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Scientific Article

A Single-Institution Prospective Study To Evaluate the Safety and Efficacy of Real- Time Image-Gated Spot-Scanning Proton Therapy (RGPT) for Prostate Cancer

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Purpose: In real-time image-gated spot-scanning proton therapy (RGPT), the dose distribution is distorted by gold fiducial markers placed in the prostate. Distortion can be suppressed by using small markers and more than 2 fields, but additional fields may increase the dose to organs at risk. Therefore, we conducted a prospective study to evaluate the safety and short-term clinical outcome of RGPT for prostate cancer.

Methods and Materials: Based on the previously reported frequency of early adverse events (AE) and the noninferiority margin of 10%, the required number of cases was calculated to be 43 using the one-sample binomial test by the Southwest Oncology Group statistical tools with the one-sided significance level of 2.5% and the power 80%. Patients with localized prostate cancer were enrolled and 3 to 4 pure gold fiducial markers of 1.5-mm diameter were inserted in the prostate. The prescribed dose was 70 Gy(relative biologic effectiveness) in 30 fractions, and treatment was performed with 3 fields from the left, right, and the back, or 4 fields from either side of slightly anterior and posterior oblique fields. The primary endpoint was the frequency of early AE (≥grade 2) and the secondary endpoint was the biochemical relapse-free survival rate and the frequency of late AE.

Results: Forty-five cases were enrolled between 2015 and 2017, and all patients completed the treatment protocol. The median follow-up period was 63.0 months. The frequency of early AE (≥grade 2) was observed in 4 cases (8.9%), therefore the noninferiority was verified. The overall 5-year biochemical relapse-free survival rate was 88.9%. As late AE, grade 2 rectal bleeding was observed in 8 cases (17.8%).

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Conclusions: The RGPT for prostate cancer with 1.5-mm markers and 3- or 4- fields was as safe as conventional proton therapy in early AE, and its efficacy was comparable with previous studies.

Introduction

Proton beam therapy (PBT) is the major treatment method of definitive radiation therapy for prostate cancer. The spot scanning PBT, in which multiple narrow proton beams (so-called "pencil beams") are used to irradiate the entire target volume, reduces the neutron exposure and the risk of secondary malignancies.[1,2] Further, this method realizes intensity modulated proton therapy (IMPT), which improves dose conformity by modulating the dose intensity within the irradiation field. However, spot-scanning PBT is highly sensitive to organ motion, which changes the water-equivalent length of the proton beams.[3] Therefore, accurate irradiation to the tumors of moving organs is difficult and may result in greater exposure to organs at risk (OARs).

It has been reported that the prostate is an organ that moves not only interfractionally[4-6] but also intrafractionally.[7-9] In addition, significant variation between patients in intrafractional prostate movement is also reported.[9-12] Although interfractional movement can be corrected using image-guided techniques such as cone beam computed tomography (CBCT), correction of intrafractional movement is a challenge. Kotte et al[7] analyzed intrafractional prostate movement by taking images at a frequency of about 1 minute from the start of treatment and found intrafractional movement more than 3 mm in a time frame of 5 to 7 minutes in 28% of fractions and also evidence of reversal of motion direction in many patients. Langen et al[10] investigated real-time intrafractional prostate movement using electromagnetic markers implanted in the prostate and reported that prostate movements of more than 3 mm were found in two-thirds (362 of 550) of all fractions. This implies that it is desirable to continuously confirm the position of the prostate during treatment, especially when a margin of 3 mm or less is used for intrafractional uncertainty.

In 2014, a therapeutic device that combines real-time tumor-tracking irradiation technology using fiducial markers and spot scanning PBT, real-time image-gated spot scanning proton therapy (RGPT), was developed.[13,14] This device could resolve the problem of intrafractional prostate movement, but when treating prostate cancer, fiducial markers made of pure gold inserted into the prostate may change the range of the proton beam and dose distribution. Matsuura et al[15] reported that the dose behind a 2-mm diameter marker can be as low as 33% of the prescribed dose and 53% behind a 1.5-mm marker. They conducted simulations using a tumor control probability model and reported that the decrease in tumor control probability could be suppressed by using a 1.5-mm diameter gold marker or using more than 2 fields for a 2-mm diameter marker. However, this result was derived from the evaluations for the dose-distortion effect caused by 1 gold marker. Further, with multiple gold markers, even with 1.5-mm markers, the dose in the prostate may further decrease with 2 opposing lateral fields. Using more than 2 fields can reduce dose uncertainties within the prostate, but adding fields will increase the dose to the bladder and rectum, leading to increases in adverse events (AE).

Here, we conducted a prospective clinical trial to verify that the frequency of AE and clinical outcomes of RGPT performed using more than 2 fields and 1.5-mm diameter fiducial markers are not inferior to conventional nonfiducial marker-based PBT.

Methods and Materials

Study design

This study was approved by the institutional review board (No. 014-0320) and then registered at the University hospital Medical Information Network Clinical Trials Registry (No. UMIN000016573). A third-party auditor (Persol Pharma Partners Ltd) conducted monitoring as a part of the clinical research quality assurance. Patients with localized prostate cancer with Eastern Cooperative Oncology Group performance status 0 to 2 were enrolled in this study. Table E1 shows the inclusion and exclusion criteria. Written informed consent was obtained from all patients before they were enrolled in the study.

Treatment machine

A PROBEAT-RT system (Hitachi Co Ltd), a synchrotron-based PBT system dedicated to discrete spot-scanning techniques with gantry-mounted 2 orthogonal x-ray units, was used.[13,14,16] In RGPT, orthogonal fluoroscopic image-tracking of a gold fiducial marker was performed.

Patient setup, image guidance, and beam gating

In all cases, 3 or 4 pure gold 1.5-mm diameter spherical fiducial markers were percutaneously inserted in the prostate about 1 week before the treatment planning CT

(TPCT). No patient had a rectal spacer inserted, as this had not been approved by national health care insurance in Japan at the time (approved in 2017). The TPCT images were acquired with a slice thickness of 1.25 mm from the supine position for all patients using Optima CT580W (GE Healthcare). A vacuum cushion was used to set the patient body and maintain the location of the legs. Patients were verbally instructed to void urine and stool as far as possible and to refrain from urination for 1 hour before the TPCT and each treatment. If residual gas was observed in the patient rectum on the x-ray fluoroscopy, the treatment was carried out after evacuation using a catheter.

Initially, registration between the treatment plan and daily setup of the patient was performed with reference to the bone structure. Then, the distance from the planned to the actual position of the fiducial markers was measured and the patient couch was moved so that the gold markers matched the position on the treatment plan. If the prostate displacement relative to the bone structure was more than 5 mm in any direction and only 4 mm in the posterior direction, a CBCT was acquired to clarify the cause of the prostate motion. Very low frequency fluoroscopy (1 Hz) was used to check the intrafractional motion with minimum x-ray exposure during the treatment. The isocenter dose from the fluoroscopy is less than 0.03 mGy per frame, so even if fluoroscopy is performed for 10 minutes (ie, 600 frames) in 1 treatment session, the total isocenter dose is less than 0.54 Gy after 30 treatment sessions. This dose is well within the threshold (5% of the therapeutic target dose) proposed in American Association of Physicists in Medicine Task Group report No. 180,[17] and the imaging dose accompanied with RGPT is considered acceptable. When a movement of 2.0 mm or more from the planned position was observed, the proton beam was automatically discontinued. If the condition persisted, the patient position was corrected again by moving the patient couch, unless the overall offset relative to the bone structure was more than 5 mm in any direction and 4 mm in the posterior direction. In case the overall offset exceeded these limits, urination and defecation was considered, depending on the probable cause based on CBCT images.

Treatment

The risk of recurrence was classified based on the National Comprehensive Cancer Network risk classification.[18] In cases where the risk of recurrence was a favorable intermediate or lower risk, only the prostate was defined as the clinical target volume (CTV), whereas in cases where the risk of recurrence was an unfavorable intermediate or higher risk, the seminal vesicle was also included as CTV.

The dose constraints for each target and OAR are detailed in Table E2. As a dose constraint for the rectum, the Quantitative Analysis of Normal Tissue Effects in the Clinic has dose constraints only for volumes of the rectum that receive 50 Gy or more, but there are reports that the fractional volumes receiving intermediate doses of 30 to 40 Gy (V30 Gy-V40 Gy) are also correlated with the frequency of early rectal AE.[19,20] Therefore, we evaluated rectum V37.5 Gy(relative biologic effectiveness [RBE]) as well as V60 Gy(RBE) based on a previous report of real-time tumor-tracking intensity modulated radiation therapy for prostate cancer.[21]

Based on institutional policy, 70 Gy(RBE) was prescribed to 99% of the CTV in 30 fractions over 7.5 weeks for all patients. This dose fractionation is equivalent to 76 Gy(RBE) in 2-Gy(RBE) fractions with an α/β ratio of 1.5. The treatment was performed with 3 fields from the left, right, and the back or 4 fields from either side of slightly anterior and posterior oblique fields. Figure 1 shows typical dose distributions for the 3- and 4-field beam arrangements. From April 2015 to July 2016, we used a 3-field technique, and from August 2016, we changed to a 4-field technique to further reduce the rectal dose. The posterior beam used in the 3-field technique had a lower weight (half of the left and right beams). In the 4-field technique, the weight of each field was set to be equal. The beam directions were determined not to pass through the intestine and bladder, which may show daily changes in volume. Three-year hormone therapy was recommended for patients with high or very high risk of recurrence.

Margins and dose optimization

The current usage of internal and setup margins for conventionally fractionated prostate radiation therapy is reported as 6 mm (range, 3-10 mm; except posteriorly 5 mm; range, 0-8 mm),[22] but relatively small margins of 3 to 5 mm are used for IMPT.[23,24] In addition, it is necessary to consider the beam range uncertainty in PBT, and margin recipes of 2.5% to 3.5% of the range plus an additional 1 to 3 mm have been reported.[25]

In RGPT, a 3-mm margin was used for internal and setup error because the fiducial markers were within 2 mm of the planned position during treatment. For single field uniform dose (SFUD) plans, distal and proximal margins calculated as 3.5% of the distal or proximal range plus 1 mm were assigned for each beam to account for range uncertainties. For the IMPT planning, robust optimization assuming a setup error of 3 mm and a range uncertainty of 3.5% was used. An example of the difference between typical PBT and RGPT margin settings is illustrated in Fig. E1.

Patients whose OAR dose constraints were difficult to achieve with SFUD were treated with IMPT. The SFUD plans were produced by adding aforementioned margins to the CTV but were not robustly optimized.

Dose calculation

Our treatment planning system uses an analytical algorithm (not a Monte Carlo–based calculation engine), and

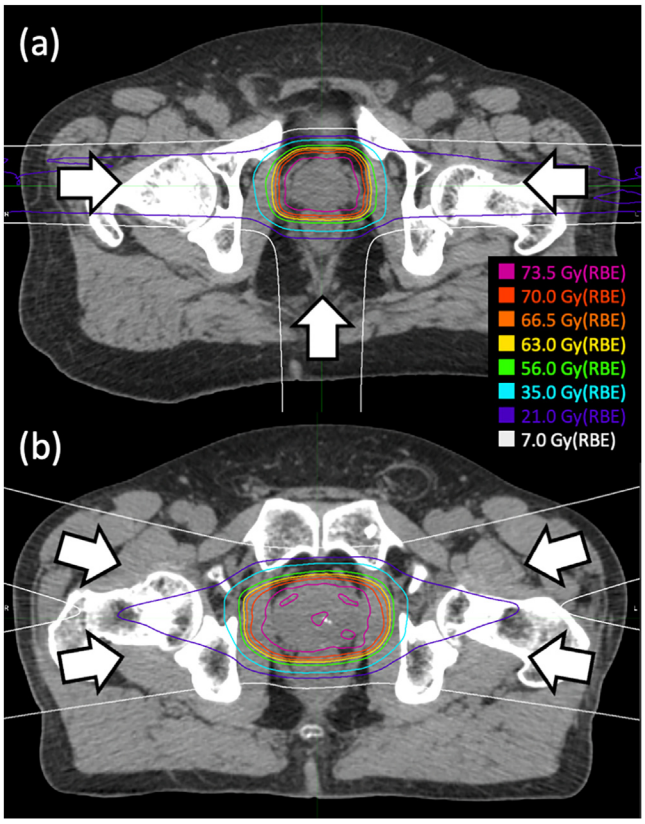

Figure 1 Examples of dose distributions for the 3- (a) and 4- (b) field beam arrangements. The white arrows indicate the direction of the proton beams. In the 3-field technique (a), the posterior beam had a lower weight (half of the left and right beams). In the 4-field technique (b), the weight of each field was set to be equal.

the resolution of the calculation is 2 mm. These make it difficult to correctly calculate the impact of a 1.5-mm diameter fiducial marker on dose distribution. In addition, the Hounsfield units (HU)-stopping power ratio conversion table registered in the treatment planning system does not correspond to the actual stopping power ratio of gold. Even if the fiducial marker HU is used for dose calculation as it is, the correct dose distribution cannot be obtained. Therefore, after confirming in advance using the Monte Carlo method that the dose-distortion effect by fiducial markers was not significant by using more than 2 fields,[15] the fiducial markers and surrounding artifacts on TPCT images were overridden with prostate HU for the dose calculations.

The RBE value was determined to be 1.1 by a previous study and used for the treatment planning here.[26]

Follow-up

The AEs based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 were evaluated weekly during the treatment, and monthly after the treatment until 3 months and every 3 months thereafter. The following items were evaluated as early rectal and bladder AE: urinary frequency, urinary incontinence, urinary retention/obstruction, urinary tract pain, urinary urgency, and rectal mucositis/anal pain. As late rectal and bladder AE, hematuria/bladder bleeding, urinary retention/obstruction, urinary urgency, and rectal bleeding were evaluated. Early and late AEs were defined as side effects occurring within 90 days and later than 90 days from the start of RGPT, respectively.

Statistics

The primary endpoint was the frequency of early AE (≥grade 2), and the secondary endpoint was the biochemical relapse-free survival rate (BRFS) and the frequency of late AE. Biochemical relapse was defined as a prostate-specific antigen (PSA) increase of at least 2 ng/mL greater than the PSA nadir (Phoenix definition) or start of any salvage therapy for PSA elevation. The BRFS rate was calculated from the initiation of RGPT to biochemical relapse or death by any cause.

Based on the previous report that the frequency of early rectal and bladder AE (≥grade 2) after prostate PBT was 12.6%,[27] the frequency of early AE (≥grade 2) of RGPT was assumed to be 7.6% because RGPT can reduce

the margins added to CTV. The noninferiority margin was set at 10%; the threshold AE occurrence rate was set at 22.6%. Because the required number of cases was calculated to be 43 using the one-sample binomial test by the Southwest Oncology Group statistical tools with the one-sided significance level of 2.5% and power 80%, the target number of cases was set to 45. Based on this assumption, the noninferiority of early safety of RGPT would be verified if the number of early AE (≥grade 2) occurrence cases is 5 or less. To assess the differences in the treatment plan due to the number of fields (3- vs 4-field) and the optimizing method (SFUD vs IMPT), the medians of dose-volume histogram (DVH) parameters were compared using the Mann-Whitney *U* test, and $P < .05$ was considered as the level of significance. The SAS software version 9.4 and JMP version 16 (SAS Institute) were used for the statistical analyses.

Results

Forty-five patients were enrolled between March 2015 and May 2017. The median follow-up was 63.0 months (range, 51.3-79.3 months). Table 1 shows patient characteristics. All patients completed the treatment protocol. Table 2 shows the median and range of DVH parameters by number of fields and optimizing methods (ie, SFUD and IMPT). The 3-field technique resulted in a significantly higher rectum V37.5 Gy(RBE) than the 4-field technique, and IMPT resulted in a significantly higher CTV maximum dose (Dmax) and rectum V37.5 Gy(RBE) than the SFUD. Representative DVH curves of setup and range perturbations applied to each of our planning techniques is shown in Fig. E2.

AEs

As early AE, grade 2 urinary frequency (2 cases) and grade 2 urinary retention/obstruction (2 cases) were observed. The overall frequency of a grade 2 early AE was 8.9% (4/45 cases) and no grade 3 early AE was observed; therefore, the noninferiority of the early safety of RGPT was verified.

As late AE, there was: rectal bleeding (grade 1 in 13 cases [28.9%], grade 2 in 8 cases [17.8%]) and bladder bleeding (grade 1 in 2 cases [4.4%]). Table 3 shows details

Table 1 Patient characteristics (n = 45)

Median age (years) (range)		62 (46-78)
Median pretreatment PSA (ng/mL) (range)		6.5 (3.1-45.1)
Gleason score — no. (%)	3+3	11 (24.4%)
	3+4	10 (22.2%)
	4+3	11 (24.4%)
	4+4	7 (15.6%)
	3+5	1 (2.2%)
	4+5	3 (6.7%)
	5+4	1 (2.2%)
	5+5	1 (2.2%)
Tumor stage — no. (%)	T1c-T2a	34 (75.5%)
	T2b-T2c	8 (17.8%)
	T3a	3 (6.7%)
NCCN risk classification — no. (%)	Very low-low	9 (20.0%)
	Favorable intermediate	7 (15.5%)
	Unfavorable intermediate	12 (26.7%)
	High-very high	17 (37.8%)
Number of fields	3	27 (SFUD 24, IMPT 3)
	4	18 (SFUD 17, IMPT 1)
Hormone therapy — no. (%)	+	17 (37.8%)
	—	28 (62.2%)

Abbreviations: IMPT = intensity modulated proton therapy; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; SFUD = single field uniform dose.

Table 2 Median and range of DVH parameters by number of fields and optimizing methods

Volume	Parameter	Number of fields	SFUD	IMPT	SFUD vs IMPT *P* value
CTV	D99 (Gy[RBE])	3	72.8 (70.9-74.3)	71.9 (70.8-74.3)	.3384
		4	73.4 (70.9-73.9)	72.3	
		3- vs 4-field *P* value	.1443		
	Dmax (Gy[RBE])	3	75.9 (73.5-77.8)	77.7 (76.3-77.9)	.0167
		4	75.6 (74.9-77.5)	76.7	
		3- vs 4-field *P* value	.2761		
Rectum	V60 Gy(RBE) (%)	3	18.2 (10.5-22.7)	17.0 (15.7-19.4)	.4977
		4	16.5 (10.4-19.8)	19.8	
		3- vs 4-field *P* value	.2611		
	V37.5 Gy(RBE) (%)	3	37.4 (23.6-51.0)	45.4 (36.6-47.6)	.0419
		4	32.2 (20.1-47.8)	42.3	
		3- vs 4-field *P* value	.0199		
Bladder	V37.5 Gy(RBE) (%)	3	24.9 (12.5-41.9)	26.8 (24.9-29.7)	.1751
		4	17.8 (7.7-34.9)	29.4	
		3- vs 4-field *P* value	.0744		

Abbreviations: CTV = clinical target volume; D99 = dose covering 99% of the target; Dmax = maximum dose; DVH = dose-volume histogram; IMPT = intensity modulated proton therapy; RBE = relative biologic effectiveness; SFUD = single field uniform dose; V60(37.5) Gy(RBE) = volume receiving more than 60(37.5) Gy(RBE).
The median DVH parameters of 3- vs 4-field arrangements and SFUD vs IMPT are compared using the Mann-Whitney *U* test.

Table 3 Early and late AEs

		Number of patients				
Grade (NCI-CTCAE v. 4.0)		0	1	2	3	4-5
Early AE						
	Urinary frequency	22	21	2	0	0
	Urinary incontinence	45	0	0	0	0
	Urinary retention/obstruction	27	16	2	0	0
	Urinary tract pain	38	7	0	0	0
	Urinary urgency	42	3	0	0	0
	Rectal mucositis/anal pain	41	4	0	0	0
Late AE						
	Hematuria/bladder bleeding	43	2	0	0	0
	Urinary retention/obstruction	43	2	0	0	0
	Urinary urgency	45	0	0	0	0
	Rectal bleeding	24	13	8	0	0

Abbreviations: AE = adverse events; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 4 Contingency tables of relationship between incidence of AEs and number of fields and optimizing method

(A) Plot of the incidence of early AE vs the number of fields				
Number of fields	**Number of grade 2 early AE**		**Total - n (%)**	***P* value**
	No - n (%)	**Yes - n (%)**		
3	26 (96.3%)	1 (3.7%)	27 (60.0%)	.1344
4	15 (83.3%)	3 (16.7%)	18 (40.0%)	
Total	41 (91.1%)	4 (8.89%)	45	
(B) Plot of the incidence of early AE vs the optimizing method				
Optimizing method	**Number of grade 2 early AE**		**Total - n (%)**	***P* value**
	No - n (%)	**Yes - n (%)**		
SFUD	37 (90.2%)	4 (9.8%)	41 (91.1%)	.5128
IMPT	4 (100%)	0 (0%)	4 (8.9%)	
Total	41 (91.1%)	4 (8.89%)	45	
(C) Plot of the incidence of late AE vs the number of fields				
Number of fields	**Number of grade 2 late AE**		**Total - n (%)**	***P* value**
	No - n (%)	**Yes - n (%)**		
3	22 (81.5%)	5 (18.5%)	27 (60.0%)	.8735
4	15 (83.3%)	3 (16.7%)	18 (40.0%)	
Total	37 (82.2%)	8 (17.8%)	45	
(D) Plot of the incidence of late AE vs the optimizing ethod				
Optimizing method	**Number of grade 2 late AE**		**Total - n (%)**	***P* value**
	No - n (%)	**Yes - n (%)**		
SFUD	33 (80.5%)	8 (19.5%)	41 (91.1%)	.3299
IMPT	4 (100%)	0 (0%)	4 (8.9%)	
Total	37 (82.2%)	8 (17.8%)	45	

Abbreviations: AE = adverse events; IMPT = intensity modulated proton therapy; SFUD = single field uniform dose.
The *P* value was calculated using χ^2 test.

of the AE. No grade 2 or higher AE due to either fiducial marker implantation or image guidance procedure was observed. No significant difference in the incidence of early grade 2 AE was observed due to differences in the number of fields or optimizing methods (χ^2 test, $P = .1344$ and $P = .5128$, respectively); this was similar for late AE (χ^2 test, $P = .8735$ and $P = .3299$, respectively). Table 4 shows the contingency tables.

Tumor control and survival

The overall 5-year BRFS was 88.9%. Figure 2 shows the Kaplan-Meier curves of BRFS by risk group. No significant difference in BRFS was observed due to differences in the number of fields or optimizing methods (log-rank test, $P = .5345$ and $P = .4134$, respectively). All but 1 patient were alive at the last follow-up; this 1 high-risk patient died of COVID-19 pneumonia at 56.6 months after the PBT without prostate cancer recurrence.

Intrafractional prostate movement

Prostate movement of 3 mm or more was observed in 10.4% of all sessions (140 of 1350) in 37 patients (82.2%). The number of proton beam discontinuations due to intrafractional prostate movement ranged from 1 to 8 times per treatment session (median, 1 time). One or more beam discontinuations were observed in 39.6% of all sessions (534 of 1350) in 44 patients (97.8%). We observed considerable intrafractional prostate movement in 1 patient (Movie E1). In this patient, the rectum was repeatedly inflated and deflated because of increases and decreases in rectal gas at short time intervals.

Discussion

The present study shows that spot scanning RGPT with more than 2 fields is noninferior to conventional

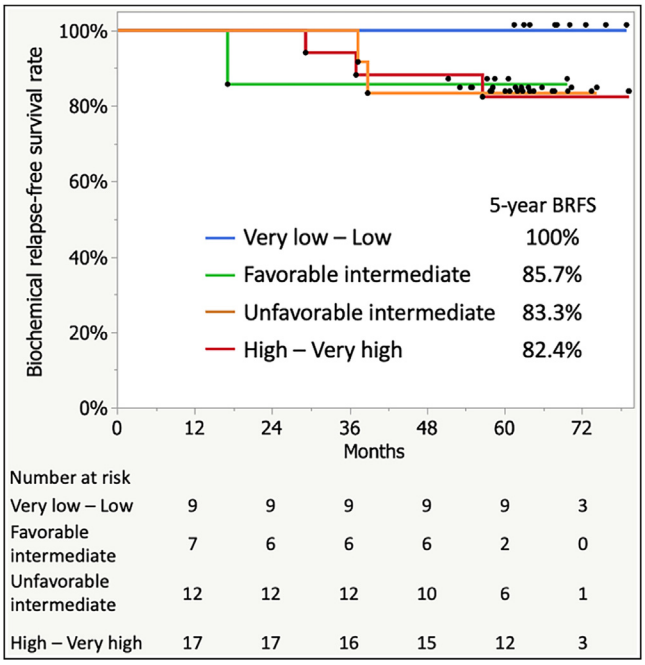

Figure 2 The Kaplan-Meier curves of biochemical relapse-free survival by risk group. The biochemical relapse-free survival rate was calculated from the initiation of real-time image-gated spot-scanning proton therapy to biochemical relapse or death by any cause. The risk of recurrence was classified based on the National Comprehensive Cancer Network risk classification.

PBT regarding the frequency of early AE. Although there are reports of passive scattering PBT[28] and spot scanning PBT[29,30] using image guidance with fiducial markers, these reports did not statistically assess the effect of the fiducial markers on treatment outcomes. In addition, to the best of our knowledge, this is the first report on the clinical results of real-time image-gated spot scanning PBT for prostate cancer. Unlike other reports, this report also includes high-risk patients, so it has the advantage that results can be generalized.

The results of recent reports on PBT for prostate cancer[27-31] are summarized in Table E3. In terms of disease control, the 4- to 5-year BRFS or freedom from biochemical progression rate is reported to be 93.5% to 96.8%. The treatment outcomes of this study (5-year BRFS 88.9%) appear slightly inferior compared with other reports; however, previous reports mainly focused on low to intermediate risk patients, while approximately one-third of the patients in this study are classified as high to very high risk. Therefore, the difference in treatment outcomes is likely attributed to the difference in the risk profiles of the patients. Regarding toxicity, the incidence of late genitourinary and gastrointestinal AE (≥grade 2) were 4% to 15% and 10% to 16%, respectively. These results suggested the secondary endpoints of this study (BRFS and the frequency of late AE) were comparable to other reports.

There are many reports of the effectiveness of image guidance, and a recent systematic review and meta-analysis showed not only a reduction in AE but also improvements in the biochemical recurrence-free rate.[32] Various image guidance methods using fiducial markers, CBCT, ultrasound, and electromagnetic transponders have been reported,[33-37] but each method has both strong and weak points. Compared with image guidance using ultrasound, the method using fiducial markers has less effect on lack of visibility due to intestinal gas, and compared with image guidance using CBCT, intrafractional movement during treatment can also be evaluated. Disadvantages of image guidance using fiducial markers include the need to implant fiducial markers and the radiation exposure associated with image guidance. In recent years, a therapeutic device combining magnetic resonance imaging and x-ray therapy has been developed, making it possible to perform continuous image guidance without embedding markers.[38] Fiducial markers may become unnecessary in the future, but a recent systematic review suggests 2-dimensional imaging plus fiducial markers could be more beneficial for late genitourinary toxicity than other types of image-guided radiotherapy.[32] Therefore, fiducial marker-based image guidance can be considered to be one of the most useful methods at present.

We experienced a case in which the prostate moved continuously on x-ray fluoroscopy during proton therapy. Shimizu et al[12] reported that the type of intrafractional motion of the prostate differed between the cases during x-ray therapy for prostate cancer. Similarly, Langen et al[10] used an electromagnetic transponder placed in the prostate to continuously observe the position of the prostate and reported drift motion, transient motion, or both simultaneously. In our cohort, 37 cases (82.2%) had at least 1

intrafractional prostate movement of 3 mm or more, and it was difficult to predict how the prostate would move before treatment. Therefore, RGPT is considered useful to improve treatment accuracy especially when a margin of 3 mm or less is used for intrafractional uncertainty.

There are several ongoing trials comparing PBT with x-ray radiation therapy for prostate cancer (NCT01617161, NCT03561220, and NCT01352429), but no clear evidence that PBT is superior to intensity modulated radiation therapy has been shown. Both appear to be comparable in both tumor control and AE frequency, based on multiple large retrospective studies.[39,40] We can assume that most of the patients in these studies underwent passive scattering PBT without image guidance considering the time the treatment was administered. Image-guided spot scanning PBT can be expected to minimize unnecessary radiation exposure and reduce AE and the incidence of secondary malignancies. However, more patients and longer follow-up are needed to be able to draw conclusions about this.

The study limitations include the small number of patients and the lack of uniformity in the number of fields and optimizing methods. The DVH parameters showed significant differences in doses to the CTV and rectum depending on the number of fields and optimizing methods. The main reason why the dose to the CTV and rectum was higher with IMPT may be that IMPT had been used in cases where dose constraints could not be met with SFUD. Although the 3-field technique resulted in a significantly higher rectum V37.5 Gy(RBE) than the 4-field technique, univariate analysis did not show significant differences in either the incidence of AE or BRFS due to the number of fields or optimizing methods. The reason why the rectal AE tended to be the same or slightly lower with the 3-field technique is not clear, but a possible reason is that the posterior beam had a lower weight and that the distal edge of the proton beam, which is known to have a higher RBE,[41] was not on the rectal side. We could not evaluate these differences by multivariate analysis because of the small number of patients and events.

Conclusion

The RGPT for prostate cancer with 1.5-mm markers and 3- or 4- fields was as safe as conventional PBT in early AE, and its efficacy is suggested to be comparable to that in previous studies. A larger number of patients and longer follow-up periods are needed to further evaluate the usefulness of RGPT.

Disclosures

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Supplementary materials

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