

# Clinical outcomes of $^{125}\text{I}$ brachytherapy with and without external-beam radiation therapy for localized prostate cancer: results from 300 patients at a single institution in Japan

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## ABSTRACT

The aim of this study was to determine the outcomes and adverse events for 300 men with prostate cancer treated with  $^{125}\text{I}$  iodine ( $^{125}\text{I}$ ) brachytherapy with and without external-beam radiation therapy (EBRT) at a single institution in Japan. Between February 2005 and November 2011, 300 consecutive patients with clinically localized prostate cancer were treated with  $^{125}\text{I}$  brachytherapy at the Nagoya University Hospital. A total of 271 men were treated with implants with doses of 145 Gy, and 29 men were treated with implants with doses of 110 Gy combined with EBRT (40–50 Gy/20–25 fractions). The median patient age was 69 years (range, 53–83 years). The median follow-up period was 53 months (range, 5–99 months). According to the National Comprehensive Cancer Network risk classification, 132 men (44%) had low-risk, 147 men (29%) had intermediate-risk and 21 men (7%) had high-risk disease. The 5-year overall survival rate, biochemical relapse-free survival rate, and disease-specific survival rates were 93.5%, 97.3% and 98.5%, respectively. Two men (0.6%) died of prostate cancer and 10 men (3.3%) died of other causes. Seventeen men (5.6%) experienced Grade 2 rectal bleeding in all: 12 (41.4%) of 29 in brachytherapy with EBRT, and 5 (1.8%) of 271 in brachytherapy alone. The rates of Grade 2 and 3 genitourinary toxicity were 1.0% and 1.7%, respectively. Excellent local control was achieved at our hospital for localized prostate cancer with  $^{125}\text{I}$  brachytherapy with and without EBRT. Gastrointestinal and genitourinary toxicities were acceptable.

**KEYWORDS:** prostate cancer, brachytherapy, external-beam radiation therapy, outcome, gastrointestinal toxicity, genitourinary toxicity

## INTRODUCTION

According to a recent report, the incidence of prostate cancer in Japan is increasing [1]. Over the last 10 years, nearly 60% of the increase in cancer in men has been the result of the increased incidence of prostate cancer. In addition, the use of radiation for prostate cancer was found to have increased by ~10%, compared with

previous Japanese studies.  $^{125}\text{I}$  Iodine ( $^{125}\text{I}$ ) permanent implants for localized prostate cancer became legally permitted in July 2003 in Japan, and more than 3000 patients per year have been treated since that time.  $^{125}\text{I}$  brachytherapy is currently one of many effective and safe treatment methods available for treating localized prostate cancer in Japan.

Several authors have reported that permanent implants for localized prostate cancer show excellent biochemical control and are associated with less severe toxicities [2–17]. According to a systematic review of randomized controlled studies, external-beam radiation therapy (EBRT), brachytherapy, and radical prostatectomy were found to be effective in the management of localized prostate cancer [18]. Furthermore, excellent biochemical outcomes have been reported with the use of combination EBRT and brachytherapy for localized prostate cancer [19–22].

In our hospital, over 300 patients with prostate cancer have been treated with  $^{125}\text{I}$  brachytherapy with and without EBRT since February 2005. In the present study, we retrospectively reviewed 300 consecutive patients treated with  $^{125}\text{I}$  brachytherapy with and without EBRT for localized prostate cancer and evaluated risk factors for overall survival (OS), biochemical relapse-free survival (bRFS), and disease-specific survival (DSS) using univariate and multivariate analyses, and also calculated OS, bRFS and DSS using Kaplan–Meier analysis. We also retrospectively reviewed gastrointestinal (GI) and genitourinary (GU) toxicities and evaluated risk factors for Grade 2 rectal bleeding and Grade 2 or 3 urethral toxicities, using univariate and multivariate analyses.

## MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Nagoya University Hospital, and all patients provided written informed consent.

### Patient selection

Between February 2005 and November 2011, 300 consecutive patients with clinically localized prostate cancer were treated with  $^{125}\text{I}$  brachytherapy with and without EBRT at Nagoya University Hospital. Patients were clinically staged by medical history, physical examination, including digital rectal examination, transrectal ultrasound (TRUS), serum prostate-specific antigen (PSA), bone scintigraphy, computed tomography (CT) of the abdomen and pelvis, and chest radiography. Magnetic resonance imaging (MRI) scans of the pelvis were performed if possible. All patients had biopsy-confirmed adenocarcinoma of the prostate, which was pathologically proven in our hospital. The UICC (Union for International Cancer Control) TNM staging system (2009) was used to assign clinical stage. Two hundred and fifty-three (84.3%) patients had T1–T2a, 38 (12.7%) patients had T2b, and 9 (3%) patients had T2c disease. No patients had T3a or higher disease. The clinical T stage was classified by physical examination, including digital rectal examination, imaging (TRUS, CT scans, and MRI imaging), and biopsy. In addition, no patients had lymph node metastasis or distant metastasis.

According to the National Comprehensive Cancer Network (NCCN) risk classification, 132 patients presented with low-risk disease (PSA 10 ng/ml, Gleason score 6, and clinical stage T2a), 147 patients presented with intermediate-risk disease (1 adverse factor: PSA 10.1–19.9 ng/ml or Gleason score 7 or clinical stage T2b) and 21 patients presented with high-risk disease (PSA 20 ng/ml or Gleason score 8 or clinical stage T2c, or 2 or 3 of the intermediate adverse features).

## Treatment

Of the 300 men, 263 (87.7%) received neoadjuvant hormonal therapy. The median duration of hormonal therapy was 10 months (range, 1–100 months). As per our treatment policy, hormonal therapy was not administered to men with low-risk disease in principle, and courses were usually short (<6 months) for men with intermediate-risk disease, and longer (>24 months) for men with high-risk disease. In cases of patients with larger prostate volume, short-term hormonal therapy was administered to minimize the volume before implant insertion. In cases of patients with longer waiting times before implant insertion, hormonal therapy was also administered.

A total of 271 (90.3%) patients received  $^{125}\text{I}$  implants with doses of 145 Gy alone, and 29 (9.7%) patients received  $^{125}\text{I}$  brachytherapy with implants with doses of 110 Gy and supplemental EBRT. EBRT was administered as a 4–5 week course after brachytherapy. The dose of EBRT was 40 Gy/20 fractions in many cases.

## Implant technique

Between February 2005 and June 2011, 277 men received modified uniform loading. After July 2011, the planning switched to peripheral loading. Twenty-three men received peripheral loading. TRUS preplanning took place ~4 weeks before implant insertion. Images were recorded every 5 mm and downloaded to a SPOT PRO® treatment planning system (Nucletron Operations B.V., Utrecht, Netherlands). On the day of the implant, intraoperative treatment planning was performed.

The dose prescribed to the planning target volume (prostate) was 145 Gy (brachytherapy monotherapy) or 110 Gy (brachytherapy combined with EBRT). Preplan and intraoperative treatment planning dosimetry aimed for 99% of the prostate to receive  $\geq 100\%$  of the prescribed dose (V100 > 99%), 90% of the prostate volume to receive 120–125% of the prescribed dose (D90), and V150 (the volume of the prostate receiving  $\geq 150\%$  of the prescribed dose) <50%. The rectal volume receiving 100% of the prescribed dose (RV100) was limited to 1.0 cm<sup>3</sup>, and the rectal dose was limited to <150% of the prescribed dose. The urethral dose was limited to <150% of the prescribed dose. Implants were generally inserted under epidural anesthesia with ultrasound and fluoroscopic guidance using a standard template. Some patients received lumbar anesthesia or sacral anesthesia. During both mapping and implant, the urethra was identified with aerated gel.

## Dosimetry

Post-implant dosimetry was performed using CT images ~4 weeks after insertion of the implant. CT images were acquired at 3-mm slice thickness and 3-mm slice spacing extending through the whole pelvis. Dosimetry was calculated using a SPOT PRO treatment planning system. For identification of the urethra, Day 1 CT images with a urinary catheter were obtained and printed. The rectum was contoured as a solid organ. The rectal wall was outlined from 9 mm above the prostate base to 9 mm below the prostate apex. The urethra was contoured as a 4-mm circle in axial views and was outlined from the prostate base to the apex. Dosimetric parameters assessed included the prostate V100, V150 and V200, as well as the D90, rectal RV100

and RV150 (the volume of the rectum receiving  $\geq 100\%$  and  $150\%$  of the prescribed dose, respectively), and urethral UD10 and UD30 [the rate (percentage) of the prescribed dose received by  $10\%$  and  $30\%$  of the urethra, respectively]. The post-implant D90 and EBRT dose were converted to prostate biological effective dose (BED) of  $\alpha/\beta$  ratio of 2 Gy (BED<sub>2</sub>) [4]. The BED<sub>2</sub> values for treatments involving both implant and EBRT were calculated by adding the BEDs computed for each treatment.

### External-beam radiation therapy

Twenty-nine (9.7%) patients received EBRT. EBRT was begun ~4–6 weeks after implant insertion. The prescription dose of EBRT was mainly 40 Gy and was delivered in 2.0-Gy fractions with 10 MV photons. One patient received a total dose of 50 Gy in 2.0-Gy fractions at an outside hospital. Planning CT images were obtained at 2-mm slice thickness and 2-mm slice spacing extending through the whole pelvis in the supine position. Treatment planning was done using the Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto, CA, USA).

Three-dimensional conformal radiotherapy (3D-CRT) with a four-field arrangement was used for the initial 27 patients. The clinical target volume (CTV) consisted of the prostate gland and whole seminal vesicles. The planning target volume (PTV) was the CTV expanded with ~10-mm margins in all directions.

Since July 2011, EBRT planning was switched to 3D-CRT with a six-field arrangement or image-guided intensity-modulated radiation therapy (IG-IMRT) using in-room CT to reduce rectal toxicity. The CTV consisted of the prostate gland and the base of the seminal vesicles. One patient was treated with 3D-CRT with a six-field arrangement, and the latest patient was treated with IG-IMRT. The rectum was contoured as a solid organ. The rectal walls were outlined from 10 mm above the prostate base to 10 mm below the prostate apex. Rectal RV30, 35 and 40 [the rate (percentage) of the volume of rectum receiving  $\geq 30$  Gy, 35 Gy and 40 Gy, respectively] were calculated. The dose–volume histogram (DVH) data for EBRT were available for 23 of 29 patients.

### Follow-up

The median follow-up period was 53 months (range, 5–99 months). Follow-up evaluations after treatment were performed at intervals of 3–6 months for 5 years, and yearly thereafter. During follow-up study, we performed a physical interview and examination, as well as serum PSA measurement. Additionally, on an as-needed basis, residual urine measurements were performed. When PSA relapse was suspected because of increased PSA levels, we performed bone scintigraphy and whole body CT. Prostate biopsy was performed in cases when local recurrence was strongly suspected.

### Analysis

GI and GU toxicities were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [23]. Kaplan–Meier analysis and curves were used to determine OS, bRFS and DSS. The bRFS was defined as a PSA nadir + 2 according to the Phoenix definition [24], with the exception of PSA bounce. The statistical significance of the

difference between risk groups for OS, bRFS and DSS was calculated using the log-rank test. The statistical difference between age  $\leq 70$  years and  $>70$  years for OS was calculated using the log-rank test. In this study, as risk factors for OS, bRFS and DSS, we analyzed age, initial PSA, Gleason score, clinical T stage, risk group, hormone therapy, cardiovascular disease, antiplatelet/anticoagulant therapy, pre-implant prostate volume, BED<sub>2</sub>, EBRT and prostate D90. Univariate analysis was used to determine the variables that predicted OS, bRFS and DSS. The rate of Grade 2 or higher late GI and GU toxicities were calculated using the Kaplan–Meier method, and its statistical difference between brachytherapy with EBRT and brachytherapy alone was calculated using the log-rank test. In this study, the following were analyzed as possible risk factors for rectal and urinary toxicity: age, hormone use, hemorrhoid diagnosis, diabetes, anticoagulation/antiplatelet therapy, preimplant prostate volume, BED<sub>2</sub>, DVH parameters of the rectum (RV100, RV150 and RV200 in brachytherapy and RV30, RV35, RV40 and rectal volume in EBRT) and the urethra (UD10, UD30), and number of seeds and needles. Categorical and continuous variables were analyzed using Fisher's exact tests and unpaired *t*-tests, respectively, for univariate analysis, and all the significant variables were evaluated using logistic regression analysis for multivariate analysis. A two-sided probability value of  $<0.05$  was considered to indicate statistical significance. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [25].

## RESULTS

### Patients

Table 1 shows the patient characteristics. The median age of patients was 69 years (range, 53–83 years). The median follow-up period was 53 months (range, 5–99 months). The median initial PSA was 7.0 ng/ml (range, 2.6–25.0 ng/ml). Table 2 shows the categorical variables. The T stage was classified based on the UICC 2009 TNM classification. The T stages of the patients were as follows: T1c–T2a (84.3%), T2b (12.7%) and T2c (3.0%). No patients had Stage T3a disease or higher. All patients had N0M0 disease. Patients were classified into low-, intermediate- and high-risk groups, based on the NCCN risk group classification. Of the 300 patients, 132 (44%) had low-risk disease, 147 (49%) had intermediate-risk disease, and 21 (7%) had high-risk disease. Table 2 shows the dosimetric summary data. DVH data for brachytherapy were available for all 300 patients. DVH data for EBRT were available for 23 of 29 patients.

### Survival analysis

OS was 93.5% at 5 years and 8 years (Fig. 1a). There were 2 deaths (0.6%) from prostate cancer and 10 deaths (3.3%) from other causes. Two patients died of prostate cancer, at 28 months and 45 months, respectively, after implant insertion. Both patients were in the high-risk group and treated with a combination of brachytherapy and EBRT with neoadjuvant short-term hormonal therapy. The

**Table 1. Patient characteristics**

Characteristics	
Age (years)	Median 69 (53–83)
Initial PSA (ng/ml)	Median 7.0 (2.6–25.0)
Risk group (NCCN)	
Low risk	132 (44%)
Intermediate risk	147 (49%)
High risk	21 (7%)
Gleason score	
≤6	179 (59.7%)
7	110 (36.7%)
≥8	11 (3.6%)
T stage (UICC2009)	
T1c–T2a	253 (84.3%)
T2b	38 (12.7%)
T2c	9 (3.0%)
Hormone therapy	
Yes	263 (87.7%)
No	37 (12.3%)
EBRT	
Yes	29 (9.7%)
No	271 (90.3%)
Follow-up period (months)	Median 53 (5–99)

PSA = prostate-specific antigen, EBRT = external-beam radiation therapy, NCCN = National Comprehensive Cancer Network, UICC = Union for International Cancer Control.

cause of death in the other 10 patients was second primary cancer in 6 (lung cancer in 3, bile duct cancer in 2, and lymphoma in 1), acute myocardial infarction in 2, epidural hemorrhage in 1, and postoperative sepsis related to another disease in 1.

OS by risk group is shown in Fig. 1b. The OS rates of the low-, intermediate- and high-risk groups were 91.0%, 97.7% and 79.3% at 5 years and 8 years, respectively ( $P = 0.864$ ). The bRFS is shown in Fig. 2. The bRFS of the entire cohort is shown in Fig. 2a, while bRFS by risk group is shown in Fig. 2b. Biochemical control was evaluated by the Phoenix definition. The bRFS was 97.3% at 5 years and 92.8% at 8 years. There were 8 (2.7%) biochemical failures. The median time to biochemical relapse was 47.5 months (range, 16–86 months). There were 8 failures of any type, including 2 local and 3 distant failures (1 lung metastasis, 1 lung and lymph node metastasis, 1 bone metastasis). The other 3 patients were diagnosed with biochemical failure alone. Two patients experienced biopsy-

**Table 2. Statistics for dosimetric data**

Characteristic	Monotherapy ( $n = 271$ )		Brachytherapy + EBRT ( $n = 29$ )	
	Median	Mean ± SD	Median	Mean ± SD
Number of seeds	56	60 ± 15.7	39	42 ± 12.5
Number of needles	27	28 ± 6.9	19	19 ± 3.2
Prostate volume (cm <sup>3</sup> )	17.6	19.5 ± 8.5	14.2	16.3 ± 7.9
V100 (%)	95.1	93 ± 5.9	94.2	93 ± 6.8
V150 (%)	56.6	57 ± 15.2	59.0	61 ± 15.6
D90 (Gy)	163.0	162 ± 19.4	121.5	121 ± 17.6
RV100 (cm <sup>3</sup> )	0.28	0 ± 0.4	0.35	0 ± 0
RV150 (cm <sup>3</sup> )	0.01	0 ± 0.1	0.02	0 ± 0.1
UD10 (%)	145.5	149 ± 27.1	151.6	157 ± 26.5
UD30 (%)	137.1	138 ± 23.0	142.7	146 ± 21.6
EBRT				
RV30 (%)			46	46 ± 21.3
RV35 (%)			35	38 ± 20.7
RV40 (%)			0	7 ± 12.8
BED <sub>2</sub> (Gy)				
Total	170.9	171 ± 21.6	206.7	207 ± 19.8
Brachytherapy	170.9	171 ± 21.6	126.7	126 ± 19.0
EBRT			80	81 ± 3.7

EBRT = external-beam radiation therapy, SD = standard deviation.

proven local recurrence at 61 and 86 months, respectively, after implant insertion and were treated with hormonal therapy. PSA bounce was recorded in 8 patients (2.7%), and the median interval to the PSA bounce was 28.5 months (range, 12–67 months).

DSS was 98.5% at 5 years and 8 years. DSS for the entire cohort is shown in Fig. 3a, and DSS by risk classification is shown in Fig. 3b. DSS of the low-risk group ( $n = 132$ ) was 100%, that of the intermediate-risk group ( $n = 147$ ) was 99%, and that of the high-risk group ( $n = 21$ ) was 87.1% at 5 and 8 years. DSS of the high-risk group was significantly lower compared with those of the low- and intermediate-risk groups ( $P = 0.001$ ).

Table 3 shows the risk factors for OS, bRFS and DSS. On univariate analysis, age was a significant risk factor ( $P = 0.017$ ) for OS. On multivariate analysis, age was the only significant risk factor for OS ( $P = 0.0198$ , odds ratio: 1.14). OS at 5 years and 8 years for patients aged ≤70 years was significantly higher (96.1%) than that of patients aged >70 years (89.4%) ( $P = 0.0321$ ). On univariate analysis, clinical T stage ( $P < 0.0001$ ) and risk group ( $P = 0.025$ ) were significant risk factors for biochemical relapse. On multivariate analysis, no significant risk factors were detected. On univariate

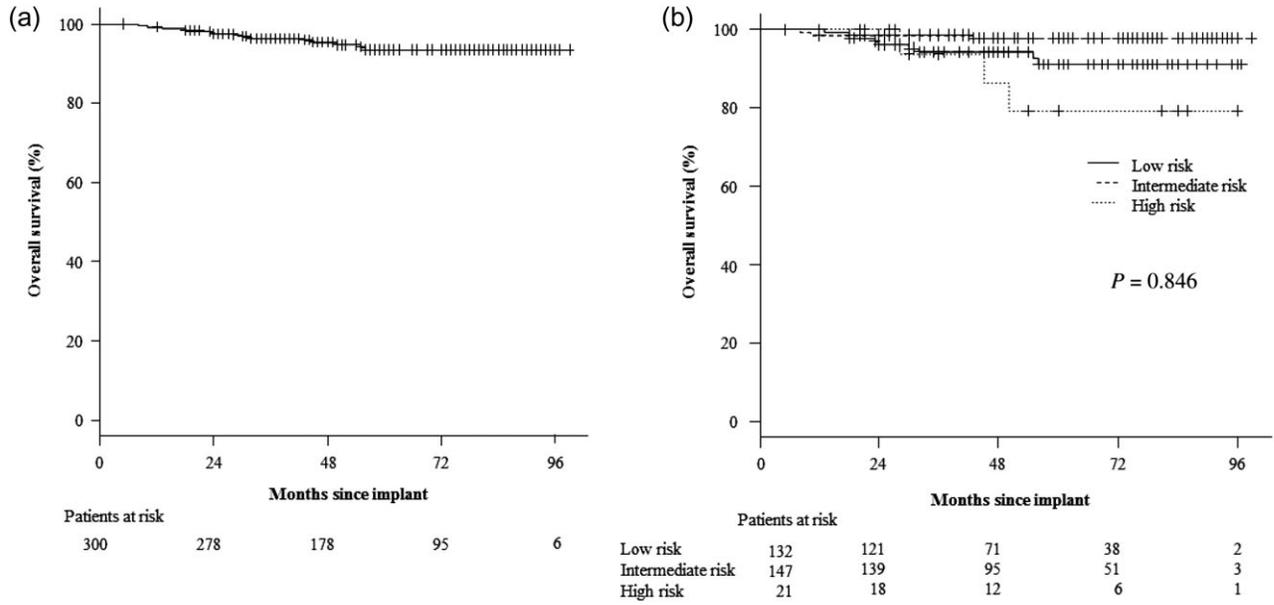


Fig. 1. Overall survival rate. (a) Overall survival of the entire cohort. (b) Overall survival by risk group.

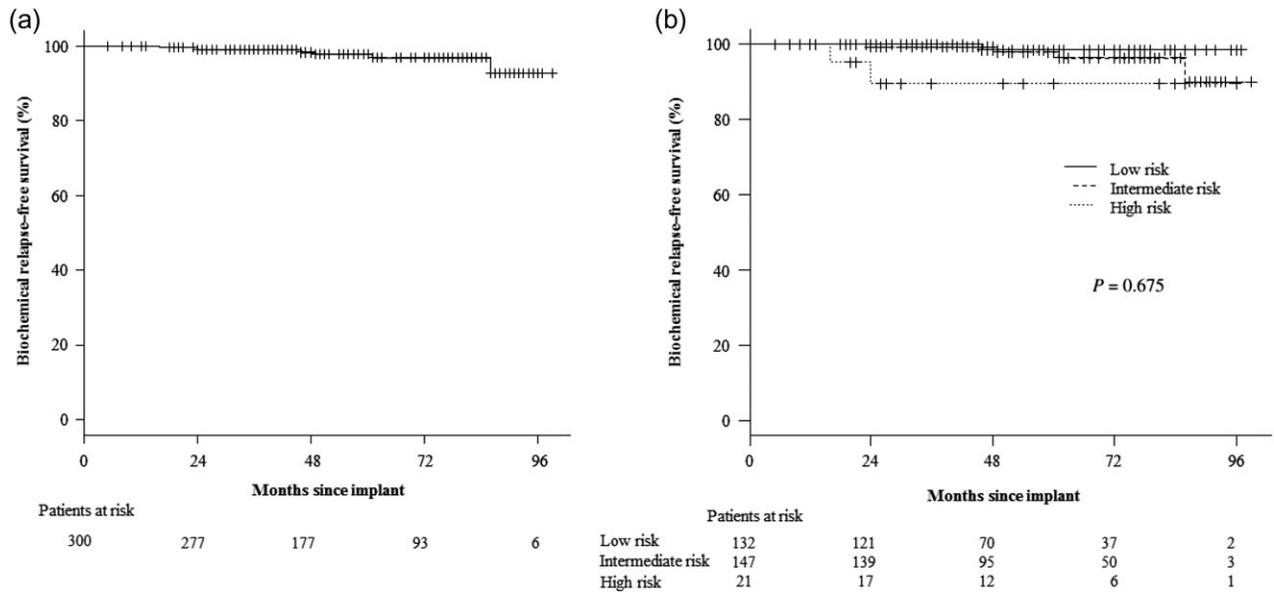


Fig. 2. Biochemical relapse-free survival rate. (a) Biochemical relapse-free survival of the entire cohort. (b) Biochemical relapse-free survival by risk group.

analysis, Gleason score ( $P = 0.006$ ), clinical T stage ( $P = 0.002$ ), risk group ( $P = 0.003$ ) and BED<sub>2</sub> ( $P = 0.028$ ) were significant risk factors for DSS. On multivariate analysis, no significant risk factors were detected.

#### Late GI toxicity

Cumulative incidence of Grade 2 late rectal bleeding is shown in Fig. 4. There was no Grade 3 or greater GI toxicity found.

Seventeen patients (5.6%) experienced Grade 2 rectal bleeding: 5 of 271 patients (1.8%) treated with brachytherapy alone, and 12 of 29 patients (41.4%) treated with brachytherapy and EBRT. Only one of all the 300 patients (0.3%) required argon-plasma coagulation (APC), and he was treated with brachytherapy and EBRT. The rate of Grade 2 rectal bleeding in patients treated with brachytherapy with EBRT was significantly higher than that in patients treated with brachytherapy alone ( $P < 0.0001$ ). All of the Grade 2 rectal bleeding was diagnosed within the 2 years following the implant.

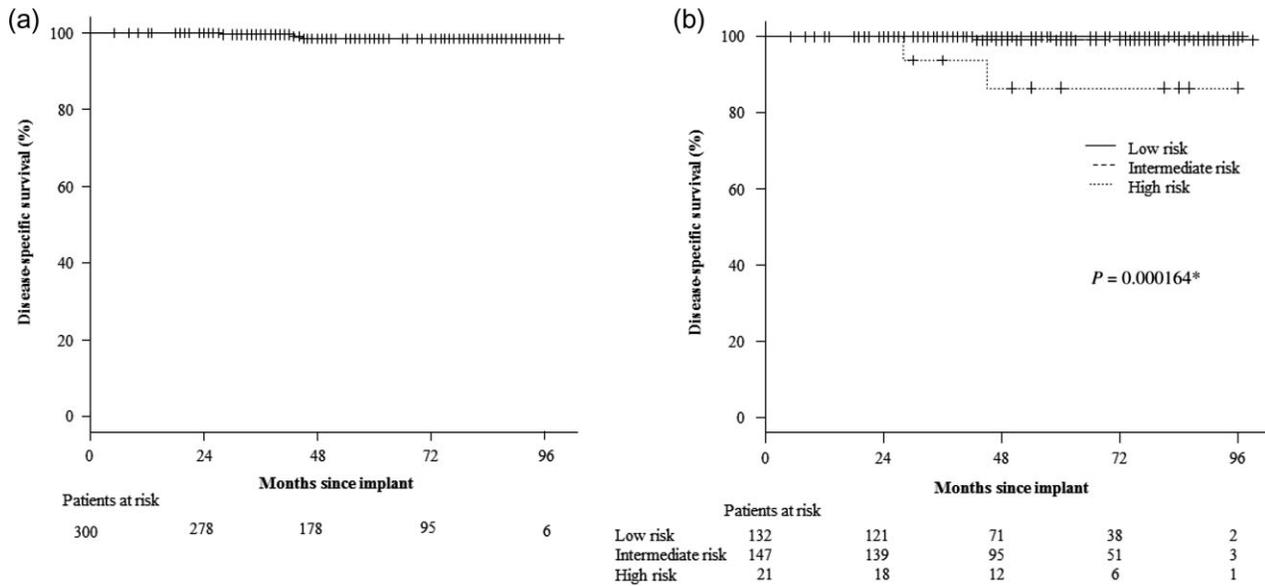


Fig. 3. Disease-specific survival rate (a) Disease-specific survival of the entire cohort. (b) Disease-specific survival by risk group.

Table 3. Univariate and multivariate analyses for OS, bRFS and DSS

Variant	Overall survival				Biochemical relapse-free survival				Disease-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	<i>P</i> value	OR	<i>P</i> value	OR	<i>P</i> value	OR	<i>P</i> value	OR	<i>P</i> value	OR	<i>P</i> value	OR
Age (years)	<b>0.017</b>		<b>0.0198</b>	<b>1.14</b>	0.410					0.095		
Initial PSA (ng/ml)	0.747				0.374					0.741		
Gleason score	0.780				0.535					<b>0.006</b>		0.260 4.28
Clinical T stage	0.909				<b>&lt;0.0001</b>		0.060 3.860			<b>0.002</b>		0.157 5.24
Risk group	0.846				<b>0.025</b>		0.675 1.420			<b>0.003</b>		0.724 1.91
Hormone	0.704	2.020			0.603					1		
Diabetes	0.722	1.265			0.330	2.035			0.422	1		
Cardiovascular disease	1	0.847			1.000	0.563			0.539	1.713		
Antiplatelet/Anticoagulant	1	0.890			0.599	0			1	0		
Pre-implant prostate volume (ml)	0.262				0.475				0.957			
BED <sub>2</sub> (Gy)	0.089				0.798				<b>0.028</b>		0.109	1.05
Addition of EBRT	0.167	2.020			0.140	3.911			0.026	19.550		
Brachytherapy												
Prostate D90 (%)	0.184				0.679				0.349			

bRFS = biochemical relapse-free survival, DSS = disease-specific survival, OS = overall survival, OR = odds ratio, PSA = prostate-specific antigen, EBRT = external-beam radiation therapy. Values in boldface are statistically significant.

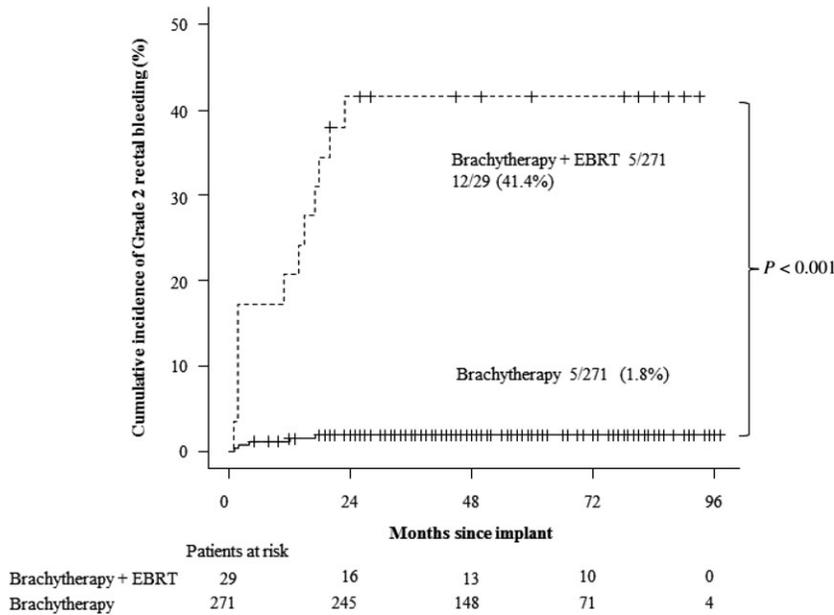


Fig. 4. Cumulative incidence of Grade 2 late rectal bleeding, stratified by therapy.

The median interval to Grade 2 rectal bleeding was 11 months (range, 1–23 months).

Table 4 shows the risk factors for Grade 2 rectal bleeding. On univariate analysis, BED<sub>2</sub> ( $P = 0.00191$ ) and addition of EBRT ( $*P < 0.0001$ ) were the significant risk factors. On multivariate analysis, addition of EBRT was the only significant risk factor ( $P < 0.0001$ , odds ratio: 70.7).

#### Late GU toxicity

Fig. 5 shows the cumulative incidence of Grade  $\geq 2$  late GU toxicities. The 5-year and 8-year cumulative incidences of Grade  $\geq 2$  late GU toxicity were 1.4% and 14.6%, respectively. Six (2.0%) patients experienced Grade 2 and 3 GU toxicity. There were no Grade 4 or greater toxicities found. All the patients who experienced Grade  $\geq 2$  GU toxicities were treated with brachytherapy alone and were treated with a modified loading technique.

Two of the 300 patients (0.7%) experienced Grade 2 toxicity. One of those patients (0.3%) had urinary retention requiring intermittent catheterization, and he also experienced Grade 3 hematuria. The other patient (0.3%) had hematuria and needed oral hemostatic agent. Five of the 300 patients (1.7%) had Grade 3 urinary toxicity. Of these five, three patients (1.0%) had hematuria: two patients needed endoscopic hemostatic treatment, and the other patient needed bladder irrigation. Two patients (0.7%) had urinary retention: one patient needed self-catheterization and transurethral resection of the prostate (TUR-P), and the other patient needed urethral dilation several times. The median interval to the Grade  $\geq 2$  GU toxicities were 23 months (range, 3–95 months) after implant.

Table 5 shows risk factors for Grade  $\geq 2$  GU toxicities. On univariate analysis, pre-implant prostate volume ( $P < 0.0001$ ), number of seeds ( $P = 0.000135$ ) and number of needles ( $P = 0.00111$ )

were the significant risk factors. On multivariate analysis, no significant risk factors were detected.

#### DISCUSSION

OS, bRFS and DSS at 5 years were 93.5%, 97.3% and 98.5%, respectively. The results of OS, bRFS and DSS were excellent and almost equivalent to those of previous reports, although our median follow-up period was not sufficient [11, 16, 19, 20].

Several reports have shown that patient age [11, 12], hypertension, diabetes and smoking [11] are related to OS. In the present study, age was the only significant risk factor indicated by univariate and multivariate analyses. OS for patients with age at implant  $\leq 70$  years was significantly higher than that for patients aged  $>70$  years. Several reports have shown that BED, D90, dose escalation [4, 6, 7, 12], Gleason score, positive core biopsy, risk group, and the treatment era [8, 11] were significant risk factors for biochemical relapse. Several reports from Japan have shown that D90 [26], initial PSA, age, T stage [27], and BED [28] were significant risk factors for biochemical relapse. No significant risk factors were found in multivariate analysis in this study. Several reports have shown that Gleason score [11], risk group, and treatment era were significant risk factors for DSS. In the present study, no significant risk factors were detected in multivariate analysis.

In this study, the Grade 2 late rectal bleeding rate was 5.6% of all patients: 1.8% in brachytherapy alone, 41.4% in brachytherapy combined with EBRT. Only one patient (0.3%) required APC. The Grade 2 rectal bleeding rate of all patients and brachytherapy alone were equivalent to those reported in the review article [29] and in reports from other institutions (3.7–10.4%, 5–7% in current studies). The rate of patients requiring endoscopic treatment was similar to that in the reports from other institutions ( $<1\%$ ). The Grade 2 rectal bleeding rate of the combined therapy group was higher than

**Table 4. Risk factors of Grade 2 late rectal bleeding**

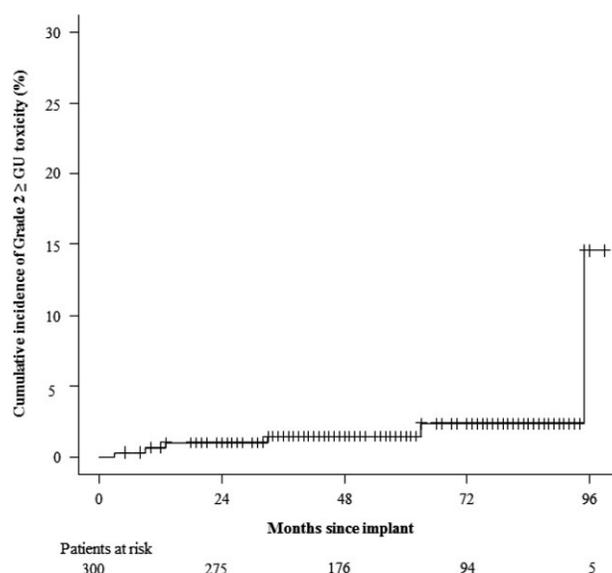
Variant	Univariate analysis		Multivariate analysis	
	P Value	OR	P Value	OR
Age	0.931			
Hormone	1	0.766		
Diabetes	1	1.058		
Antiplatelet/Anticoagulant	1	0.765		
Cardiovascular disease	0.771	0.719		
Pre-implant prostate volume (ml)	0.620			
Addition of EBRT	<b>&lt;0.0001</b>	<b>36.334</b>	<b>&lt;0.0001</b>	<b>70.7</b>
BED <sub>2</sub> (Gy)	<b>0.0019</b>		0.260	0.984
Brachytherapy				
RV100 (cm <sup>3</sup> )	0.778			
RV150 (cm <sup>3</sup> )	0.910			
EBRT				
RV30 (%)	0.295			
RV35 (%)	0.392			
RV40 (%)	0.441			
Rectal volume (cm <sup>3</sup> )	0.368			

OR = odds ratio, CI = confidence interval, EBRT = external-beam radiation therapy, BED<sub>2</sub> = biological effective dose of  $\alpha/\beta$  ratio 2, RV100 = rectal volume (cm<sup>3</sup>) receiving  $\geq 100\%$  of the prescribed dose, RV150 = rectal volume (cm<sup>3</sup>) receiving  $\geq 150\%$  of the prescribed dose, RV30 = percentage of the rectal volume receiving  $\geq 30$  Gy; RV35 = percentage of the rectal volume receiving  $\geq 35$  Gy; RV40 = percentage of the rectal volume receiving  $\geq 40$  Gy. Values in boldface are statistically significant.

that in previous reports from other institutions in Japan. Katayama *et al.* [30] reported the incidence of the rectal toxicity in 2339 patients with prostate cancer undergoing <sup>125</sup>I brachytherapy with or without EBRT in a nationwide prospective cohort study in Japan (J-POPS). The 3-year cumulative incidences for  $\geq$ Grade 2 rectal toxicity were 2.88%, 1.76% and 6.53% in all subjects, the brachytherapy group and the EBRT combination therapy group, respectively. In the report by Shiraishi *et al.* [31] on <sup>125</sup>I brachytherapy combined with EBRT, 9.7% developed Grade 2 rectal bleeding.

In the present study, BED<sub>2</sub> and addition of EBRT were the significant risk factors for Grade 2 rectal bleeding in univariate analysis. Addition of EBRT was the only significant ( $P < 0.0001$ ) risk factor in multivariate analysis. Lawton *et al.* [21] reported that the addition of EBRT was the significant risk factor in the RTOG00-19 trial.

Several reports have shown that development of rectal bleeding is dependent on rectal dose volume. Snyder *et al.* [32] reported that the prescription dose (160 Gy) delivered to  $\leq 1.3$  cm<sup>3</sup> of rectal

**Fig. 5. Cumulative incidence of Grade  $\geq 2$  late GU toxicity.**

tissue resulted in a 5% rate of proctitis at 5 years vs 18% for volumes  $>1.3$  cm<sup>3</sup>. Keyes *et al.* [33] reported late rectal RTOG  $\geq 2$  was associated with the presence of acute toxicity, higher RV100 and learning curve. In a report from Japan, Shiraishi *et al.* [31] reported that the Grade 2 rectal bleeding rate was 4.2% for a RV100  $\leq 0.5$  ml and a V30  $\leq 35\%$ , whereas it was 22.4% for an RV100 of  $>0.5$  ml and a V30 of  $>35\%$ . Harada *et al.* [34] reported that for an RV100 kept below 1.0 ml, no Grade 2 morbidity developed in their study. Based on their results, Katayama *et al.* [30] proposed that an RV100 of  $<1$  ml in both brachytherapy and EBRT combination therapy groups may be effective in decreasing the incidence of rectal toxicity. Ohashi *et al.* [35] reported that a rectal dose  $>160$  Gy was correlated with Grade 2 rectal morbidity. Tanaka *et al.* [36] reported that higher RV100 was a significant predictor of late GI toxicity. Aoki *et al.* [37] reported that Grade 2 rectal bleeding increased significantly at D90  $>130$  Gy, but rectal dose volume was not found to be a significant risk factor for Grade 2 late rectal bleeding in our study. Age, existence of an acute side effect (urinary retention), and use of an anticoagulant were also reported as risk factors of Grade 2 or greater late rectal bleeding.

In the present study, the Grade 2 late rectal bleeding rate of patients treated with a combination of brachytherapy and EBRT was significantly higher than that of patients treated with brachytherapy alone. We considered two possible causes for the higher bleeding rate in combination therapy patients. First, the target of EBRT was large; the CTV included the prostate and the whole seminal vesicles; and using the four-field box-like field arrangement, the margin of the rectal side was expanded, as in other directions. Forsythe *et al.* [38] reported that IMRT causes fewer side effects than 3D-CRT when used in combination with brachytherapy. In their findings, Grade  $\geq 2$  rectal bleeding was reported by 11% of 3D-CRT patients and 7% of IMRT patients. In our study, we minimized the CTV to the whole prostate and the base of the seminal vesicles and

**Table 5. Risk factors of Grade  $\geq 2$  late GU toxicity**

Variant	Univariate analysis		Multivariate analysis	
	P value	OR	P value	OR
Age (years)	0.079			
Hormone	0.027	0.132		
Diabetes	1	1		
Antiplatelet/Anticoagulant	1	1.167		
Cardiovascular disease	1	0.678		
Pre-implant prostate volume (ml)	<b>&lt;0.0001</b>		0.184	1.110
BED <sub>2</sub> (Gy)	0.274			
UD10 (%)	0.255			
UD30 (%)	0.255			
Addition of EBRT	1	0		
Number of seeds	<b>0.000135</b>		0.989	0.999
Number of needles	<b>0.00111</b>		0.513	1.050

OR = odds ratio, CI = confidence interval, BED<sub>2</sub> = biological effective dose of  $\alpha/\beta$  ratio 2, EBRT = external-beam radiation therapy, UD10 = percentage of the prescribed dose received by 10% of the urethra, UD30 = percentage of the prescribed dose received by 30% of the urethra. Values in boldface are statistically significant.

used a 3D-CRT six-field beam arrangement or IG-IMRT to minimize the rectal dose. Second, the EBRT dose was fixed regardless of the post-implant dosimetry. The BED<sub>2</sub> of patients who experienced Grade 2 rectal bleeding ( $191.7 \pm 23.9$  Gy) was higher than that of patients who did not experience bleeding ( $173.3 \pm 23.5$  Gy) ( $P = 0.0019$ ). Stone *et al.* [39] recommended customized dose prescription for permanent prostate brachytherapy. In low-risk patients, achieving a BED of  $\geq 140$  Gy might be adequate for PSA control. However, high-risk disease might require a BED dose of  $\geq 200$  Gy. In our study, in the treatment with combination therapy, we adjusted the EBRT component based on the post-implant dosimetry of D90. The total BED<sub>2</sub> will be between 200 and 220 Gy. A BED<sub>2</sub> of  $>220$  Gy was avoided to reduce late rectal bleeding.

In the present study, 1.0% of the 300 patients experienced Grade 2 urinary toxicity and 1.7% experienced Grade 3 urinary toxicity. Late urethral adverse effects can occur 5 years or more after implant, so careful follow-up is needed. The percentages of Grade 2 or 3 GU toxicities we found were similar to reports from the MD Anderson Cancer Center (RTOG-Grade 2: 6.5%, Grade 3: 1.7%, Grade 4: 0.5%) [40] and other institutions in Japan. Ohashi *et al.* [41] reported in the urinary toxicity profiles of J-POPS, analyses of 2339 patients, Grade 2+ late urinary toxicities developed in 5.75% of the patients. Yorozu *et al.* [42] reported the outcomes for 1313 men treated with <sup>125</sup>I brachytherapy at a single institution in Japan: the 7-year Grade 3+ GU toxicity was 2%; patients who experienced

Grade 2 or greater urinary toxicity had a larger prostate volume and needed a larger number of needles and seeds in this study, but no significant risk factors were detected in multivariate analysis. In reports from other institutions, patients with larger prostate volume, higher baseline International Prostate Symptom Score (IPSS), higher D90, the presence of acute toxicity, age  $>70$  years, higher prostate V100, or higher prostate V150 had more  $\geq$ Grade 2 late GU toxicity [40, 43–45]. Reports from Japan have indicated that baseline IPSS [46, 47], neoadjuvant androgen deprivation therapy, seed density [47], combination with EBRT [36], and prostate V100 [46] were predictive factors for Grade 2 late urinary toxicity.

In conclusion, we reported our single-institution experience and evaluated the outcomes for 300 men treated with <sup>125</sup>I brachytherapy with and without EBRT on OS, bRFS and DSS using Kaplan–Meier analysis. In this study, age was the only significant risk factor for OS in univariate and multivariate analyses. Although longer follow-up period is required, the results of OS, bRFS and DSS were excellent, and almost equivalent to those of previous reports. Late GI and GU toxicity levels were acceptable.

### CONFLICT OF INTEREST

None declared.

### FUNDING

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