Role of Novel Risk Classification Method, Prostate Cancer Risk Index (PRIX) for Clinically Localized Prostate Cancer After High-dose-rate Interstitial Brachytherapy as Monotherapy

KEN YOSHIDA[1], HIDEYA YAMAZAKI[2], SATOAKI NAKAMURA[2], KOJI MASUI[2], TADAYUKI KOTSUMA[3], HIRONORI AKIYAMA[3], EIICHI TANAKA[3] and YASUO YOSHIOKA[4]

[1]*Department of Radiology, Osaka Medical College, Takatsuki-City, Osaka, Japan;*
[2]*Department of Radiology, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, Japan;*
[3]*Department of Radiology, National Hospital Organization, Osaka National Hospital,Osaka City, Osaka, Japan;*
[4]*Department of Radiation Oncology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan*

Abstract. *Aim: To examine the role of the new grading system Prostate Cancer Risk Index (PRIX) with existing risk-grouping after high-dose-rate interstitial brachytherapy (HDR-ISBT) as monotherapy for localized prostate cancer. Patients and Methods: We analyzed outcome in 100 patients treated by HDR-ISBT as monotherapy using PRIX and compared this with D'Amico, the National Comprehensive Cancer Network (NCCN), and Seattle classifications. The median follow-up was 74 (range=48-109) months. Results: Five-year prostate-specific antigen control and overall survival rates were 94% and 98%, respectively. PRIX separated the risks statistically significantly (p=0.004), while D'Amico (p=0.319), NCCN 2002 (p=0.126), NCCN 2012 (p=0.052) and Seattle (p=0.112) classifications failed to show a statistically significant separation. Conclusion: PRIX is a more useful risk classification system in high-risk patient selection than existing risk classification system in clinically localized prostate cancer after HDR-ISBT as monotherapy.*

Prostate cancer is one of the major malignancies of men in Western countries. Interstitial brachytherapy (ISBT) can deliver a higher radiation dose to the prostate gland avoiding surrounding normal tissue and is, therefore, regarded as an effective treatment option among different types of radiotherapy (1-3). High-dose-rate ISBT (HDR-ISBT) monotherapy would definitely be the most efficient method of achieving good dose distribution with a high degree of conformity, even for adjacent tissue invasion (seminal vesicle or extracapsular extension), with short overall treatment time. We have implemented HDR-ISBT as monotherapy and reported excellent outcome (4, 5).

For risk factor classification, a simplified categorization with three risk groups is widely used, known as low-, intermediate-, and high-risk groups. This grouping is very simple and usable, but entails problem. With the advent of modern treatment modalities, dose escalation and hormonal therapy have improved biochemical control and overall survival rate of patients with localized prostate cancer. Generally, the high-risk groups of conventional groupings include cases so heterogeneous that it often makes it difficult to choose the most appropriate treatment from many alternatives. Yoshioka *et al.* proposed a new grouping method, namely Prostate Cancer Risk Index (PRIX), with an additional number of risk categories, which should be fully compatible with the existing data such as the Partin Table (6). The aim of the current study was to examine the role of PRIX by comparison with the existing risk-grouping methods such as D'Amico (7), the National Comprehensive Cancer Network (NCCN) 2005 (8), NCCN 2012 (9), and Seattle (10) classifications in assessment of outcome after HDR-ISBT monotherapy.

Patients and Methods

Between July 2003 and May 2008, 100 patients were treated by HDR-ISBT as monotherapy at the National Hospital Organization Osaka National Hospital. Patients' characteristics are shown in Table I. The median patient age was 71 (range=52-86) years and median follow-up time was 74 (range=48-109) months. Using the UICC classification of 2002, most patients had stage T2 disease or higher (11). All patients were histologically-proven to have adenocarcinoma. Gleason scores were 7 or more in most patients (62%). The median pre-treatment

Correspondence to: Hideya Yamazaki, MD, Department of Radiology, Kyoto Prefectural University of Medicine, 465 Kajiicho Kawaramachi Hirokoji, Kamigyo-ku, Kyoto, Kyoto 602-8566 Japan. Tel: +81 752515618, Fax: +81 752515840, e-mail: hideya10@hotmail.com

Key Words: High-dose-rate brachytherapy, prostate cancer, risk classification.

Table I. *Patients' characteristics.*

Variable	
Age (years)	
Median (range)	71 (52-86)
Follow-up period (months)	
Median (range)	73 months (48-109)
Gleason score	
≤6	38
7	42
8≤	18
Unknown	2
T-stage	
T1	34
T2	49
T3	16
T4	1
Initial prostate-specific antigen (ng/ml)	
Mean±SD	19±19 (3.8-98.6)
<10	39
10-20	31
>20	30
Dose/fraction (Gy/fractions)	
38 Gy/4 fractions	4
49 Gy/7 fractions	69
54 Gy/9 fractions	26
40 Gy/5 fractions	1
Androgen deprivation therapy	
Neoadjuvant only	81
Adjuvant only	0
Neoadjuvant+Adjuvant	10
No	9

Table II. *Patients' distribution among risk classification systems.*

Variable	
NCCN 2002	
Low	21
Intermediate	35
High	44
NCCN 2012	
Low	21
Intermediate	35
High	38
Super high risk	6
D' Amico	
Low	15
Intermediate	33
High	52
Siatle	
Low	21
Intermediate	27
High	52
PRIX	
0	15
1	20
2	14
3	20
4	16
5	10
6	3

NCCN; National Comprehensive Cancer Network, PRIX: Prostate Cancer Risk Index.

prostate-specific antigen (PSA) was 19 (range=3.8-98.6) ng/ml. Androgen deprivation therapy (ADT) was performed in 91 patients as neoadjuvant or adjuvant treatment (median=7 months; range=3-25 months). The detailed method of applicator implantation was described elsewhere (5). All patients underwent a computed tomographic (CT) examination before planning. The CT-based planning with or without magnetic resonance imaging (MRI) assistance was performed by computer optimization (Nucletron an Elekta Company, Veenendaal, the Netherlands; PLATO® and Oncentra® brachy, Elekta AB, Stockholm, Sweden) with or without manual modification. The prescribed dose was 38 Gy in four fractions, 40 Gy in five fractions, 54 Gy in nine fractions in five days, and 49 Gy in seven fractions. The treatment machine used was the microSelectron-HDR® (Nucletron).

The new grading system consists of three factors (6). The first factor is for PSA of 4.1-10.0 ng/ml (score 0), 10.1-20.0 ng/ml (score 1), and >20.0 ng/ml (score 2). The second is for Gleason score (GS) of 6 (score 0), 7 (score 1), and 8-10 (score 2). The third is T classifications (UICC 2002) of T1c–T2a (score 0), T2b–T2c (score 1), and T3a (score 2). The sum of the three scores derives the PRIX. Definition of the following three risk-grouping systems, which seemed the most widely accepted currently, were examined in this study.

D'Amico defines low-risk patients as having disease stage T1c, 2a, PSA level ≤10 ng/ml and GS ≤6; intermediate-risk as T2b or GS 7 or PSA level >10 and ≤20 ng/ml; and high-risk as T2c or PSA level >20 ng/ml or GS ≥8 (7).

The NCCN defines recurrence risk as follows: low: T1-T2a and GS 2-6 and PSA <10 ng/ml; intermediate: T2b-T2c or GS 7 or PSA 10-20 ng/ml; high: T3a or GS 8-10 or PSA >20 ng/ml (8); and very high: T3–T4 (9).

The Seattle group defines risk categories as follows: low: PSA ≤10 ng/ml, GS <7, and stage <T2c; intermediate: PSA >10 ng/ml or GS ≥7 or stage ≥T2c (one intermediate risk factor); and high: two or more intermediate risk factors (10). Table II shows the patient distribution by each risk classifications.

Statistical analysis. All statistical analyses were performed using Statview 5.0 (SAS Institute, Inc., Cary, NC, USA) and IBM SPSS statistics 20 software (IBM, Armonk, NY, USA). Frequencies were analyzed using the χ^2 test. Means were compared using Student's *t*-test for normally-distributed data and the Mann–Whitney *U*-test for skewed data. Survival data and cumulative incidences were estimated by the Kaplan–Meier method and examined for significance using the log-rank test. The cut-off value was set at the average or the median value of each variable unless otherwise stated. All analyses used the conventional $p<0.05$ level of significance.

Results

All ISBT was finished without skipping treatment sessions or reducing planned doses. The 5-year PSA control rate was 94%. No PSA failure was found among low-risk patients by any risk classification system. Nine PSA failures occurred

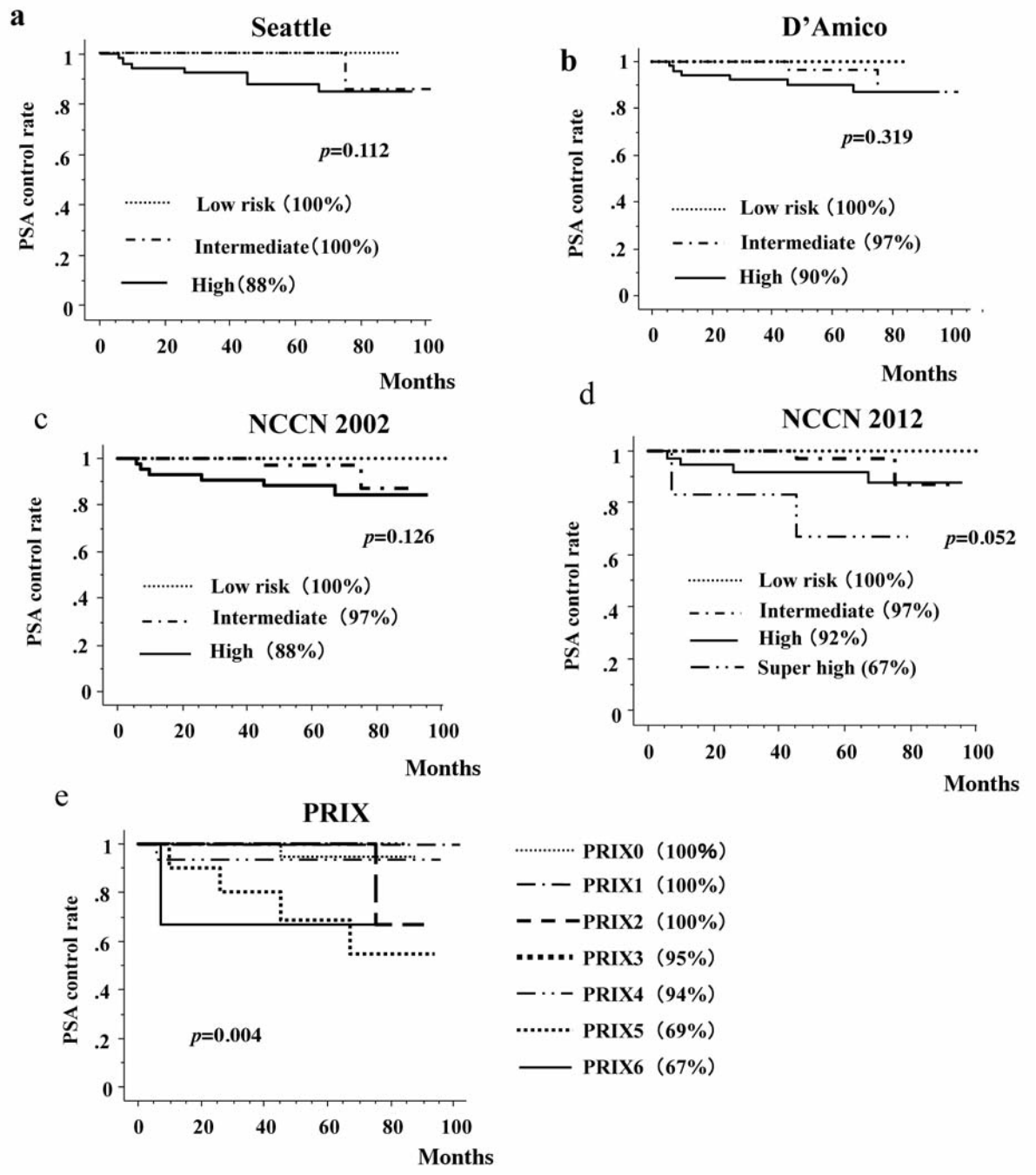

Figure 1. *PSA control rates according to Seattle (a), D'Amico (b), NCCN 2002 (c) NCCN 2012 (d) and PRIX (e) risk classification systems. Five-year PSA control rates are given in parentheses. PRIX separated the risks statistically significantly (p=0.004), while the D'Amico (p=0.319), NCCN 2002 (p=0.126), NCCN 2012 (p=0.052) and Seattle (p=0.112) risk classifications failed to show statistically significant separation.*

and seven of those were observed within 48 months. The 5-year biochemical control rate was 100%, 93% and 82% for T1-2a, T2b and 2c and T3-4 (p=0.015). The 5-year biochemical control rate was 100%, 95% and 78% for Gleason score <7, 7 and >7, respectively (p=0.037). The 5-year biochemical control rate was 100%, 90% and 90% for PSA<10, PSA=10-20 and PSA >20 ng/ml (p=0.074). The 5-year biochemical control rate was 100%, 100%, 100% , 95%, 94%, 69% and 67% for PRIX 0-6 (Figure 1, p=0.004), whereas the other risk classification systems (D'Amico:

p=0.319, NCCN 2002: p=0.126, NCCN 2012: p=0.052 and Seattle: p=0.112 classifications failed to show a statistically significant separation.

The 5-year overall survival rate was 98%; six patients died 40 to 76 months after HDR-ISBT. Only one patient was dead due to prostate cancer. The other five patients died due to concurrent disease (second cancer: 4, brain vascular disease: 1).

Grade 2 late gastrointestinal complications (rectal bleeding) occurred in two patients (2%). No grade 3 or more late gastrointestinal complication was observed.

Discussion

Until recently, HDR-ISBT as monotherapy was mainly used for low-intermediate risk patients (1, 2). The Osaka University Group initiated clinical investigation to expand eligibility criteria to all risk groups in 1995 (4). The recent treatment results (5-year PSA control rates) were 85%, 93% and 79% for low-, intermediate- and high-risk patients (NCCN 2002) (3) data which concur with our data.

Several other groups also reported good outcomes. Challapalli *et al*. reviewed the treatment results of combined HDR-ISBT and external-beam radiotherapy and showed that 4-10 year biochemical control rates were 82-100% for low-intermediate risk and 62-97% for high-risk patients (NCCN 2002) (11). Zamboglou *et al*. investigated HDR-ISBT monotherapy in over 700 patients and obtained 5-year biochemical control rate 95%, 95% and 93% for low-risk, intermediate-risk and high-risk groups (D'Amico) (12). Therefore, HDR brachytherapy is now one of the highly curative potential treatments, not only for low- and intermediate-risk patients, but also for high-risk patients. In addition, some phase III trials demonstrated that neoadjuvant or adjuvant hormone therapy for 'locally advanced prostate cancer' is associated with a significant improvement in cause-specific survival or overall survival, compared to radiotherapy alone (13-15). The definitions of 'locally advanced prostate cancer' in these trials are different. We should decide which patients really benefit from the addition of hormone therapy or intensive treatment such as HDR-ISBT, in future experimental clinical trials. PRIX may contribute to finding more consistent answers by specifying that patients with, for example, a given PRIX or greater would benefit, and others not (6).

However, several limitations remain. Firstly, this was a retrospective single-Institute analysis dealing with a rather small number of patients. To confirm reliability and potential for PRIX, longer follow-up with a larger number of patients is required before reaching concrete conclusions.

In conclusion, PRIX is a useful risk classification system after HDR-ISBT as monotherapy for prostate cancer patients.

Acknowledgements

This work was supported by JSPS Grant-in-Aid for Scientific Research (KAKENHI) (C) Grant Number 25461931.

References

1 Zelefsky M, Valicenti L, Hunt M and Perez C: Low-risk prostate cancer. In: Perez and Brady's Principle and Practice of Radiation Oncology, Fifth Edition. Halperin E, Perez C and Brady L (eds.). Philadelphia, Lippincott Williams and Wilkins, pp. 1439-1482, 2008.

2 Chung H, Speight J and Roach M: Intermediate- and high-risk prostate cancer. *In*: Perez and Brady's Principle and Practice of Radiation Oncology, Fifth Edition. Halperin E, Perez C and Brady L (eds.). Philadelphia, Lippincott Williams and Wilkins, pp. 1483-1502, 2008.

3 Yoshioka Y, Yoshida K, Yamazaki H, Nonomura N and Ogawa K: The emerging role of high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer. J Radiat Res *54*: 781-788, 2013.

4 Yoshioka Y, Nose T, Yoshida K, Inoue T, Yamazaki H, Tanaka E, Shiomi H, Imai A, Nakamura S, Shimamoto S and Inoue T: High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: Treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys *48*: 675-681, 2000.

5 Yoshida K, Nose T, Shiomi H, Yoshioka Y, Fujita Y, Kuroda S, Yoshida M, Takahashi T, Kitamura M, Akai H, Oka T and Hosoki T: New ambulatory implant technique of high-dose-rate interstitial brachytherapy for prostate cancer. Radiat Med *24*: 595-599, 2006.

6 Yoshioka Y and Inoue T: Prostate Risk Index (PRIX) as a new method of risk classification for clinically localized prostate cancer. Strahlenther Onkol *183*: 490-496, 2007.

7 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ and Wein A: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA *280*: 969-974, 1998.

8 National Comprehensive Cancer Network. Prostate cancer – version 2.2005. NCCN Clinical Practice Guidelines in Oncology. Jenkintown, PA, USA: NCCN, 2005 (http:// www.nccn.org/ index.html). Common Terminology Criteria for Adverse Events, Version 3.0: http://ctep.cancer.gov/ protocoldevelopment/ electronic_applications/docs/ctcaev3.pdf.

9 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) prostate cancer 2012 version 4. http://www.nccn.org/ professionals/physician_gls/f_guidelines.asp#prostate.

10 Sylvester JE, Blasko JC, Grimm PD, Meier R and Malmgren JA: Ten-year biochemical relapse-free survival after external beam radiation and brachytherapy for localized prostate cancer: the Seattle experience. Int J Radiat Oncol Biol Phys *57*: 944-952, 2003.

11 Challapalli A, Jones E, Harvey C, Hellawell GO and Mangar SA: High-dose-rate prostate brachytherapy: an overview of the rationale, experience and emerging applications in the treatment of prostate cancer. Br J Radiol *85*: 18-27, 2012.

12 Zamboglou N, Tselis N, Baltas D, Buhleier T, Martin T, Milickovic N, Papaioannou S, Ackermann H and Tunn UW:

High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. Int J Radiat Oncol Biol Phys *85*: 672-678, 2013.

13 Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Mattelaer J, Lopez Torecilla J, Pfeffer JR, Lino Cutajar C, Zurlo A and Pierart M: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet *360*: 103-106, 2002.

14 Pilepich MV, Winter K, John MJ, Mesic JB, Sause W, Rubin P, Lawton C, Machtay M and Grignon D: Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys *50*: 1243-1252, 2001.

15 Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, Hug EB, Asbell SO and Grignon D: Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys *61*: 1285-1290, 2005.

Received February 2, 2014
Revised April 3, 2014
Accepted April 4, 2014