# PREDICTION AND STRATIFICATION OF THE BIOCHEMICAL RECURRENCE IN PATIENTS WITH HIGH-RISK PROSTATE CANCER AFTER LOW DOSE RATE PERMANENT SEED IMPLANTATION

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## Abstract

### *Introduction and Objective*

Treatment of high-risk prostate cancer (PCa) remains challenging for urologists. The present study was undertaken to identify risk factors for the biochemical recurrence (BCR) in patients with high-risk PCa who underwent low dose rate permanent seed implantation brachytherapy with iodine-125 (LDR).

### *Methods*

Medical records of 335 patients with high-risk PCa identified by National Cancer Care Network (NCCN) risk stratification and treated with LDR during the period of 2003–2015 at single institution have been reviewed. All patients received external beam radiation therapy (EBRT) after LDR. Possible risk factors assessed for the future BCR including age, PSA, prostate volume, histological findings of biopsy specimens, neoadjuvant hormone therapy, and local extent of disease evaluated by pelvic MRI. BCR free survival rates were determined using the Kaplan–Meier method. Risk factors for BCR were calculated by multivariate Cox proportional hazard model.

### *Results*

The Kaplan–Meier analysis showed that the 5- and 10-year BCR free survival rates were 86.7%, and 78.8%, respectively. Multivariate analysis demonstrated that WHO histological grade group 5 (Hazard ratio; HR 3.75, p<0.01), ≥cT3 (HR 2.03, p<0.05), PSA >20ng/ml (HR 2.45, p<0.01) and no neoadjuvant hormonal therapy (HR 2.16, p<0.05) were significant prognostic factors for BCR. Using these factors, the patients were stratified into a good- (0-1 risk factor), intermediate- (2-3 risk factors), and poor-risk group (4 risk factors). The 5- and 10-year BCR free survival rates were 92.4% and 83.1%, 75.3% and 72.5%, 26.7% and 26.7% in good-, intermediate-, and poor-risk patients, respectively.

### *Conclusion*

These results indicate that grade group 5, ≥cT3, PSA>20ng/ml, and no neoadjuvant hormonal therapy were independent risk factors for the BCR in patients with high-risk PCa treated with LDR. The combination of these factors may be helpful to identify candidates for additional treatments to prevent disease progression.

## Introduction and Objective

The majority of patients newly diagnosed as PCa exhibit clinically localized disease due to the widespread use of PSA screening test. Some patients are classified into high-risk PCa by NCCN risk stratification, and they are have higher incidence of biochemical failure and prostate cancer death. Radical prostatectomy and radiation therapy including LDR have been performed for localized high-risk PCa.

We started LDR in Japan, and have achieved over 3,000 cases until end of 2017. In this study, we summarized the results of high-risk PCa patients who underwent LDR, and identified the risk factors for BCR and developed a prognostic factor-based risk stratification model.

## Patients and Methods

From September 2003 to December 2015, total 2680 patients with adenocarcinoma of PCa received LDR at Tokyo Medical Center. Among them, 335 patients were classified into high risk group according to the NCCN risk stratification, Gleason score ≥8 and/or PSA >20ng/ml and/or ≥cT3a. Patients' characteristics were summarized in Table 1.

By the pre-planing or intraoperative planning methods to determine the seed location , we performed LDR using an ultrasound-guided technique with the Mick applicator or QUICKLINK. Iodine-125 seeds were administered as a prescription dose of 100-110 Gy, and EBRT with 45 Gy in 25 fractions (1.8X25) covering the prostate and seminal vesicles followed 1 month later.

Neoadjuvant hormonal therapy including use of androgen antagonists, LH-RH agonists or antagonists, both have been performed for 3 to 95 months in 264 patients with the aim of prostate volume reduction, high-grade PCa or a longer waiting time.

The primary outcome was BCR defined as a PSA level over the nadir plus 2 ng/ml (the Phoenix Definition of Biochemical Failure). Possible risk factors assessed for the future development of BCR included age, prostate volume (ml), initial PSA >20 (ng/ml), no neoadjuvant hormonal therapy, ≥cT3a and grade group 5. BCR free survival rates were constructed using the Kaplan-Meier method. Risk factors for BCR were evaluated by the log-rank test and multiple Cox proportional hazard model with a stepwise selection. All statistical analyses were performed with IBM SPSS Statistics® with a 2-sides p <0.05 considered significant.

## Results

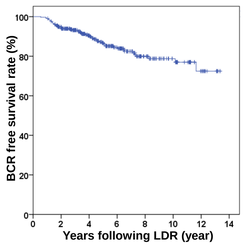
**Table 1. Patients characteristics**

| | Total | Grade group ≤4 | Grade group 5 | p value |
|---|---|---|---|---|
| Age (year) | 69.4±6.9 | 69.2±6.8 | 69.8±7.5 | 0.52 |
| Initial PSA (ng/ml) | 19.6±15.2 | 20.5±15.0 | 15.7±14.3 | 0.14 |
| Follow (year) | 5.6±3.2 | 5.8±3.1 | 4.7±3.2 | 0.08 |
| Prostate volume (ml) | 28.4±12.5 | 25.9±11.3 | 23.8±9.4 | 0.15 |
| Clinical T stage | | | | |
| T1.T2 | 255 | 196 | 59 | 0.91 |
| T3 | 80 | 62 | 18 | |
| Neoadjuvant hormonal therapy | | | | |
| Yes | 71 | 56 | 15 | 0.67 |
| No | 264 | 202 | 62 | |

**Table 2. Univariate and multivariate analysis for BCR**

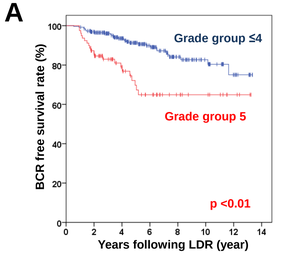
| | Univariate | Multivariate | | |
|---|---|---|---|---|
| | p value | Hazard ratio | 95% CI | p value |
| Age (year) | 0.347 | | | |
| Prostate volume (ml) | 0.959 | | | |
| Initial PSA >20 (ng/ml) | 0.259 | 2.45 | 1.3-4.5 | <0.01 |
| No neoadjuvant hormonal therapy | 0.117 | 2.16 | 1.1-4.1 | <0.05 |
| ≥cT3a | 0.096 | 2.03 | 1.1-3.9 | <0.05 |
| Grade group 5 | <0.01 | 3.75 | 2.1-6.8 | <0.01 |

**Fig 1. (A) BCR free survival rate curve, and (B) the incidences of BCR in all patients**




| | 5-year BCR free survival rate | 10-year BCR free survival rate |
|---|---|---|
| 335 | 86.7% | 78.8% |

**Fig 2. (A) BCR free survival rate curve, and (B) the incidences of BCR in grade group ≤4 and grade group 5**



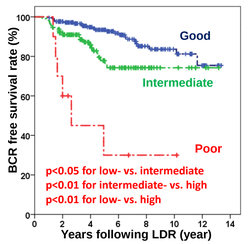

| Grade group | 5-year BCR free survival rate | 10-year BCR free survival rate |
|---|---|---|
| ≤4 (N=258) | 91.2% | 82.6% |
| 5 (N=77) | 70.1% | 65.0% |

**Fig 3. (A) Risk stratification of BCR using statistically significant variables, (B) BCR free survival curve, and (C) the incidences of BCR according to the three risk groups**

A

| Risk stratification | Number of risk factors | Hazard ratio |
|---|---|---|
| Good (N=213) | 0-1 | 0-3.8 |
| Intermediate (N=112) | 2-3 | 4.7-21.8 |
| Poor (N=10) | 4 | 43.8 |

B




C

| Risk stratification | 5-year BCR free survival rate | 10-year BCR free survival rate |
|---|---|---|
| Good | 92.4% | 83.1% |
| Intermediate | 75.3% | 72.5% |
| Poor | 26.7% | 26.7% |

## Summary of findings

1. *Incidence of BCR* The 5- and 10-year BCR free survival rates high risk PCa patients were 86.7%, and 78.8%, respectively.
2. *Grade group 5* Patients with grade group 5 PCa were significantly lower 5- and 10-year BCR free survival rate than one with grade group ≤4 PCa (p<0.01).
3. Risk factors for BCR The multivariate analysis revealed that grade group 5 (HR 3.75, p<0.01), ≥cT3 (HR 2.03, p<0.05), PSA >20ng/ml (HR 2.45, p<0.01) and no neoadjuvant hormonal therapy (HR 2.16, p<0.05) were significant risk factors for BCR.
4. *Risk stratification* Using these statistically significant factors in the multivariate Cox regression analysis, we developed a prognostic factor-based risk stratification model for BCR in high-risk PCa patients treated with LDR.

## Conclusion

This study revealed the independent predictive factors for BCR including grade group 5 among the high-risk PCa patients treated with LDR. The Grading System help us predict BCR after LDR more accurately.