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National survey of radiation oncologists' practice patterns regarding hormone-naïve prostate cancer with bone metastases

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Abstract

Objective: To explore radiation oncologists' attitudes and practice patterns of radiotherapy for hormone-naïve prostate cancer with bone metastases in Japan.

Methods: An internet-based survey was distributed to board-certified radiation oncologists of the Japanese Society of Radiation Oncology. Three hypothetical cases were assumed: hormone-naïve prostate cancer with single, three or multiple non-symptomatic bone metastases. The respondents described their attitude regarding such cases, treatment methods and the radiotherapy dose fractionation that they would recommend.

Results: Among the 1013 board-certified radiation oncologists in Japan, 373 (36.8%) responded to the questionnaire. Most of the respondents (85.0%) believed that radiotherapy may be applicable as a primary treatment for hormone-naïve prostate cancer with bone metastases in some circumstances. For Case 1 (single bone metastasis), 55.0% of the respondents recommended radiotherapy for the prostate and bone metastasis. For Case 2 (three bone metastases), only 24.4% recommended radiotherapy for all lesions, and 31.4% recommended radiotherapy for the prostate only. For Case 3 (multiple bone metastases), 49.1% of the respondents stated that there was no indication for radiotherapy. However, 34% of the respondents still preferred to administer radiotherapy for the prostate. The radiotherapy techniques and dose fractionations varied widely among the respondents.

Conclusion: Most of the respondent radiation oncologists believed that radiotherapy may be beneficial for hormone-naïve prostate cancer with bone metastases.

Key words: radiotherapy, prostate cancer, metastasis, neoplasm metastasis

Introduction

In the treatment of prostate cancer with bone metastases (bmPCa), radiotherapy has traditionally been used only for palliation, but several recent studies have reported the possibility of improving the prognosis of patients with oligometastatic prostate cancer by treating all lesions with radiotherapy (1,2). There is also evidence indicating that the addition of local therapy such as surgery or radiotherapy to systemic therapy may improve the prognosis (3,4). Recent randomized trials compared systemic therapy versus systemic therapy plus local radiotherapy in patients with hormone-sensitive metastatic prostate cancer (5,6), and although radiotherapy to the prostate did not improve the patients' overall survival, local radiotherapy tended to improve the survival of the patients with low-volume metastases (7). The role of radiotherapy administered to the primary tumor and/or sites of oligometastases for patients with hormone-sensitive bmPCa has been discussed, and clinical trials have examined the efficacy of radiotherapy for patients' metastatic prostate cancer (8,9).

However, it is unclear how radiotherapy is actually applied in clinical settings for patients with bmPCa (10). To our knowledge, no previous surveys have focused on the attitude of radiation oncologists regarding the treatment of bmPCa. In the present study, we distributed a questionnaire survey about the use of radiotherapy for bmPCa to board-certified radiation oncologists in Japan to investigate their current patterns of practice and their attitudes about radiotherapy for bmPCa.

Materials and methods

The national survey was designed and conducted by the Urologic Oncology Group of the Japanese Radiation Oncology Study Group, and the survey was approved by the Japanese Society of Radiation Oncology. An e-mail notifying recipients about this internet-based survey on radiotherapy for bmPCa was sent to 1013 Japanese board-certified radiation oncologists on 12 December 2017. The survey's questions included whether the respondent would recommend radiotherapy aiming at the improvement of the prognosis of patients with bmPCa, whether the respondent had treated patients with bmPCa by using radiotherapy with radical intent in the past and how radiotherapy would be given to three hypothetical cases. All three of the hypothetical cases were uncomplicated cases of 60-year-old patients with hormone-sensitive primary bmPCa.

We hypothesized that bone metastases were osteoblastic, with the absence of mass formation, pain and the fear of spinal cord compression. There were also no visceral or lymph node metastases. Case 1 had a single bone metastasis. Case 2 had three bone metastases. Case 3 had multiple bone metastases (Fig. 1). The survey asked the following: when the prostate-specific antigen (PSA) value of the hypothetical patients tended to decline after the start of hormonal therapy, how and where would the respondent administer radiotherapy, on the condition that ideal treatment techniques can be used without any limitation from the medical insurance system.

The survey was closed on 9 January 9 2018, and 372 radiation oncologists responded (36.7% of all board-certified radiation oncologists in Japan). To compare the different dose fractionation schedules, we calculated the biologically effective dose (BED) based on the linear-quadratic formula using an α/β ratio of 1.5 Gy for a tumor.

Results

The respondents included 55 radiation oncologists (14.8%) with 1–4.9 years of experience as a radiation oncologist after board certification, 70 radiation oncologists (18.8%) with 5–9.9 years, 151 (40.6%) with 10–19.9 years and 96 (25.8%) with ≥20 years. For the question of whether external beam radiotherapy or brachytherapy (not including radium-223) has the ability to improve the overall survival of bmPCa patients, 317 of the 372 respondents (85.2%) responded that radiotherapy might improve survival in some circumstances, and 20 (5.4%) responded that radiotherapy did not contribute to the improvement in prognosis. Thirty-five respondents (9.4%) replied that they did not know or were unable to answer this question. Interestingly, slightly lower percentage of radiation oncologists with 1–4.9 years of experience responded that radiotherapy might improve survival, than those with 5–9.9 years, 10–19.9 years or ≥20 years of experience (80.0% versus 88.6, 86.1, 84.4%, respectively), because radiation oncologists with 1–4.9 years of experience tended to reply that they were unable to answer this question compared with those with longer experiences (12.7% versus 5.7, 7.9, 8.3%, respectively).

For the question of whether the respondent had any experience(s) in which radiotherapy with radical intent had been applied for bmPCa, 252 radiation oncologists (67.7%) answered Yes, 100 (26.9%) answered No and 20 (5.4%) replied that they did not know or were unable to answer.

The recommended treatment strategies of radiotherapy for Cases 1–3 are shown in Table 1. The respondents' responses regarding the dose per fraction and the total BED to the prostate and/or bone (when a respondent recommended radiotherapy) are shown in Figs 2 and 3. For Case 1 (a single bone metastasis), 54.8% of the radiation oncologists responded that both the prostate and bone metastasis should be irradiated, and only 11.3% felt that this patient was not a candidate for radiotherapy. For Case 2 (three bone metastases), 24.5% of the respondents recommended radiotherapy for both the prostate and bone metastases, and 31.5% believed that only the prostate should be irradiated. Interestingly, for Case 3 (multiple bone metastases), 34.1% of the respondents still recommended radiotherapy for the prostate only, whereas 48.9% responded that radiotherapy was not indicated.

Regarding the prostate, most respondents chose the conventional fractionation of 2 Gy using intensity-modulated radiotherapy (IMRT). The survey responses indicated that a dose fraction of 3 Gy or more using three-dimensional conformal radiotherapy (3DCRT) tended to be applied to the bone lesions. A high BED to the prostate was administered in all three cases, and a lower BED tended to be selected for bone metastases as the number of metastases increased. Stereotactic ablative body radiotherapy

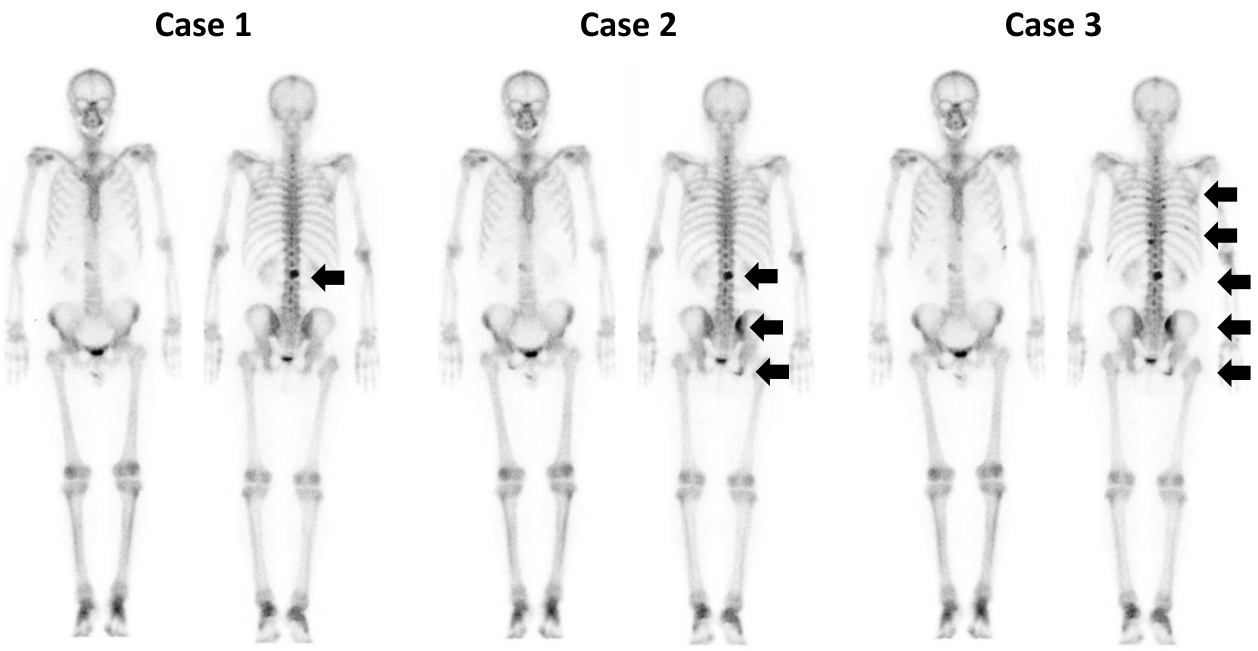

Figure 1. Bone scintigraphic images of the hypothetical cases. Case 1 had a single bone metastasis. Case 2 had three bone metastases. Case 3 had multiple bone metastases.

Table 1. The recommended treatment strategies of radiotherapy for the three hypothetical cases

	Case 1	Case 2	Case 3
Do you intend to perform radiotherapy?			
Yes, prostate only	76 (20.4%)	117 (31.5%)	127 (34.1%)
Yes, prostate and bone metastasis	204 (54.8%)	91 (24.5%)	8 (2.2%)
Yes, bone metastasis only	29 (7.8%)	30 (8.1%)	20 (5.4%)
No indication	42 (11.3%)	107 (28.8%)	182 (48.9%)
Others	21 (5.6%)	26 (7%)	34 (9.1%)
If yes, what is a treatment method for the prostate?			
3DCRT	41 (14.6%)	35 (16.8%)	28 (20.7%)
IMRT	225 (80.4%)	162 (77.9%)	97 (71.9%)
SABR	9 (3.2%)	6 (2.9%)	7 (5.2%)
HDR brachytherapy	1 (0.4%)	1 (0.5%)	1 (0.7%)
LDR brachytherapy	0 (0%)	0 (0%)	1 (0.7%)
Others	4 (1.4%)	4 (1.9%)	1 (0.7%)
What is a treatment method for bone metastasis?			
3DCRT	129 (56.1%)	78 (64.5%)	20 (71.4%)
IMRT	67 (29.1%)	31 (25.6%)	1 (3.6%)
SABR	27(11.7%)	4(3.3%)	1 (3.6%)
Others	7 (3%)	8 (6.6%)	6 (21.4%)

Because there were some missing data, the total numbers of each category may not agree with each other. 3DCRT, three-dimensional conformal radiotherapy; HDR, high dose rate; IMRT, intensity-modulated radiotherapy; LDR, low dose rate; SABR, stereotactic ablative body radiotherapy.

(SABR; 6 Gy per fraction or more) was rarely used for the prostate.

Discussion

Because prostate cancer frequently metastasizes to the bone, the management of patients with bmPCa is very important. The traditional main roles of radiotherapy for bone metastases have been pain control, the prevention of pathologic fractures and as treatment of spinal cord compression associated with bone metastases. However, several research groups have suggested that the addition of radiotherapy may prolong the survival of patients with bmPCa. For example, using the SEER-Medicare linked database, Satkunasivam et al. reported that local therapy including radical prostatectomy and IMRT was associated with a survival benefit in men with metastatic prostate cancer (4). In their propensity score analysis using the National Cancer Database, Rusthoven et al. demonstrated

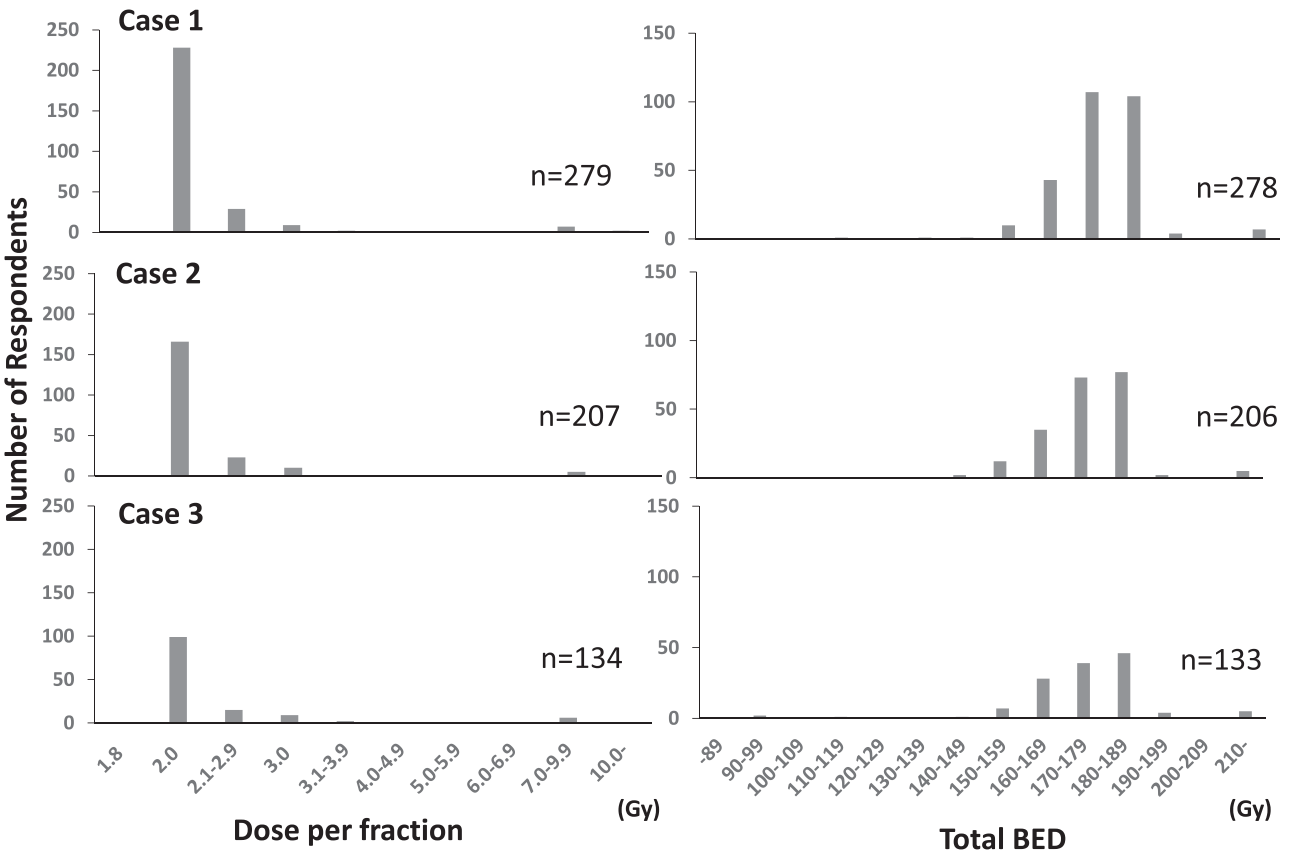

Figure 2. The dose per fraction and total biologically effective dose (BED) to the prostate among the respondents who recommended radiotherapy.

that patients with metastatic prostate cancer who received local radiotherapy and androgen deprivation therapy (ADT) achieved substantially longer survival than the patients treated with ADT alone (3).

Clinical trials have been conducted based on these retrospective studies. In the HORRAD trial, Boevé et al. examined whether overall survival was improved by adding local irradiation to ADT in patients with bmPCa (5). Most of the 432 patients enrolled in that trial had advanced bmPCa with the median PSA level of 142 ng/ml and more than five bone metastases. Although the median time to PSA progression in the radiation group was significantly improved, no significant between-group difference was found in overall survival. In the STAMPEDE trial, Parker et al. compared systemic therapy with or without local radiotherapy in patients with newly diagnosed metastatic prostate cancer (6); the systemic therapy included lifelong ADT with or without docetaxel. Although local radiotherapy did not improve the survival of the unselected patients, overall survival was improved significantly in the patients with low-volume metastases. Parker et al. concluded that radiotherapy to the prostate should be a standard treatment option for prostate cancer patients with a low-metastatic burden.

The optimum total dose and radiation technique for the prostate in patients with low-volume metastatic prostate cancer are uncertain. The radiation dose fractionation and techniques used in the clinical trials evaluating prostate radiotherapy for patients with primary metastatic prostate cancer are summarized in Table 2 (5,6,11). Compared with the currently applied dose schedules for localized prostate cancer such as 78 Gy/39 fraction (BED 182) or 60 Gy/20 fraction (BED 180), the radiation doses applied in the clinical trials are slightly lower, because the standard schedule would be too burdensome for patients with metastatic prostate cancer (6) or the overall survival would not be improved by dose escalation (5). Therefore, the US National Comprehensive Cancer Network guideline for prostate cancer states that a dose escalation beyond the BED equivalents used in the STAMPEDE trial is not recommended (12). On the other hand, higher dose schedules are commonly used in patients with high-risk localized prostate cancer (13,14).

The recent development of more sensitive imaging techniques using radiotracers targeting a prostate-specific membrane antigen revealed that patients with high-risk prostate cancer frequently have lymph node or distant metastases, which cannot be detected by conventional imaging modalities (15). In these cases, it has been demonstrated that radiotherapy in addition to lifelong ADT improves overall survival (16,17). As shown in Fig. 2, a number of Japanese radiation oncologists tend to prefer to use a total BED that is as high as the currently applied dose schedules for high-risk prostate cancer. In addition to the dose schedules, the definitions of the clinical target volume (CTV) and the margins of the planning target volume (PTV) from the CTV seems to be also important (Table 2). Although the definition of the CTV has varied among the clinical trials, the PTV margins were the same as the currently applied margins (Table 2). It seems likely that the PTV margin can be diminished—in cases with metastatic lesions that are not irradiated—to decrease the incidence of adverse effects. Further studies are needed to evaluate the impact of the dose fraction schedules and the treatment planning in prostate cancer cases.

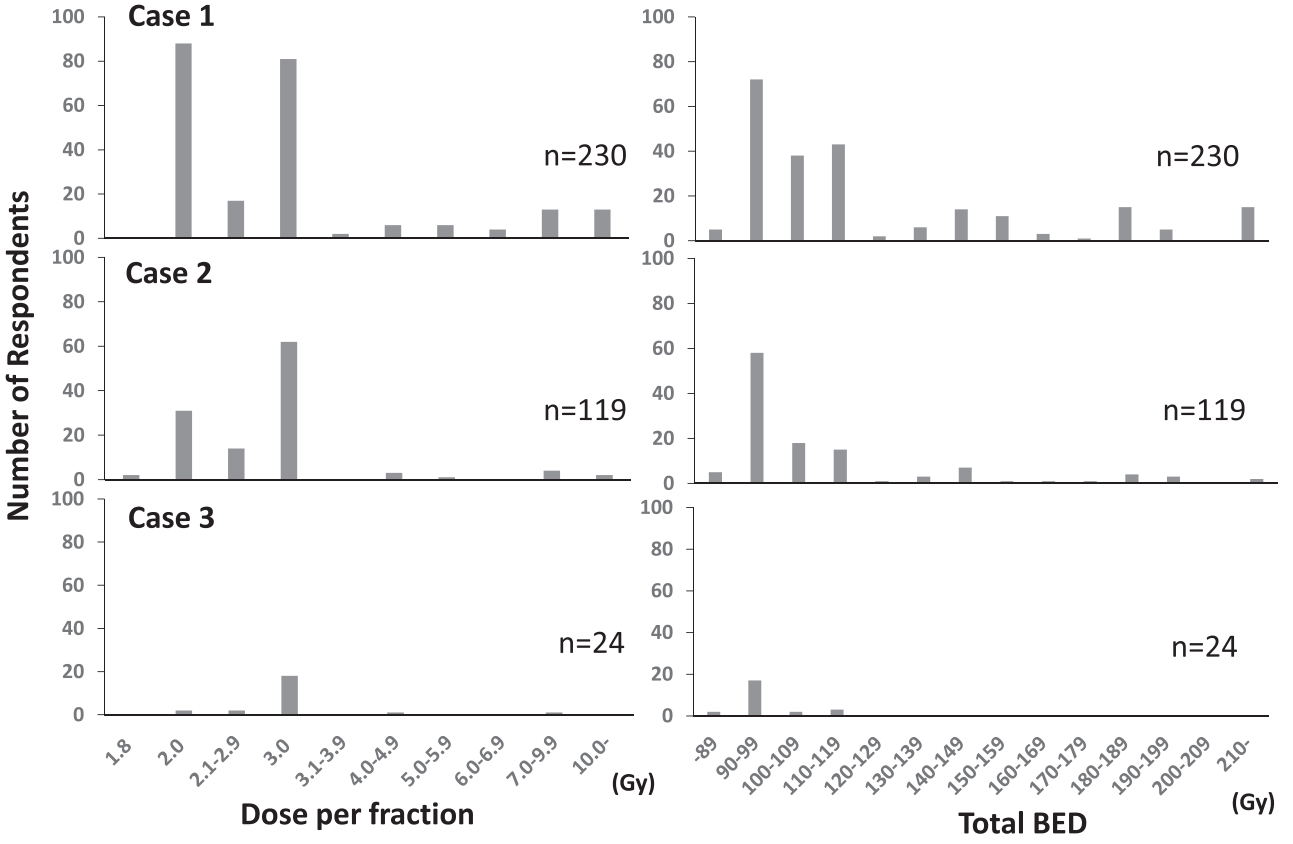

Figure 3. The dose per fraction and total BED to the bone lesions among the respondents who recommended radiotherapy.

Table 2. Radiation dose fractionation and techniques in clinical trials evaluating prostate radiotherapy for patients with primary metastatic prostate cancer

Protocol	Dose schedule	BED (Gy)	Technique	CTV	PTV margin from CTV
HORRAD	70 Gy/35 fraction/daily/7 weeks	163.3	3DCRT or IMRT	P + SV base	8 mm (with gold marker) or 1 cm
	57.76 Gy/19 fraction/3×/week/6 weeks	174.8			
STAMPEDE	55 Gy/20 fraction/daily/4 weeks	155.8	n.s.	P only	1 cm with 8 mm posteriorly
	36 Gy/6 fraction/1×/week/6 weeks	180.0			
PEACE-1	74 Gy/37 fraction/daily/7–8 weeks	172.7	3DCRT or IMRT	n.s.	n.s.

BED was calculated using an α/β ratio of 1.5 Gy for tumor. The effect of time factor was not taken into account. n.s., not specified; P, prostate; SV, seminal vesicles.

Radiotherapy to all lesions is an emerging treatment option for oligometastatic prostate cancer. However, the evidence regarding whether there is a further benefit of radiotherapy to all oligometastatic lesions in addition to the prostate is limited. SABR is frequently used as a radiation technique for patients with oligometastatic prostate cancer. Siva et al. treated 33 patients with oligometastatic prostate cancer by using a single fraction of 20-Gy SABR to each lesion (1). They reported that a single SABR session was feasible and associated with low morbidity at a follow-up period of 2 years. The ongoing ORIOLE trial has been evaluating the safety and efficacy of SABR in oligometastatic hormone-sensitive prostate cancer, using the SABR doses in one to five fractions in

accordance with the American Association of Physicists in Medicine Task Group 101 recommendations (2). Tsumura et al. treated 40 patients with oligometastatic prostate cancer by using high-dose rate prostate brachytherapy with or without metastases-directed external beam radiotherapy (18), and although the total doses to the metastatic lesions were 30–50 Gy with the conventional fractionation of 2–3 Gy per fraction, the 5-year castration-resistant prostate cancer-free survival rate was improved in the patients treated with brachytherapy and metastases-directed radiotherapy. As shown in Fig. 3, the radiation doses to the bone lesions varied quite widely among the radiation oncologists who responded to our survey, with a trend toward a lower BED than those applied to the prostate. However, SABR to oligometastatic lesions have just been covered by Japanese health insurance since April 2020. Further survey is expected to reveal the changes in trends of radiotherapy to the bone lesions.

In the SMAMPEDE trial examining patients with high-volume metastatic prostate cancer, radiotherapy to the prostate did not improve overall survival or failure-free survival (6). As shown in Table 1, even for Case 3 with multiple metastases, 34% of our respondents (i.e. Japanese radiation oncologists) reported feeling that radiotherapy to the prostate may improve the overall survival. Our survey was distributed before the results of the STAMPEDE and HORRAD trials were published (5,6). If the survey had been distributed after the publication of these trials' findings, the percentage of radiation oncologists who believed in the beneficial effect of local radiotherapy on overall survival might be different. However, the median follow-up periods in these trials were too short to evaluate the effects of local radiotherapy on symptomatic local events (5,6), and future analyses should explore whether local radiotherapy might still be useful for the prevention of symptomatic local events.

One limitation of this study is that the treatment strategy and fractionation schedules may have been affected by a medical insurance system. The respondents to our survey tended to use IMRT to the prostate and 3DCRT to bone lesions (not SBAR to these lesions), although the survey instructions noted that ideal treatment techniques can be used without any limitation from the medical insurance system. In principle, reimbursement in Japan depends on the number of fractions, and the medical reimbursement fee for SABR to bone lesions used to be the same as the fees for conventional techniques. However, we believe that our findings are important because the survey revealed the attitude of radiation oncologists toward local radiotherapy for hormone-naïve prostate cancer with multiple bone metastases. The respondents' reported radiotherapy techniques and dose fractionation varied widely, and our study results indicate that radiation oncologists should determine the adequate dose fraction schedules and treatment planning, including the definition of the targets and the target margins.

Appendix

In addition to the authors listed on the first page, the following authors contributed equally to this study.

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Conflict of interest statement

None declared.

References

1. Siva S, Bressel M, Murphy DG, et al. Stereotactic abative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. *Eur Urol* 2018;74:455–62.
2. Radwan N, Phillips R, Ross A, et al. A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE). *BMC Cancer* 2017;17:453.
3. Rusthoven CG, Jones BL, Flaig TW, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol* 2016;34:2835–42.
4. Satkunasivam R, Kim AE, Desai M, et al. Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis. *J Urol* 2015;194:378–85.
5. Boevé LM, Hulshof MC, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol* 2019;75:410–8.
6. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018;392:2353–66.
7. Burdett S, Boevé LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol* 2019;76:115–24.
8. Kothari G, Ost P, Cheung P, et al. Trends in management of oligometastatic hormone-sensitive prostate cancer. *Curr Oncol Rep* 2019;21:43.

9. Foster CC, Weichselbaum RR, Pitroda SP. Oligometastatic prostate cancer: reality or figment of imagination? *Cancer* 2019;125:340–52.
10. Sinha S, Muralidhar V, Feng FY, Nguyen PL. Characteristics and national trends of patients receiving treatment of the primary tumor for metastatic prostate cancer. *Prostate Int* 2017;5:89–94.
11. ClinicalTrials.gov. A Phase III Study for Patients With Metastatic Hormone-naïve Prostate Cancer (PEACE1). https://clinicaltrials.gov/ct2/show/NCT01957436 (5 April 2020, date last accessed).
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer version 1, 2020. http://www.nccn.org/ (5 April 2020, date last accessed).
13. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85:686–92.
14. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015;16:320–7.
15. Calais J, Kishan AU, Cao MF, et al. Potential impact of 68Ga-PSMA-11 PET/CT on the planning of definitive radiation therapy for prostate cancer. *J Nucl Med* 2018;59:1714–21.
16. Fosså SD, Wiklund F, Klepp O, et al. Ten-and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of the Scandinavian Prostate Cancer Group-7. *Eur Urol* 2016;70:684–91.
17. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* 2011;378:2104–11.
18. Tsumura H, Ishiyama H, Ki T, et al. Long-term outcomes of combining prostate brachytherapy and metastasis-directed radiotherapy in newly diagnosed oligometastatic prostate cancer: a retrospective cohort study. *Prostate* 2019;79:506–14.