

## **Influence of the treatment schedule on the physicians' decisions to refer bone metastases patients for palliative radiotherapy: a questionnaire survey of physicians in various specialties**

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### ABSTRACT

We investigated whether the treatment schedule influences physicians' decisions to refer their patients for radiotherapy. We presented a questionnaire to 104 physicians in various specialties at three hospitals. It included three hypothetical patients with uncomplicated painful bone metastasis: patients with an expected life span of one year (case 1), 6 months (case 2), and 2 months (case 3). The physicians were asked whether they would refer their patients for radiotherapy when a radiation oncologist presented three different treatment schedules: a short (8 Gy/1 fraction/1 day)-, a medium (20 Gy/5 fractions/1 week)-, and a long (30 Gy/10 fractions/2 weeks) schedule. We used Cochran's Q-test to compare the percentage of physicians across the three schedules and a mixed-effect logistic model to identify predictors of the selection of only the one-day schedule. Of the 104 physicians, 68 (65%) responded. Of these, 37 (54%), 27 (40%), and 26 (38%) chose to refer patients for radiotherapy when the short-, medium-, and long schedules, respectively, were proposed in case 1 ( $p = 0.14$ ). These numbers were 44 (65%), 29 (43%), and 15 (22%) for case 2 ( $p < 0.001$ ), and 59 (87%), 12 (18%), and 1 (1%) for case 3 ( $p < 0.001$ ). Hypothetical patient and the physicians' years of practice and perspective regarding side effects were independently predictive of the selection of only the one-day schedule. In conclusion, the treatment schedule influenced the physicians' decisions to refer patients for radiotherapy.

**Key Words:** radiotherapy, bone metastasis, palliative care, pain, questionnaire

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### INTRODUCTION

Radiotherapy (RT) plays a crucial role in palliating the symptoms of bone metastases (BM)<sup>1-3</sup> and in randomized clinical trials, single- and multiple fraction RT was shown to have similar pain-palliating effects.<sup>4,7</sup> However, the under-use of single-fraction RT has been demonstrated.<sup>8-15</sup> This trend is marked in Japan and the United States; in questionnaire studies, radiation oncologists chose single-fraction RT in only 1–15.6% of hypothetical patients.<sup>13,16,17</sup>

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Patient convenience, reduced treatment expenses, and a decrease in the RT department workload were cited as advantages of the single-dose schedule.<sup>18-20</sup> When the patients' expected life span is short or their performance status is poor, longer treatment schedules may be inappropriate.<sup>9,21,22</sup> We wondered whether the burden imposed by delivering RT over the course of a few weeks results in the physicians' reluctance to refer some BM patients for RT. To our knowledge, the influence of the treatment schedule on the physicians' preference for treatment has not been investigated.

In this study, we investigated whether the treatment schedule influences physicians' decisions to refer their patients for RT. In many Japanese hospitals, there are no medical oncologists. Many BM patients are managed by physicians in various specialties and they usually refer patients to radiation oncology for consultation about palliative RT. We invited physicians in specialties other than radiation oncology to participate in a questionnaire survey.

## MATERIALS AND METHODS

### *Questionnaire and respondents*

Three radiation oncologists developed our anonymous questionnaire. It asked the participants to identify their specialty, place of work, years of practice, and experience with palliative RT. It also included seven factors to estimate their expectations from RT (Table 1). Respondents were asked to rate, on a five-point scale, the importance of seven factors for the delivery of palliative RT to BM patients. The questionnaire presented three hypothetical patients with a solitary painful right iliac metastasis (Table 2). Their age, primary BM site, prognosis, pain intensity, and the amount of analgesics were different and no patient was at risk for fracture. Three RT schedules were presented in the questionnaire, i.e. a short (8 Gy/1 fraction/1 day)-, a medium (20 Gy/5 fractions/1 week)-, and a long (30 Gy/10 fractions/2 weeks) schedule and the respondents were asked whether they would refer their patients for RT. They were allowed to select one or more schedules for each patient and they could indicate that they considered none of the schedules appropriate.

The questionnaire was mailed to 104 physicians whose specialty involved the palliation of BM pain. Of these, 77 served at a single university hospital and 12 and 15 at two non-academic general hospitals. To supplement the respondents' potential knowledge deficiencies with respect to palliative RT the three radiation oncologists included a description of the RT dose fractionation in patients with BM in the cover letter (see Appendix). Briefly, it indicated that in patients with uncomplicated BM, the pain-palliating effect of single- and multiple-fraction RT is similar and that the re-treatment rate after single-fraction RT is high, probably because radiation oncologists tend to recommend re-irradiation after single-fraction RT. The questionnaire and cover letter were written in Japanese and translated into English for this manuscript.

### *Data analysis*

We used Cochran's Q-test to compare the percentage of respondents who chose to refer patients for RT across the three schedules for each hypothetical patient. When only the one-day schedule (8 Gy/1 fraction/1 day) but none of the other schedules was selected, we recorded the respondent as considering the patient eligible for RT only if the one-day schedule was presented. To predict the respondents' selection of only the one-day schedule a mixed-effect logistic model was fitted with respondent as a random effect. To identify factors independently associated with the selection of only the one-day schedule we performed multivariate- after univariate analysis using the backward elimination method with a  $p < 0.20$  criterion for retention. A value of  $p <$

## Schedule's impact on physicians' choices

**Table 1** Factors to estimate respondents' expectations from radiotherapy for bone metastasis

Rate the importance of each of factor when you refer patients with bone metastasis to radiation oncology (0 = not important, 5 = most important).			
Factor	Respondents		
		n	%
1. Great reduction of pain	0	0	0
	1	1	2
	2	0	0
	3	7	10
	4	60	88
	Median		4
2. Long duration of pain relief	0	0	0
	1	1	2
	2	4	6
	3	27	40
	4	36	53
	Median		4
3. Prevention of pathological fracture	0	1	2
	1	2	3
	2	9	13
	3	33	49
	4	23	34
	Median		3
4. Prevention of compression of nerves such as spinal cord	0	0	0
	1	2	3
	2	10	15
	3	23	34
	4	33	49
	Median		3
5. Minimization of acute side effects of radiotherapy including dermatitis, diarrhea, and fatigue	0	0	0
	1	4	6
	2	25	37
	3	25	37
	4	14	21
	Median		3
6. Minimization of myelosuppression due to radiotherapy	0	1	2
	1	4	6
	2	37	54
	3	15	22
	4	11	16
	Median		2
7. Shortening of radiotherapy schedule to reduce patient burden	0	0	0
	1	0	0
	2	8	12
	3	35	52
	4	25	37
	Median		3

**Table 2** Hypothetical patients

Check the treatment schedule if you would choose to refer patients for radiotherapy. Assume that all schedules offered by the radiation oncologist provide equal pain relief. More than one schedule can be checked. If you would not refer patients for radiotherapy, do not check any schedule.

Hypothetical patient	Treatment schedule	Respondents who would choose to refer patients for radiotherapy		
		n	%	
Case 1 50 y.o. female; breast cancer; ECOG performance status = 1; expected life span = one year; solitary painful right iliac metastasis with no risk of fracture; NRS <sup>a</sup> = 6; 20 mg oxycodone per day; no pain when in supine position for radiotherapy	8 Gy/1 fraction /1 day	37	54	p=0.14
	20 Gy/5 fractions/1 week	27	40	
	30 Gy/10 fractions/2 weeks	26	38	
Case 2 65 y.o. male; colon cancer; ECOG performance status = 2; expected life span = 6 months; solitary painful right iliac metastasis with no risk of fracture; NRS <sup>a</sup> = 8; 60 mg oxycodone per day; daytime drowsiness associated with opioid use; tolerable pain when in supine position for radiotherapy	8 Gy/1 fraction /1 day	44	65	p<0.001
	20 Gy/5 fractions/1 week	29	43	
	30 Gy/10 fractions/2 weeks	15	22	
Case 3 80 y.o. male; lung cancer; ECOG performance status = 3; expected life span = 2 months; solitary painful right iliac metastasis with no risk of fracture; NRS <sup>a</sup> = 9; 100 mg oxycodone per day; refractory constipation associated with opioid use; opioid rescue dose needed when in supine position for radiotherapy	8 Gy/1 fraction /1 day	59	87	p<0.001
	20 Gy/5 fractions/1 week	12	18	
	30 Gy/10 fractions/2 weeks	1	1	

ECOG, eastern cooperative oncology group; NRS, numeric rating scale.

<sup>a</sup> Pain intensity rated on a scale from 0 to 10.

As the respondents were allowed to select more than one schedule for each hypothetical patient, the sum of the percentages is greater than 100 for each patient. The respondents were allowed to select none of the proposed schedules.

0.05 was considered statistically significant. For Cochran's Q-test and the mixed-effect logistic model we used SPSS version 21 (SPSS, Chicago, IL, USA) and SAS version 9.2 (SAS Institute, Cary, NC, USA), respectively.

## RESULTS

### *Respondents*

The response rate was 65% (68 of 104 physicians). The respondent characteristics are shown in Table 3. The respondents' first and second-most frequent specialties were gastroenterological surgery and pulmonology. Most of the respondents (56/68, 82%) worked at a university hospital. The distribution of the physicians' clinical experience was relatively even; 24% had ≤ 10 years and 29% had ≥ 17 years of experience. The majority of respondents had referred 1–5 BM patients for radiotherapy during the past year.

### *Factors to estimate the respondents' expectations from radiotherapy*

As shown in Table 1, the respondents placed a high priority on the extent of pain reduction

**Table 3** Respondent characteristics

Characteristic	Respondents	
	n	%
Total respondents	68	100
Specialty		
Pulmonology	13	19
Thoracic surgery	4	6
Gastroenterology	7	10
Gastroenterological surgery	14	21
Breast surgery	6	9
Urology	5	7
Gynecology	8	12
Otolaryngology	2	3
Oral and maxillofacial surgery	2	3
Dermatology	2	3
Orthopedics	2	3
Anesthesiology	2	3
Missing	1	1
Place of work		
University hospital	56	82
Non-academic general hospital	12	18
Years in practice		
Median		13.5
Interquartile range		11–17
Range		3–31
No. of patients with bone metastasis referred for radiotherapy in the past year		
0	13	19
1–5	44	65
6–10	6	9
11–	5	7

(median score 4) and the duration of pain relief (median score 4). They also considered important the prevention of pathological fracture (median score 3) and of compression of nerves such as the spinal cord (median score 3), the minimization of acute RT side effects (median score 3), and shortening the RT schedule to reduce the patient burden (median score 3). The minimization of myelosuppression was rated as less important (median score 2).

#### *Hypothetical patients*

Table 2 shows the percentage of respondents who would choose to refer their patients for

RT when different treatment schedules were presented. Because they could select more than one schedule for each hypothetical patient, the sums of the percentages exceeded 100 for each patient. In case 1 there was no statistically significant difference between the percentage of respondents who chose to refer their patients for RT among the three schedules. In cases 2 and 3, significantly more respondents chose to refer their patients for RT when the proposed protocol was shorter ( $p < 0.001$ ); this trend was marked in case 3.

#### *Predictors of the selection of only the one-day schedule*

Table 4 presents the results of the uni- and the multivariate mixed-effect logistic model for predictors of the selection of only the one-day schedule (only the one-day schedule (8 Gy/1 fraction/1 day) but none of the other schedules was selected). For each predictor we assessed 204 answers made by 68 respondents with respect to the three hypothetical patients; 103 of the selections (50%) involved the one-day schedule. Multivariate analysis using the backward elimination method showed that the final model included five predictors, two were the hypothetical patient and the physician's years of practice. The other three factors to estimate the respondents' expectations were the prevention of compression of nerves, minimization of acute side effects of RT, and shortening of RT schedule to reduce patient burden. All but the prevention of compression of nerves were independent factors predictive of the selection of only the one-day schedule.

**Table 4** Predictors of the selection of only the one-day schedule

Predictor	No. of responses <sup>a</sup>	Selection of only the one-day schedule <sup>b</sup>		Univariate mixed-effect logistic model			Multivariate mixed-effect logistic model		
		n	%	Odds ratio			Odds ratio		
				Point estimate	95% CI	p value	Point estimate	95% CI	p value
<b>Hypothetical patient</b>									
1	68	21	31	Reference	–	< 0.001	Reference	–	< 0.001
2	68	28	41	1.90	0.81 to 4.48		2.44	0.88 to 6.78	
3	68	54	79	19.45	7.45 to 50.76		51.75	14.84 to 180.50	
<b>Respondent characteristics</b>									
Specialty									
Pulmonology	39	15	38	Reference	–	0.014			
Gastroenterological surgery	42	13	31	0.68	0.19 to 2.39				
Others	123	75	61	2.68	0.97 to 7.40				
Place of work									
University hospital	168	87	52	Reference	–	0.538			
Non-academic general hospital	36	16	44	0.72	0.26 to 2.05				
Years in practice									
–10	48	23	48	Reference	–	0.052	Reference	–	0.016
11–13	54	25	46	0.94	0.31 to 2.81		0.24	0.037 to 1.53	
14–16	42	14	33	0.52	0.16 to 1.72		0.14	0.019 to 1.03	
17–	60	41	68	2.53	0.85 to 7.54		2.20	0.39 to 12.50	
No. of bone metastasis patients managed with radiotherapy in the past year									
0	39	20	51	Reference	–	0.888			
1–5	132	69	52	1.04	0.36 to 2.99				
6–10	18	8	44	0.75	0.15 to 3.84				
11–	15	6	40	0.59	0.10 to 3.51				

## Schedule's impact on physicians' choices

Factors to estimate respondents' expectations from radiotherapy										
1. Great reduction of pain										
≤ 3	24	10	42	Reference	–	0.482				
4	180	93	52	1.55	0.45 to 5.35					
2. Long duration of pain relief										
≤ 2	15	8	53	Reference	–	0.980				
3	81	41	51	0.88	0.17 to 4.49					
4	108	54	50	0.85	0.17 to 4.20					
3. Prevention of pathological fracture										
≤ 2	36	14	39	Reference	–	0.151				
3	99	46	46	1.41	0.47 to 4.27					
4	69	43	62	2.84	0.88 to 9.17					
4. Prevention of compression of nerves such as spinal cord										
≤ 2	36	17	47	Reference	–	0.946	Reference	–	0.118	
3	69	35	51	1.17	0.36 to 3.82		0.71	0.11 to 4.74		
4	99	51	52	1.21	0.39 to 3.70		0.19	0.026 to 1.29		
5. Minimization of acute side effects										
≤ 2	87	38	44	Reference	–	0.001	Reference	–	0.007	
3	75	30	40	0.84	0.37 to 1.93		0.69	0.17 to 2.86		
4	42	35	83	6.99	2.26 to 21.64		20.75	2.72 to 158.24		
6. Minimization of myelosuppression due to radiotherapy										
≤ 2	126	51	40	Reference	–	0.001				
3	45	23	51	1.59	0.64 to 3.92					
4	33	29	88	11.74	3.18 to 43.33					
7. Shortening of radiotherapy schedule to reduce patient burden										
≤ 2	24	6	25	Reference	–	0.010	Reference	–	0.049	
3	105	47	45	2.60	0.69 to 9.77		10.12	1.05 to 97.64		
4	75	50	67	6.85	1.74 to 27.05		21.17	1.86 to 241.54		

<sup>a</sup> For each predictor there were 204 responses (68 respondents × 3 hypothetical patients).

<sup>b</sup> Respondents checking only the one-day schedule.

Multivariate analysis with backward elimination selection ( $p < 0.20$  for retention) was performed to identify factors independently associated with the selection of only the one-day schedule.

## DISCUSSION

We found that in two of our three hypothetical BM patients (cases 2 and 3) the treatment schedule influenced the respondents' decision to refer their patients for RT. For hypothetical patients with a poorer prognosis and performance status and more intractable pain, the respondents tended to choose the one-day RT schedule. This indicates that in BM patients not considered able to undergo longer-term palliative RT the respondents chose single-fraction RT. Our findings show that the more frequent offer of a short RT schedule by radiation oncologists may influence the RT referral among physicians with various specialties. Because RT is an effective treatment which has a unique mechanism of action in pain-palliation,<sup>23-25)</sup> its increased use will contribute to better patient care.

In our study, the hypothetical patient, the respondents' years in practice, their perception of RT side effects, and the burden imposed on patients were independent factors predictive of the selection of only the one-day RT schedule. The schedule's influence on the physicians' choices of treatment probably depends on the patients' characteristics. We are not sure why many physicians with long experience ( $\geq 17$  years) chose only the one-day schedule. Experienced physicians may perhaps know various treatment options for pain relief and prefer these options to long-term palliative RT. With respect to the influence of the physicians' expectations, respondents who placed a high priority on the minimization of acute side effects tended to select only the one-day schedule. This may reflect their thinking that a lower total radiation dose elicits fewer side effects. However, a systematic review of randomized controlled trials in patients with BM revealed no statistically significant difference in the acute toxicity of single- and multiple-fraction RT.<sup>7)</sup>

Most earlier questionnaire studies on palliative RT solicited the opinion of radiation oncologists,<sup>12-16,19)</sup> although a few assessed the treatment preferences of physicians in specialties other than radiation oncology.<sup>26-28)</sup> Many BM patients are managed by physicians in various specialties<sup>26)</sup> and they usually refer patients to radiation oncology for consultation about palliative RT.<sup>27)</sup> Information on single-fraction treatment must be promulgated to increase the opportunity for patients to receive palliative RT.

In the present study we presented three hypothetical patients with differences in their prognosis, performance status, pain intensity, analgesics, and the adverse effects of opioids. Other factors include the need for hospitalization,<sup>29,30)</sup> the travel distance to the hospital,<sup>31,32)</sup> and the wait at the facility delivering RT.<sup>19,33,34)</sup> Further studies are warranted to examine the effects of these factors on the delivery of palliative RT.

Our study has some limitations. The number of participating physicians was small. Also, as data were collected from only three institutions and many of the respondents worked at the same hospital, generalization is limited. Consequently, our findings must be confirmed. Description of the RT dose fractionation in patients with BM was mailed as a cover letter with the questionnaire. It indicated that for patients with a poor prognosis, single-fraction RT is recommended. This could have influenced the respondents' choices particularly for Case 3. The cover letter was necessary because the study was designed to investigate the treatment preferences of physicians in specialties other than radiation oncology.

In summary, our study on hypothetical patients showed that the treatment schedule affected the physicians' decision to refer their patients for palliative RT. For patients with a poor prognosis and performance status, many respondents chose to refer patients for RT only when the one-day schedule was presented. Our findings shed new light on the delivery of single- vs. multiple fractions in the treatment of BM pain by palliative RT and our study bears repeating at different facilities and in different countries.

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#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.



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#### Appendix. Description of the Radiotherapy Dose Fractionation in Patients with Bone Metastasis

When providing radiotherapy (RT) to patients with bone metastasis without fracture or spinal cord compression, the pain-palliating effect of irradiation with 8 Gy in a single fraction, 30 Gy in 10 fractions, and 20 Gy in five fractions is similar. The time to pain progression, the quality of life, and acute and late adverse effects are also similar in patients receiving single- or multiple-fraction RT. According to earlier studies, spinal cord compression tended to occur less frequently when RT was delivered in multiple- rather than single fractions although the difference was not statistically significant. With respect to pathological fracture there was no trend favoring multiple fractions. In patients with neuropathic pain the palliative effect of single-fraction RT may be inferior to multiple-fraction RT. The retreatment rate after single-fraction RT is high, probably because radiation oncologists tend to offer re-irradiation after single-fraction treatment. For patients with a poor prognosis, single-fraction RT is recommended because the treatment schedule is shorter. In patients with a good prognosis, there are no data supporting the use of multiple-fraction RT, except in patients with the risk for spinal cord compression or neuropathic pain.