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Comparison of pain-relieving effects by number of irradiations, through propensity score matching and the international consensus endpoint

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ABSTRACT

Background: Palliative radiotherapy for bone metastases utilizes various dose fractionation schedules. The pain-relieving effects of a single fraction (SF) and multiple fractions (MF) are largely debated due to the difficulty in matching patients' backgrounds and in assessing the effectiveness of pain relief. This study aimed to compare the pain-relieving effects of SF and MF palliative radiotherapy for bone metastases using propensity score matching and the international consensus endpoint (ICE).

Materials and methods: Our study included 195 patients irradiated for bone metastasis. The primary endpoint was the pain-relieving effects used by ICE. In addition, the evaluation was performed by using responder (complete response/partial response) and non-responder (pain progression/indeterminate response) categorization. The secondary endpoints were the discharge or transfer rate at one month after irradiation–and postirradiation pathological fracture rate. Propensity score matching was used to adjust patient's characteristics and reduce selection bias.

Results: After adapting propensity score matching, the total number of patients was 74. There was no significant difference in the pain-relieving effects between SF and MF ($p = 0.184$). There were no significant differences in them between SF and MF when using responder and non-responder categorization ($p = 0.163$). Furthermore, there were no differences in the discharge or transfer rates ($p = 0.693$) and pathological fracture rates ($p = 1.00$).

Conclusions: The combination of propensity score matching and ICE revealed no significant difference in the pain-relieving effects between SF and MF for bone metastases, thus, SF has no significant disadvantage compared to MF in pain-relieving effects.

Key words: radiotherapy; bone metastases; the international consensus endpoint; propensity score matching

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Introduction

Bone metastasis is a relatively common complication of cancer [1], which often causes severe pain [2–4] and can seriously deteriorate the patients' quality of life; therefore, pain-relieving interventions are essential [5, 6]. Palliative radiation for bone metastases is an effective and common treatment approach worldwide [7]. Although various dose fractionation schedules are used in radiation therapy for bone metastases [8, 9], many studies have suggested that there is no difference in the pain-relieving effects between single fraction (SF) and multiple fraction (MF) regimens [10–12]; moreover, there is one report indicating that SF provides better pain-relieving effects [13].

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Furthermore, SF requires less patient effort to treat compared to MF and is considered to provide benefit to the patient. Patients with severe pain from bone metastases often have difficulty moving, the fewer treatments that might require, the less the burden on the patient. However, the percentage of patients receiving SF is still low compared to MF [14, 15].

Moreover, in the past, the evaluation of palliative irradiation for pain in bone metastases was not standardized. Thus, it is extremely difficult to make comparisons between trials. In 2002, the International Bone Metastases Consensus Working Party published the first consensus on palliative irradiation [16] and the consensus was then updated and proposed as the international consensus endpoint (ICE) in 2012. ICE considered the amount of analgesic medications required by individual patients in assessing pain response [17]. However, the majority of research studies have not combined propensity score matching with ICE, suggesting that the respective findings may suffer from significant bias. We hypothesized that pain-relieving effects evaluation combined with propensity score matching and ICE may be useful to verify that SF has no significant disadvantage compared with MF. This study aimed to compare the pain-relieving effects of SF and MF palliative radiotherapy for bone metastases using propensity score matching and ICE.

Materials and methods

Patients

Patients that underwent irradiation for bone metastases at our institution between 2013 and 2019 were considered eligible to participate in this study. The total number of patients was 462. As far as the choice of fraction dose is concerned, in general, SF is often chosen when the expected survival is a few months, and MF is often chosen when the expected survival is longer than it is in patients treated with SF. Specifically, if the Karnofsky Performance Status (KPS) is less than 70, the prognosis is considered poor and SF is often chosen. Even if the KPS is 80 or higher, SF may be chosen if the patient is awaiting chemotherapy and would like to finish the short period or if the patient lives far away from our hospital and hospital visits are difficult. The primary endpoint was the pain-relieving effects defined by ICE. Discharge or transfer rate at one month after irradiation and postirradiation pathological fracture rate-were the secondary endpoints. This study was approved by our institutional research ethics committee in accordance with the principles of the Declaration of Helsinki (approval number: 20145). Furthermore, written informed consent was not deemed necessary by the ethics committee due to the retrospective and noninvasive nature of this study.

Evaluation of the pain-relieving effect

In this study, we evaluated the pain-relieving effects according to ICE, the response categories are depicted in Table 1 [18]. In addition, responder and non-responder are defined as follows: responder is complete response (CR) or partial response (PR), non-responder is indeterminate response (IR) or pain progression (PP). We compared the number of each response categories in SF and MF groups. The pain scale before and after treatment reflects those described in the medication dates of our hospital. The pain rating was on an 11-point scale from 0–10, with 0 corresponding to no pain and 10 to the worst possible pain, and was self-reported by the patient. Evaluation

Table 1. Response categories

Term	Definition
Complete response	A pain score of 0 at treated site with no concomitant increase in analgesic intake [stable or reducing analgesics in daily oral morphine equivalent (OMED)]
Partial response	Pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or Analgesic reduction of 25% or more from baseline without an increase in pain.
Pain progression	Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline
Indeterminate response	Any response that is not captured by the complete response, partial response, or pain progression definitions

of pretreatment and post-treatment pain scale was performed just prior to starting the irradiation and within a month after the end of irradiation, respectively. Pre- and post-treatment analgesic data were obtained from individual prescriptions and medical data, and morphine equivalents were calculated based on the method proposed by Helena et al. [18].

Factors that could be related to pain

Propensity score matching was used to adjust patients' baseline characteristics and reduce selection bias. All items that could be related to pain were included in the variables [19], including age, sex, primary site, site of lesion, pre-radiation KPS, pain scale and lactate dehydrogenase (LDH), pre-radiation and during or after-radiation use of corticosteroid (within one month), bone resorption inhibitors, non-opioids opioids, and patient status (outpatient or inpatient).

Statistical analysis

The Mann-Whitney U test was used for continuous variables, the chi-square test or Fisher's exact test was used for categorical variables, as applicable. Furthermore, a p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics [20].

Roles of authors

The role of each author is described below. Yuki Aoki's role is manuscript writing, Michihiro Nakayama's role is data analysis, Kaori Nakajima and Masaaki Yamashina's role is patients' management and Atsutaka Okizaki's role is statistical analysis and manuscript editing.

Results

Of the initial 462 patients considered for the study 211 patients were ineligible due to missing pre- and post-radiation pain scale data, missing pre- and post-radiation analgetic drug data and drugs that cannot be converted to morphine were used. Twenty-three patients were excluded due to oligometastases and hematological malignancies in the primary tumor, thirty-three due to fraction dose other than 8 Gy/1 fr or 30 Gy/10 fr (Fig. 1).

The patients' baseline characteristics are summarized in Table 2. The origins of the primary tumors were the lung, breast, prostate, kidney, liver, thyroid, salivary gland, larynx, hypopharynx, esophagus, stomach, gallbladder, pancreas, cholangiocellular, renal pelvic, renal cell, urethra, bladder, colon, rectal, uterine cervix, endometrium, soft tissue, skin, bone, and unknown. Items with significant differences in the distribution of each group were pre-radiation KPS, LDH, use of corticosteroids and use of opioid analgesics.

After adapting propensity score matching, the total number of patients was 74. Our findings revealed no significant difference between the pain-relieving effect and the aligned background factors (Tab. 3). There was no difference in them between SF and MF when using responder and non-responder categorization (Tab. 4). Table 5 demonstrates the discharge or transfer rates at one month after irradiation and postirradiation pathological fracture rate. No significant differences were observed in these parameters.

Discussion

Our findings demonstrate that there was no significant difference in the pain-relieving effect between the SF and MF groups when considering both ICE and propensity score matching. Therefore, we believe that this study will spread awareness regarding the usefulness of SF and encourage clinicians to employ this approach in radiation practice. Furthermore, there were no differences in the discharge or transfer rates and pathological fracture rates. These results are consistent with previous reports.

For instance, Elsbeth et al. prospectively compared the analgesic effects between 24 Gy/6 fr and 8 Gy/1 fr and found no difference between them [10]. The authors used an 11-point scale to evaluate the analgesic effect, and patients with a decrease in the pain scale of at least 2 points before treatment were considered to have an analgesic effect. However, the amount of analgesic medication was not reflected in the evaluation. Similarly, Chow

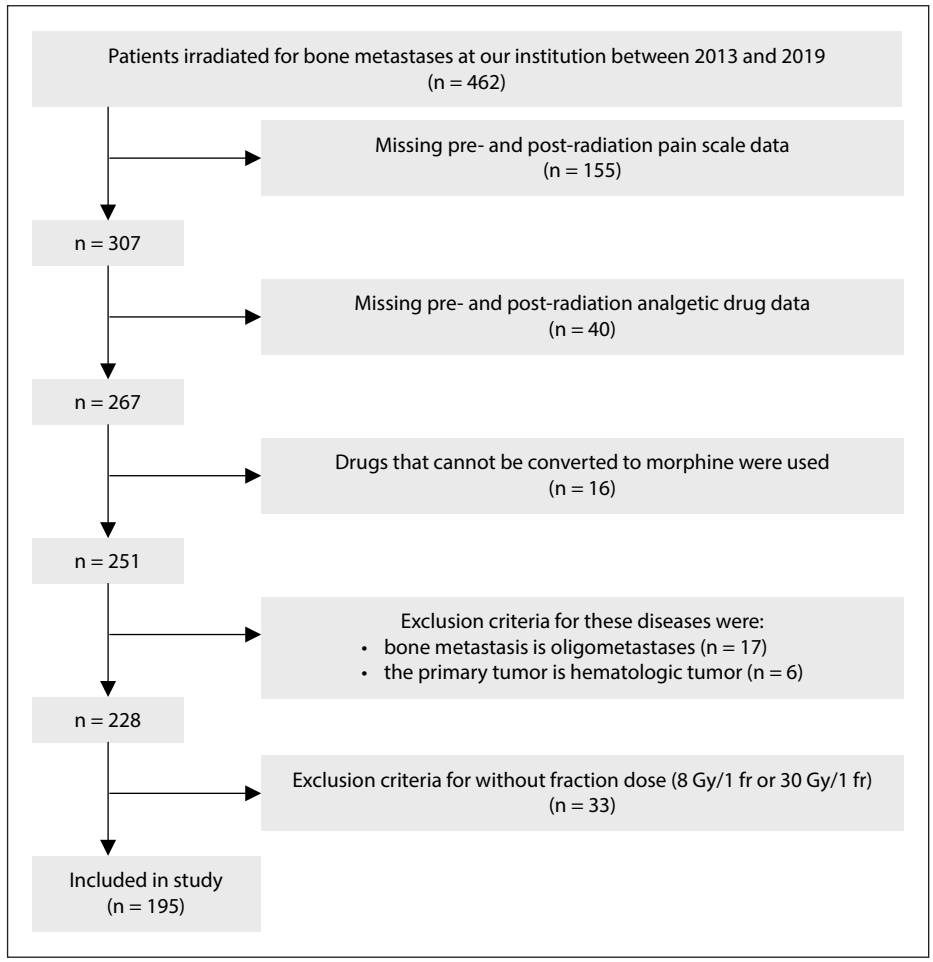

Figure 1. Flowchart of patients' inclusion

et al. [12] performed a meta-analysis of 25 palliative irradiation trials for bone metastases published between 1950 and 2010, and found no difference in pain relief between SF and MF. Filippo et al. [13] performed a meta-analysis of 15 palliative irradiation trials for bone metastases published be-

Table 2. Baseline characteristics of the patients included in this study

Characteristics	Single fraction (%)	Multiple fraction (%)	p-value
Number of patients	61	134	
Age (years)	19–91 (M:70)	32–90 (M:67)	0.258
Sex (male/female)	35 (57.4)/26 (42.6)	68 (50.7)/66 (49.3)	0.441
Fraction dose	8 Gy/1 fr (BED[a]:14.4)	30 Gy/10 fr (BED:39)	
Primary site			
Lung(non small cell)	21 (34.4)	42 (31.3)	0.215
Breast	9 (14.8)	30 (22.4)	
Prostate	5 (8.2)	16 (11.9)	
Kidney	2 (3.3)	6 (4.5)	
Liver	0 (0.0)	5 (3.7)	
Thyroid	0 (0.0)	3 (2.2)	
Other	24 (39.3)	32 (24.0)	

Table 2. Baseline characteristics of the patients included in this study

Characteristics	Single fraction (%)	Multiple fraction (%)	p-value
Site of lesion			
Spine	37 (60.7)	85 (63.4)	0.157
Pelvic bone	17 (27.9)	23 (17.2)	
Limb bones	3 (4.9)	15 (11.2)	
Rib, sternum, clavicle, scapula	4 (6.5)	6 (4.5)	
Skull	0 (0.0)	5 (3.7)	
Pre-radiation KPS			
100	2 (3.3)	12 (9.0)	0.00000488
90	7 (11.5)	47 (35.1)	
80	13 (21.3)	40 (29.9)	
≤ 70	39 (63.9)	35 (26.0)	
Pre-radiation pain scale			
0–3	5 (8.2)	31 (23.1)	0.0395
4–7	32 (52.5)	59 (44.0)	
8–10	24 (30.3)	44 (32.8)	
Pre-radiation LDH [U/L]	150-6644 (M:307)	133-996 (M:224)	0.00125
Pre-radiation use of bisphosphonates			
Yes	4 (6.6)	8 (6.0)	1
No	57 (93.4)	126 (94)	
Pre-radiation use of denosumabs			
Yes	15 (24.6)	20 (14.9)	0.111
No	46 (75.4)	114 (85.1)	
Pre-radiation use of corticosteroids			
Yes	24 (39.3)	22 (16.4)	0.0009
No	37 (60.7)	112 (83.6)	
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Yes	37 (60.7)	65 (48.5)	0.125
No	24 (39.3)	69 (51.5)	
Pre-radiation use of non-opioid analgesics			
Yes	50 (82.0)	109 (81.3)	1
No	11 (18.0)	25 (18.7)	
Pre-radiation use of opioid analgesics			
Yes	39 (63.9)	64 (47.8)	0.0443
No	22 (36.1)	70 (52.2)	
In/out patient			
Inpatient	41 (67.2)	88 (65.7)	0.872
Outpatient	20 (32.8)	46 (34.3)	

[a]α/β was calculated as 10; M — median; fr — fraction; BED — biological equivalent dose; KPS — Karnofsky Performance Status; LDH — lactate dehydrogenase

tween 1986 and 2014, and found that SF provided superior pain relief compared to MF. These studies demonstrate that the pain-relieving effect of SF is equal or greater than that of MF, and ASTRO largely recommends SF considering its cost and QOL [22]. The analysis of responders and non-responders also showed no difference between SF and MF, which is consistent with the analysis published by van der Velden et al. [23] in a prospective cohort of unselected patients with bone metastases.

Consistent with these findings, the present study underlines that SF should not be considered infe-

Table 3. The Results of the pain-relieving effect with the background factors

	CR	PR	IR	Total	p-value
Single fraction	1	14	22	37	0.184
Multiple fraction	4	18	15	37	

CR — complete response; PR — partial response; IR — indeterminate response

Table 4. The results of the responder or non-responder with the background factors aligned

	Responder	Non-responder	Total	p-value
Single fraction	15	22	37	0.163
Multiple fraction	22	15	37	

Note: Responder include complete response (CR) and partial response (PR), non-responder include indeterminate response (IR) and pain progression (PP)

Table 5. Secondary endpoints

	Single fraction		Multiple fraction		p-value
	N	%	N	%	
Number of inpatient	23		21		
Discharge or changing hospital (< 1 M)					
Possible	20	87.0	17	81.0	0.693
Impossible	3	13.0	4	19.0	
Pathological fracture					
Present	0	0.0	1	4.8	1.00
Absent	37	100.0	36	95.2	

M — months

rior to MF. Although the proportion of SF is gradually increasing in clinical practice, it still remains significantly low [8, 14], which may be explained by the fact that 30 Gy/10 fr is still widely and frequently used, perhaps due to the high reirradiation rate after SF irradiation [12].

Pain-relieving effects are critical in palliative irradiation of bone metastases, postirradiation pathological fracture rate is also vital with respect to the quality of life after treatment. Therefore, we set these rates as the secondary endpoint. The results of the present study did not show any significant differences between SF and MF in postirradiation pathological fracture rate

Considering the medical economics, the discharge or transfer rate at one month after irradiation are important factors; therefore, the discharge or transfer rate was set as the secondary endpoint. Our findings did not show any statistical differences between SF and MF.

We excluded hematological tumors from this study due to their extreme radiosensitivity [24]. Additionally, radiation therapists at our institution tend to use single fraction regardless of the underlying condition. We also excluded oligometastases because the clinical state of this metastatic disease includes cases that are irradiated as modified radical treatment rather than palliation [25]. Finally, conversion of abstral and methadone to morphine is very challenging; hence, patients using these drugs were excluded from this study.

Whether the use of corticosteroids has an effect on the pain-relieving effects of radiotherapy is controversial [26–28], therefore, the using or not using of corticosteroids was added as variables in the propensity score matching in this study.

Our study has certain limitation. First, the study was a single-institution retrospective study, and the characteristic of patients in SF and MF groups were not homogeneous. To adjust for the differences in background factors, propensity score matching was used. Second, the study observation period may have been too short to evaluate the events using time series analyses. The design

of this study was to evaluate pain-relieving effects at one month after irradiation. Therefore, only onetime point was analyzed and no time series analysis was performed. We are confident that our findings may encourage clinicians to perform SF in clinical practice. In the future, time series data will be evaluated to further verify the results presented in this study.

Conclusion

The combination of propensity score matching and ICE revealed no significant difference in the pain-relieving effects between SF and MF for bone metastases. Thus, SF has no significant disadvantage compared to MF in pain-relieving effects.

Conflict of interest

The authors have no conflicts of interest directly relevant to the content of this article.

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