

## Original Article

Prostate Int 2014;2(2):70-75 • <http://dx.doi.org/10.12954/PI.14042>

# Predictive factors of unfavorable prostate cancer in patients who underwent prostatectomy but eligible for active surveillance

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**Purpose:** To investigate the predictive factors of unfavorable prostate cancer in Korean men who underwent radical prostatectomy but eligible for active surveillance according to Epstein criteria.

**Methods:** We retrospectively reviewed the medical records of 2,036 patients who underwent radical prostatectomy for prostate cancer between 1994 and 2011. Among these, 233 patients were eligible for active surveillance based on Epstein criteria. Unfavorable prostate cancer was defined as pathologic Gleason sum  $\geq 7$  or non-organ-confined disease. We investigated pathologic outcomes and predictive factors for unfavorable prostate cancer.

**Results:** Of 233 cases, 91 patients (39.1%) were pathologic Gleason sum  $\geq 7$ , 11 (4.7%) had extracapsular extension, and three (1.3%) had seminal vesicle invasion. Ninety-eight patients (42.1%) had unfavorable prostate cancer. When comparing clinically insignificant and significant prostate cancer, there were significant differences in mean age ( $P=0.007$ ), prostate volume ( $P=0.021$ ), prostate-specific antigen (PSA) density ( $P=0.03$ ), maximum tumor volume in biopsy core ( $P<0.001$ ), and rate of two positive cores ( $P=0.001$ ). On multivariate analysis, age ( $P=0.015$ ), PSA density ( $P=0.017$ ) and two positive cores ( $P=0.001$ ) were independent predictive factors for unfavorable prostate cancer.

**Conclusions:** A significant proportion of patients who were candidates for active surveillance had unfavorable prostate cancer. Age, PSA density, and two positive cores were independent significant predictive factors for unfavorable prostate cancer. These factors should be considered when performing active surveillance.

**Keywords:** Prostatic neoplasms, Surveillance, Prostatectomy, Pathology, Neoplasm grading

## INTRODUCTION

Low-risk prostate cancer is a very indolent disease with a limited impact on life expectancy. The Scandinavian Prostate Cancer Group Study Number 4 reported that among men in the low-risk group, radical prostatectomy did not significantly reduce the rate of death from prostate cancer [1]. The Prostate Cancer Intervention versus Observation Trial compared the outcome of prostatectomy and observation and showed no

difference in cancer-specific survival among men with low-risk cancers [2]. These studies advocate the use of active surveillance (AS) and AS is now considered a viable treatment option for low-risk prostate cancer. However, these data are not directly applicable to Asian men. Center et al. [3] reported international variation in prostate cancer incidence and mortality rates. Prostate cancer incidence rates in Asia are among the lowest worldwide but the annual percent change in incidence in the Republic of Korea was 13.8%. Byun et al. [4] re-

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Submitted: 26 February 2014 / Accepted after revision: 14 April 2014

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pISSN: 2287-8882 • eISSN: 2287-903X

ported that Korean men with prostate cancer now have better clinicopathologic parameters than previously. Nonetheless, they showed worse pathologic features than Western men: approximately 50% of Western men had a pathologic Gleason sum of 6 or lower compared with only approximately 30% of Korean men. Thus, although AS is a treatment option for low-risk prostate cancer in the western world it is doubtful whether this applies to Asian men. We analyzed the pathologic features of possible candidates for AS among Korean prostate cancer patients and investigated the predictive factors of unfavorable prostate cancer.

## MATERIALS AND METHODS

### 1. Patients

We retrospectively reviewed the medical records of 2,036 patients who underwent radical prostatectomy for prostate cancer at Samsung Medical Center between September 1995 and December 2011. Patients who underwent neoadjuvant therapy and those with no biopsy slide or incomplete data were excluded. In total 233 patients fulfilled the inclusion criteria for AS defined by Carter et al. [5], which are defined as clinically localized (T1) disease, prostate-specific antigen (PSA) density  $\leq 0.15$  ng/mL<sup>2</sup>, Gleason score  $\leq 6$ , fewer than three cores containing prostate cancer, and lower than 50% cancer involvement in any core [6]. We compared the pathological findings between prostate biopsies and specimens after radical prostatectomy.

Three different radical prostatectomy methods were used: 38.6% of patients (90/233) had open radical prostatectomy, 52.8% (123/233) had robot-assisted laparoscopic prostatectomy, and 8.6% (20/233) had laparoscopic radical prostatectomy. Neurovascular bundle saving was done in 78.5% (183/233). Unfavorable prostate cancer was defined as pathologic Gleason score sum  $\geq 7$  or non-organ-confined disease (extracapsular extension or seminal vesicle invasion) after radical prostatectomy. Our institutional pathologists reviewed all biopsy slides from other institutions. The percentage of tumor volume in each biopsy core was measured. Prostate volume was determined by transrectal ultrasound or magnetic resonance imaging using the formula  $\pi/6 \times \text{width} \times \text{height} \times \text{length}$ . PSA density was calculated as preoperative PSA divided by prostate volume. Biochemical recurrence (BCR) was defined as an initial serum PSA level  $\geq 0.2$  ng/mL with a second confirmatory serum PSA level  $> 0.2$  ng/mL [7]. We investigated pathologic outcomes and predictive factors for unfavorable prostate cancer. Clinical and pathologic staging was assigned according to the 2002 TNM staging system.

### 2. Statistical analyses

Continuous variables were compared using the Mann-Whitney *U*-test, and categorical variables were compared using the chi-square test. Potential predictors for unfavorable prostate cancer were analyzed by univariable and multivariable logistic regression models. For logistic regression analysis PSA density was replaced with the transformed value of PSA density  $\times 10$  (PSAD10). The 5-year BCR-free survival rate was estimated using the Kaplan-Meier method and compared using the Log-rank test. All *P*-values were two-sided, and a value of *P*  $< 0.05$  was considered statistically significant. All data analyses were performed with IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA).

### 3. Ethics statement

The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2012-07-068). Informed consent was waived by the IRB.

## RESULTS

Table 1 shows the clinical characteristics of 233 patients included in this study. Majority of enrolled patients (222/233, 95.7%) underwent radical prostatectomy after January 2005. The mean age at the time of surgery was 64.6 years (range, 43–73 years). Mean PSA level and PSA density were 4.3 ng/

**Table 1.** Clinical and needle biopsy characteristics of patients

Characteristic	Value
No. of patients	233
Age (yr)	64.6 $\pm$ 6.2 (43–77)
Body mass index (kg/m <sup>2</sup> )	24.6 $\pm$ 2.7 (17.5–39.4)
PSA (ng/mL)	4.3 $\pm$ 1.5 (0.91–10.80)
Prostate volume (mL)	45.1 $\pm$ 19.4 (18.4–173.0)
PSA density (ng/mL <sup>2</sup> )	0.10 $\pm$ 0.03 (0.031–0.149)
Maximum tumor volume in biopsy core (%)	24.6 $\pm$ 12.5 (1–50)
No. of biopsy cores	
<10	24 (10.3)
$\geq 10$	209 (89.7)
Biopsy Gleason score	
<6	6 (2.6)
6	227 (97.4)
No. of positive cores	
1	168 (72.1)
2	65 (27.9)
Laterality of biopsy cores	
Unilateral	212 (91.0)
Bilateral	21 (9.0)

Values are presented as mean  $\pm$  standard deviation (range) or number (%).

PSA, prostate specific antigen.

mL and 0.10 ng/mL<sup>2</sup> respectively. All patients had a minimum of six biopsy cores and 89.7% had 10 or more biopsy cores. Most patients (72.1%) had one positive core, 27.9% had two positive cores, and 9.0% had positive cores on both sides of the prostate.

Table 2 shows the clinicopathologic findings after radical prostatectomy. Ninety-eight of 233 patients (42.1%) had unfavorable prostate cancer. Among these, 91 patients (39.1%) had pathologic Gleason score sum  $\geq 7$ , 11 (4.7%) had extracapsular extension, and three (1.3%) had seminal vesicle invasion. One patient (0.4%) had Gleason score sum of 9. We did lymph node dissection in 48 patients (20.6%) and no patient had a positive pelvic lymph node.

**Table 2.** Postprostatectomy pathologic outcomes

Variable	No. (%)
Unfavorable prostate cancer	98 (42.1)
Pathologic up-staging	14 (6.0)
Extracapsular extension	11 (4.7)
Seminal vesicle invasion	3 (1.3)
Pathologic up-grading	91 (39.1)
3+4	83 (35.6)
4+3	7 (3.0)
4+5	1 (0.4)
Positive surgical margin	11 (4.7)
Lymph node invasion	
Negative	48 (20.6)
Not performed	185 (79.4)

When comparing favorable and unfavorable prostate cancer, there were significant differences in mean age (63.7 vs. 65.9,  $P=0.007$ ), prostate volume (47.1 mL vs. 42.2 mL,  $P=0.021$ ), PSA density (0.096 ng/mL<sup>2</sup> vs. 0.104 ng/mL<sup>2</sup>,  $P=0.03$ ), maximum tumor volume in biopsy core (11.6% vs. 18.3%,  $P<0.001$ ), and percentage of patients with two positive cores (19.3% vs. 39.8%,  $P=0.001$ ) (Table 3). There was no difference in laterality of positive biopsy cores. The patients who had family history of prostate cancer were 4.7% (11/223) and there was no difference between favorable and unfavorable prostate cancer (3.7% vs. 6.1%,  $P=0.534$ ).

We used logistic regression analysis to identify predictive factors for unfavorable prostate cancer. On univariable analysis, age (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.02–1.11;  $P=0.009$ ), PSA density (OR, 2.88; 95% CI, 1.11–7.43;  $P=0.029$ ), maximum tumor volume (OR, 1.05; 95% CI, 1.02–1.07;  $P<0.001$ ), and two positive cores (OR, 2.77; 95% CI, 1.54–4.99;  $P=0.001$ ) were predictors of unfavorable prostate cancer. On multivariable analysis, age (OR, 1.06; 95% CI, 1.01–1.11;  $P=0.015$ ), PSA density (OR, 3.41; 95% CI, 1.25–9.30;  $P=0.017$ ), and two positive cores (OR, 2.83; 95% CI, 1.54–5.20;  $P=0.001$ ) were independent predictive factors for unfavorable prostate cancer (Table 4). The median follow-up was 30 months and the 5-year BCR-free survival rates were estimated to be 96.8% for favorable prostate cancer and 98% for unfavorable prostate cancer, with no significant difference ( $P=0.734$ ).

**Table 3.** Comparison of preoperative variables between patients with favorable and unfavorable prostate cancer

Variable	Favorable PCa	Unfavorable PCa	P-value
No. of patients	135	98	
Age (yr)	63.7 (49–77)	65.9 (43–77)	0.007
Body mass index (kg/m <sup>2</sup> )	24.6 (17.5–39.4)	24.7 (18.3–30.1)	0.459
PSA (ng/mL)	4.3 (0.91–9.00)	4.2 (0.93–10.80)	0.606
Prostate volume (mL)	47.1 (18.4–173.0)	42.2 (20.0–113.0)	0.021
PSA density (ng/mL <sup>2</sup> )	0.096 (0.040–0.148)	0.104 (0.031–0.149)	0.030
Maximum tumor volume in biopsy core (%)	11.6 (1.0–50.0)	18.3 (2.0–50.0)	<0.001
No. of biopsy cores			0.967
<10	14 (10.4)	10 (10.2)	
$\geq 10$	121 (89.6)	88 (89.8)	
Biopsy Gleason score			1.000
<6	4 (3.0)	2 (2.0)	
6	131 (97.0)	96 (98.0)	
No. of positive cores			0.001
1	109 (89.7)	59 (60.2)	
2	26 (19.3)	39 (39.8)	
Laterality of biopsy cores			0.142
Unilateral	126 (93.3)	86 (87.8)	
Bilateral	9 (6.7)	12 (12.2)	

Values are presented as mean (range) or number (%). PCa, prostate cancer; PSA, prostate specific antigen.

**Table 4.** Logistic regression analysis for favorable prostate cancer

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.06	1.02–1.11	0.009	1.06	1.01–1.11	0.015
BMI	1.01	0.92–1.11	0.834			
PSA	0.93	0.79–1.11	0.432			
Prostate volume	0.99	0.97–1.00	0.061			
PSAD10	2.88	1.11–7.43	0.029	3.41	1.25–9.30	0.017
Maximum tumor volume	1.05	1.02–1.07	<0.001			
No. of biopsy cores	1.02	0.43–2.40	0.967			
Biopsy Gleason score	1.47	0.24–8.17	0.663			
No. of positive cores	2.77	1.54–4.99	0.001	2.83	1.54–5.20	0.001
Laterality of biopsy cores	1.95	0.79–4.84	0.148			

OR, odds ratio; CI, confidence interval; BMI, body mass index; PSA, prostate specific antigen; PSAD10, PSA density  $\times$  10.

## DISCUSSION

Widespread use of PSA screening has increased detection rates of low-risk prostate cancer. Although screening has resulted in a significant decrease in prostate cancer mortality [8], it has also brought the new problems of overdiagnosis and overtreatment. The cost of diagnosis and treatment for potentially nonharmful disease is another problem. A recent report showed no difference in survival between expectant treatment and radical prostatectomy [2]. These findings have resulted in increased use of AS. AS has many advantages including avoidance of side effects of definite therapy or unnecessary treatment of indolent cancers, retained quality of life, and decreased treatment costs. However, it also has several disadvantages including the possibility of missing the chance of cure, possible cancer progression, and increased anxiety over untreated cancers. Therefore, patient selection criteria are a critical aspect of successful AS. Many studies are being conducted and many contemporary AS criteria are available. In a meta-analysis of conservative management of clinically localized prostate cancer, Chodak et al. [9] reported that the 10-year cancer-specific survival rate was 87% for low-grade prostate cancer and 81% for metastasis-free survival. However, their study reported long-term results of conservative management and the concept of AS is different. Reports of AS studies have a relatively short follow-up duration. Klotz et al. [10] reported long-term results of AS of 450 patients with a median follow-up of 6.8 years (1 to 13 years). Overall survival was 78.6% and the 10-year prostate cancer actuarial survival

was 97.2%. Thirty percent of the patients were offered definitive therapy, and 72% and 62% of patients were maintained on AS at 5 and 10 years respectively from the beginning of the study. Carter et al. [5] reported results of AS of 407 men: 59% remained on AS at a median follow-up of 3.4 years, 25% underwent curative intervention, 3% were lost to follow-up, and 11% withdrew from the program. Other studies on AS generally showed that 30% of patients receive curative therapy and cancer-specific mortality was low during 5 to 10 years of follow-up. However, these data are not conclusive and the studies were conducted in western populations thus their direct application to Asian men may be inappropriate.

Compared with western patients, a higher proportion of Korean prostate cancer patients have high-grade disease. Song et al. [11] reported that more than 60% of American men have Gleason scores of 6 or lower, whereas 58.8% of Korean men have Gleason scores of 7 or greater. Furthermore, 50% of Korean patients with PSA level  $<$  4.0 ng/mL and 56.4% of patients with PSA level between 4.1 and 10.0 ng/mL have Gleason scores of 7 or greater. Similar results were reported in other Asian countries: 46.7% of Chinese men (57/122) and 56.2% of Japanese men (100/178) had Gleason score of 7 or greater in radical prostatectomy specimens. Lee et al. [12] analyzed 131 Korean men who met the Epstein criteria and underwent prostatectomy. Of these, 30.5% (40/131) had pathologically unfavorable prostate cancer, defined as either Gleason sum 7 or non-organ-confined disease. In contrast, Jeldres et al. [13] reported a similar study with European men in which 24% (88/366) had unfavorable pathologic outcomes. Analysis of the CaPSURE database (UCSF, Urology Outcomes Research Group and TAP Pharmaceutical Products, Inc., Lake Forest, IL, USA) showed that 24% of men (30/125) who met the Epstein criteria had pathologic upstaging or upgrading [14]. Our data showed that 42.1% (98/233) had pathologically unfavorable prostate cancer. These differences between western series and Korean series may be due to different PSA screening rates or differences in intrinsic cancer biology.

Similar studies conducted in Europe or the United States showed a higher rate of pathologic upgrading. Mufarrij et al. [15] reported 205 men who met the Epstein criteria, among which 45.9% showed pathologic upgrading to Gleason score 7 or greater, and Kane et al. [16] reported an upgrading rate of 36%. However, these studies did not report the total number of biopsy cores among the inclusion criteria and the tumor volume in biopsy cores. Freedland et al. [17] reported that 42% of patients had pathologic upgrading from Gleason 6 to 7 and patients with more than eight biopsy cores had a significantly lower rate of upgrading (OR, 0.62; 95% CI, 0.43–0.89;

$P=0.01$ ). Abouassaly et al. [18] also showed that a high number of biopsy cores are related to reduced Gleason upgrading. Our study also included men with fewer than 10 biopsy cores, but they represented only about 10% of the population and 3% (7/233) had fewer than eight biopsy cores.

Many studies have been conducted to analyze the pathologic outcomes of radical prostatectomy in possible candidates for AS. However, most of these studies were conducted in Western countries and only a few were performed in Asia. Few studies suggested predictive factors for unfavorable disease. Beauval et al. [19] showed that prostate volume was significantly predictive for insignificant prostate cancer. Our study showed that older age, PSA density, and two positive cores were independent predictors of unfavorable disease. Although these results will not alter the criteria for AS, they might help in the decision making process for patients considering AS. Further studies based on a large population might suggest different criteria for AS.

In the current study, the 5-year BCR-free survival rate was estimated to be 97.3%, compared with 92% to 100% in other similar studies [14,15,19,20]. Despite the high proportion of pathologic upgrading, BCR-free survival rates were high. This could be because the data are based on low-risk prostate cancer and a favorable BCR rate was the natural result, or because of the relatively short follow-up period (approximately 2.5 years). Other studies showed no significant difference in BCR rate using different inclusion criteria [21,22]. Iremashvili et al. [21] compared pathologic cancer characteristics in patients grouped according to five different contemporary AS criteria and showed no significant difference in BCR-free survival. Ploussard et al. [22] also compared pathologic findings of candidates for AS who were divided into three different groups based on biopsy criteria and showed no significant difference in BCR-free survival rates. However, because these studies had short follow-up durations, further investigations are necessary to reveal the relationship between different AS criteria and BCR-free survival. In addition, Thaxton et al. [23] reported that a biopsy Gleason score greater than 6 had a 2.74- to 3.19-fold increased hazard ratio for biochemical progression.

This study has several limitations. First, this was a retrospective study performed at a single center. Second, there was heterogeneity in the biopsy cores and no cutoff values. This study included men with six or more biopsy cores but 89.7% of them (209/233) had 10 or more biopsy cores. When analyzed separately, older age, PSA density, and two positive cores were independent predictors of unfavorable disease. The relatively short follow-up duration is another limitation and long-term pathologic data are required.

In conclusion, AS is a promising treatment option for low-risk prostate cancer patients because it avoids overtreatment or complications of prostatectomy or radiation therapy but it is not directly applicable to Korean men. Further definitive studies are required and stricter criteria should be established. Our study reported the rates of pathologic features or upgrading in Korean patients and suggested predictive factors of unfavorable prostate cancer. Our findings could provide guidance when deciding whether to perform AS instead of other treatment options.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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