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A Single or Short Course of Palliative Radiotherapy Increases the Risk of Pain Flare

Osamu Tanaka,[1,*] and Masahiko Oguchi[2]

[1]Department of Radiation Oncology, Gifu Municipal Hospital, 7 - 1 Kashima-Cho Gifu, Japan, 500 - 8513
[2]Department of Radiation Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3 - 10 - 6 Ariake Koutoh Ward, Tokyo, Japan 135 - 8550

[*]*Corresponding author*: Osamu Tanaka, Department of Radiation Oncology, Gifu Municipal Hospital, 7 - 1 Kashima-Cho Gifu, Japan, 500 - 8513. Tel: +81-582511101, Fax: +81-582511101, E-mail: c.bluered@gmail.com

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Abstract

Objectives: To evaluate the incidence of pain flare after palliative radiation for painful osseous metastases, and whether a single or short course of radiotherapy increases the risk of pain flare using a physician-based assessment.
Methods: A series of 55 consecutive patients who underwent palliative radiotherapy were included in this analysis. Their treatments were as follows: 8 Gy, single fraction (n = 5), 20 Gy, 5 fractions (n = 11), 30 Gy, 10 fractions (n = 39). Pain flare was defined as a 2-point increase in the present pain intensity (PPI) with no decrease in analgesic score or a 25% increase in the analgesic score with no decrease in PPI for at least 2 consecutive days. The assessment was performed by a radiation oncologist.
Results: Using the definition of pain flare, 8 out of 34 (24%) patients experienced a pain flare with a median duration of 3 days (range: 2 to 6 days). The median onset of pain flare was the day after the start of radiotherapy (day 2; range, day 1 to 3). Two of the 5 (40%) patients and 4 of the 11 (36%) patients who received total doses of 8 Gy and 20 Gy, respectively, experienced a pain flare. In contrast, 2 of the 39 (5%) patients who received a total dose of 30 Gy experienced a pain flare.
Conclusions: Pain flare is common after palliative radiotherapy for bone metastases. Single fraction or short course radiotherapy may be associated with a higher risk of pain flare.

Keywords: Pain Flare, Bone Metastasis, Radiotherapy

1. Background

The role of radiotherapy (RT) in the palliation of symptomatic bone metastasis is well established. A wide variety of dose schedules have been used, varying from one fraction of 6 - 10 Gy to multiple fractions, most often 30 Gy delivered in 10 fractions. For more than two decades the optimal radiotherapy regimen has been the subject of ongoing discussion (1-3). The first randomized study assessing the effect of one fraction of 8 Gy versus multiple fractions (3 Gy x 10) was published in 1986 (1). No difference was found between the regimens with regard to the onset or duration of pain. Although re-irradiation is generally needed for single fraction radiotherapy, it is well recognized that single fraction radiotherapy has advantages over multiple fraction radiotherapy in its lower cost and its association with fewer toxic events (2-11).

Although pain flare has at times been mentioned as a potential side effect of radiotherapy, it has seldom been well-documented in previous studies. Pain flare has sometimes been reported in association with total body irradiation (TBI) and radionuclide therapy, but rarely in association with local radiotherapy. Recently, some reports on the subject of pain flare after palliative radiotherapy for bone metastasis were written by a Canadian group, American group and Netherland group (12-14). Loblaw et al. noted that 15 of 44 (34%) patients experienced a pain flare that lasted a median of 3 days. In their patient series, 10 of 23 (44%) and 5 of 21 (24%) patients who received 8 Gy, in a single fraction and 20 Gy, 5 fractions, respectively, experienced pain flare (9). They concluded that pain flare is common after palliative radiotherapy for bone metastasis. Single fraction radiotherapy may be associated with a higher risk of pain flare. However, the authors did not investigate the incidence with a dose of 30 Gy in a 10 fraction schedule. No such studies have been reported from Japan. Besides, Pain flare is most frequency occurs after stereotactic body radiation therapy (SBRT), and Chiang et al. reported pain flare was observed in 68% of patients, most commonly on day one after spine SBRT (12). Pan et al. reported that was observed in 23% of patients after spine SBRT (9).

A temporary worsening of pain, shortly after palliative radiotherapy, is clinically common and can be problem-

atic, particularly for patients who receive single fraction therapy. In this analysis, we evaluated the incidence of pain flare after palliative radiation for painful bone metastases and investigated the incidence of pain flare after single fraction (9-11), short course (20 Gy, 5 fractions), or long course (30 Gy, 10 fractions) radiotherapy using a physician-based assessment.

2. Methods

2.1. Pretreatment Patient Characteristics

A total of 34 consecutive patients with bone metastasis who were treated with external beam radiotherapy were analyzed in this study. The patient's characteristics are shown in Table 1. All patients provided written informed consent in relation to the use of a questionnaire, the ethical committee of radiation oncology department approval number, H19-01. Patients with pathological fractures and spinal cord compression were excluded from the study. Female patients with breast adenocarcinoma were predominantly included in this analysis due to the fact that they comprise the majority of the patients who are treated in our hospital. The radiotherapy dose fractionations were 8 Gy, single fraction, or multiple fractions of 20 - 30 Gy. The fractionation was determined by the patient's prognosis; multiple fractions were administered to patients with longer life expectancy, while patients with a shorter life expectancy received a single fraction. Although some patients received hormonal therapy or bisphosphonate during the course of the radiotherapy, these therapies were not taken into account for the analysis. Three-dimensional conformal radiotherapy was performed in all patients.

2.2. Estimation of the Pain Flare

One week after the start of radiotherapy, each patient was asked whether he or she experienced a worsening of pain. If the patient experienced the worsening of the pain, the radiation oncologist explained the definition of pain flare as a 2 point increase in the pain scale of 0 - 10 (0 indicating the absence of pain and 10 indicating the worst possible pain) in comparison to baseline levels with no decrease in analgesic intake or a 25% increase in analgesic intake (employing the daily oral morphine equivalent) with no decrease in pain score. If the patient met the criteria of the definition then a pain flare was determined to have occurred. Patients with a baseline pain score of 9 or 10 were not observed in this analysis. To distinguish an incidence of pain flare from the progression of pain, we required the pain score to return back to baseline after the pain flare.

Table 1. Patient Characteristics (n = 55)

Patient Characteristics	Value
Gender	
Male	15 (22%)
Female	40 (78%)
Age (y)	
Median	62
Range	27 - 74
Primary cancer site	
Breast	27 (50%)
Colon	10 (18%)
Limbs	3 (5%)
Lung	5 (9%)
Others	8 (15%)
Unknown	2 (4%)
Pathology	
Adenocarcinoma	41 (75%)
Sarcoma	3 (5%)
Others	11 (20%)
Performance status (ECOG)	
0	31 (56%)
1	18 (33%)
2	6 (11%)

3. Results

The incidence of pain flare in relation to the radiotherapy fractions and sites of irradiation is shown in Table 2. Of the 34 patients, 8 (24%) experienced a pain flare (according to the above-noted definition) that lasted a median of 3 days (range: 2 to 6 days). The median onset of pain flare was the day after the start of radiotherapy (day 2; range, day 1 - 3). Two of 5 (40%) and 4 of 11 (36%) patients who received total doses of 8 Gy and 20 Gy, respectively, experienced a pain flare. In contrast, only 2 of 39 (5%) patients who received a total dose of 30 Gy experienced a pain flare. The site of irradiation was found to have no impact on the occurrence of the pain flare.

4. Discussion

The results of the present study were similar to those reported by Loblaw et al. in terms of hypofraction 8 Gy single and 20 Gy in 5 fractions (9). They reported that 10 of 23 (44%) and 5 out of 21 (24%) patients who received 8 Gy

Table 2. Radiotherapy Methods and Incidence of Pain Flare[a]

		Pain Flare	Site	
Radiation dose	**Number**	**Yes**	**No**	
8 Gy single fraction	5 (4)[b]	2 (40%)	3	Spine 2
20 Gy in 5 daily fractions	11	4 (36%)	7	Spine 3, Pelvis 1
30 Gy in 10 daily fractions	39	2 (5%)	37	Spine 2
Total	55	8 (15%)	47	
Irradiated site		**Yes**	**No**	
Spine	23	4 (15%)	19	
Limbs	12	3 (25%)	9	
Pelvis	11	1 (9%)	10	
Others	9	0 (0%)	9	

[a]The dexamethasone dose was 6 mg for 3 days from the day of radiotherapy. No pain flare was observed in any of the patients.
[b]Four patients were prescribed dexamethasone for the prevention of pain flare.

single fraction and 20 Gy 5 fractions, respectively, experienced a pain flare. In our series, 2 of 5 (40%) and 4 of 11 (36%) patients who received 8 Gy and 20 Gy, respectively, experienced a pain flare. On the other hand, we included 30 Gy in 10 fractions (long time course) and the occurrence of pain flare occurred only 5% (2 of 39). Some studies showed hypofraction RT was the one of risk factor of pain flare (2, 6, 9, 14)

However this our retrospective study included a very small number of patients, and only five patients were treated with single fraction therapy (8 Gy). Thus we could not reach a definitive conclusion. A large-cohort study of the Japanese population is needed.

This study used physician-based assessment. Recently, the use of this method is unusual. We employed the physician-based assessment because patient self-assessment systems such as the numeric rating scale, which has been authorized by ASTRO, CARO and other international groups, is not clarified. It is necessary for both the physician and the patient to investigate instances of pain. Due to the limited data that were collected in relation to the patients' characteristics, we could not clearly describe the number of patients with multiple bone metastasis, who were treated with hormonal therapy, bisphosphonate or chemotherapy during radiotherapy. We needed to describe the numbers of patients at each pain score level and who were taking oral morphine or NSAIDs before radiotherapy.

In the pain flare study by Chow et al. (8), 88 patients who provided pain scores and analgesic data daily for 2 weeks were studied prospectively. Most patients received one or five fractions of RT (6% received ten fractions). They defined pain flare as an increase in the 0 -10 pain scale of $\geq$ 2 without an increase in the analgesic score or an increase in the analgesic score of 25% or greater with no decrease in the pain score. Despite their use of the same definition as the present study, they reported a lower incidence of pain flare: 14.0 vs. 15.6% for patients who receive single fraction vs. multiple fraction radiotherapy, respectively. They reported that only 1 out of 5 (20%) patients who received 30 Gy in 10 fractions experienced a pain flare. In our series, 2 out of 39 (5%) patients who received 30 Gy in 10 fractions experienced a pain flare.

The differences between the studies were caused by the definition of pain flare as well as patient characteristics. Our population consisted mostly of breast adenocarcinoma patients (47%). Breast cancer patients sometimes require hormonal therapy, which might impact the results. The 2 previous studies (2, 9), involved a patient-based analysis, while ours was based on a physician's assessment. This might have caused an overestimation or underestimation of the incidence of pain flare. In our series, many patients with breast cancer received bisphosphonate after the occurrence of bone metastasis. The use of bisphosphonate reduces the pain of bone metastasis; however, we did not take the use of bisphosphonate into account for this analysis. Furthermore, a better comparison of the 8 Gy and 20 Gy doses with the 30 Gy dose could have been made if there were differences in their radiation field sizes.

These results show the incidence of pain flare to be controversial. What is clear, however, is that pain flare occurred, especially after short-course radiotherapy. Chow et al. reported, in their pilot study of patients who were treated with 8 Gy (single fraction) for bone metastasis, that the patients took 8 mg dexamethasone before the radiation treatment (10). A total of 10 out of 33 patients showed

a progressive worsening of pain during the entire 10-day period of the follow-up. A total of 8 patients (24%) experienced a pain flare during the 10-day follow-up period. They concluded that dexamethasone might be effective in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases. In our series, 2 patients took dexamethasone after the occurrence of pain flare. The 2 patients were rescued from the temporal worsening of the pain after receiving the medication. It might be reasonable to use dexamethasone after the onset of pain flare, however, it is inconvenient for patients with single fraction radiotherapy to return to the hospital to receive medications. Therefore in terms of convenience and cost, the prophylactic use of dexamethasone might be worthwhile.

In conclusion, development of radiotherapy systems makes more accurate and short course radiotherapy easy. The importance of prophylactic dose of dexamethasone was reported by Westhoff et al. by using randomized control trial (13). Therefore, we need prophylactic dose of steroid in short course radiotherapy in Japanese population.

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