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Research Article

Patient age as a predictive factor in biochemical recurrence following brachytherapy: Oncological outcomes at a single center

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ABSTRACT

Background: Iodine-125 low-dose-rate brachytherapy (LDR-BT) is a treatment modality utilized in both localized and advanced prostate cancer (PCa). We aimed to evaluate the long-term oncological outcomes in patients with PCa who underwent LDR-BT, at a single institution in Japan.

Methods: We retrospectively reviewed the clinical records of 340 consecutive patients with localized PCa who underwent LDR-BT between August 2004 and December 2014 at our institution. Patients with low-risk PCa who had a pretreatment prostate volume >50 mL received neoadjuvant androgen deprivation therapy (ADT) for at least 3 months before LDR-BT. Patients with intermediate-risk PCa were treated with a combination of LDR-BT and/or external beam radiation therapy (EBRT) and/or ADT for 9 months. Patients with high-risk PCa underwent LDR-BT, EBRT, and ADT for 24 months. The endpoints of this study were biochemical recurrence-free survival (BRFS) and overall survival (OS). Additionally, the association between biochemical recurrence (BCR) and clinical/pathological covariates was analyzed.

Results: At the end of the follow-up period, nine patients (2.6%) showed BCR, and six patients (1.8%) developed secondary cancers after LDR-BT. The 5-year and 10-year BRFS rates were 99.4% and 95.3%, respectively. Factoring in the patients' ages, the 5-year and 10-year BRFS rates were 99.1% and 99.1%, respectively, in patients aged >63 years. The rates were 100% and 89.4% in those aged ≤63 years, respectively. In the multivariate analysis, age ≤63 years was identified as a significant independent predictor of BCR after LDR-BT.

Conclusion: Age ≤63 years was a significant predictor of BCR following LDR-BT. Although the risk of secondary malignant neoplasms should be considered when opting for LDR-BT in younger patients with PCa, the prevalence of them in these patients is relatively low. Therefore, clinicians should weigh the risks and benefits of definitive therapy in PCa, particularly in younger patients.

1. Introduction

Iodine-125 low-dose-rate brachytherapy (LDR-BT) is a treatment modality used in both localized and advanced prostate cancer (PCa).[1,2] Over the past two decades, the radiation dose delivered by either external beam radiation therapy (EBRT) or brachytherapy has increased, resulting in decreased biochemical recurrence (BCR).[3] According to the D'Amico risk stratification[4] and the Phoenix definition,[5] the 5-year biochemical recurrence-free survival (BRFS) in patients with PCa who underwent LDR-BT with or without androgen deprivation therapy (ADT) and/or EBRT was 92.1–98.6% in low-risk PCa, 86.0–97.3% in intermediate-risk PCa, and 78–95.2% in high-risk PCa.[6,7]

Although excellent oncological outcomes are achieved in patients with PCa who underwent LDR-BT, a certain number of patients have continued to suffer from BCR followed by local recurrence or distant metastasis.[8,9] Several studies have reported that age, biopsy Gleason score (GS), nadir prostate-specific antigen (PSA) level, and the use of ADT, EBRT, and biologically effective dose (BED) are associated with BRFS.[6–12] In contrast, younger patients with PCa (≤60 years) have achieved excellent long-term PCa control with a low rate of treatment-related adverse events following LDR-BT.[6,11,13]

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Therefore, we aimed to evaluate the long-term oncological outcomes in patients with PCa who underwent LDR-BT at a single center in Japan.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the institutional review board of Gifu University (Number: 29-106). We reviewed the clinical records of 340 consecutive patients with PCa who underwent LDR-BT between August 2004 and December 2014 at Gifu University Hospital. The enrolled patients had clinical T1c/T2 PCa without lymph node involvement or distant metastases, according to the 2010 American Joint Committee on Cancer Staging Manual.[14] All patients were stratified into risk groups as per the classification model proposed by D'Amico.[4] Preoperative information obtained included age, PSA level, clinical T-stage, biopsy GS, risk classification, prostate volume (PV), ADT status, and follow-up duration. Patients who had previously undergone transurethral prostate resection and had <10 mL/s based on uroflowmetry examination did not undergo LDR-BT as an out-of-treatment indication. Complete colonoscopy was performed in all patients before LDR-BT, in April 2010, if the patient had not undergone a colonoscopy within the previous two years.[15]

2.2. Treatment

Patients with low-risk PCa who had a pretreatment PV > 50 mL received neoadjuvant ADT for at least three months before LDR-BT. Patients with intermediate-risk PCa were treated with a combination of LDR-BT and/or EBRT and/or ADT for nine months. Patients with high-risk PCa underwent LDR-BT, EBRT, and ADT for 24 months. Patients were implanted with loose ^{125}I radioactive seeds (Oncoseed, Nihon Mediphysics, Tokyo, Japan) using a Mick applicator (Mick Radio-Nuclear Instruments, Bronx, NY, USA) or with linked seeds using a ProLink® delivery system (C. R. Bard, Inc., Murray Hill, NJ, USA) using a real-time transrectal ultrasound-guided transperineal technique.[16] The prescribed minimum peripheral doses were 145 Gy for patients who underwent LDR-BT alone, and 104 Gy for those who underwent LDR-BT combined with EBRT. EBRT (40 Gy in 2 Gy fractions) was administered to the prostate and seminal vesicles within 1 month of LDR-BT. In all cases, seed implantation was performed after pre-planning using modified peripheral loading techniques.[17]

2.3. Post-dosimetric evaluation

Therapeutic planning and post-implant dosimetric evaluations were performed using the updated American Association of Physicists in Medicine Task Group 43 protocol and VariSeed version 7.1 (Varian Medical Systems, Palo Alto, CA, USA). A post-implant dosimetric study using computed tomography (CT) and magnetic resonance imaging (MRI) was performed one month following LDR-BT. CT was performed using a CT scanner with 16 or 64 detector arrays (LightSpeed Ultra 16/Discovery CT 750 HD; GE Healthcare, Milwaukee, WI, USA).[18] MRI was performed using a 5-channel SENSE cardiac coil under easy breathing with a slice thickness of 3 mm and no intersectional gap (Intera Achieva 1.5 T/Intra Achieva Nova Dual 1.5 T Pulsar; Philips Medical Systems, Eindhoven, The Netherlands).[18] The dosimetric parameters analyzed in this study were the minimal percentage of the dose received by 90% of the prostate gland (D90), the percentage of PV receiving 100% of the prescribed minimal peripheral dose (V100), the rectal volume receiving 100% of the prescribed dose (RV100), and BED.

2.4. Follow-up schedule

All patients were followed-up every 3–6 months for 5 years and every 6–12 months thereafter. Follow-up consisted of interval history, physical examination, and PSA measurement. Testosterone levels were also measured in patients who underwent ADT. The follow-up period was defined as the time from the completion of RT to the last available follow-up date or the date of death. BCR after LDR-BT was defined as any PSA increase greater than 2 ng/ml above the nadir, as per the Radiation Therapy Oncology Group-Phoenix definition.[5] PSA bounce, defined as a temporary rise in PSA, was excluded from being classified as BCR.

2.5. Statistical analysis

The endpoints of this study were BRFS, overall survival (OS), and the association between BCR and clinical/pathological covariates. JMP 14 (SAS Institute Inc., Cary, NC, USA) was used for the data analyses. The Kaplan–Meier method was used to determine the BRFS following LDR-BT. OS was defined as the time from LDT-BT to death due to any cause. The cut-off values for covariates were defined as the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ according to the area under the receiver operating characteristic curve.[19] Survival according to subgroup analysis was analyzed using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards model. Statistical significance was set at a two-sided p-value of <0.05.

3. Results

3.1. Patient characteristics

The demographic data of the participants are presented in Table 1. All patients were diagnosed with PCa based on histological examination of specimens obtained during prostate biopsy. Among them, six patients (1.8%) had PSA ≥20 ng/mL and 22 (6.5%) had GS ≥ 8.

3.2. Patients' dosimetric data

Dosimetric and anatomical data are shown in Table 2. Of the enrolled patients in this study, the median D90, V100, and BED

Table 1
Patient characteristics

	All (n = 340)
Age (year, median, IQR)	66.0 (62.0-71.0)
Prostate-specific antigen (ng/mL, median, IQR)	6.4 (5.0-8.7)
Clinical T-stage (number, %)	
T1c	223 (65.6)
T2a	74 (21.8)
T2b	17 (5.0)
T2c	26 (7.6)
Gleason score (median, IQR)	7 (6-7)
D'Amico risk classification (number, %)	
Low	146 (42.9)
Intermediate	160 (47.1)
High	34 (10.0)
Prostate volume at LDR-BT (mL, median, IQR)	22.4 (17.5-29.5)
Neoadjuvant ADT (number, %)	235 (69.1)
Adjuvant ADT (number, %)	100 (29.4)
Follow-up period (months, median, IQR)	90.0 (72.0-120.0)

Abbreviations: ADT, androgen deprivation therapy; LDR-BT, Iodine-125 low-dose-rate brachytherapy; IQR, interquartile range; n, number.

were 118.9% (interquartile range [IQR], 110.2–127.8%), 96.1% (IQR, 94.1–97.3%), and 193.3 Gy_2 (IQR, 176.1–208.2 Gy_2), respectively. According to the anatomic data of the enrolled patients, the median RV100 was 0.36 mL (IQR, 0.10–0.82 mL).

3.3. Oncological outcomes

At the end of the follow-up period, nine patients (2.6%) showed BCR, even though serum testosterone levels had recovered at 5 years following LDR-BT in all patients who underwent neoadjuvant or adjuvant ADT. Overall, six patients (1.8%) had developed secondary cancers after LDR-BT: bladder cancer in four (one patient aged ≤63 years and three patients aged >63 years), anal canal cancer in one patient aged ≤63 years, and rectal cancer in one patient aged >63 years. The 5-year and 10-year BRFS rates were 99.4% and 95.3%, respectively (Fig. 1A). According to the D'Amico risk stratification, the 10-year BRFS rates were 96.1% in patients with low-risk PCa, 95.4% in those with intermediate-risk PCa, and 93.4% in those with high-risk PCa (Fig. 1B). However, none of the enrolled patients died from PCa, and 11 patients succumbed to (3.2%) of other causes. The 5-year and 10-year OS rates were 98.2% and 95.9%, respectively (Fig. 2).

When patients' age was taken into account, the 5-year and 10-year BRFS rates were 100% and 89.4%, respectively, in those aged ≤63 years. However, the 5-year and 10-year survival rates were 99.1% and 99.1%, respectively, in patients aged >63 years (Fig. 3).

As per the multivariate analysis, age ≤63 years was a significant independent predictor of BCR following LDR-BT (Table 3).

4. Discussion

In this study, patients with PCa who underwent LDR-BT with or without ADT and EBRT achieved good oncological outcomes including BRFS and OS. Additionally, age ≤63 years was significantly associated with BRFS following LDR-BT.

Based on previous studies, age is a useful predictor of BCR after LDR-BT.[6,11,13] Reis et al reported that age <50 years was significantly associated with BCR as well as PSA nadirs at one year after LDR-BT.[11] However, only a small number of patients <50 years (7.87%) were included in this study.[11] Based on a prospective cohort study of 2,316 patients undergoing LDR-BT at 42 institutions in Japan, younger age was significantly associated with BCR only in patients with low-risk PCa.[6] This study suggests that younger-onset PCa may be more aggressive and possess several different biological and genetic features when compared to older-onset PCa.[6] In the multivariate analysis, age was significantly associated with BCR based on the Phoenix definition, whereas the risk group and BED independently affected BCR based on the nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS) definition (PSA of more than 1.0 ng/mL that is increasing over three measurements).[5,20] In case of high-risk PCa, PSA level, GS, and BED were significantly associated with BCR, but age was not.[7] GS was a significant independent predictor of metastasis following LDR-BT in patients with high-risk or high-grade PCa.[7–9] Therefore, the use of patient age as a predictive factor remains controversial.

Several epidemiological studies have documented a small but significantly elevated risk of developing second malignant neoplasms following RT as a treatment in PCa.[21,22] The magnitude of this excess absolute risk was estimated to be approximately one in 290, representing an increased relative risk of developing a second malignant tumor of approximately 6%, and this risk increased to one in 70 on long-term follow-up (>10 years).[21] In addition, the risk of developing a second cancer five years after treatment with LDR-BT was not significantly different from that of patients with PCa who were treated without RT.[22] Based on a single institution study of 348 patients with PCa who underwent LDR-BT and had a median follow-up period of 10.5 years, the absolute excess risk was represented as 35 cancers per 10,000 patients or one in 286.[22] As per the generally accepted mechanism of metastasis from primary malignant tumors, Kim et al reported that a primary tumor can act as the source of circulating tumor cells, with the potential of "self-seeding" of the primary tumor.[23] Another hypothesis is based on seed and soil theories.[24] Primary tumors metastasize by disseminating tumor cells into circulation and preparing the so-called "premetastatic niche" for metastasis implantation.[24] The proliferation of metastasis at distant sites is stimulated and maintained by compounds secreted into circulation by the primary tumor.[25] From this perspective, the absolute increased risk of secondary cancers appears to be low.[14] In this study, only 1.9% of the patients aged ≤63 years developed secondary cancers following LDR-BT. However, the need for long-term follow-up may be important in deciding the indication of LDR-BT in extremely young patients with PCa due to the risk of them developing secondary malignant neoplasms or distant metastasis following treatment with RT.[26]

In addition to comparing oncological outcomes among the various treatments for PCa, post-treatment quality of life (QOL) issues are important in younger patients with a life expectancy of ≥20 years.[27,28] In younger patients, LDR-BT has higher post-operative potency rates and QOL parameters than other treatment options.[28] Litwin et al reported that LDR-BT resulted in better sexual function, whereas maintenance of potency was equivalent for LDR-BT and bilateral nerve-sparing radical prostatectomy (RP).[29] According to QOL analysis after various treatments for PCa, patients who received LDR-BT had the highest quality of post-treatment sexual function, which resulted in a significantly

Table 2
Patient dosimetric data of radiation therapy

Dosimetric parameter	
The minimal percentage of the dose received by 90% of the prostate gland (%, median, interquartile range)	
LDR-BT	119.6 (111.0-127.1)
LDR-BT + EBRT	119.1 (108.7-128.7)
The percentage prostate volume receiving 100% of the prescribed minimal peripheral dose (%, median, interquartile range)	
LDR-BT	96.1 (94.2-97.6)
LDR-BT + EBRT	96.2 (92.9-97.9)
The rectal volume receiving 100% of the prescribed dose (mL, median, interquartile range)	
LDR-BT	0.39 (0.10-0.88)
LDR-BT + EBRT	0.35 (0.09-0.73)
Total biologically effective dose (Gy_2, median, interquartile range)	
LDR-BT	182.4 (170.0-195.8)
LDR-BT + EBRT	207.1 (198.3-215.3)

Abbreviations: EBRT, external beam radiation therapy; LDR-BT, Iodine-125 low-dose-rate brachytherapy.

Table 3
Predictive factors of biochemical recurrence in patients with prostate cancer who underwent brachytherapy

	N	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
Age							
≤63	105	6.42	1.33 − 31.0	0.021	6.44	1.31 − 31.6	0.022
>63	235	1(ref.)	-	-	1(ref.)	-	-
D'Amico risk classification							
Low-risk	146	1(ref.)	-	-	1(ref.)	-	-
Intermediate-risk	160	1.23	0.28 − 5.49	0.78	0.46	0.04 − 5.22	0.54
High-risk	34	4.11	0.67 − 25.2	0.13	1.44	0.09 − 25.8	0.80
Treatment of radiation therapy							
LDR-BT	201	1(ref.)	-	-	1(ref.)	-	-
LDR-BT + EBRT	139	2.54	0.19 − 10.2	0.19	4.29	0.36 − 51.5	0.25
Neoadjuvant androgen deprivation therapy							
No	105	1(ref.)	-	-	1(ref.)	-	-
Yes	235	0.99	0.25 − 3.96	0.99	1.15	0.28 − 4.81	0.84
Biologically effective dose							
<177.7Gy_2	89	1(ref.)	-	-	1(ref.)	-	-
≥177.7Gy_2	251	0.79	0.20 − 3.15	0.74	0.52	0.11 − 2.51	0.41

Abbreviations: CI, confidence interval; EBRT, external beam radiation therapy; HR, hazard ratio; LDR-BT, Iodine-125 low-dose-rate brachytherapy; n, number.

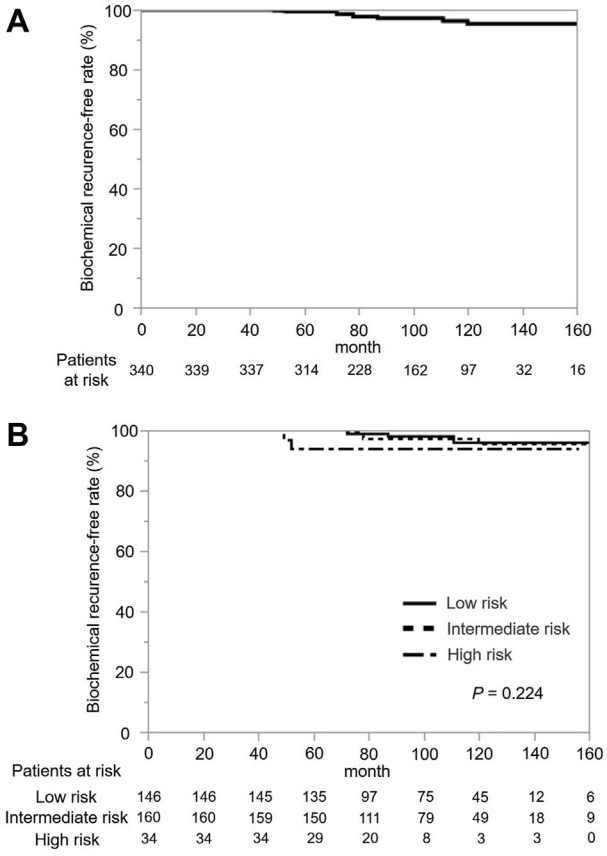

Fig. 1. Kaplan−Meier estimates of biochemical recurrence-free survival (BRFS). (A) The 5-year and 10-year BRFS rates were 99.4% and 95.3%, respectively. (B) As per the D'Amico risk stratification, the 10-year BRFS rate was 96.1% in patients with low-risk prostate cancer (PCa), 95.4% in those with intermediate-risk PCa, and 93.4% in those with high-risk PCa.

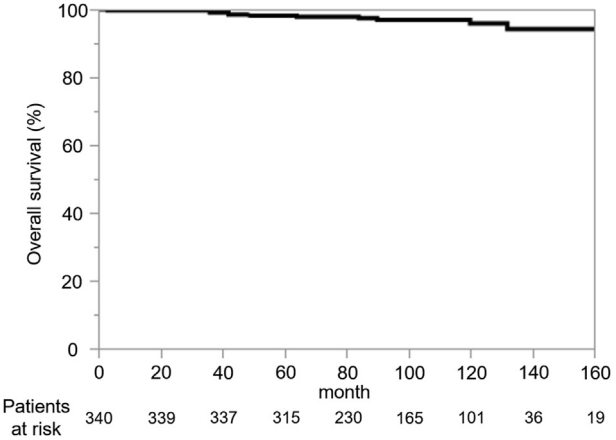

Fig. 2. Kaplan−Meier estimates of overall survival (OS). The 5-year and 10-year OS rates were 98.2% and 95.9%, respectively.

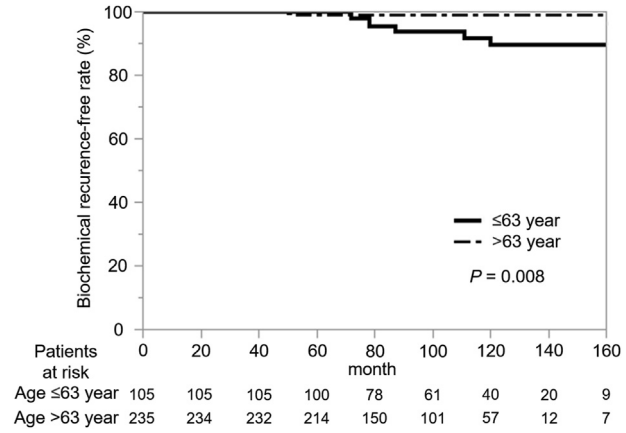

Fig. 3. Kaplan−Meier estimates of biochemical recurrence-free survival (BRFS) according to patients' age at the time of undergoing LDR-BT. The 5-year and 10-year BRFS rates were 100% and 89.4%, respectively, in patients aged ≤63 years. The 5-year and 10-year survival rates were 99.1% and 99.1%, respectively, in patients aged >63 years.

higher rate of overall satisfaction with the treatment, even though LDR-BT was associated with urinary symptoms.[30]

Our study has certain limitations. Firstly, it was a retrospective study performed at a single institution, which means the potential selection bias cannot be excluded. Secondly, the study had a relatively small sample size, especially of patients with high-risk PCa. Thirdly, we did not investigate QOL parameters after LDR-BT. Finally, no control group of patients received RP, EBRT, or ADT alone for the treatment of PCa.

In conclusion, age ≤63 years was a significant predictor of BCR following LDR-BT. Although the risk of secondary malignant neoplasms should be considered when selecting LDR-BT as a treatment option in younger patients with PCa, the prevalence of the same in these patients is relatively low. Therefore, clinicians should weigh the risks and benefits of definitive therapy for PCa, particularly in younger patients. The findings of this study should be validated using a larger prospective dataset to aid surgeons further in clinical decision-making.

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Conflict of interest

The authors have no conflicts of interest to declare and received no financial support for this study.

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