46\% \text{ multi-fraction vs. 32\% single-fraction}) \) was lower than that seen in other multicentre trials.

Despite the high-level evidence published in the international literature, several practice-pattern surveys conducted among radiation oncologists in various countries have shown limited use of single fractions for bone metastases \( ^{5-7} \). Haddad et al. studied a Canadian specialized academic palliative RT program and demonstrated that, even in that program, only one third of palliative RT courses for bone metastases were prescribed using a single fraction \( ^{11} \).

Chow et al. argued that, instead of further dose fractionation trials in bone metastases, perhaps resources could be better invested in other research areas \( ^{12} \). For example, the strong preference of clinicians to use multiple fractions for spinal metastases is likely a result of concern for the intermediate complications of bone metastases such as subacute cord compression and pathologic fracture. A systematic review by Sze et al. \( ^9 \) demonstrated a rate of pathologic fracture in single-fraction RT patients that was 1.82 times the rate in multi-fraction patients, although the absolute rate of difference was only 1.3%. In addition, the meta-analysis mentioned earlier showed a trend for increasing rates of spinal cord compression in both single- and multi-fraction patients, but the number of events was too small to allow for testing of the difference. Future studies are needed to determine the optimal choice of dose fractionation with respect to these outcomes \( ^{13} \).

The overall response rate to palliative RT in the Iranian patients in our trial was 71%, which accords with the results reported in the international literature. In the Dutch Bone Metastasis Study \( ^2 \), the overall response rate was also 71%. In the Bone Pain Trial Working Party report \( ^3 \), 78% of patients experienced some degree of pain relief; in the RTOG 97-14 trial \( ^8 \), the overall response rate was 66%; and in the systematic review by Sze et al. \( ^9 \), the rate was 59%–60%. The complete
response rate in our trial (14%) was lower than that in either the Dutch (35%) or the Working Party (57%) trial and that in the systematic review (32%–34%), but it was very similar to the response rate in the RTOG 97-14 trial (17%). This finding might be related to differences in the questionnaires used, the timing of the pain evaluation after RT, the definition of complete response, or the small number of patients in our trial.

Our trial showed better pain relief in patients 50 years of age and younger (Figure 1). That effect of age remained significant in the multiple regression analysis and might be the result of better performance status in younger patients or just an incidental statistical finding. An effect of age was not discussed in reports of the three multicentre trials, the meta-analysis by Wu et al., and the systematic review by Sze et al.

Some studies have reported variable responses to palliative RT in bone metastases from different primaries, especially breast and prostate cancer as compared with lung cancer. We saw no difference in that regard in our trial, but the number of patients in our trial was not large enough to properly test the issue (we had only 1 patient with a lung primary; this tumour is less common in Iran than in Western countries). We also could not test the effect of performance status on our results, because those data were not recorded.

The main limitations of our trial were the relatively small number of patients accrued and the inability to contact some of them after RT. Randomized clinical trials are a relatively unfamiliar issue for Iranian patients (and even physicians), and our centres typically lack the support personnel required for such trials. In addition, the long distances sometimes travelled by patients to reach specialized treatment centres in this vast country complicate this matter further.

5. CONCLUSIONS

Our trial showed no significant difference in pain relief after palliative RT with 1 or with 10 fractions in Iranian patients, a result that accorded with reports from other countries. The overall response rate was 71%, similar to results in the international literature. Younger patients experienced better pain relief.

6. ACKNOWLEDGMENTS

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7. REFERENCES


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