

Treatment results of radiotherapy to both the prostate and metastatic sites in patients with bone metastatic prostate cancer

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ABSTRACT

Although systemic therapy is the standard treatment for metastatic prostate cancer, a randomized controlled trial showed radiotherapy to the prostate improved overall survival of metastatic prostate cancer patients with the low metastatic burden. Additionally, a randomized phase II trial showed that metastasis-directed therapy for oligo-recurrent prostate cancer improved androgen-deprivation therapy (ADT)-free survival. Therefore, administering radiotherapy to both prostate and metastatic regions might result in better outcomes. Thus, we report the treatment results of radiotherapy to both prostate and metastatic regions. Our institutional database was searched for patients who received radiotherapy to the prostate and metastatic regions. We summarized patient characteristics and treatment efficacy and performed statistical analysis to find possible prognostic factors. A total of 35 patients were included in this study. The median age was 66 years, and the median initial prostate-specific antigen (PSA) level was 32 ng/ml. The Gleason score was 7 in 10 patients, 8 in 13 patients, and 9 in 12 patients. The median radiotherapy dose was 72 Gy to the prostate and 50 Gy to the metastatic bone region. The 8-year overall survival, cause-specific survival, progression-free survival, and freedom from biochemical failure rate were 81, 85, 53, and 57%. Among the 35 patients, 12 were disease-free even after ADT was discontinued. In selected patients with metastatic prostate cancer, ADT and radiotherapy to the prostate and metastatic sites were effective. Patients with good response to ADT may benefit from radiotherapy to both prostate and metastatic regions.

Keywords: prostate cancer; metastatic prostate cancer; radiotherapy for both prostate and bone metastasis; radiotherapy for bone metastasis

INTRODUCTION

The standard of care for metastatic prostate cancer is mainly systemic treatment [1–7]; nevertheless, prostate cancer develops castration

resistance over several years and median survival was reported to be several years [1,3–5,8–10]. A randomized controlled trial showed that radiotherapy to the prostate improved the overall survival of the

prespecified low metastatic burden subgroup in the metastatic prostate cancer [11]. Additionally, there is a study that showed metastasis-directed therapy improved androgen-deprivation therapy (ADT)-free survival in patients with oligo-recurrent prostate cancer when compared with surveillance [12]. Therefore, radiotherapy to not only the prostate but also the metastatic regions has the potential to improve outcome [13]. In our institution, definitive radiotherapy is sometimes administered to the prostate including the metastatic bone region when bone metastasis was observed near the pelvis or when the number of bone metastasis was small. The rationale is that some patients with metastatic prostate cancer show the symptoms associated with local invasion of prostate cancer such as urinary obstruction or hematuria and symptoms related to bone metastasis such as pain or fracture as the disease progresses. Moreover, we administered whole pelvic radiotherapy for locally advanced prostate cancer [14]. Therefore, administering radiotherapy to the metastatic sites that were located within and near the pelvis did not seem to increase the toxicity. The current study was conducted to analyze the efficacy of radiotherapy on prostate cancer with bone metastasis by irradiating both the prostate and the metastatic regions.

MATERIALS AND METHODS

Our institutional database was searched for patients who underwent radiotherapy to both the prostate and metastatic regions. We summarized the patient and treatment characteristics, treatment efficacy, and adverse effects related to radiotherapy. The metastatic burden was categorized according to the definition used in the CHAARTED trial [3].

The freedom from biochemical failure (FFBF) rate, progression-free survival (PFS) rate, overall survival (OS) rate, and cause-specific survival (CSS) rate were calculated with the Kaplan–Meier method from the start of treatment. Biochemical failure was defined as the nadir prostate-specific antigen (PSA) level plus 2 ng/ml using the Phoenix definition [15]. A PFS event was defined as the observation of any clinical failure (local, nodal, or distant recurrence) or death. Univariate analysis was performed to determine the possible prognostic factors for FFBF, PFS, OS, and CSS by using the log-rank test. The analyzed possible factors were age < 66 years vs ≥ 66 years, PSA level < 80 ng/ml vs ≥ 80 ng/ml, Gleason score (GS) ≤ 8 vs ≥ 9, diagnosis before 2005 vs after 2006, PSA level before radiotherapy < 1 ng/ml vs ≥ 1 ng/ml, and the duration of ADT, neoadjuvant ADT, and adjuvant ADT. A *P*-value < 0.05 was considered statistically significant. Morbidities were classified according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Acute adverse events were defined as any adverse events that occurred within 3 months from the start of radiotherapy. Late adverse events were defined as any adverse events that occurred after 3 months from the start of radiotherapy. Statistical analyses were performed with JMP® 14 (SAS Institute Inc., Cary, NC, USA). Our Institutional Review Board (National Cancer Center, Tokyo, Japan) approved this study. All treatments were performed after obtaining patient consent.

Table 1. Patients characteristics

Characteristics	
Age, years	Median 66 (44–76)
PS (0–1)	35
Year of diagnosis	
1995–2001	4
2002–2005	14
2006–2009	5
2010–2014	7
2015–2017	5
PSA, ng/ml	Median 32 (5–11750)
GS	
7	10
8	13
9	12
T stage	
T1	3
T2	5
T3	18
T4	8
Tx	1
N stage	
N0	24
N1	11
The location of bone metastasis	
Pelvic bone	27
Pelvic bone + lumbar vertebra	1
Pelvic bone + lumbar and thoracic and cervical vertebra	1
Pelvic bone + lumbar vertebra and rib	1
Pelvic bone + rib + cranial bone	1
Femoral bone	1
Lumbar vertebra	2
Lumbar and thoracic vertebra and rib	1
PSA value before radiotherapy, ng/ml	
< 1	25
1 ≥	10
Follow up period, months	Median 94 (12–256)

RESULTS

A total of 35 patients were treated with radiotherapy by irradiating the prostate and the metastatic bone regions in our institution between 1995 and 2017. The patient characteristics are summarized in Table 1. The median age was 66 years (range: 44–76 years), and the median initial PSA level was 32 ng/ml (range: 5–11 750 ng/ml). The GS was 7 in 10 patients, 8 in 13 patients, and 9 in 12 patients. Bone metastasis was located in the pelvic bone in 27 patients and outside the pelvis in 8 patients. Two patients were classified into the high metastatic burden group, while the remaining 33 patients were classified into the low metastatic burden group. Twenty five patients had PSA value before radiotherapy < 1 ng/ml and ten patients ≥ 1 ng/ml.

The treatment characteristics are shown in Table 2. Radiotherapy to the prostate was performed with conventional fractionation but only 1 patient with high-dose-rate (HDR) brachytherapy. Regarding bone

Table 2. Treatment characteristics

Characteristics	N
RT method	
2D	11
2D + 3DCRT	8
3DCRT	2
IMRT	10
IMRT+3DCRT	3
IMRT+HDR brachytherapy	1
RT dose	
Prostate	
15 Gy/1fraction (HDR brachytherapy) + 46 Gy	1
80 Gy	2
78 Gy	8
72 Gy	12
66 Gy	5
64 Gy	1
50 Gy	6
Pelvic lymph node region	
For metastatic lymph node	
65 Gy	1
60 Gy	6
54 Gy	2
50 Gy	1
46 Gy	1
For prophylactic	
50 Gy	6
46 Gy	23
40 Gy	4
Metastatic bone	
72 Gy	1
66 Gy	1
65 Gy	1
63 Gy	1
60 Gy	5
56 Gy	1
55.2 Gy	1
54 Gy	1
50 Gy	7
46 Gy	10
40 Gy	4
30 Gy	2
Neo adjuvant ADT	34 patients
	Median 9 months (2–44 months)
Adjuvant ADT	25 patients
	Median 17 months (2–94 months)

2D = 2 dimensional.

3DCRT = 3 dimensional conformal radiotherapy.

IMRT = Intensity-modulated radiotherapy.

HDR = High-dose-rate.

ADT = Androgen-deprivation therapy.

metastasis, intensity-modulated radiotherapy (IMRT) was performed in 12 patients and 2D or 3D radiotherapy planning in 23 patients with various dose fractionation.

The median radiotherapy dose to the prostate was 72 Gy (range: 50–80 Gy, 1 patient was treated with HDR brachytherapy of 15 Gy / 1 fraction and IMRT) and that to the metastatic bone region was 50 Gy (range: 30–72 Gy). In 33 patients, prophylactic irradiation to the pelvic lymph node regions was performed with a median dose of 46 Gy (range: 40–50 Gy). ADT was administered to all 35 patients. Neoadjuvant ADT was administered to 34 patients with a median length of 9 months (range: 2–44 months). Adjuvant ADT

was administered to 25 patients with a median length of 17 months (range: 2–94 months). The median follow-up duration was 94 months (range: 12–256 months). The FFBE, PFS, OS, and CSS rates were 68, 88, 94, and 94% at 3 years and 57, 53, 81, and 85% at 8 years (Fig. 1). Of the 35 included patients, 12 were free from disease after discontinuing ADT, and the median length of being disease-free after discontinuing ADT was 102 months (range: 16–162 months). Univariate analyses showed that a PSA level before radiotherapy < 1 ng/ml was a good prognostic factor for FFBE, PFS, OS, and CSS (Fig. 2, Table 3, and Table 4).

Adverse events related to radiotherapy are summarized in Table 5. A grade 3 acute adverse event was observed in 3 patients. A grade 3 late adverse event was observed in 1 patient.

DISCUSSION

The results of the current study proved that some patients with metastatic prostate cancer could be long-time survivors after receiving radiotherapy to both the prostate and metastatic regions, indicating that radiotherapy has the potential to improve the FFBE, PFS, OS, and CSS rates of patients with prostate cancer with bone metastasis. A PSA level before radiotherapy < 1 ng/ml was a good prognostic factor for FFBE, PFS, OS, and CSS.

Several retrospective and prospective studies have evaluated the efficacy of local therapy for prostate cancer which is considered to be a systemic disease [11, 16–18]. For example, the STAMPEDE trial showed that local radiotherapy to the prostate improved the overall survival in patients with a low metastatic burden [11]. Moreover, there is a study that reported metastasis-directed therapy for oligo-recurrent prostate cancer improved ADT-free survival when compared with surveillance [12]. In our institution, the use of whole pelvic irradiation for locally advanced prostate cancer was previously evaluated [14]. It has often been used for locally advanced prostate cancer. Hence, 33 of 35 patients (94%) in this study received elective pelvic lymph node irradiation. This treatment was performed after adequate discussion of treatment with urologists and radiation oncologists. The reasons for administering this treatment were mainly the good response to ADT (as determined by good reduction in PSA levels, good radiological results, and no new lesions after ADT), the small metastatic volume, and the easy inclusion of the target regions in the radiation field (meaning that whole pelvic irradiation and additional small radiation fields were sufficient to cover the lesions).

In the STAMPEDE trial, the patients who were allocated radiotherapy had a 3-year failure-free survival rate of 50%, PFS rate of 63%, OS rate of 81%, and CSS rate of 86% in the low metastatic burden group [11]. In the current study, the 3-year FFBE rate was 68%, PFS rate was 88%, OS rate was 94%, and CSS rate was 94%. Furthermore, 12 of 35 patients were disease-free after discontinuing ADT, which has a strong impact on the clinical practice for prostate cancer with bone metastasis. Therefore, the treatment strategy of radiotherapy to both the prostate and metastatic regions seems a promising method, and this study could be the basis for phase II and III well-designed prospective studies on the use of radiotherapy to the prostate and metastatic regions in patients with metastatic prostate cancer.

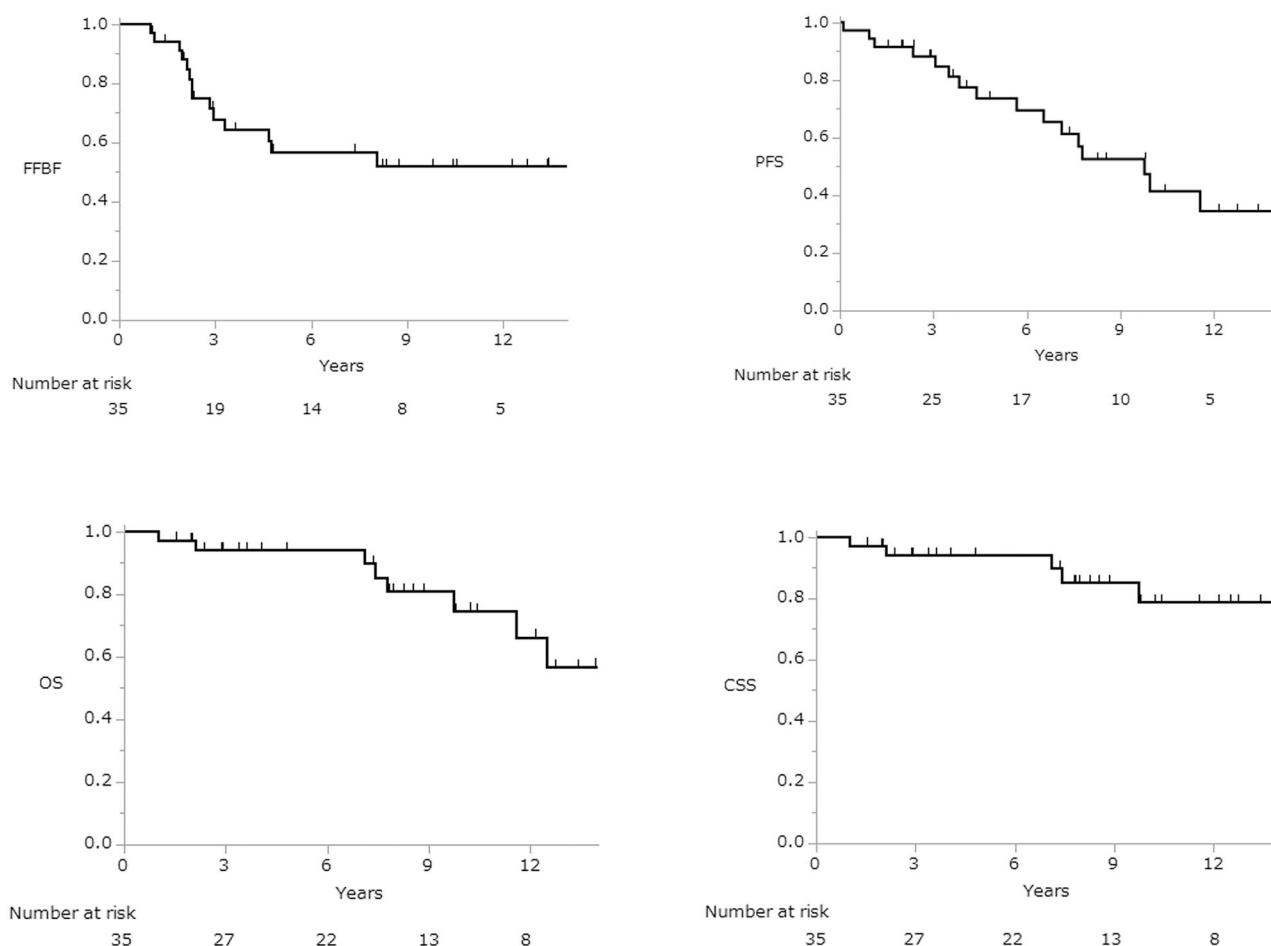


Fig. 1. Freedom from biochemical failure (FFBF), progression-free survival (PFS), overall survival (OS), and cause-specific survival (CSS) for all patients.

Table 3. Statistical analysis of freedom from biochemical failure (FFBF) and progression-free survival (PFS)

Factors	N	FFBF		PFS	
		Univariate analysis		Univariate analysis	
		3 year (8 year) FFBF	P value (log-rank test)	3 year (8 year) PFS	P value (log-rank test)
GS ≥ 9 vs ≤ 8	(12/23)	49% (49%) vs 77% (61%)	0.56	81% (52%) vs 91% (53%)	0.44
PSA ≥ 80 ng/ml vs < 80 ng/ml	(12/23)	45% (23%) vs 81% (76%)	0.0062	83% (38%) vs 91% (61%)	0.23
Diagnosis year before 2005 vs diagnosis year after 2006	(18/17)	67% (50%) vs 67% (67%)	0.28	89% (50%) vs 86% (64%)	0.69
Age ≥ 66 years vs age < 66 years	(21/14)	65% (46%) vs 71% (71%)	0.54	90% (46%) vs 86% (59%)	0.73
Length of ADT ≥ 1 year vs < 1 year	(29/6)	68% (54%) vs 67% (67%)	0.57	86% (51%) vs 100% (60%)	0.63
Length of neoadjuvant ADT ≥ 6 months vs < 6 months	(25/9)	69% (54%) vs 65% (65%)	0.87	88% (54%) vs 100% (50%)	0.99
Length of adjuvant ADT ≥ 6 months vs < 6 months	(19/6)	70% (56%) vs 80% (53%)	0.92	83% (47%) vs 83% (42%)	0.99
PSA value before radiotherapy ≥ 1 ng/ml vs < 1 ng/ml	(10/25)	54% (20%) vs 73% (68%)	0.0076	70% (0%) vs 95% (68%)	< 0.0001

ADT: Androgen-deprivation therapy

GS: Gleason score

Our study has several limitations in addition to the retrospective nature and small sample size. The main limitation is selection bias. This treatment was performed in a limited population. Many patients in this

study had small bone metastasis located within and near the pelvis, and they showed a good response to ADT; such patients account for a small number of patients with metastatic prostate cancer. Therefore,

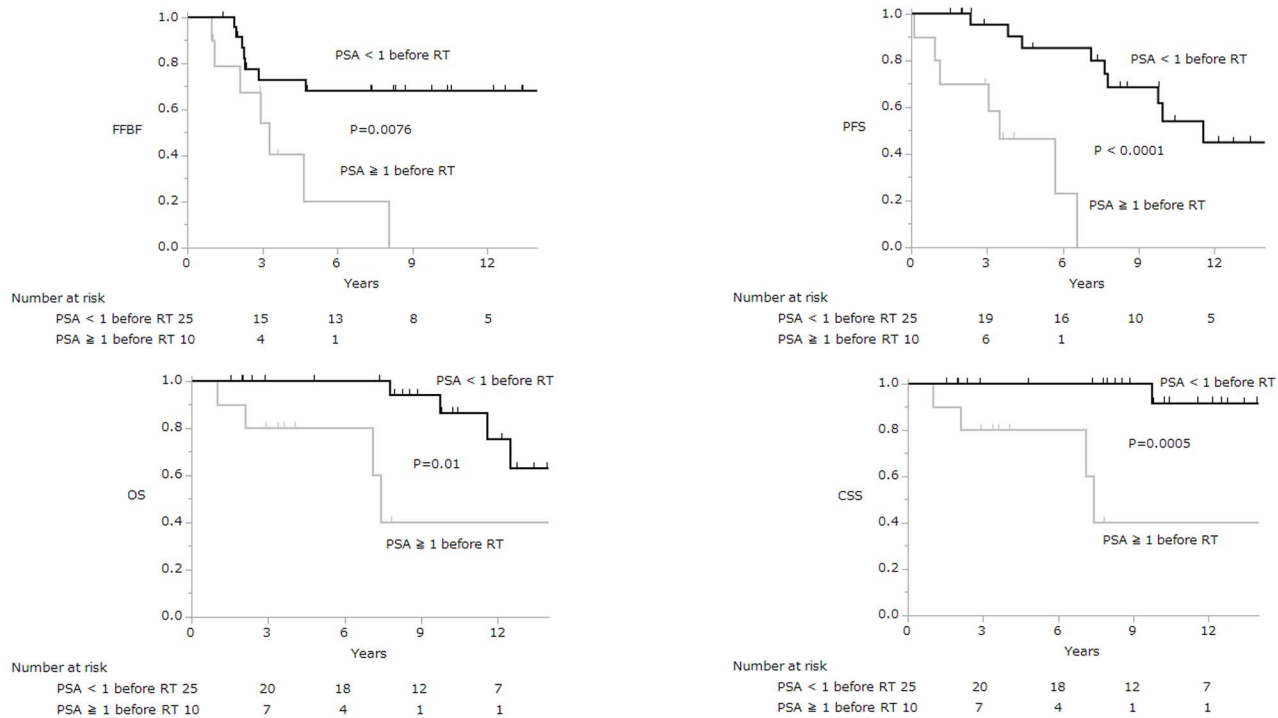


Fig. 2. Freedom from biochemical failure (FFBF), progression-free survival (PFS), overall survival (OS), and cause-specific survival (CSS) for the PSA level before radiotherapy ≥ 1 ng/ml vs < 1 ng/ml.

Table 4. Statistical analysis of overall survival (OS) and cause-specific survival (CSS)

Factors	N	OS Univariate analysis		CSS Univariate analysis	
		3 year (8 year) OS	P value (log-rank test)	3 year (8 year) CSS	P value (log-rank test)
GS ≥ 9 vs ≤ 8	(12/23)	90% (68%) vs 96% (85%)	0.46	90% (90%) vs 96% (85%)	0.77
PSA ≥ 80 ng/ml vs < 80 ng/ml	(12/23)	100% (100%) vs 91% (72%)	0.14	100% (100%) vs 91% (78%)	0.48
Diagnosis year before 2005 vs diagnosis year after 2006	(18/17)	94% (78%) vs 94% (94%)	0.51	94% (83%) vs 94% (94%)	0.61
Age ≥ 66 years vs age < 66 years	(21/14)	95% (87%) vs 93% (73%)	0.70	95% (87%) vs 93% (84%)	0.93
Length of ADT ≥ 1 year vs < 1 year	(29/6)	93% (76%) vs 100% (100%)	0.50	93% (81%) vs 100% (100%)	0.21
Length of neoadjuvant ADT \geq 6 months vs < 6 months	(25/9)	92% (79%) vs 100% (80%)	0.72	92% (86%) vs 100% (80%)	0.88
Length of adjuvant ADT \geq 6 months vs < 6 months	(19/6)	94% (72%) vs 83% (63%)	0.62	94% (72%) vs 83% (83%)	0.91
PSA value before radiotherapy \geq 1 ng/ml vs < 1 ng/ml	(10/25)	80% (40%) vs 100% (94%)	0.01	80% (40%) vs 100% (100%)	0.0005

OS: Overall survival

CSS: Cause-specific survival

GS: Gleason score

ADT: Androgen-deprivation therapy

further research is needed on how these results could be applied to the treatment of metastatic prostate cancer. However, the important finding obtained in this study is that some patients with metastasis could obtain a good outcome after definitive radiotherapy to both the prostate and metastatic regions. In addition, another limitation is the low dose of 30 or 40 Gy to the metastatic bones in some patients. It does not seem to be enough dose to control the tumor. These patients

were treated with 2D or 3D radiotherapy planning which was difficult to prescribe a high dose. Further research regarding dose to metastatic sites is needed.

In conclusion, we reported good results of ADT and radiotherapy to both the prostate and metastatic regions in patients with prostate cancer with a few bone metastasis. In selected prostate cancer patients with bone metastasis, ADT and radiotherapy to the prostate and the

Table 5. Acute and late adverse events

Adverse events	N	
	Grade 2	Grade 3
Acute adverse events		
Diarrhea	10	3
Anal pain	7	0
Rectal hemorrhage	0	0
Urinary frequency	7	–
Urinary incontinence	1	0
Urinary tract pain	1	0
Nausea	1	0
Fatigue	1	0
Anorexia	0	0
Stomach pain	1	0
Dermatitis radiation	3	0
Late adverse events		
Rectal hemorrhage	1	1
Diarrhea	1	0
Fecal incontinence	0	0
Hematuria	2	0
Urinary frequency	4	–
Urinary retention	1	0
Urinary incontinence	1	0
Urinary tract obstruction	1	0
Spinal fracture	1	0

metastatic bone regions could be a promising treatment. Patients with a good response to ADT may benefit from radiotherapy to both the prostate and metastatic regions.

CONFLICT OF INTEREST

Dr. Inaba reports grants from Elekta K.K., outside the submitted work. Dr. Igaki reports grants from HekaBio and personal fees from ITOCHU, outside the submitted work. Dr. Nakayama reports personal fees from AstraZeneca, outside the submitted work. Dr. Itami reports personal fees and non-financial support from Kay J, personal fees from Alpha Tau, personal fees from HekaBio, grants from Elekta, and grants from ITOCHU, outside the submitted work. The other authors have no conflicts of interest to declare.

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