Practice Patterns for Postoperative Radiation Therapy in Patients with Metastases to the Long Bones: Survey of the Japanese Radiation Oncology Study Group

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Abstract

Background

Because of the lack of evidence on practice patterns of postoperative radiation therapy (PORT)in patients with metastases to the long bones, it is essential to characterize the current practice patterns and identify factors affecting dose-fractionation to aid future clinical trials.

Methods

The palliative radiation therapy subgroup of the Japanese Radiation Oncology Study Group conducted an internet-based survey to determine the prescription practices and various dose-fractionations used for PORT. Additionally, responders were asked to recommend dose-fractionations in four hypothetical cancer cases, wherein each case represented a patient with impending pathological fractures and one of the four features: limited prognosis, solitary metastasis, radio-resistant primary tumor, or long-term survival. Responders were asked to indicate their preferred irradiation fields and the reasons for choosing long-course radiotherapy over short-course radiotherapy (RT).

Results

Eighty-nine radiation oncologists from 67 institutions and 151 RT plans were included. Twenty-two different dose-fractionations were used; the most commonly used and recommended dose-fractionation was 30 Gy in 10 fractions. “Local control” was most the common reason for preferring longer course RT. While fractionated higher-dose regimens were preferred in case of oligometastasis, low dose regimens were preferred in case of limited prognosis; single fraction RT was never preferred. Most respondents recommended involvement of “the entire orthopedic prosthesis.”

Conclusion

For PORT of metastases to the long bones, 30 Gy in 10 fractions for the entire orthopedic prosthesis is preferred in current practice. Oligometastasis and a limited prognosis influence the selection of high- and low-dose regimens, respectively. Single fraction RT is never preferred.

Background

Bone metastases (BMs) are a frequent complication of cancer [1–3], and cause variable symptoms such as pain, pathologic fractures, and spinal cord compression. These symptoms negatively affect the patient's quality of life (QOL) and diminish performance status (PS). Radiation therapy (RT) is recognized as a highly effective standard therapy for BMs providing pain relief in approximately 60–80% patients as per the evidence from randomized trials [4], with slightly lower response rates (55%) as per the real-world evidence [5].

BMs of the long bones can result in pathologic fractures. Surgical interventions are often required to stabilize the long bones with impending or existing pathological fractures, which may provide pain relief as well as restore functional status [6]. In general, one of the following surgical strategies is commonly used: endoprosthetic reconstruction or internal fixation with either intramedullary nailing or plate/screw fixation devices. Indication of postoperative RT (PORT) after endoprosthetic reconstruction is equivocal because it has been reported to cause prevention of new bone formation in case of proximal femur metastasis [7]. Meanwhile, PORT for metastases to the long bones is commonly practiced, and a few retrospective studies have reported that it lessens pain, improves functional status, decreases re-operation, and slows down further local progression of metastases [8–11]. Further, these studies proposed PORT as one of the effective treatment options. However, the optimal dose-fractionation as well as irradiation fields of PORT have not been reported.

Further, due to the lack of clear evidence, clinical trials of PORT for indication of metastases to the long bones would be essential in the future. While conducting a clinical trial, it is important to understand the radiation oncologists' decision-making patterns and the existing standards of care. To our knowledge, no previous studies have focused on these practice patterns in the PORT for indication of metastases to the long bones.

Thus, the purpose of this study was to characterize the current practice patterns in the PORT for indication of metastases to the long bones and to identify factors that affect the dose-fractionation.

Methods

Palliative radiation therapy subgroup of the Japanese Radiation Oncology Study Group (JROSG) conducted an internet-based survey among the members of JROSG who are practicing radiation oncologists. The respondents were asked to provide their name, institution, and years of experience in radiation oncology practice as well as the frequency of performing PORT in each institution for the indication of metastases to the long bones in 2017 along with the actual administered dose-fractionation. They were also asked for the dose-fractionation they would recommend in each of the four hypothetical cancer cases provided in the study.

The hypothetical cases described impending pathological fractures in the lower limb due to BM, but differed in factors such as nature of malignancy, number of metastases and survival (Table 1). While Case 1 (relatively limited survival) described a case with impending pathological fractures in the lower limb from non-small cell lung cancer with multiple metastases, Case 2 (presence of oligometastasis) investigated whether management for a case of solitary BM would be different from that of Case 1. Case 3 (presence of radio-resistant primary tumor) was identical with Case 2 except for the radio-resistant primary tumor: renal cell carcinoma (RCC). Case 4 (expectation of long survival) involved a patient with BM from breast cancer who was expected to survive longer. Additionally, radiation oncologists who did not recommend short-course RT (e.g., 8 Gy in 1 fraction or 20 Gy in 5 fractions) for Case 1 were asked to explain why they considered long-course RT to be superior to short-course RT.

Table 1
Hypothetical cases

Case 1	**Patients with relatively limited survival**
	65-year-old man with squamous cell lung cancer had been treated by radical surgery 1 year earlier. Patient had right femoral pain, and examination shows lytic BM in right femoral bone, multiple lung mets and right adrenal met. Internal fixation was performed for right femoral BMs due to the impending fracture. He now has a little pain. His ECOG PS is 1.
Case 2	Patient with oligometastasis
	65-year-old man with squamous cell lung cancer had been treated by radical surgery 1 year earlier. Patient had right femoral pain, and examination shows solitary lytic BM in right femoral bone. Internal fixation was performed for right femoral BM due to the impending fracture. He now has a little pain. His ECOG PS is 1.
Case 3	Patient with the radio-resistant primary tumor
	65-year-old man with renal cell carcinoma had been treated by radical surgery 1 year earlier. Patient had right femoral pain, and examination shows lytic BM in right femoral bone and multiple lung. Internal fixation was performed for right femoral BM due to the impending fracture. He now has a little pain. His ECOG PS is 1.
Case4	Patient with expected long survival
	50-year-old woman had right femoral pain. Examination showed left breast tumor and multiple lytic lesions including right femoral bone. She was diagnosed as breast cancer (ER positive/PR positive/Her-2 negative/Ki-67 5%) and multiple BMs. Internal fixation was performed for right femoral BM due to the impending fracture. She now has a little pain. Her ECOG PS is 2.

For analysis, the actual prescribed dose-fractionation as well as the recommended dose-fractionation for the four hypothetical cases were classified into following five categories: “single fraction”, “fractionated low dose”, “30 Gy in 10 fr”, “fractionated intermediate dose”, and “fractionated high dose” as per the biologically effective dose (BED10) (Table 2). “Single fraction” included 14.4 Gy (BED10), “fractionated low dose” included ≥ 22.5 Gy and ≤ 37.5 Gy (BED10), “30 Gy in 10 fr” included 39 Gy (BED10), “fractionated intermediate dose” included ≥ 39.2 Gy and ≤ 59.5 Gy (BED10), and “fractionated high dose” included ≥ 60 Gy (BED10).

Table 2
Classification of dose-fractionations prescribed dose-fractionation used in each institution and recommended for hypothetical cases

Total dose (Gy)	No. of fractions	Dose per fraction (Gy)	BED10
Single fraction			
8	1	8	14.4
Fractionated low dose			
15	3	5	22.5
20	5	4	28
20	4	5	30
24	6	4	33.6
25	5	5	37.5
30 Gy in 10 fractions			
30	10	3	39
Fractionated intermediate dose			
28	7	4	39.2
24	3	8	43.2
36	12	3	46.8
37.5	15	2.5	46.88
30	5	6	48
40	16	2.5	50
39	13	3	50.7
42	14	3	54.6
40	10	4	56
45	18	2.5	56.25
45	15	3	58.5
35	5	7	59.5
Fractionated high dose			
50	25	2	60
48	12	4	67.2

Total dose (Gy)	No. of fractions	Dose per fraction (Gy)	BED10
60	30	2	72
50	10	5	75
60	24	2.5	75
65	25	2.6	81.9

In addition, we asked all respondents which irradiation field was recommended out of the following three options: “the range where tumors existed preoperatively,” “the entire orthopedic prosthesis,” or “the entire affected bone.”

Results

Eighty-nine radiation oncologists from 67 institutions (50% of JROSG participating facilities) responded. The study responders’ median experience in radiation oncology was 20 years (range; 2.5–40 years). Of all the RT plans used at these institutions in 2017, 152 were eligible for this study. Except for the one RT plan with an unknown prescribed dose-fractionation, the rest 151 were enrolled in the study. There were 21 different dose-fractionation regimens ranging from 8 Gy in one fraction to 65 Gy in 25 fractions in these 151 RT plans (Supplemental table 1). Among the five classified categories of those dose-fractionation regimens, the most commonly actual used dose-fractionation was 30 Gy in 10 fractions (n = 75; 50%), followed by fractionated low dose (Fig. 1). The commonest dose-fractionation in fractionated low dose was 20 Gy in five fractions (n = 29; 19%). Single-fractioned RT was prescribed only in 3% of cases (n = 4), whereas the remaining 97% patients (n = 147) received fractioned RT.

For the four hypothetical cases, 15 different dose-fractionations were recommended by study responders, ranging from 8 Gy in one fraction to 60 Gy in 30 fractions (Supplemental table 2). For all the four cases, the most common recommended dose-fractionation was 30 Gy in 10 fractions (Fig. 2). For case 1, fractionated low dose regimens were recommended only by 17 respondents (19%). Sixty-eight respondents (76%) did not recommend short course RT (e.g., 8 Gy in 1 fraction or 20 Gy in 5 fractions) for Case 1. Figure 3 summarizes the reasons why these respondents regarded longer course RT more than 20 Gy in 5 fractions as superior to short course RT for Case 1. “Local control”was the most often cited reason (n = 37; 54%), followed by “incidence of re-irradiation” (n = 23; 34%), and “time until first increase in pain” (n = 13; 19%). Fractionated dose regimens more than 30 Gy in 10 fractions were relatively recommended in case of oligometastasis (n = 47; 53%), compared to those with radio-resistant tumors (n = 30; 34%) and those with expected long-term prognosis (n = 22; 25%). Fractionated intermediate dose regimens were recommended for oligometastasis (Case 2) or radio-resistant primary tumor (Case 3) in comparison with other cases. Especially, fractionated high dose regimens were recommended for oligometastasis (n = 11; 12%), while none of the respondents recommended high dose per fraction for radio-resistant primary tumor. Fifty-nine respondents (66%) recommended 30 Gy in 10 fractions for expected long survival (Case 4), which was similar with comparatively limited survival (Case 1) (n = 60;

67%). The irradiation field recommended for PORT by the majority of responders was “the entire orthopedic prosthesis” (n = 66; 74%), followed by “the range where tumors existed preoperatively” (n = 9; 10%) and “the entire affected bone” (n = 8; 9%) (Fig. 4).

Discussion

The results of this study show that 30 Gy in 10 fractions has been most commonly used for PORT of metastases to the long bones in current practice in Japan. Half of the RT plans irradiated at JROSG institutes were prescribed 30 Gy in 10 fractions. In addition, the majority of the respondents also recommended this regimen in hypothetical cases (67% for Case 1, 45% for Case 2, 53% for Case 3, and 66% for Case 4). Our results are similar to those reported by previous retrospective studies about PORT for metastases to the long bones [8–11]. In most of these studies fractioned RT, such as 30 Gy in 10 fractions or 20 Gy in 5 fractions, ranging from 8 Gy to 56 Gy was used. In addition, as per the American College of Radiology (ACR) Appropriateness Criteria for Non-Spine BMs [12], which is based on multidisciplinary expert opinion, while there are no definitive data to suggest the most appropriate radiotherapy dose, 30 Gy in 10 fractions seems to be a reasonable option with the goal of eradicating microscopic residual disease. In the expert opinion, 8 Gy in 1 fraction to 35 Gy in 14 fractions are also equally appropriate.

Among the hypothetical cases, case 2 that described a single oligometastasis of non-small-cell lung cancer in the long bone, was mostly recommended for higher dose regimens (fractionated intermediate dose regimens: 40% or fractionated high dose regimens: 12%) in comparison to other hypothetical cases. Recently, SAbR-COMET study [13] showed that stereotactic body radiotherapy (SBRT) for oligometastasis provided a survival benefit (standard of care alone vs. SBRT arm; 28 vs. 41 months of median overall survival). Another previous study [14] has shown that high dose prescription by SBRT yields high rates of great local control of greater than 85% for non-spine BMs. Thus, the higher dose PORT regimens might also lead to good local control as well as survival benefit in case of oligometastasis.

Case 3

in our study was identical with Case 1 except for the radio-resistant primary tumor. In current study, none of the respondents recommended high-dose-per-fraction (greater than 5 Gy) for Case 3. Although RCC is traditionally reported to be radio-resistant to RT [15], it has been previously reported that high-dose-per-fraction RT could overcome this relative radio-resistance in RCC [16]. Similar findings for melanoma, also considered as a radio-resistant primary tumor, have also been reported [17]. However, Rades et al reported escalation of the radiation dose beyond 30 Gy in 10 fractions did not significantly improve motor function and local control of metastatic spinal cord compression in case of radio-resistant tumors including renal cell carcinoma, colorectal cancer, and malignant melanoma [18]. Therefore, whether to escalate radiation dose for radio-resistant primary tumors in a palliative care setting remains unclear.

Case 4

in our study described a patient with expected long-term survival. Sixty-six percent of respondents recommended 30 Gy in 10 fractions for Case 4, which were similar to recommendations for Case 1 with comparatively limited survival (67%). Fractioned intermediate dose or high dose was recommended by 24% of the respondents, which was higher than that recommended for Case 1 with limited survival (9%). However, according to the data reported for pain relief of bone metastases for 320 patients with painful BM surviving > 52 weeks, Van der Linden et al. reported that the responses were similar in both single and multiple fraction schedules (87% after 8 Gy, and 85% after 24 Gy) [19]. Single fraction schedule is the standard palliative treatment for all patients with painful bone metastases, including patients with an expected favorable prognosis [19]. However, the research on optimal dose fractionation in the PORT setting should also be conducted in patients with an expected favorable prognosis.

Three-quarters of respondents recommended “the entire orthopedic prosthesis” for irradiation fields during PORT. Two retrospective studies about PORT for long bones mention about irradiation fields; Townsend et al. reported that 21 out of 25 fields (84%) included the entire orthopedic prosthesis [8], and Drost et al. reported that 72 out of 74 fields (97.3%) included the entire orthopedic prosthesis [10]. It is thus common in practice to include at least the entire orthopedic prosthesis.

Although the objective of the PORT for long bones is not clear, Townsend et al. and Adamietz et al. retrospectively reported the efficacy of PORT based on the functional status of the extremities [8, 11]. Other potential objective is to reduce local progression and prevent prosthesis displacement, hence reducing the need for second surgery [10]. Our study also suggests that many Japanese radiation oncologists (54%) considered that long-course RT was preferred in PORT for the long bones due to better “local control.” However, in the palliative setting, the primary object of palliative RT is not mainly local control but benefits such as improved QOL, reduction in symptoms, and overall survival. For example, Rades et al reported on 265 patients treated with RT for metastatic spinal cord compression that 1-year local control was significantly better in long-course RT compared with short-course RT, while short-course RT and long-course RT had no significant difference with respect to the effect of RT on motor function [20].

The biggest limitation of the present study was the lack of clinical follow-up data. Especially, recommendations for hypothetical cases might not truly reflect clinical management. However, understanding the patterns of practices will be important for future clinical trials. Because there is no clear evidence for the efficacy or optimal dose-fractionation of PORT for the indication of BMs of the long bones, clinical trials to examine the efficacy or optimal dose-fractionation of PORT would be necessary in the future.

Conclusion

We found that 30 Gy in 10 fractions for the entire orthopedic prosthesis was preferred in current practice in Japan. Based primarily on local control of the tumor, most Japanease radiation oncologists regard long course RT as superior to short course RT. Fractioned high dose regimens may be preferred for the indication of oligometastasis, and fractioned low dose regimens may be preferred for cases with limited survival. Single fraction RT was not preferred in this palliative setting. These results will be important to future clinical trials of PORT for the indication of metastases to the long bones. Because of the lack of evidence, research should be performed to evaluate whether PORT has a beneficial palliative effect, and to identify the optimal dose-fractionation for PORT.

Declarations

Ethics approval and consent to participate:

All respondents consented to participate in this survey.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests: Dr. Harada received grants from Japanese Radiation Oncology Study Group; personal fees from AstraZeneca and BrainLab, outside the submitted work. Dr. Tago received grants from Bayer Yakuhin, Ltd., Daiichi Sankyo Company, Ltd. and Eisai Co., Ltd., outside the submitted work. For the remaining authors none were declared.

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Authors' contributions:HK and NN designed this survey and made major contributions in collecting and analyzing the data and writing the manuscript. NS was a major contributor in writing the manuscript. HH, HN, JH, TK and TS made contributions in creating the questionnaires. AT, HW, KI, MN, MT, MF, NU, NA, SS, TT and KY collaborated in the discussion. All authors read and approved the final manuscript.

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Figures

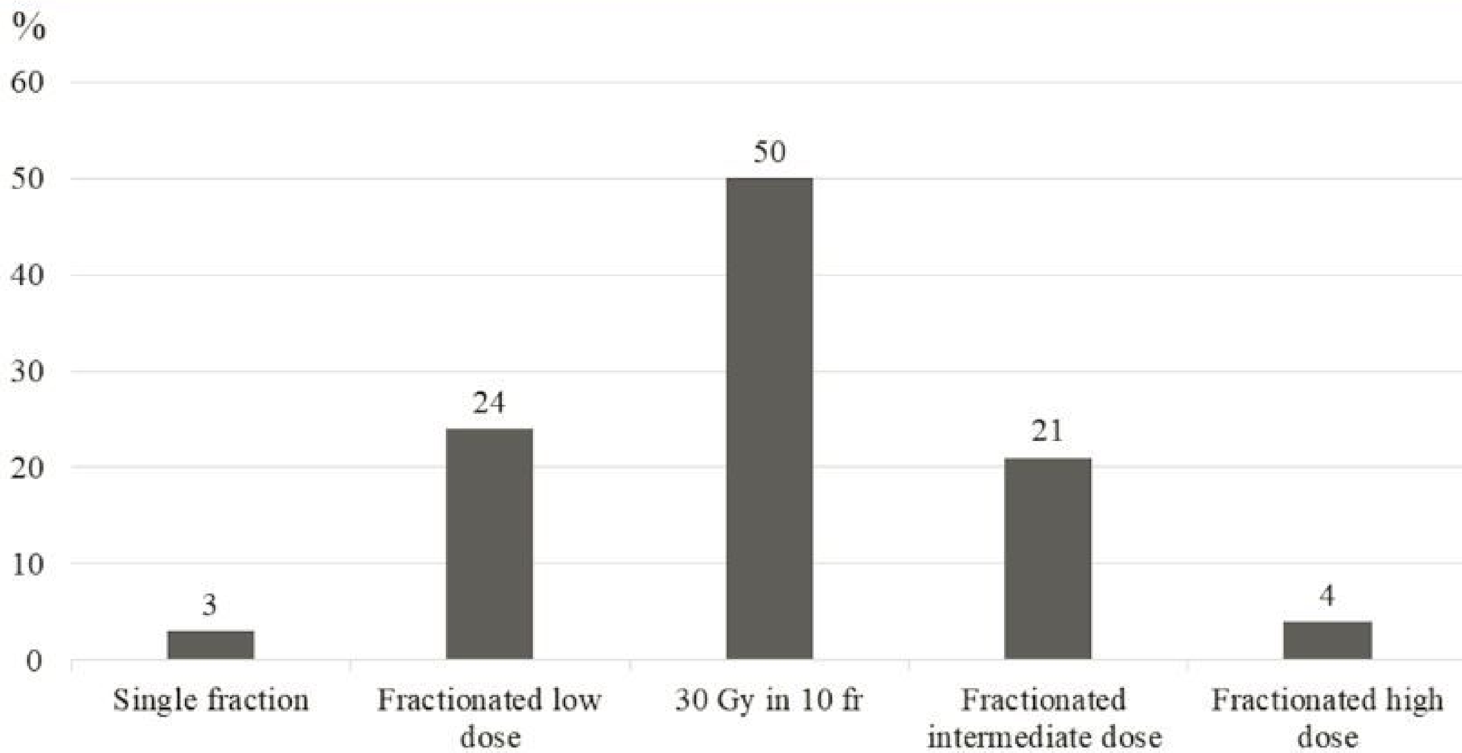

Figure 1

Dose-fractionation regimens used at the Japanese Radiation Oncology Study Group institutions Details of categories: “single fraction” includes 14.4 Gy (BED10), “fractionated low dose” includes ≥ 22.5 Gy and ≤ 37.5 Gy, “30 Gy in 10 fr” includes 39 Gy (BED10), “fractionated intermediate dose” includes ≥ 39.2 Gy and ≤ 59.5 Gy, and “fractionated high dose” includes ≥ 60 Gy.

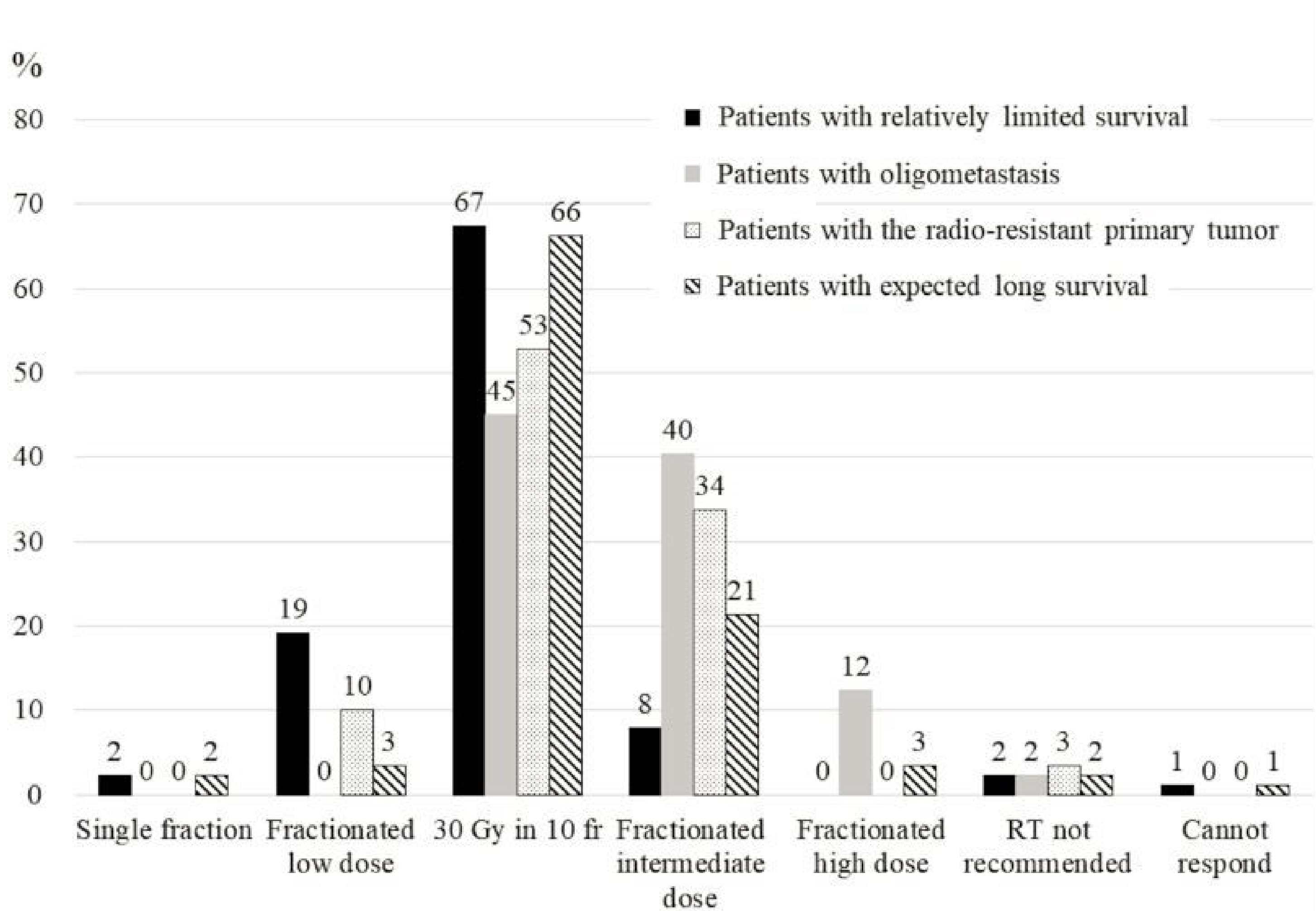

Figure 2

Dose-fractionation regimens recommended for hypothetical cases. The black bar represents the case 1 (relatively limited survival), the gray bar represents the case 2 (presence of oligometastasis), the dot pattern bar represents the case 3 (radio-resistant primary tumor), and the hatched pattern bar represents the case 4 (expected long survival). Details of categories: “single fraction” includes 14.4 Gy (BED10), “fractionated low dose” includes ≥ 22.5 Gy and ≤ 37.5 Gy, “30 Gy in 10 fr” includes 39 Gy (BED10), “fractionated intermediate dose” includes ≥ 39.2 Gy and ≤ 59.5 Gy, and “fractionated high dose” includes ≥ 60 Gy.

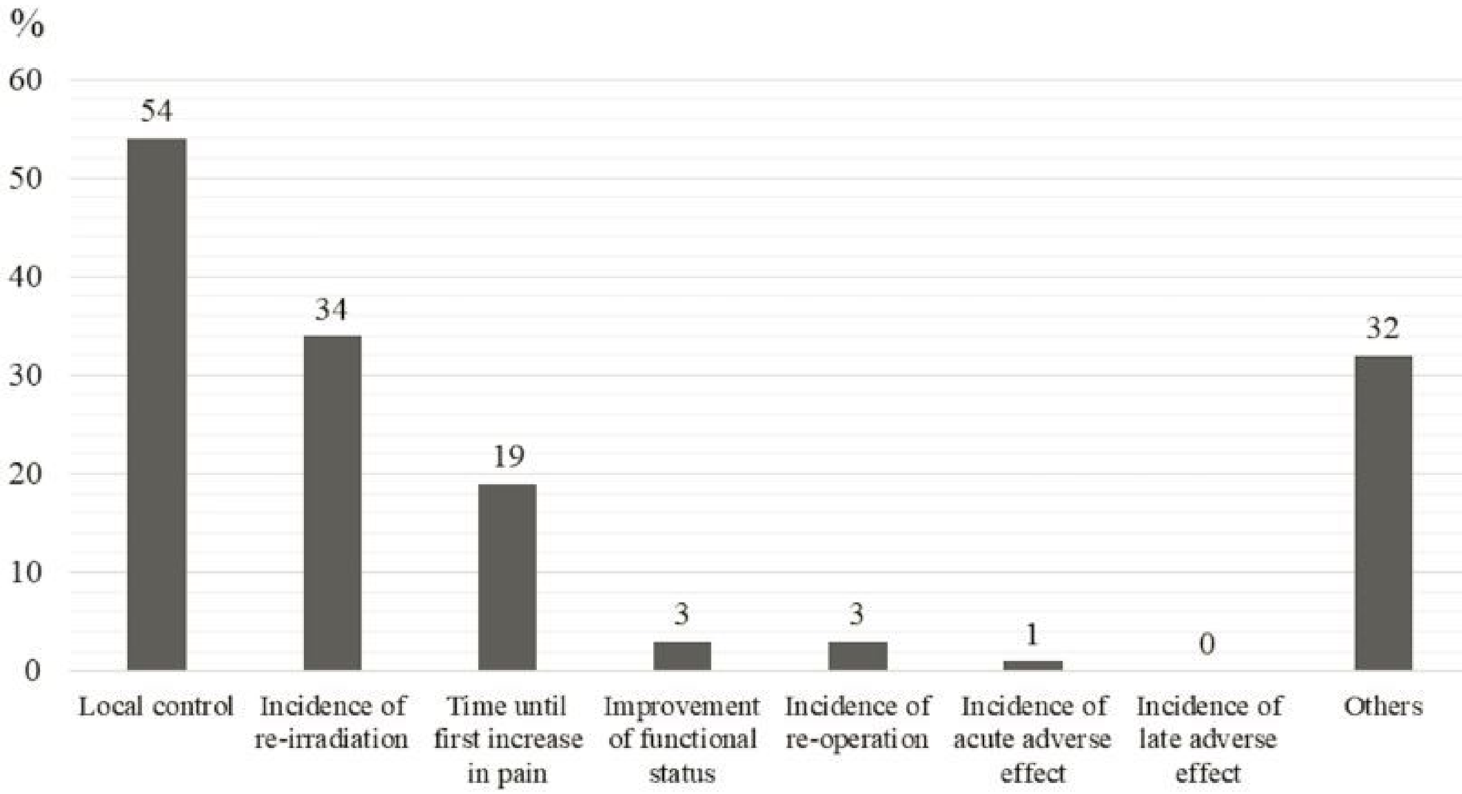

Figure 3

Respondents' reasons for not recommending short course RT for Hypothetical Case 1 Multiple choices were allowed in this question. Sixty-eight respondents recommended long course RT for Case 1.

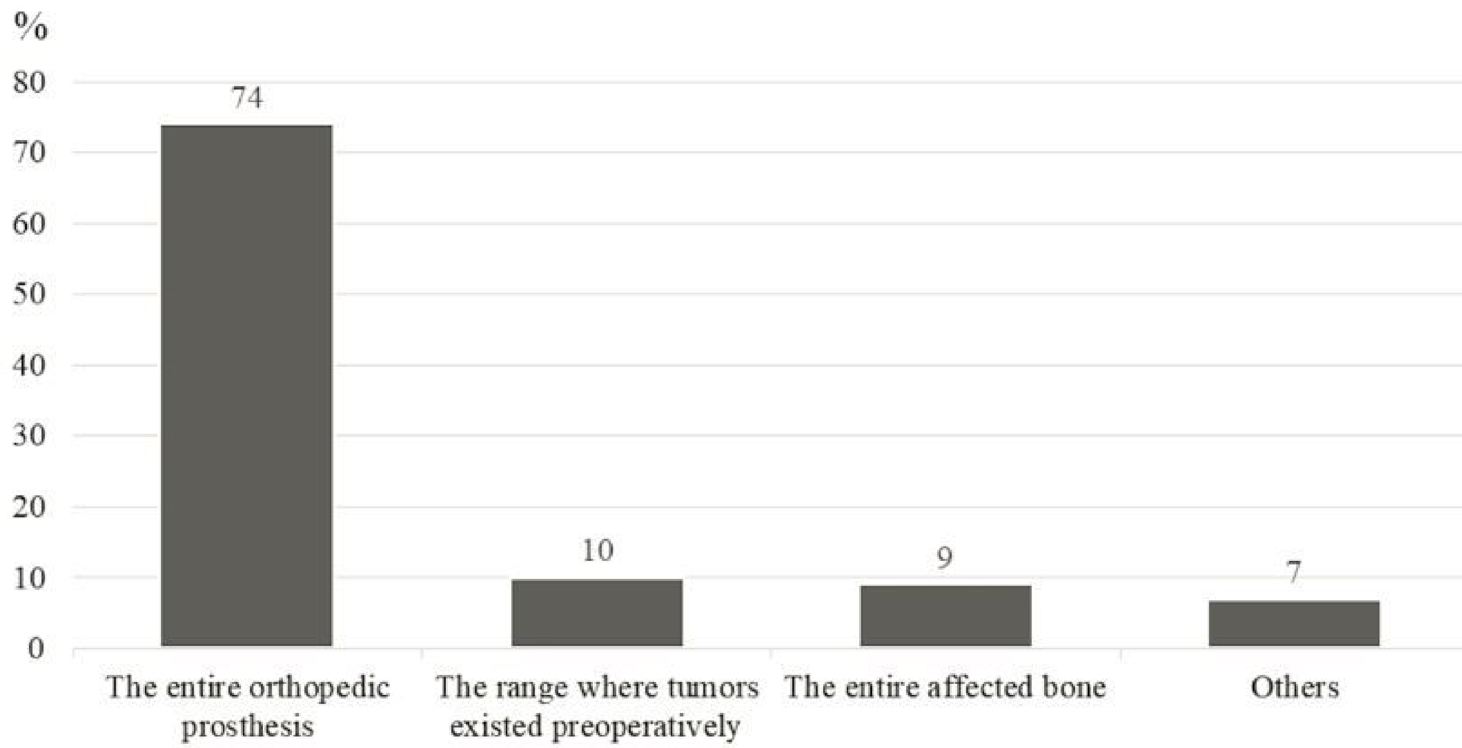

Figure 4

Recommended irradiation field for PORT

Supplementary Files

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- radiationoncologySupplementaltable2.docx
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