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ORIGINAL ARTICLE

Efficacy and time course of palliative radiotherapy for pain relief in 70 patients with bone metastases*

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Abstract

Objective The aim of this study was to evaluate the efficacy and time course of radiotherapy for pain relief in patients with bone metastases.

Methods A total of 70 patients with painful bone metastases were investigated between January 2013 and August 2015. The patients were divided into 3 groups and each group was treated with radiotherapy using 30 Gy in 10 fractions, 20 Gy in 5 fractions, or a single dose of 8 Gy. The pain over the irradiated site was assessed using a numerical rating scale (NRS) ranging from 0 to 10. Pain relief was assessed every 5 days based on a pain questionnaire.

Results Complete pain relief was achieved in 14.3% (10/70) patients; partial pain relief in 74.3% (52/70); and no response in 11.4% (8/70). The overall response rate was 88.6%. No significant difference was observed between single fraction radiotherapy and multifraction radiotherapy. There was no relationship between the pain relief and treated sites. The pain score gradually decreased and most patients reached a moderate pain score (NRS < 7) on day 10–15.

Conclusion Local radiotherapy is a very rapid and effective palliative treatment for painful bone metastases; however, the optimal dose and fractionation regimen remain debatable. Individualized therapy for painful bone metastases should be considered according to the patient's condition and life expectancy.

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Key words: bone metastases; radiotherapy; pain relief; time course

Bone is the most common site of cancer dissemination, and about 80% patients dying of cancer have bone metastases [1–2]. Cancer pain is one of the most unbearable symptoms of advanced cancer, and may severely impair the quality of life of the patients who suffer from it. Bone metastases lead to skeletal-related events, which include fractures, pain, spinal cord compression, and hypercalcemia. Moreover, severe bone pain may result in prolonged bed rest and deep vein thrombosis. External beam radiotherapy plays a major role in the treatment of painful bone metastases. Previous studies have shown that pain relief can be expected in 70%–90% of the patients with painful bone metastases [3]. However, the optimal dose/fraction regimen remains debatable, and the time course of pain relief provided by radiotherapy is not well known. This study was performed not only to confirm the previous results but also to determine the time course of pain relief after radiotherapy.

Materials and methods

Patients

This retrospective study included 70 patients who had undergone palliative radiotherapy at Tongji Hospital from January 2013 to August 2015. The patients who were diagnosed with cancer and had cancer pain due to bone metastases were enrolled in this study. Bone metastases were confirmed using radiography, computed tomography (CT), magnetic resonance imaging, or skeleton emission CT scan. Patients with the Eastern Cooperative Oncology Group performance status [1–4] and with clear consciousness were included in this study. Informed consent was obtained from all the patients.

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Radiotherapy

All the patients were treated with external beam radiotherapy using an ELEKTA linear accelerator with 6 MV or 10 MV photons or 6–15 MeV electron beams. The choice of radiotherapy technique was left to the discretion of the treating physician and radiation therapist. Single-field, two parallel-opposed field, or intensity-modulated radiation therapy techniques were allowed. For single-field irradiation, the dose was specified on the lesion depth, whereas for parallel-opposed fields, the dose was specified in the mid-plane. No restrictions were implemented regarding the machine or photon energy used for irradiation. Radiotherapy was administered and targeted the lesions in patients who complained of pain.

All the patients were assigned to 1 of the following 3 dose fractionation schedules: 8 Gy delivered in a single fraction (8 Gy/1), 30 Gy in 10 fractions (30 Gy/10), or 20 Gy in 1 week (400 cGy × 5). Irradiation was performed once per day from Monday to Friday (5 days per week). If radiotherapy was synchronously or asynchronously administered more than once in the same patient because of multiple lesions, the evaluation of pain relief was independently performed in each lesion.

Assessment of pain

Cancer pain was assessed using the patients' self-rated pain scores from 0 (no pain) to 10 (the worst pain) from day 1 of radiotherapy. The effect of radiotherapy on pain relief is known to occur in a month and this effect generally stabilizes in approximately 1 to 2 months. In this study, the pain score was assessed every 5 days for 5 weeks (on days 5, 10, 15, 20, 25, 30, and 35). The pain score was defined by assessing the pain due to the lesion(s) for which radiotherapy was administered or the pain associated with the lesion(s). Pain not related to the irradiated lesion(s) was not evaluated (radiotherapy was administered to the site with the most painful lesion).

Pain relief was assessed using a pain questionnaire and by evaluating the types and the decrease in the doses of the analgesic drugs. Pain relief was defined as a decrease in the pain score recorded by the patient or a significant decrease in the doses of the analgesic drugs with stable pain level. Complete response was defined as the complete disappearance of pain and withdrawal of all the analgesic drugs. Partial pain relief was defined as a greater than 50% reduction in medication as well as a significant decrease in the pain score.

Statistical analysis

The pain score was analyzed using a repeated measures analysis of variance. The chi-square test was used to evaluate the treatment differences (30 Gy/10 vs. 20 Gy/5 vs. 8 Gy/1) in the distribution of pain response at 0.05 significance level.

Results

General information

The 70 patients included 37 men and 33 women, and their median age was 59 years. The sites of the primary tumor were breast cancer in 27 patients, respiratory system in 23, prostatic cancer in 6, multiple myeloma in 2, nasopharyngeal carcinoma in 4, cervical cancer in 2, gastric cancer in 3, and occult primary tumors in 3. The detailed characteristics of the 70 patients are listed in Table 1.

Response to radiotherapy

The response to treatment was assessed in the 70 patients with painful bone metastases. The overall rates of complete pain relief, partial pain relief, and no response were 14.3% (10/70), 74.3% (52/70), and 11.4% (8/70), respectively. The overall response rate (ORR) was 88.6%.

Of the enrolled patients, 53 received 30 Gy in 10 fractions, and the ORR was 90.6% (48/53), while 12 received 20 Gy in 5 fractions, and the ORR was 83.3% (10/12). Only 5 patients received 8 Gy single-fraction radiotherapy (SFRT), and the ORR was 80% (4/5) (Table 2). No significant differences in the response rates were observed among different radiotherapy schedule groups. The following sites were irradiated: vertebral column (51.4%), pelvis (22.9%), arms and legs (21.4%), and chest wall (4.3%). The overall response rates of bone pain at different treatment sites were 94.4% (spine), 87.5% (pelvis), 80.0% (limbs), and 66.7% (chest wall) (Table 3). Similarly, no statistical difference was found in the pain relief rates among the differing treatment sites.

Time course of pain relief

Pain scores of the 70 patients were recorded from the beginning to the end of radiotherapy. The mean ± standard deviation pain scores at days 5, 10, 15, 20, 25, 30, and 35 were 8.20 ± 1.12, 6.60 ± 1.27, 5.12 ± 1.24, 3.34 ± 1.24, 2.03 ± 1.08, 1.20 ± 0.91, and 1.03 ± 0.75, respectively (Fig. 1). In the analysis of all time points, a significant difference was observed in the time course of pain score during and after radiotherapy. The pain score gradually decreased and most patients reached a moderate pain score (NRS < 7) on day 10–15.

Discussion

Radiotherapy is one of the most important and effective treatment methods for painful bone metastases. It is effective in decreasing the pain due to bone metastases and causing tumor shrinkage or growth inhibition. Many studies have shown that the total rate of pain relief provided by radiotherapy is 80%–90% and the rate of complete pain relief is 27%–50%. In addition, the pain score gradually but significantly decreases weekly and the pain

Table 1 Patient characteristics

Variable	No. of patients	%
Sex		
Male	37	53
Female	33	47
Median age (years)	59 (26–76)	
Primary Tumor		
Breast	27	38.6
Lung, trachea	23	32.9
Prostate	6	8.6
Bone marrow	2	2.8
Nasopharynx	4	5.7
Cervix	2	2.8
Stomach	3	4.3
Unknown	3	4.3
Site		
Vertebral bone	36	51.4
Pelvis	16	22.9
Limbs	15	21.4
Chest wall	3	4.3
NRS score		
7–10	52	74.3
4–6	18	25.7

Table 2 Pain response after radiotherapy

Does/fractions	*n*	CR	PR	NR	ORR (%)
30 Gy/10 F	53	6	42	5	90.6
20 Gy/5 F	12	3	7	2	83.3
Single 8 Gy	5	1	3	1	80.0

Table 3 Remission of pain due to bone metastases at different sites after radiotherapy

	CR+ PR	NR	ORR (%)
Vertebral bone	34	2	94.4
Pelvis	14	2	87.5
Limbs	12	3	80.0
Chest wall	2	1	66.7

relief could last for at least 3 months in about 70% of the patients. In the past few years, a dose of 2 to 8 Gy/fraction has been used in palliative radiotherapy for pain control. For pain control in bone metastases, there are 3 different but commonly used radiotherapy dose fractionation regimens, which include a single dose of 8 Gy radiation and 2 multifraction schemes of 30 Gy in 10 fractions and 20 Gy in 5 fractions. Although many studies suggest no differences in pain relief and toxicity depending on the dose/fraction, the optimal and recommended palliative treatment regimen for painful bone metastases is still debatable.

The largest trial comparing the treatment effects of different radiotherapy schedules in palliative treatment for bone metastases was performed by the Radiation Therapy

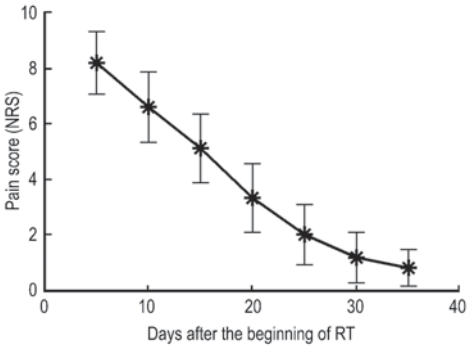

Fig. 1 Time course of pain score in 70 patients from the onset to the end of radiotherapy

Oncology Group. A total of 759 metastatic sites were evaluated for pain relief produced by 5 different fractionation schedules: 40 Gy in 15 fractions, 20 Gy in 5 fractions, 30 Gy in 3 fractions, 27 Gy in 5 fractions, and 25 Gy in 5 fractions. None of the regimens was significantly superior over the others in terms of response rates and pain relief duration. Subsequent reanalysis of this data with different statistical methods and different endpoints demonstrated a relationship between higher doses in more fractions and improved pain control [4]. A further study indicated that protracted dose-fractionation schedules are more effective than a short course regimen. Kaasa *et al* observed similar pain relief outcomes with SFRT (8 Gy/1) schedules compared to longer courses of palliative radiation for previously un-irradiated bone metastases. Patients with a pain score of 3–4 could benefit from SFRT for pain relief due to increased convenience and decreased medical expenditure [5]. However, SFRT has a higher rate of re-treatment and bone fracture than multi-fraction radiotherapy (MFRT) [6].

Thus, SFRT might be appropriate for patients with poor performance status (pain score > 3), limited life expectancy, and severe cancer pain, while MFRT with a total dose ≥ 30 Gy is recommended to patients with a pain score of 1–2 and a long life expectancy [7].

SFRT has not yet gained overwhelming support in China; the reasons for this are as follows: a reluctance to adapt a new practice after long experience with MFRT, concerns about risks of acute morbidity, concerns about late central nervous system toxicity and bone fracture, and physician's preferences. In the present study, 75.7% (53/70) patients received 30 Gy in 10 fractions, 17.2% (12/70) received 20 Gy in 5 fractions, and 7.1% (5/70) received 8 Gy single radiation. No differences in the pain score, fatigue, or overall quality of life were found among the 3 treatment regimens; this result was similar to the observation in Wu *et al* meta-analysis [8]. Prospective studies suggest that radiotherapy provides pain relief after 10–14 days of treatment. Significant improvement in the

pain score was observed in 70% of the patients in 2 weeks after the treatment. Remarkable pain relief was observed in 90% of the patients in the later 3 months [9–10]. In this study, the pain score in 70 patients with bone metastases gradually but significantly decreased weekly over 4–5 weeks.

The mechanism of the pain-relieving effect of radiotherapy is incompletely understood. There is no direct correlation between the effectiveness of radiotherapy and the radiosensitivity of the tumor or the administered dose. Tumor shrinkage and inhibition of the release of chemical pain mediators seem to be the main mechanisms of action of radiotherapy. The rapid onset of pain relief, within days or even hours, is attributed to the decrease in the level of various chemical pain mediators, whereas tumor shrinkage and recalcification of osteolytic bone lesions contribute towards the long-lasting effect [11].

In conclusion, radiotherapy is the single most effective oncological treatment of cancer pain. For bone metastases treatment, the pain-relieving efficacy of both external radiotherapy and systemic radionuclide therapy is well–documented [12]. However, there is no consensus regarding the most appropriate way of delivering radiotherapy for painful bone metastases. It is important to strike a balance between the treatment efficacy, patient convenience, and cost. Individualized therapy for painful bone metastases should be considered according to the patient's condition and life expectancy.

Conflicts of interest

The authors declared no potential conflicts of interest.

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