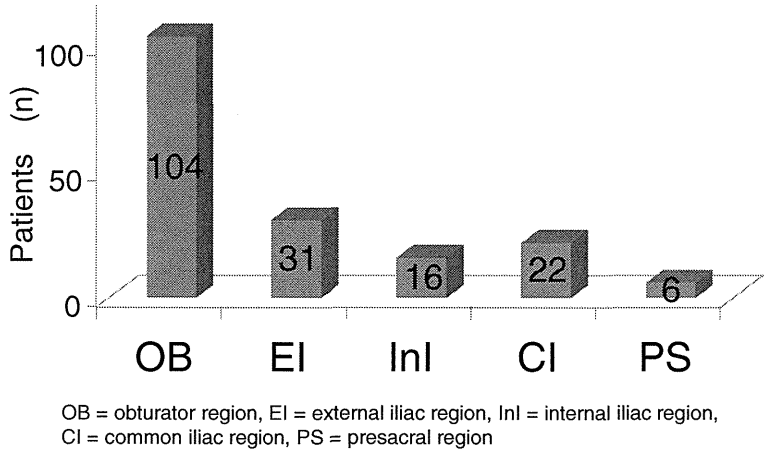

Figure 2 Incidence of clinically metastatic pelvic lymph nodes in each region. *Including duplication.

regions or sub-regions. We defined each of these regions as a NSR (non-solitary region). Patients with NSR metastases had high FIGO stages or a large number of positive nodes. Patients with high FIGO-stage disease (III, IVA) had a significantly higher frequency of positive nodes in the NSR (23/54, 43%) compared with patients who had low FIGO-stage disease (15/60, 25%) (P=0.047). The average number of metastatic lymph nodes was 3.7 for patients with NSR and 1.9 for patients with non-NSR. There was no significant relationship between tumor diameter and the incidence of NSR metastases: 6/18 (30%) for tumors≤40 mm, 20/58 (34%) for tumors 41–60 mm, and 15/38 (38%) for tumors≥61 mm. All 16 patients with nodal metastases in less common (≤ 6/114, 5%) areas (presacral, caudal obturator, and caudal/lateral external iliac regions) had large tumors (> 4 cm), of which all 9 cases who had NSR metastases in the lateral external iliac and presacral regions were stage IIB or more. In addition, all 9 cases with NSR metastases in the caudal obturator or caudal external iliac regions also had positive lymph nodes in the ipsilateral cranial obturator or medial external iliac region, and all 3 cases with NSR metastases in the lateral external iliac region had positive nodes in the ipsilateral intermediate external iliac region.

Discussion

To minimize the risk of inter-planner variability on pelvic node CTV contouring, consensus-based CTV guidelines have been developed for patients with cervical cancer [2-4]. Modification of the standard CTV guidelines based on the probability of subclinical disease, in other words, risk of recurrence is the next challenge for individualized treatment planning.

The CTV could be divided into subgroups, e.g., high-risk CTV and low-risk CTV, according to the probability of recurrence. The high-risk CTV would be defined as the volume that involves frequent metastases, and should be treated for every patient. In contrast, the low-risk CTV would be defined as a region with rare disease involvement, and might be able to be excluded from the CTV in certain situations. The arrangement of CTV nodes could reduce the dose/volume of organs at risk (OAR) and lead to lower side effects. In the previously published guidelines, the CTV nodes cover the entire anatomical pelvic node distribution [2-4,6]. The guidelines did not emphasize the actual probability of nodal involvement, in other words, the risk of recurrence. In head and neck cancers, individualization of CTV nodes for 3D planning was proposed according to the primary

Table 2 Number of patients* with clinically pelvic nodal metastases # by region/subdivided region

	Total	OB		EI				InI	CI	PS
		Cranial	Caudal	Med	Int	Lat	Caudal			
Positive nodes in other regions	82	76	5	10	13	3	6	16	22	6
No positive nodes in other regions	32	28	0	2	2	0	0	0	0	0
Total	114	104	5	12	15	3	6	16	22	6

*including duplication, # assesed by CT/MRI (>= 10 mm in shortest diameter).
OB = obturator region, EI = external iliac region, InI = internal iliac region, CI = common iliac region, PS = presacral region, Med = medial, Int = intermediate, Lat = lateral.

site or T/N stage [8]. For uterine cervical cancer, in an attempt at dose reduction for OAR, small pelvic field irradiation has been investigated [9,10]. The treatment fields were designed to exclude the common iliac region. In this study, we tried to analyze the 3D distribution patterns of positive nodes in the pelvis assessed by pretreatment CT/MRI to quantify the nodal metastasis probability in patients with uterine cervical cancer.

Some surgical series have indicated that the obturator and external iliac regions have the highest frequency of metastatic lymph nodes [11,12]. This is consistent with the findings demonstrated in the present study. We subdivided the obturator and external iliac regions according to craniocaudal distribution at the border of the femoral head. Analyses with this subdivision revealed that positive lymph nodes were rarely seen on the caudal side, and most were observed on the cranial side. Benedetti and colleagues also subdivided the obturator region into deep and superficial regions. They demonstrated that there were few metastatic lymph nodes in the deep region [12]. Our results are consistent with that report. No previous study supports our finding that the caudal external iliac sub-region rarely had positive nodes. However, the present results suggest the appropriateness of the definition of the external iliac region in the RTOG and JCOG guidelines, which set the lower end of the external iliac region at the top of the femoral head [2,4].

For the external iliac region above the aspect of the femoral head, 3 anatomically subdivided regions have been proposed [6,7]. According to the definition, positive nodes in the medial external iliac and intermediate external iliac regions were frequent in contrast to the lateral external iliac regions in our study. This observation was also made by Graham et al. [13]. Taylor et al. demonstrated that the normal node distribution extended more than 10 mm laterally to the external iliac artery and veins in their USPIO MRI study. Based on this finding, they recommended that the CTV should expand 17 mm laterally from the vessels to cover the region sufficiently [6]. However, our present study demonstrated that positive nodes were rare in the lateral external iliac region, and suggested that the expansion that Taylor proposed could be omitted in some cases.

Based on the findings from our present analyses, high-risk regions such as the cranial obturator and the medial and intermediate external regions must be irradiated sufficiently in all cases. In contrast, the caudal external iliac, caudal obturator, lateral external iliac and presacral regions, which demonstrated a very low incidence (≤ 5%) of positive nodes, might be allowed to be excluded in patients who satisfy all of the following criteria: small tumor size (≤ 4 cm) and no positive nodes on CT/MRI. The CTV shrinkage might help to reduce complications in the surrounding organs. Further investigation is needed to justify such modification in clinical practice. In the other remaining regions (i.e., common iliac, internal iliac), although no patient in this study had a solitary positive lymph node, the positive rate was not low. Therefore, we suggest that the common iliac and internal iliac regions should continue to be included in all cases for radical radiotherapy for patients with uterine cervical cancer.

This study has some limitations. First, the insufficient sensitivity of CT/MRI is critical. Bellomi and colleagues reported that the sensitivity and specificity of CT were 64% and 93%, respectively, and those of MRI were 72% and 93%, respectively [14]. The results of this study should be interpreted carefully due to the inadequate sensitivity and specificity of these methods. Meanwhile, Choi and coworkers compared the sensitivity and specificity of MRI and positron emission tomography/computed tomography (PET/CT) [15]. With MRI, the sensitivity and specificity were 30% and 92%, respectively, and with PET/CT, the sensitivity and specificity were 57% and 92%, respectively. Further study using PET/CT is encouraged. Second, the absence of histopathological confirmation is a serious weakness of the present study. Although some surgical series presented detailed data on the pathological positive node distribution [11,12], data for inoperable advanced-stage patients were sparse. In addition, it is difficult to apply the distribution of metastatic nodes from surgical findings directly to the 3D distribution on CT/MRI images for accurate CTV contouring. For these reasons, despite its insufficient sensitivity and specificity, some surrogate information could be obtained from the study using CT/MRI. Third, this study consists of a relatively small number of patients and a heterogenous population (i.e. stage, tumor size). Various systematic and random errors due to multicenter assessment over a long time period might negatively affect the validity of the study.

Conclusions

The present study demonstrated distribution patterns of positive pelvic nodes in patients with cervical cancer treated with definitive radiotherapy/chemoradiotherapy. The findings might contribute to future investigations for the individualization of CTV node contouring.

Abbreviations

3D: Three-dimensional; CT: Computed tomography; MRI: Magnetic resonance imaging; FIGO: Federation Internationale de Gynecologie et de Obstetrique; RTOG: Radiation Therapy Oncology Group; UK: United Kingdom; JCOG: Japan Clinical Oncology Group; CTV: Clinical target volume; NSR: Non-solitary region; OAR: Organs at risk; PET: Positron emission tomography.

Competing interests

The authors declare that they have no competing interests regarding this manuscript.

Authors' contributions
GK and TT designed this study, assembled the data, performed the statistical analysis and interpretation, and wrote the manuscript. KF, TK, TO, YK, RY, and TU provided study materials from each institution and proofed the manuscript. AY participated as a diagnostic radiologist and confirmed the distribution of positive lymph nodes. SI and MH helped to revise the manuscript. All authors read and approved the final manuscript.

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Clinical Investigation

A Dose–Response Analysis of Biochemical Control Outcomes After ^{125}I Monotherapy for Patients With Favorable-Risk Prostate Cancer

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Summary

Low-dose-rate brachytherapy is a widely accepted treatment for localized prostate cancer. Although excellent long-term results have been obtained, the dose–response relationship remains controversial. This retrospective study demonstrated that a high prostate dose after ^{125}I implantation produces better treatment outcomes and acceptable toxicity. We propose herein several prostate dose cutoff points for better biochemical control.

Purpose: To define the optimal dose for ^{125}I prostate implants by correlating postimplantation dosimetry findings with biochemical failure and toxicity.

Methods and Materials: Between 2003 and 2009, 683 patients with prostate cancer were treated with ^{125}I prostate brachytherapy without supplemental external beam radiation therapy and were followed up for a median time of 80 months. Implant dose was defined as the D90 (the minimal dose received by 90% of the prostate) on postoperative day 1 and 1 month after implantation. Therefore, 2 dosimetric variables (day 1 D90 and day 30 D90) were analyzed for each patient. We investigated the dose effects on biochemical control and toxicity.

Results: The 7-year biochemical failure-free survival (BFFS) rate for the group overall was 96.4% according to the Phoenix definition. A multivariate analysis found day 1 D90 and day 30 D90 to be the most significant factors affecting BFFS. The cutoff points for day 1 D90 and day 30 D90, calculated from ROC curves, were 163 Gy and 175 Gy, respectively. By use of univariate analysis, various dosimetric cutoff points for day 30 D90 were tested. We found that day 30 D90 cutoff points from 130 to 180 Gy appeared to be good for the entire cohort. Greater D90s were associated with an increase in late genitourinary or gastrointestinal toxicity $\geq$ grade 2, but the increase was not statistically significant.

Conclusions: Improvements in BFFS rates were seen with increasing D90 levels. Day 30 D90 doses of 130 to 180 Gy were found to serve as cutoff levels. For low-risk and low-tier intermediate-risk prostate cancer patients, high prostate D90s, even with doses exceeding 180 Gy, achieve better treatment results and are feasible.

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Introduction

Whereas no prospective dose escalation clinical trials have been conducted on permanent prostate brachytherapy for prostate cancer, much of the published data support a dose–response relationship with improvements in biochemical control being associated with increasing doses (1-12). A commonly used dosimetric parameter to describe the prostatic delivered dose is prostate D90, the minimum dose received by 90% of the postimplantation computed tomography (CT)-based prostate volume.

The Mount Sinai group suggested increased efficacy with greater biologically effective doses in prostate brachytherapy (2). They prescribe 160 Gy for their real-time planning, and they recommend D90 values of at least 180 Gy (3). However, the need for a prostate D90 of 180 Gy or more has not been established in low-risk patients (4). Morris et al (13) reviewed their experience with 2000 consecutive ^{125}I prostate implants to determine which pretreatment-related and treatment-related factors influenced prostate-specific antigen (PSA) control, and they concluded that D90 was not predictive of disease-free survival. The optimal D90 cutoff for postimplantation dosimetry thus remains a debated issue (14, 15). In this report, we present our updated brachytherapy results for localized prostate cancer and discuss the optimal dose for ^{125}I monotherapy by correlating postimplantation CT dosimetry with biochemical control and toxicity.

Methods and Materials

Between 2003 and 2009, 1313 consecutive patients with clinically localized prostate cancer were treated with permanent interstitial seed implants at Tokyo Medical Center, National Hospital Organization. The patients were classified into prognostic risk groups according to the National Comprehensive Cancer Network (www.nccn.org). In general, low-risk and low-tier intermediate-risk (defined as organ-confined disease, PSA <10 ng/mL, and Gleason score 3 + 4 with biopsy positive core rate <33%) patients received permanent prostate brachytherapy as monotherapy. In total, 686 patients with low-risk or low-tier intermediate-risk prostate cancer were given brachytherapy as monotherapy. Three patients were excluded from the analysis, 2 because follow-up was less than 1 year and the other because the patient died of cancer within 1 year after implantation. The remaining 683 patients were included in this analysis. Two hundred fifty-four patients (37.2%) received neoadjuvant androgen deprivation therapy (ADT) with the aim of prostate volume reduction or a longer waiting time. Because the Japanese national policy for patient discharge criteria mandates that total seed activity be kept below 1300 MBq, patients with prostate volumes >40 cc usually must undergo hormonal therapy to downsize the prostate before implantation (16). None of our present patients received adjuvant hormone therapy.

The implantation technique was previously described in detail (16, 17). Early in the study period, the preplanning method was used in the first 125 patients, and from December 2004 onward, the real-time planning method was used (18). All procedures were conducted with the use of ^{125}I free seeds, the only approved radioisotope available for permanent prostate brachytherapy in Japan. The prescribed dose was 145 Gy for the 324 patients treated through 2006 and 160 Gy for 359 patients after 2007. The entire prostate with no periprostatic margins was defined as the planning target volume. Intraoperative planning dosimetry aimed for 99% of the prostate to receive 100% of the prescribed dose (V100) and for 90% of the prostate (D90) to receive 110% to 120% of the prescribed dose. Postimplantation CT scans were obtained on both postoperative day 1 and 1 month after implantation, so that 2 dosimetric variables (day 1 D90 and day 30 D90) were analyzed for each patient. A single radiation oncologist (A.Y.) contoured the prostate on postimplantation CT scans in all patients and identified the seeds in the VariSeed treatment planning system (Varian Medical Systems, Palo Alto, CA) using a combination of manual and automated techniques.

Planned follow-up was by PSA blood tests and physical examination every 3 months for the first 2 years and every 6 months thereafter. The primary outcome measure was biochemical failure-free survival (BFFS). Biochemical failure was determined by use of the nadir +2 ng/mL definition (the Phoenix definition) (19). Patients with early rises in PSA that triggered the Phoenix definition but with subsequent declines in PSA values to <0.5 ng/mL without intervention were classified as having a benign bounce and were excluded from the analysis of failure. Genitourinary (GU) and gastrointestinal (GI) toxicities were prospectively assessed by the Common Terminology Criteria for Adverse Events version 4.0. Acute toxicity was defined as occurring within the first 12 months after implantation, with late toxicity developing after 12 months.

Statistical significance was tested with the unpaired t test for continuous variables and the χ^2 test for categorical variables. Actuarial survival curves were calculated by the Kaplan-Meier method to determine BFFS, and differences between time-adjusted rates were evaluated with the log-rank test. Univariate and multivariate Cox regression analyses were used to assess potential predictors of biochemical failure. Analyses were carried out with IBM SPSS Statistics Version 22 (IBM Corp., Chicago, IL). All tests were 2-sided, and statistical significance was set at the level of $P<.05$.

Results

The clinical features and the treatment and dosimetric parameters for the 683 patients included in the analysis are

Table 1 Clinical features and treatment and dosimetric parameters

Characteristic	Low-risk (n=455)		Low-tier intermediate- risk (n=228)			Total (n=683)	
	Median	Range/count, %	Median	Range/count, %	*P*	Median	Range/count, %
Continuous variable							
Age, y	66	38-83	68	49-87	.055	67.0	38-87
Pretreatment PSA, ng/mL	6.63	1.1-9.9	7.64	3.4-19.0	<.001	6.86	1.1-19.0
Positive biopsy rate, %	20.0	5.0-100	21.0	4.0-100	.542	20.0	5.0-100
Prostate volume, cc	25.0	8.5-45.6	23.3	9.6-49.4	.091	24.5	8.5-49.4
Day 1 D90, Gy	157.8	91.8-194.8	159.2	104.6-196.2	.307	158.4	91.8-196.2
Day 30 D90, Gy	185.0	131.3-223.3	184.1	126.4-233.6	.857	184.7	126.4-233.6
Categorical variables							
Gleason sum					<.001		
≤6		455 (100%)		89 (39.0%)			544 (79.6%)
7		0		139 (61.0%)			139 (20.4%)
Clinical T stage					<.001		
T1c		358 (78.7%)		147 (64.5%)			505 (73.9%)
T2a		97 (21.3%)		43 (18.9%)			140 (20.5%)
T2b		0		36 (15.8%)			36 (5.3%)
T2c		0		2 (0.9%)			2 (0.3%)
Neoadjuvant ADT					.839		
No		287 (63.1%)		142 (62.3%)			429 (62.8%)
Yes		168 (36.9%)		86 (37.7%)			254 (37.2%)
Planning technique					.075		
Preplanning		92 (20.2%)		33 (14.5%)			125 (18.3%)
Real-time planning		363 (79.8%)		195 (85.5%)			558 (81.7%)
Prescribed dose					.726		
145 Gy		218 (47.9%)		106 (46.5%)			324 (47.4%)
160 Gy		237 (52.1%)		122 (53.5%)			359 (52.6%)

Abbreviations: ADT = androgen deprivation therapy; D90 = the minimal dose received by 90% of the prostate; PSA = prostate-specific antigen.

detailed in Table 1. The median follow-up time was 80 months (range, 12-125 months). The follow-up time was at least 3 years for 672 patients (98.4%).

At the time of data extraction (January 1, 2014), 23 patients (3.4%) had experienced biochemical failure. The median time to biochemical failure in these patients was 52 months (range, 9-111 months). The 5-year and 7-year BFFS rates for the group overall were 97.9% and 96.4%, respectively, according to the Phoenix definition. The 7-year BFFS rates for low-risk and low-tier intermediate-risk patients were 97.5% and 94.3%, respectively ($P=.052$) (Fig. 1).

Multivariate Cox regression analysis including age, Gleason score, T stage, PSA, risk group, neoadjuvant ADT administration, planning technique, prescribed dose, day 1 prostate D90, and day 30 prostate D90 was conducted to test for predictors of BFFS. Day 1 D90 and day 30 D90 were both independent predictors of BFFS by the Phoenix definition (Table 2).

The day 1 D90s ranged from 91 to 196 Gy (median, 158 Gy) and the day 30 D90s from 126 to 233 Gy (median, 185 Gy). The ratios of the day 30 D90s to the day 1 D90s (day 30 D90/day 1 D90 ratio) ranged from 0.85 to 1.71 (median, 1.17). There was a significant correlation between the day 1 D90 and the day 30 D90 (correlation coefficient = 0.708; $P<.001$).

To estimate the predictive utilities of the day 1 D90 and the day 30 D90, we constructed a receiver operating characteristic (ROC) curve and determined the corresponding area under the curve (AUC). When applied to the entire cohort, day 1 D90 and day 30 D90 accrued AUC of 0.622 (95% confidence interval [CI], 0.502-0.742; $P=.047$) and 0.763 (95% CI, 0.672-0.853; $P<.001$), respectively (Fig. 2A). The cutoff points for the day 1 D90 and the day 30 D90 calculated from the ROC curves were 163 Gy and 175 Gy, respectively. Similar ROC curves for the low-risk and low-tier intermediate-risk patients are shown in Figure 2B and 2C. For the low-risk patients, although the day 30 D90 was associated with improved biochemical control (AUC = 0.704; 95% CI, 0.551-0.858; $P=.021$), the day 1 D90 was not predictive (AUC = 0.552; 95% CI, 0.350-0.754; $P=.554$). For the low-tier intermediate-risk patients, both the day 1 D90 (AUC = 0.703; 95% CI, 0.578-0.828; $P=.018$) and the day 30 D90 (AUC = 0.821; 95% CI, 0.731-0.911; $P<.001$) were associated with improved biochemical control.

To explore the dose–response relationship further, various dosimetric cutoff points for day 30 D90 were tested by univariate Cox regression analysis, as shown in Table 3. In the entire cohort, all cutoff points were associated with improved BFFS. Although all cutoff points were also associated with improved BFFS in the low-tier

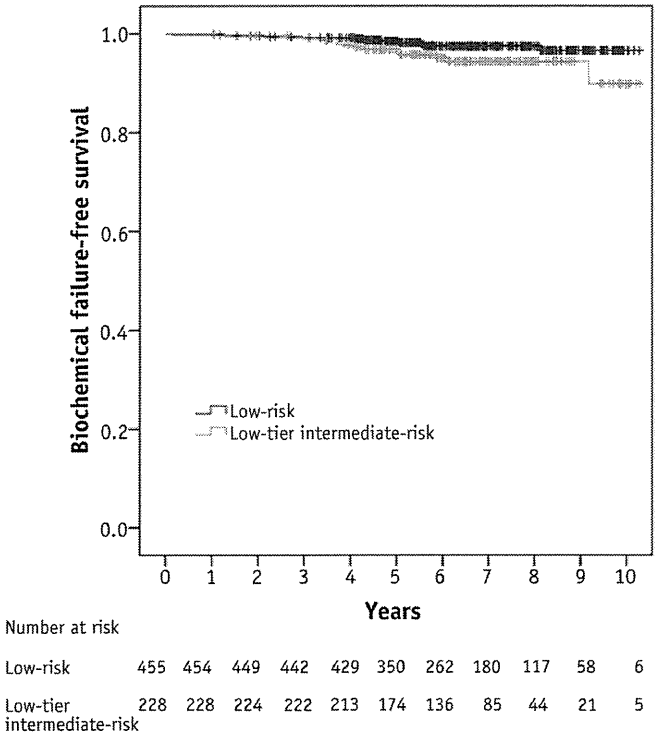

Fig. 1. Biochemical failure-free survival for the low-risk and low-tier intermediate-risk prostate cancer patients ($P=.052$).

intermediate-risk group, only 140 Gy and 160 Gy were statistically significant cutoff points in the low-risk group. When the entire patient population was divided into 3 groups by day 30 D90 dose categories, there was a significant difference for biochemical control: <160 Gy (n=85), 160 to <180 Gy (n=195), and ≥180 Gy (n=403). As shown in Figure 3, the BFFS rates at 7 years were 91.2%, 95.1%, and 98.5% for day 30 D90 doses <160 Gy, 160 to <180 Gy, and ≥180 Gy, respectively ($P=.001$).

Although no grade 3 or greater acute toxicity was observed, 42 patients (6.1%) required catheterization during the acute period after brachytherapy. Late grade 2-3 GU toxicity was experienced by 55 patients (8.1%). Late grade 3 GU toxicity occurred in 7 patients (1.0%) who experienced urinary retention requiring urethral dilatation, internal urethrotomy, or transurethral resection of the prostate. The late grade 2 GU toxicities were urinary urgency or retention. The incidences of late GU toxicities of grade 2-3 were 4.7% for the day 30 D90 doses <160 Gy, 6.2% for 160 to <180 Gy, and 9.7% for ≥180 Gy ($P=.159$). Late grade 2 GI toxicity was experienced by 9 patients (1.3%), but none experienced grade 3 GI toxicities. The late grade 2 GI toxicities primarily involved rectal bleeding. The rates of late grade 2 GI toxicities were 0% for the day 30 D90 doses <160 Gy, 1.0% for 160 to <180 Gy, and 1.7% for ≥180 Gy ($P=.405$).

Table 2 Cox regression analysis for biochemical failure according to the Phoenix definition

Variable	*P*	HR	95% CI
Age	.506	0.979	0.919-1.043
Risk group (low vs intermediate)	.402	1.820	0.448-7.388
Gleason score (≤6 vs 7)	.964	1.034	0.237-4.513
Clinical T stage (T1c/T2a vs T2b/c)	.523	1.656	0.352-7.782
Initial PSA	.658	1.047	0.855-1.281
Positive biopsy rate	.275	3.081	0.409-23.20
Neoadjuvant ADT (no vs yes)	.789	0.858	0.280-2.629
Planning technique (preplanning vs real-time)	.479	0.637	0.183-2.216
Prescribed dose (145 Gy vs 160 Gy)	.838	1.009	0.929-1.095
Day 1 D90	.030	1.045	1.004-1.088
Day 30 D90	.000	0.929	0.896-0.963

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; D90 = the minimal dose received by 90% of the prostate; HR = hazard ratio; PSA = prostate-specific antigen.

Discussion

Brachytherapy has come to be widely accepted for treating localized prostate cancer. Excellent long-term results have been obtained in many centers (2-5,9-13, 20, 21). Whereas no prospective dose escalation clinical trials have been conducted in cases receiving ^{125}I brachytherapy for prostate cancer, ample retrospective data confirm the importance of dosimetry for outcomes. In our current study, improvements in biochemical control rates were seen with increasing D90 levels in post-implantation dosimetry on day 1 or day 30. On multivariate analysis, only the actual delivered dose (D90) was found to affect biochemical control (Table 2).

To the best of our knowledge, this is the first report documenting significant biochemical control based on both the day 1 and the day 30 dosimetry evaluation. ROC analyses showed day 30 D90 to be more predictive than day 1 D90 of improved biochemical control. The American Brachytherapy Society (ABS) recommends that CT-based postoperative dosimetry be performed within 60 days of implantation and that the optimal CT timing to minimize edema-derived dosimetry error is radionuclide specific: 30 ± 7 days for ^{125}I (22). Our methods with respect to the timing of post-implantation dosimetry are considered to be consistent with the ABS recommendation. Our planning technique showed an average D90 of 156 Gy (standard deviation, 16) at day 1 and 183 Gy (standard deviation, 18) at day 30; the difference was large at 17%. Waterman et al (23) examined D90 based on the CT dosimetry performed on the implantation day and on day 46 (±23 days) for 50 consecutive patients treated with ^{125}I implants. The mean D90 increased from the values obtained on the implantation day by 15 ± 17%, consistent with expected edema resolution. The increase in D90 was found to be proportional to the magnitude of edema and

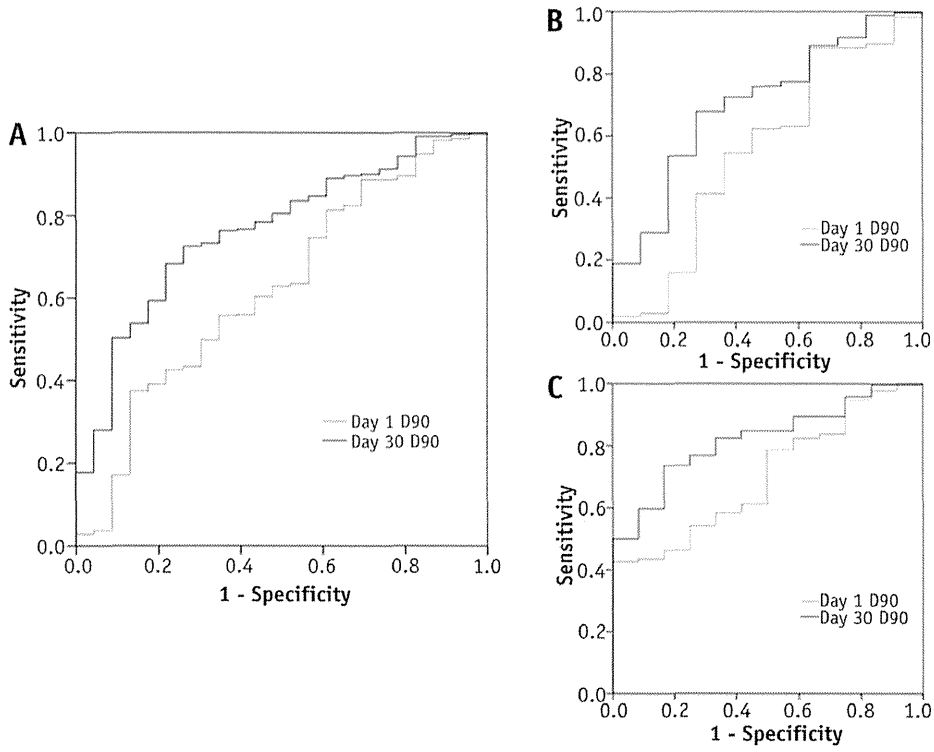

Fig. 2. Receiver operating characteristic (ROC) curves showing the relationship between biochemical control and D90. (A) ROC curves for the entire cohort. (B) ROC curves for low-risk patients. (C) ROC curves for low-tier intermediate-risk patients.

the implant-day D90 value. However, the amounts of increase varied widely among patients; the standard deviation for the increase in D90 was ±24 Gy. They concluded that predicting the D90 from the implant-day values would be a poor substitute for actual post-implantation dosimetry performed on a later day. D90 values change markedly from day 0 through day 30 after implantation, and the effect of imaging timing on dose reporting should be considered when variable dose—response thresholds are being compared.

In a recent large series reported by Morris et al (13), D90 values lower than 130 Gy at day 0 or day 28 were predictive of an increased risk of recurrence in the non-ADT subset, but none of the other cutoff points was predictive in subset analysis. In their study, 23% of patients had day 0 dosimetry, whereas 77% had 1-month post-implantation dosimetry. D90 values change greatly from 0 through 30 days after implantation, and it may not be advisable to regard D90 values with different dosimetry timings as identical. Implantation philosophy may also have an effect on dose—response thresholds associated with better biochemical outcomes. The planning algorithm applied by Morris et al sought to raise the 144 Gy isodose surface to cover treatment margins of 3 to 5 mm beyond the prostate. As in their study, adding margins on the prostate to define the planning target volume and then implanting many seeds outside the gland may require even lower D90 values to optimize local control.

Table 3 Biochemical failure-free survival for various day 30 D90 cutoff points

	Subgroup								
	Low-risk (n=455)			Low-tier intermediate-risk (n=228)			Total (n=683)		
Cutoff point	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI
130 Gy				.024	0.093	0.012-0.729	.006	0.061	0.008-0.456
140 Gy	.002	0.083	0.018-0.387	.024	0.093	0.012-0.729	.000	0.107	0.032-0.364
150 Gy	.067	0.238	0.051-1.106	.024	0.174	0.038-0.795	.008	0.231	0.078-0.686
160 Gy	.045	0.282	0.082-0.970	.029	0.272	0.085-0.874	.003	0.271	0.116-0.632
170 Gy	.220	0.472	0.142-1.567	.010	0.201	0.060-0.679	.006	0.307	0.133-0.707
180 Gy	.091	0.316	0.083-1.200	.016	0.154	0.033-0.708	.004	0.229	0.085-0.622

Abbreviations: CI = confidence interval; D90 = the minimal dose received by 90% of the prostate; HR = hazard radio.

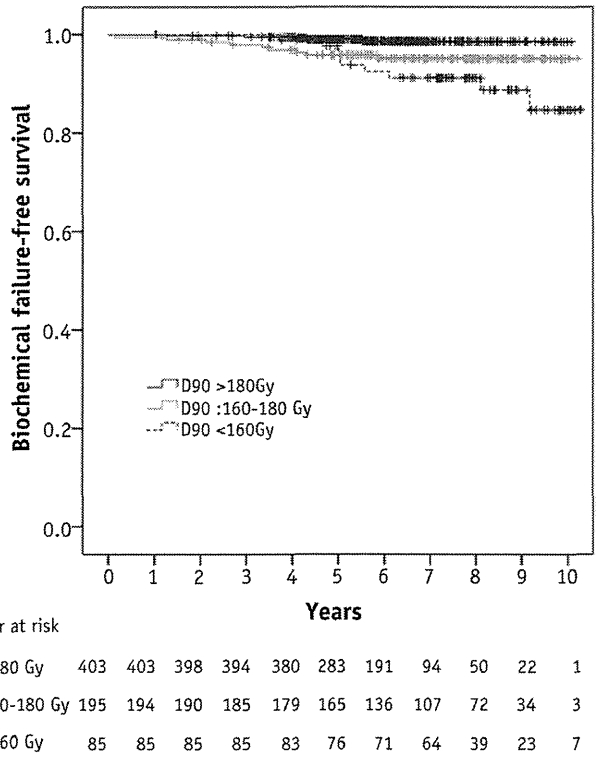

Fig. 3. Biochemical failure-free survival according to the prostate D90 dosimetric assessment ($P = .001$).

Butler et al (24) also reported that the biologically equivalent dose (BED) was not a predictor of biochemical progression in a population of 1473 consecutive permanent brachytherapy patients. Their treatment plans involved the use of a large number of extraprostatic seeds, assuring that the prescribed dose completely covered an explicit target volume enlarging the prostate >4 mm laterally and anteriorly, and implants were also placed in the proximal seminal vesicles. In Japan, ^{125}I seed implants were approved in 2003, but only a Mick applicator technique was available at that time. The higher D90 threshold of 180 Gy, as in our study, may be required for implants with seeds only inside the prostate to raise the dose enough to treat extracapsular extension of the disease. According to the original Partin data obtained with use of the Roach formula, even low-risk patients can have an extracapsular extension exceeding 40% at the time of radical prostatectomy (25). This may have accounted for the differences in the required dose being more pronounced in higher-risk patients, given that the incidence of extracapsular extension increases with risk group.

In our current study, day 30 D90 levels of 130 to 180 Gy appeared to be good cutoff points for the entire cohort including the low-risk and the low-tier intermediate-risk patients. Our study is the first, to our knowledge, to demonstrate significant cutoff values at dose levels as high as 180 Gy. ROC analyses (Fig. 2) and Cox regression analyses (Table 3) showed day 30 D90 to be more predictive in the low-tier intermediate-risk patients with improved biochemical control than in the low-risk patients. These results suggest dose escalation to be more beneficial in higher risk patients.

In a multi-institutional series reported by Stone et al (5), patients with Gleason scores of 8 to 10 demonstrated improved overall and metastasis-free survival if a greater BED was delivered. The recent publication by Spratt et al (26), which compared the use of high-dose intensity modulated radiation therapy (IMRT) alone and brachytherapy combined with IMRT (combo-RT), showed enhanced dose escalation using combo-RT to be associated with superior distant metastasis-free survival outcomes for intermediate-risk patients. These 2 studies are arguably more relevant than prior investigations because they obtained data that included "hard" clinical endpoints, not just biochemical recurrence. These data seem to indicate that primary control of prostate cancer not only improves biochemical control but also decreases subsequent metastases and death. Although we cannot show improvements in overall survival as yet, improvements in biochemical control with increasing D90 levels may lead to better overall survival in longer follow-up of patients with favorable-risk prostate cancer.

There are reports showing the feasibility, safety, and oncologic results of prostate D90 of 180 Gy or greater (27, 28). In a report on doses of ≥180 Gy, 5-year biochemical disease-free survival was very favorable but not superior to the results for brachytherapy with a D90 of 140 to 180 Gy (27, 28). The report by Kao et al (27) on doses of ≥180 Gy described toxicities within the expected range, with the rate of rectal bleeding of grade 2 or greater at 5 years being 11.5%, that of acute urinary retention being 10.7%, and a maintenance of potency rate of 73.4% at 5 years after implantation. Another report showed that D90s from 180 to 200 Gy were apparently well tolerated without an increase in the incidence of toxicity (28). In the present study, higher D90s were found to be associated with a small increase in late toxicity ≥ grade 2, but there were no significant differences between our D90 groups. This observation supports the feasibility, safety, and better treatment results of high D90s (ie, 160 to 180 Gy or even greater) for favorable-risk patients. By contrast, a small increase in late toxicity with dose escalation may lead to a significant increase in toxicity for the overall population. Unjustifiable dose escalation ignoring dose-volume constraints must be avoided. Given the high doses delivered to the prostate, the practitioner needs to apply a meticulous technique adhering to dose-volume constraints for the rectum and urethra in an effort to minimize toxicity.

Conclusion

Improvements in biochemical control rates were seen with increasing D90 levels in postimplantation dosimetry on both day 1 and day 30. Day 30 D90 was shown to be more predictive than day 1 D90 with improved biochemical control. Day 30 D90 levels of 130 to 180 Gy appeared to be

good cutoff points. Although greater D90s are associated with a small increase in late toxicity ≥ grade 2, the differences did not reach statistical significance. Our results show the feasibility, safety, and better treatment results of high D90s, with 160 to 180 Gy or even greater doses.

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Patterns of Practice in the Radiation Therapy for Bladder Cancer: Survey of the Japanese Radiation Oncology Study Group (JROSG)

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Objective: To retrospectively analyze the clinical outcomes of radiation therapy with or without chemotherapy for bladder cancer in Japan.
Methods: A questionnaire-based survey of patients with pathologically proven bladder cancer treated by definitive radiation therapy between 2002 and 2006 was conducted by the Japanese Radiation Oncology Study Group, and the clinical records of 159 patients were collected from 17 institutions. Concurrent intra-arterial chemoradiotherapy and concurrent systemic chemoradiotherapy were administered in 51 and 33 patients, respectively.
Results: The 5-year overall survival and bladder preservation rates were 48 and 39%, respectively. Eighty-nine (56%) patients developed recurrence (bladder, 48; regional lymph nodes, 4; distant sites, 41). The results of multivariate analysis revealed that adoption of chemotherapy was the only significant prognostic factor for overall survival (relative risk = 0.615 [95% confidence interval: 0.439–0.862], $P = 0.005$). The type of chemotherapy administered did not significantly affect the local control or overall survival rates. The actuarial 5-year overall survival rates and bladder preservation in the radiation therapy combined with intra-arterial chemotherapy group were 64 and 58%, respectively, and the corresponding rates in the radiation therapy combined with systemic chemotherapy group were 67 and 42%, respectively.
Conclusions: The results of this survey revealed the current status of practice of radiation therapy for bladder cancer in Japan. A multi-institutional prospective study is needed based on the results of this study to determine the optimal radiotherapeutic approach, including the need for concurrent chemotherapy and the appropriate chemotherapy regimen for invasive bladder cancer.

Key words: bladder cancer – radiation therapy – systemic chemotherapy – intra-arterial chemotherapy

INTRODUCTION

In Japan, the actual annual incidence of bladder cancer has increased in recent years to approximately 7.6 per 100 000 people (1). Radiation therapy (RT) is used fairly frequently for patients with bladder cancer, despite the lack of mature clinical evidence regarding its effectiveness as compared with that of standard therapies, including radical cystectomy. The standard treatment for invasive bladder cancer is radical cystectomy, however, patients in whom surgery is contraindicated due to intercurrent disease or who refuse to undergo surgery are treated by definitive RT as an alternative treatment option.

Concurrent chemotherapy with RT has become established as an effective bladder-preserving approach (2–11). However, RT has been used with or without chemotherapy to treat invasive bladder cancer in Japan. Hence, we collected clinical data from institutions that belong to the Japanese Radiation Oncology Study Group (JROSG), to clarify the treatment trends and methods, including the dose of the RT and usage of chemotherapy concurrently with RT in Japan. In this study, we retrospectively analyzed the clinical data, especially focusing on the impact of the RT and use of concurrent chemotherapy on the clinical outcomes, with the aim of clarifying the optimal radiotherapeutic approach for invasive bladder cancer.

PATIENTS AND METHODS

Patient Selection

A questionnaire-based survey of patients with pathologically proven bladder cancer who were treated by definitive RT between 2002 and 2006 was conducted by the JROSG at one of the 17 institutions belonging to the group. The facilities that participated in this study included 13 university hospitals, 2 cancer centers, and 2 public hospitals. From a total of 189 registered cases, we analyzed the data of 159 patients whose follow-up duration was 6 months or longer after the completion of RT. Regarding the eligibility criteria for this survey, patients whose prescribed dose was 30 Gy or more were considered to be eligible, because a relatively low total RT dose has generally been used in patients receiving concurrent intra-arterial chemotherapy (IAC) (12–14).

As for histological diagnosis, 150 patients received transurethral resection of bladder tumor (TUR-BT) and 9 patients were diagnosed in cytological examination of the urine.

In this study, we classified the RT approaches as follows: RT alone, RT with concurrent systemic chemotherapy (RT + SC; SCR) or RT with concurrent IAC (RT + IAC; intra-arterial chemoradiotherapy (IACR)). The patient characteristics are listed in Table 1. Bladder preservation or local control was defined as the state in which there was no recurrent or persistent tumor in the bladder.

Table 1. Patient characteristics

	RT $n = 75$	SCR $n = 33$	IACR $n = 51$	Total $n = 159$
Follow-up (months)				
Median	20	32	49	27
Range	6–88	6–93	6–92	6–93
Age				
Median	79	75	73	76
Range	52–92	38–84	43–90	38–92
Sex				
Male	53 (71)	23 (70)	41 (80)	117 (74)
Female	22 (29)	10 (30)	10 (20)	42 (26)
T-stage				
Tis	3 (4)	0	0	3 (2)
T1	2 (3)	4 (12)	9 (18)	16 (10)
T2	29 (39)	10 (30)	19 (37)	58 (36)
T3	27 (36)	13 (39)	17 (33)	57 (36)
T4	14 (19)	6 (18)	6 (12)	26 (16)
N-stage				
N0	69 (92)	26 (79)	47 (92)	142 (89)
N1	4 (5)	3 (9)	3 (6)	10 (6)
N2	2 (3)	4 (12)	1 (2)	7 (4)
Stage				
0is	3 (4)	0	0	3 (2)
I	2 (3)	3 (9)	9 (18)	14 (9)
II	29 (39)	9 (27)	18 (35)	56 (35)
III	26 (35)	14 (42) *T4a: 2	16 (31) *T4a: 1	56 (35)
IV	15 (20)	7 (21)	8 (16)	30 (19)
Grade				
1	4 (5)	1 (3)	2 (4)	7 (4)
2	18 (24)	11 (33)	19 (37)	48 (30)
3	44 (59)	19 (58)	23 (45)	86 (54)
Unknown	9 (12)	2 (6)	7 (14)	18 (11)
Pathology				
Urothelial cancer	70 (93)	33 (100)	45 (88)	148 (93)
SCC	3 (4)	0	4 (8)	7 (4)
Small cell cancer	0	0	2 (4)	2 (1)
Other	2 (3)	0	0	2 (1)

Data are presented as the number of patients, with percentages indicated in parentheses.
RT, radiation therapy; SCR, systemic chemoradiotherapy; IACR, intra-arterial chemoradiotherapy; SCC, squamous cell carcinoma.

Statistical Analysis

Survival was calculated by the Kaplan–Meier method, and differences were expressed at a 5% significance level with a two-tailed log-rank test. Multivariate analysis of the data was performed using a Cox proportional hazards model. All calculations and survival displays were conducted using the SPSS 15.0J statistical software (SSPS Inc., Chicago, IL, USA). Late

complications were graded according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC), Version 3.0 (15).

RESULTS

Radiation Therapy

First, we evaluated the differences in the RT protocol, including the RT field and total RT dose, etc., in the collected records. Among all the patents included in the analyses, 50% received whole-pelvis RT, or small-pelvis RT, in which the radiation field encompassed the superior border at the bottom of the ileo-sacral joint to just below the obturator foramen, while the others, except four patients (0.3%) in whom the RT field remained unknown, received local RT for the entire urinary bladder without pelvic lymph node irradiation. The total RT dose ranged from 30 to 66 Gy (median, 60 Gy), administered on 5 days of the week in fractional doses of 1.8–2 Gy. Three patients were treated by hyperfractionated RT using two daily fractions of 1.3–2 Gy, administered on 5 days of the week. The RT protocols, including the RT field and total RT dose are summarized in Table 2.

Concurrent Chemoradiotherapy

Thirty-three patients (21%) received concurrent chemoradiotherapy. Among these, 30 patients (91%) were treated with platinum-based chemotherapy regimens; 16 of these patients (48%) received weekly (35 mg/m^2) or monthly (100 mg/m^2) cisplatin alone combined with RT. With regard to the response to concurrent chemoradiotherapy, complete response was obtained in 23 patients (70%), excluding 3 patients in whom the response could not be determined because diagnostic cystoscopy was not performed.

Table 2. Summary of the RT approaches

	RT alone $n = 75$	SCR $n = 33$	IACR $n = 51$	Total $n = 159$
Technique				
Entire bladder	31 (41)	14 (42)	33 (65)	78 (49)
Small pelvis	33 (44)	11 (33)	9 (18)	53 (33)
Whole pelvis	10 (13)	7 (21)	7 (14)	24 (15)
Unknown	1 (1)	1 (3)	2 (4)	4 (3)
Dose (Gy)				
Median	60	60	50	60
Range	30–66	40–66	30–65	30–66
30≤, <50	30–50: 3 (4)	40–50: 3 (9)	30–40: 25 (49)	31 (19)
50≤, <60	17 (23)	9 (27)	6 (12)	32 (20)
60	29 (39)	9 (27)	13 (25)	51 (32)
60<	26 (35)	12 (12)	7 (14)	45 (28)

Data are presented as the number of patients with percentages indicated in parentheses.

Intra-arterial Chemoradiotherapy

Fifty-one patients (32%) were treated by IACR, and the regimens used were as follows: cisplatin alone in 36 (71%) patients, and cisplatin/carboplatin plus an anthracycline in 13 (25%) patients. Among the patients receiving intra-arterial cisplatin, 24 (47%) received the intra-arterial chemotherapy combined with systemic chemotherapy. Regarding the response to intra-arterial chemoradiotherapy, complete response was obtained in 41 patients (80%).

Overall Survival

The 2-year and 5-year rates of OS for all patients were 65 and 48%, respectively (Fig. 1). The 5-year survival rates of the patients treated by RT alone, RT + SC and RT + IAC were 26, 67 and 64%, respectively (Fig. 2). Regarding the recurrence pattern, the locoregional recurrence rate of RT alone, RT + SC and RT + IAC were 39, 27 and 27%, respectively. The extrapelvic recurrence rates of RT alone, RT + SC and RT + IAC were 27, 18 and 22%, respectively. In this respect, both the locoregional and extrapelvic recurrence rates were higher in the RT alone group than in the RT + SC or RT + IAC group (Table 3). The results of multivariate analysis revealed that adoption of concurrent chemotherapy was the only significant prognostic factor for OS (Table 4).

In the present study, the 2-year and 5-year rates of bladder preservation for all patients were 51 and 39%, respectively (Fig. 3), and the corresponding rates in the RT alone, RT + SC and RT + IAC groups were 24, 42 and 58%, respectively (Fig. 4).

When the bladder preservation rate was compared between the two types of chemotherapy, the rate in the IACR was numerically better than that in the SCR, although this difference did not reach statistical significance ($P = 0.55$).

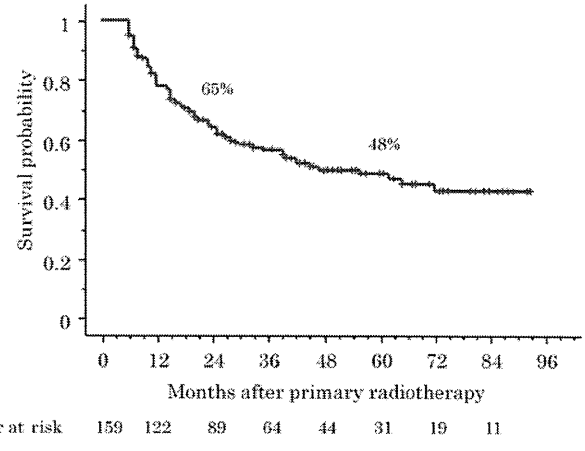


Figure 1. Overall survival curve of all patients.

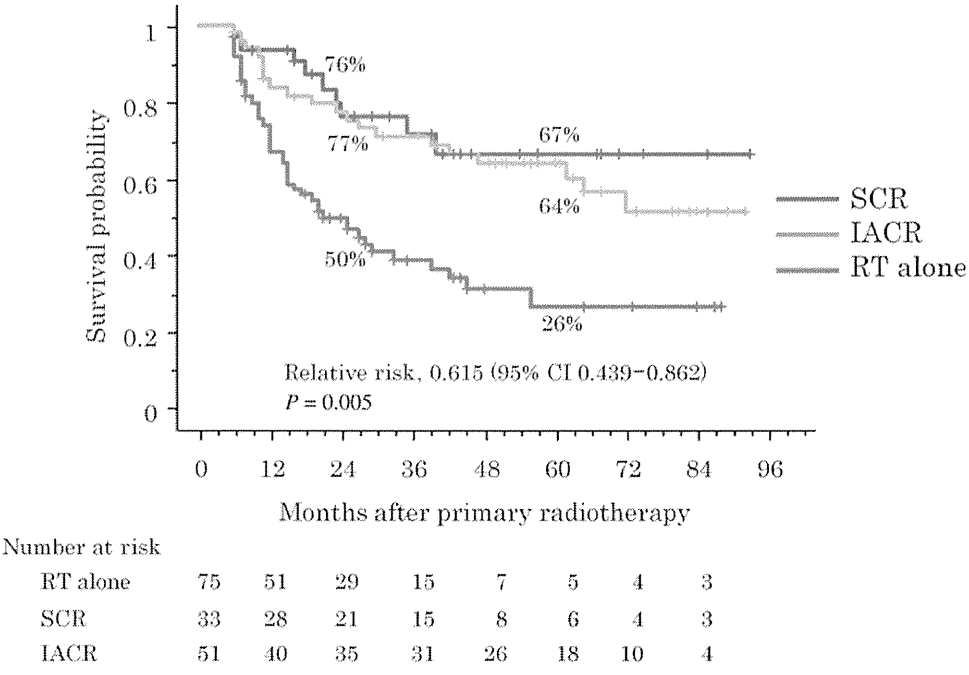


Figure 2. Overall survival in the RT alone, SCR and IACR groups. *P* values were calculated by the log-rank test stratified according to the radiation therapy treatment group. RT, radiation therapy; SCR, systemic chemoradiotherapy; IACR, intra-arterial chemoradiotherapy.

Table 3. Pattern of recurrence

	Rec./Meta.	Case	Incidence rate	Type of failure
RT alone $n = 75$	None	19	(25%)	Pelvic LN meta: 1 (out of field)
	Locoregional	29	39%	
	Extrapelvic	20	27%	
	Unknown	7		
SCR $n = 33$	None	16	(49%)	All cases recurred locally.
	Locoregional	9	27%	
	Extrapelvic	6	18%	
	Unknown	2		
IACR $n = 51$	None	24	(47%)	Pelvic LN meta: 3 (out of field)
	Locoregional	14	27%	
	Extrapelvic	11	22%	
	Unknown	2		

LN, lymph node.

Usage and Regimen of Chemotherapy and Salvage Treatment

Twelve patients (8%) were administered neoadjuvant chemotherapy with platinum-based regimens (Table 5).

Due to recurrent or residual tumor, nine patients received cisplatin-based IACR or SCR following RT alone, while four underwent TUR-BT. Three of these patients subsequently underwent cystectomy.

Table 4. Multivariate analysis

Factor	*P* value	RR (95.0% CI)
T-stage	0.378	1.119 (0.872–1.435)
N-stage	0.015	1.714 (1.108–2.650)
Grade	0.783	0.996 (0.759–1.231)
Pathology	0.395	1.422 (0.632–3.198)
Total dose	0.638	0.993 (0.963–1.023)
Sex	0.232	0.701 (0.402–1.247)
Chemotherapy	0.005	0.615 (0.439–0.862)
Age	0.014	1.036 (1.007–1.066)

RR, relative risk; CI, confidence interval.

Adverse Events

Regarding late adverse events, four patients (3%) experienced Grade 3 gastrointestinal toxicities (ileus in two and rectal bleeding in two patients). The RT doses in these patients who received concurrent chemotherapy were 59.6 and 66 Gy. Five patients (3%) experienced Grade 3 genitourinary toxicities (cystitis in three and urethral stricture in two patients). The RT approach in these patients was RT alone in three patients, RT + SC in one patient and RT + IAC in one patient.

DISCUSSION

Radical cystectomy is established as the standard treatment for muscle-invasive bladder cancer, although an estimated

approximately 40% of patients with organ-confined disease at cystectomy develop recurrences (16–18). Regarding the indications of RT with or without chemotherapy, patients who are not suitable candidates for radical cystectomy due to general comorbidities or extension of the disease are treated by RT with or without chemotherapy, with radical or palliative intent. Hence, the treatment outcomes of RT with or without chemotherapy for bladder cancer are considered to be unsatisfactory. According to this survey, the 5-year rates of bladder preservation and OS for all patients were 39 and 48%, respectively. The results in RT for invasive bladder cancer in this survey were similar to other findings of the clinical trials (7). According to this survey, the 5-year rates of bladder preservation and OS associated with RT alone were 24 and 26%, respectively, with a median survival time of 20 months. Thus, the reported clinical outcomes of RT for invasive bladder cancer are inferior to those of the radical surgical approach (19). One of the major reasons for this difference may be that the total dose of RT could not be increased due to the maximum tolerated dose of the urinary bladder, indicating that an excessive dose to the whole bladder can result in the occurrence of severe bladder atrophy and functional bladder impairment, even after eradication of the primary tumor. The results of this survey revealed that the median total dose of RT was 60 Gy (range 30–66 Gy), however, the RT protocol, including the RT field and the number of portals differed greatly among the institutions.

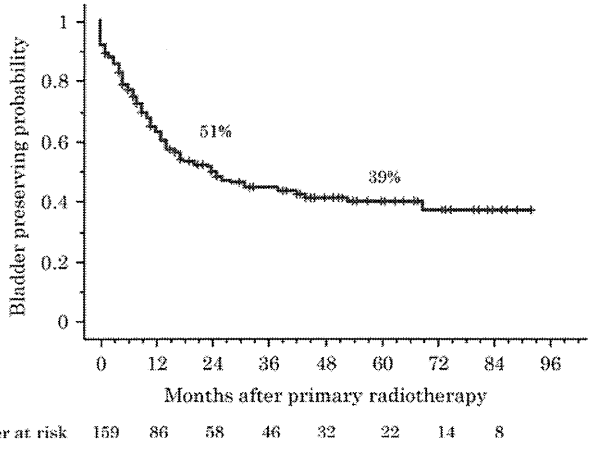
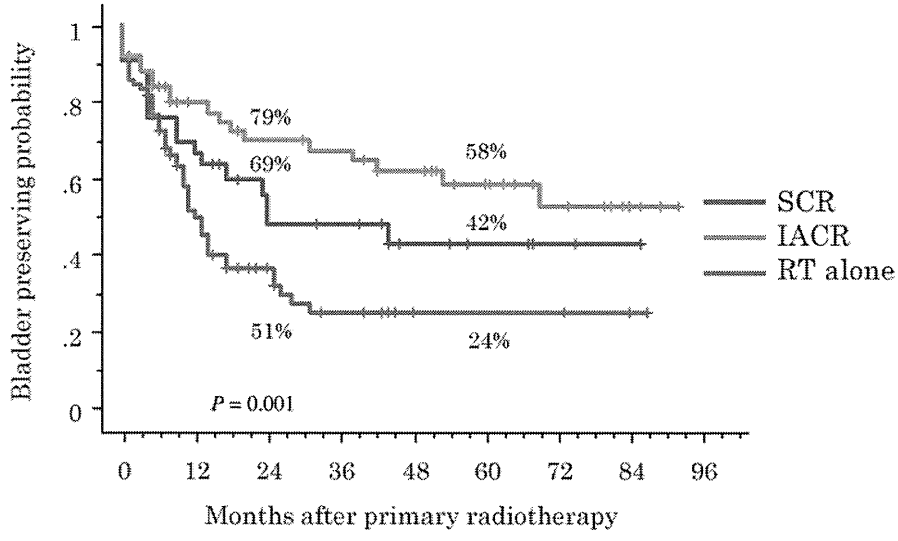


Figure 3. Bladder preservation curve of all patients.

Concerning the method of RT, it was thought that having a radiation field with the entire bladder or small pelvis was sufficient, although only one report of a single-institution experience randomized study was made regarding the radiation field (20), except that studies regarding the radiation dose were published (21–24). The present study also failed to yield any significant results concerning the optimal radiation field. Thus, RT alone has not been established as an optimal treatment method for obtaining satisfactory local control or improved survival rates in patients with invasive bladder cancer (25).

Regarding the usage of chemotherapy, RT with concurrent chemotherapy has been established as the standard approach for bladder preservation. The major roles of chemotherapy are to improve the local control and reduce the likelihood of distant metastases. Concurrent chemotherapy with RT has been investigated in an attempt to take advantage of the radiosensitizing capabilities of drugs in patients with invasive



Number at risk

RT alone	75	30	17	9	4	3	3	2
SCR	33	22	14	11	7	4	2	1
IACR	51	33	28	26	21	16	9	5

Figure 4. Bladder preservation in the RT alone, SCR and IACR groups. *P* values were calculated by the log-rank test stratified according to the radiation therapy treatment group.

Table 5. Chemotherapy regimens for neoadjuvant chemotherapy

	$n = 12$	RT alone	SCR	IACR
CDDP + ADM (IAC)	4	3	0	1
CDDP (SC)	1	0	1	0
CDDP (IAC)	1	0	0	1
MVAC	4	1	2	1
MEC	1	0	1	0
Combination chemotherapy	1			
CDDP (IAC) and MVAC		0	0	1

SC, systemic chemotherapy; IAC, intra-arterial chemotherapy; CDDP, cisplatin; ADM, doxorubicin; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; MEC, methotrexate, epirubicin and cisplatin.

bladder cancers, and concurrent chemotherapy has been well-recognized to improve the clinical outcomes through improvement of the local control rates without compromising the quality of life (QOL) (26–28). In this multi-institutional survey, the actuarial 5-year survival rates of RT plus concurrent chemotherapy was 65%, which was significantly better than that obtained with RT alone. In addition, IAC has been well utilized for the treatment of invasive bladder cancer in Japan, as compared with USA or Europe. Based on clinical experience, the total dose of RT in RT + IAC is often lower than that in RT plus SC (12–14). In this survey, the total dose of RT in patients receiving RT + IAC was approximately 30 Gy. However, the survivals rates in the patients who were treated by SCR or IACR were almost similar despite the large difference in the total dose of RT. Similar results have been reported from other studies (12–14). Hence, IACR might be an effective alternative to the radiotherapeutic approach for invasive bladder cancer. As described in the Results, the results of multivariate analysis revealed that adoption of concurrent chemotherapy was the only significant prognostic factor for OS, but we consider that a definite conclusion cannot be drawn. Main reasons are retrospective nature of this study, indicating that selection bias such as the difference in the pattern of clinical practice according to each institution, and also the difference in follow-up duration according to each treatment modality.

Regarding the recurrence patterns, the intrapelvic recurrence rates in patients treated by IACR and SCR were almost similar, at 27%. Similarly, the rates of extrapelvic recurrence, including distant metastasis and extrapelvic lymph node metastasis, were also similar. This may be explained by the fact that local injection of high-dose anticancer drugs resulted provided a higher concentration of the drugs in the cancer cells, resulting in a high capability for enhancement of the radiosensitivity. Therefore, usage of concurrent chemotherapy, irrespective of whether systemic or intra-arterial, is mandatory to obtain a satisfactory local control rate, if RT is selected as a bladder preservation therapy. This has also been confirmed by previous reports (2–11).

Concerning the use of TUR-BT, it is important as one of the therapeutic methods for the bladder cancer (11). However, detailed information regarding resection status after TUR-BT or the role of TUR-BT as a treatment modality is unclear.

The results of this survey demonstrated large differences in the RT technique used and usage/method of chemotherapy among the institutions (29). This may be partly attributed to the fact that no standard treatment approach for invasive bladder cancer has been established yet in Japan. Therefore, the results of this survey may represent reference information for radiotherapeutic management of invasive bladder cancer, and a multi-institutional prospective study is necessary, based on the result of this study, to determine the optimal radiotherapeutic approach, including the chemotherapy regimens for concurrent use, for the treatment of invasive bladder cancer.

CONCLUSIONS

In conclusion, this survey revealed the current pattern of adoption of radiotherapeutic approaches for bladder cancer in Japan. A multi-institutional prospective study is needed based on the results of this study to determine the optimal radiotherapeutic approach, including appropriate chemotherapy regimen for invasive bladder cancer.

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Conflicts of interest statement

None declared.

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RADIATION ONCOLOGY

RESEARCH Open Access

Combined brachytherapy and external beam radiotherapy without adjuvant androgen deprivation therapy for high-risk prostate cancer

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Abstract

Background: To report the outcomes of patients treated with combined iodine-125 (I-125) brachytherapy and external beam radiotherapy (EBRT) for high-risk prostate cancer.

Methods: Between 2003 and 2009, I-125 permanent prostate brachytherapy plus EBRT was performed for 206 patients with high-risk prostate cancer. High-risk patients had prostate-specific antigen ≥ 20 ng/mL, and/or Gleason score ≥ 8, and/or Stage ≥ T3. One hundred and one patients (49.0%) received neoadjuvant androgen deprivation therapy (ADT) but none were given adjuvant ADT. Biochemical failure-free survival (BFFS) was determined using the Phoenix definition.

Results: The 5-year actuarial BFFS rate was 84.8%. The 5-year cause-specific survival and overall survival rates were 98.7% and 97.6%, respectively. There were 8 deaths (3.9%), of which 2 were due to prostate cancer. On multivariate analysis, positive biopsy core rates and the number of high-risk factors were independent predictors of BFFS. The 5-year BFFS rates for patients in the positive biopsy core rate <50% and ≥50% groups were 89.3% and 78.2%, respectively ($p = 0.03$). The 5-year BFFS rate for patients with the any single high-risk factor was 86.1%, compared with 73.6% for those with any 2 or all 3 high-risk factors ($p = 0.03$). Neoadjuvant ADT did not impact the 5-year BFFS.

Conclusions: At a median follow-up of 60 months, high-risk prostate cancer patients undergoing combined I-125 brachytherapy and EBRT without adjuvant ADT have a high probability of achieving 5-year BFFS.

Keywords: Prostate cancer, Brachytherapy, High risk, Androgen deprivation therapy

Background

The prognosis for men with clinically localized, high-risk prostate cancer treated with external beam radiotherapy (EBRT) has improved significantly over the last 15 years [1-7]. Most notably, the addition of androgen deprivation therapy (ADT) to standard dose EBRT has been shown in several large, randomized studies to increase cause-specific survival (CSS) and overall survival (OS) [1,2]. In addition, increasing the external beam dose to 78–80 Gy has led to improvements in biochemical failure-free survival (BFFS) [3-6]. However, even with these improvements, high-risk prostate cancer remains a therapeutic challenge for both urologists and radiation oncologists.

Stock et al. documented results for a series of patients with high-risk disease receiving trimodality therapy consisting of brachytherapy, EBRT and ADT, reporting excellent biochemical and pathologically confirmed local control [8]. Their group also reported a recent series showing favorable distant control and disease-specific survival in men with Gleason score 8–10 disease [9], and long-term biochemical control in men with extraprostatic disease [10]. Brachytherapy provides a means to further raise the local dose and has been used in an attempt to improve results in men with high-risk disease. With high biologic effective doses (BED) being achievable with EBRT plus brachytherapy, BFFS rates of

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85–90% have reportedly been obtained in large cohorts of men with high-risk disease [11,12]. Some previous studies demonstrated a benefit of ADT used in conjunction with EBRT to treat locally advanced prostate cancer [1,2,13]. However, these studies, which demonstrated an advantage with the addition of ADT, were conducted during a period when radiation doses may have been inadequate to control all local disease. Clear evidence for using adjuvant ADT when much higher radiation doses are delivered is thus lacking.

The use of permanent prostate brachytherapy employing iodine-125 (I-125) seeds has expanded rapidly in Japan since the establishment of guidelines for this treatment modality and revision of the dosimetric regulations related to radiation hazards and safety in 2003. In this report, we summarize the clinical outcomes of patients in our experience receiving combined therapy consisting of permanent prostate brachytherapy and EBRT without adjuvant ADT.

Methods

Between September 2003 and June 2009, 206 consecutive Japanese patients with high-risk localized prostate cancer were treated with combined modality therapy consisting of I-125 permanent seed implantation and supplemental EBRT at either the National Hospital Organization Tokyo Medical Center or the National Hospital Organization Saitama Hospital. These patients included men with a prostate-specific antigen (PSA) level higher than 20 ng/mL, and/or Gleason score ≥ 8, and/or Stage T3. Clinical T stage was classified by combination of magnetic resonance imaging finding and digital examination by urologist. There were no treatment policy discrepancies between the National Hospital Organization Tokyo Medical Center and National Hospital Organization Saitama Hospital. One hundred and one patients (49.0%) received neoadjuvant ADT with the aim of prostate volume reduction or a longer waiting time. Regarding the aim of volume reduction, patients with prostate volumes >40 cc usually underwent ADT because Japanese national policy for patient discharge criteria mandates that total seed activity be kept below 1,300 MBq. None of our present patients received adjuvant ADT. ADT consisted of luteinizing hormone-releasing hormone agonist alone or in combination with an anti-androgen. The length of ADT duration was decided at the discretion of the treating urologist, and the median duration of ADT was 4 months (range, 3–86 months). This retrospective study was approved by the each hospital's local Institutional Review Board.

The implant technique and dose constraints were previously described in detail [14-16]. Early in the study period, the preplanning method was used in the first 25 patients, and from December 2004 onward, the procedure was changed to the real-time planning method. All procedures were conducted utilizing I-125 free seeds, being the only approved radioisotope available for permanent prostate brachytherapy in Japan. The prescribed minimum peripheral doses were 100 Gy in the preplanning method era and 110 Gy in the real-time planning method era, respectively. Post-implant dosimetry was performed 1 month after implantation, and the minimal dose received by 90% of the prostate (prostate D90) was the post-implant variable analyzed.

Supplemental EBRT was delivered 4 to 8 weeks after implantation. In general, EBRT consisted of a median dose of 45 Gy (range, 28.8–50.4 Gy) delivered in 1.8 Gy fractions using 6–10 MV photons delivered via a three-dimensional conformal technique. For all patients, the target volume consisted of the prostate gland and seminal vesicles. The BED was calculated from the prostate D90 and the EBRT dose using an α/β ratio of 2 (Gy2), applying the formulas described previously by Stock et al. [17]. The total BED for the combination therapy was the sum of the BED from the implant and that from the EBRT.

Planned follow-up was by PSA blood tests and physical examination every 3 months for the first 2 years, every 6 months thereafter. The primary outcome measure was BFFS. Biochemical failure was determined using the nadir +2 ng/mL definition (the Phoenix definition). Patients meeting the criteria for biochemical failure but showing a subsequent decrease to <0.5 ng/mL without intervention were classified as having a benign bounce, and were excluded from the analysis of failure. Acute toxicity was considered to be symptoms developing within the first year after implantation. Late toxicity was defined as any symptom developing after the first year, or symptoms that developed during the first year and persisted ≥12 months. Toxicity was scored by the Common Terminology Criteria for Adverse Events version 4.0.

Actuarial survival curves were calculated by the Kaplan-Meier method to determine BFFS, CSS, and OS. Multivariate Cox regression analysis including age, PSA level, Gleason score, positive biopsy core rates, number of high-risk factors, neoadjuvant ADT, prostate D90, and BED was conducted to test for predictors of BFFS. Analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided, and statistical significance was set at $p < 0.05$.

Results

Clinical, treatment and dosimetric parameters for the 206 patients included in the analysis are detailed in Table 1. The median follow-up time was 60 months (range, 9–112 months).

Of the 206 patients, 30 developed PSA failure, yielding an actuarial BFFS rate of 84.8% at 5 years (Figure 1). The median time to biochemical failure was 37.2 months

Table 1 Clinical, treatment and dosimetric parameters

	Median (range)	Count (%)
Continuous variables		
Age (years)	70 (54–86)	
Initial PSA (ng/mL)	11.95 (3.7–48.0)	
Positive biopsy rate (%)	33.0 (13.0–100)	
Prostate D90 (Gy)	124.8 (100.0–206.5)	
BED (Gy2)	213.5 (178.5–245.5)	
Categorical variables		
PSA level in ng/mL		
<10		86 (41.7%)
10-20		39 (19.0%)
≥ 20		81 (39.3%)
Gleason score		
5-6		26 (12.6%)
7		54 (26.2%)
8-10		126 (61.2%)
Clinical T stage		
T1-T2a		142 (69.0%)
T2b-T2c		46 (22.4%)
T3a		18 (8.6%)
No. of high-risk features		
1		186 (90.3%)
2		19 (9.2%)
3		1 (0.5%)
Neoadjuvant ADT		
Yes		101 (49.0%)

Abbreviations: PSA = prostate specific antigen; D90 = the minimal dose received by 90% of the prostate; BED = biologically effective dose; ADT = androgen deprivation therapy.

in those who failed. Of the 30 patients with PSA failure, 20 underwent post-treatment biopsy. Five of these 20 patients had pathologically-proven local recurrence. The patterns of clinical failure were local recurrence in 4 patients, distant metastases in 13, and both in 1. There were 8 deaths (3.9%), of which 2 were due to prostate cancer. The 5-year CSS for the entire cohort was 98.7%. The 5-year OS for the entire cohort was 97.6%.

Acute grade 2 gastrointestinal (GI) and genitourinary (GU) toxicity was experienced by 12 patients (5.8%) and 20 patients (14.5%), respectively. Late grade 2 GI and GU toxicity was experienced by 18 patients (8.8%) and 21 patients (10.2%), respectively. None of the patients experienced Grade ≥3 acute or late toxicity. The late grade 2 GI toxicities primarily related to rectal bleeding and the late grade 2 GU toxicities consisted of urinary urgency or retention. Rectal or urethral doses were not associated with the development of grade 2 GI or GU toxicity on univariate analysis.

On multivariate Cox regression analysis, positive biopsy core rates and number of high-risk factors were independent predictors of BFFS by the Phoenix definition (Table 2). The positive biopsy core rates were divided into subgroups: <50% (n = 130, 63.1%) and ≥50% (n = 76, 36.9%). As shown in Figure 2, the 5-year BFFS rates for patients in the positive biopsy core rate <50% and ≥50% groups were 89.3% and 78.2%, respectively (p = 0.03). Figure 3 shows BFFS stratified by numbers of high-risk factors (any 1 vs. any 2 or all 3). The 5-year BFFS rates for patients with any single high-risk factor was 86.1%, compared with 73.6% for those with any 2 or all 3 high-risk factors (p = 0.03). Neoadjuvant ADT did not improve the 5-year BFFS (87.1% vs. 82.1%, p = 0.11), according to analysis employing the log-rank test.

Discussion

Although some patients with high-risk factors may have subclinical distant metastatic disease at diagnosis, prior trials reported improved BFFS for patients with high-risk prostate cancer who received higher doses of EBRT [4-6]. This finding refutes the hypothesis that most patients with high-risk factors have subclinical distant metastases at diagnosis, but rather, supports an aggressive loco-regional treatment approach. In addition, Do et al. reported a 5-year biochemical progression-free survival rate of 20% for patients with Gleason scores of 8–10 who were treated with radical prostatectomy and a rate of 30% for those given conventional doses of EBRT [18]. However, 65% of patients undergoing prostatectomy with adjuvant EBRT were biochemically free of disease at 5 years. This study also supports an aggressive loco-regional treatment approach.

Brachytherapy provides a means to further escalate the local dose and has been used in an effort to improve results in men with high-risk disease [11,12]. Stone et al. reported a multicenter cohort study of 3,928 brachytherapy patients with a median follow-up of 42 months [11]. For the cohort as a whole, the respective BFFS rates for low-, intermediate-, and high-risk patients were 84%, 77%, and 64%. However, the 1,100 men who received a higher BED of >200 Gy via their implant, with or without EBRT, had much more favorable outcomes. Among these men, BFFS for low-, intermediate-, and high-risk patients were 88%, 94%, and 90%, respectively. The range seen in BED values is mostly due to inherent inaccuracies in the implant procedure itself, with the resulting variation in dosimetry developing after implantation. The EBRT dose variation stems mainly from the policy of adjusting these doses based on the final dosimetric outcome of the implant. As a result of these adjustments, the combination of brachytherapy and EBRT resulted in very high BED (median 213.5 Gy2, range 178.5–245.5 Gy2) in our study. This dose is much higher