

Urological Oncology

Impact of Prostate Size on Pathologic Outcomes and Prognosis after Radical Prostatectomy

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Purpose: We investigated prostate size and its correlation with final pathologic outcomes and prognosis.

Materials and Methods: From 1993 to 2009, 830 consecutive patients who underwent radical prostatectomy with follow-up duration of 12 months or more were included in this study. Patients were categorized according to prostate size as follows: group 1, prostate size ≤ 40 g (n=458), and group 2, prostate size > 40 g (n=472). Preoperative parameters and postoperative pathologic outcomes were compared between groups. Multivariate analysis with Cox proportional hazards regression model was used to identify the pathologic and clinical factors affecting biochemical recurrence.

Results: Patients in group 1 had higher pathologic T stage (pT2a=17.7% vs. 23.9%, pT2b=1.1% vs. 0%, pT2c=40.4% vs. 39.8%, pT3a=29.5% vs. 21.0%, pT3b=10.7% vs. 13.2%, p=0.003) and higher positive surgical margin (40.3% vs. 33.1%, p=0.033) than did patients in group 2. Pathologic Gleason score was not significantly different between the two groups. The 5-year biochemical-recurrence-free survival was 62.3% for patients in group 1 and 73.2% for patients in group 2 (p=0.005). Multivariate Cox regression analysis showed that prostate size of 40 g or less (hazard ratio [HR], 1.378; 95% confidence interval [CI], 1.027 to 1.848; p=0.032), extracapsular extension (HR, 1.592; 95% CI, 1.147 to 2.209; p=0.005), positive surgical margin (HR, 2.348; 95% CI, 1.701 to 3.242; p<0.001), and pathologic Gleason sum (HR, 1.507; 95% CI, 1.292 to 1.758; p<0.001) were independent predictors of biochemical recurrence.

Conclusions: Smaller prostate size was associated with increased risk of higher pT stage and positive surgical margin after radical prostatectomy. Also, prostate size less than 40 g was an independent prognostic factor for biochemical recurrence.

Key Words: Prognosis; Prostate; Prostatectomy

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INTRODUCTION

Radical prostatectomy is the most common treatment for localized prostate cancer. Several factors have been developed to predict biochemical recurrence (BCR) after radical prostatectomy, including preoperative prostate-specific antigen (PSA) and pathologic variables [1,2]. Recently, many studies have focused on prostate size as a potential covariate for predicting pathologic features or prognosis after prostatectomy. However, the particular effects of pros-

tate size on oncologic outcomes are not completely defined. Some studies have demonstrated a relationship between prostate size and either adverse pathologic features or response to therapy [3-5], whereas others have found no additional benefit to the use of this parameter [6,7].

Given the discordant findings in the published literature, we hypothesized that prostate size would be related to pathologic outcomes or risk of recurrence after radical prostatectomy. In an effort to clarify the hypothesis, we used our database of 830 patients who underwent radical

prostatectomy and examined the effects of prostate size on pathologic outcomes and BCR by use of a multivariate model.

MATERIALS AND METHODS

From 1993 to 2009, 830 consecutive patients who underwent radical prostatectomy with follow-up duration over 12 months were included in this study. None of the patients received preoperative radiation, androgen deprivation therapy, or previous prostatic surgery. After approval by the Institutional Review Board (H-1102-003-349), clinical and pathologic data from the eligible patients were retrieved from the patients' medical records and were reviewed retrospectively.

Radical prostatectomy specimens were handled and processed in a standard manner. All specimens were subjected to weighing to determine the exact prostate volume after the seminal vesicles were excised. The tumors were graded according to the Gleason grading system [8] and were staged according to the 2002 American Joint Committee on Cancer tumor-node-metastasis grading system [9]. Patients with lymph node metastasis were excluded in this study. Tumor volume was reported as the estimated percentage of prostate tissue involved by prostate cancer [10]. Serum PSA levels were measured at 3, 6, and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually. BCR was defined as two consecutive rises in PSA level greater than 0.2 ng/ml.

Patients were categorized according to prostate size as follows: group 1, prostate size ≤ 40 g (n=458), and group 2, prostate size > 40 g (n=472). Preoperative parameters (age, body mass index [BMI], PSA, biopsy Gleason score, etc) and postoperative pathologic outcomes (pathologic T stage, pathologic Gleason score, surgical margin status, prostate size, etc) were compared between the 2 groups. Differences in demographics and clinical and pathological factors were examined by using the Student's t-test and chi-square test for continuous and categorical variables, respectively. Survival curves for BCR relative to prostate size were estimated by use of the Kaplan-Meier method and were compared by using the log rank test. Significant prognostic factors for BCR were assessed by multivariate analysis by the Cox proportional hazard regression model. All p-values were 2-sided and $p < 0.05$ (IBM SPSS ver. 19.0 [IBM Co., Armonk, NY, USA]) was considered significant.

RESULTS

Mean age, BMI, and preoperative PSA were 65.2 years (range, 41 to 85 years), 24.2 kg/m² (range, 16.2 to 33.3 kg/m²), and 12.3 ng/ml (range, 1.2 to 45.7 ng/ml), respectively. Nerve-sparing procedures were performed in 481 patients (58.0%): bilateral in 356 (42.9%) and unilateral in 125 (15.1%). Mean prostate weight was 42.0 g (range, 11.8 to 132.0 g).

Comparisons of demographic characteristics according

TABLE 1. Demographic characteristics according to prostate weight

Characteristic	Group 1: Prostate ≤ 40 g (n=458)	Group 2: Prostate > 40 g (n=472)	p-value
Age (yr)	64.3 (± 6.7)	66.4 (± 6.3)	< 0.001
ASA score (%)			0.371
1	200 (43.7)	149 (40.2)	
2	237 (51.7)	209 (56.3)	
3	21 (4.6)	13 (3.5)	
BMI (kg/m ²)	24.1 (± 2.7)	24.3 (± 2.7)	0.544
Serum PSA (ng/ml)	9.8 (± 8.8)	15.4 (± 4.7)	< 0.001
Clinical stage (%)			0.465
T1a	1 (0.2)	0 (0)	
T1b	2 (0.4)	0 (0)	
T1c	277 (60.5)	233 (62.8)	
T2a	166 (36.2)	121 (32.6)	
T2b	1 (0.2)	1 (0.3)	
T2c	6 (1.3)	10 (2.7)	
T3a	2 (0.4)	4 (1.1)	
T3b	3 (0.7)	2 (0.5)	
Biopsy Gleason score (%)			0.388
≤ 6	217 (47.7)	191 (51.9)	
7	145 (31.9)	102 (27.7)	
≥ 8	93 (20.4)	75 (20.4)	

Values are presented as mean (\pm SD) or number (%).

ASA, American Society of Anesthesiologists; BMI, body mass index; PSA, prostate-specific antigen.

to prostate weight are shown in Table 1. When compared with their lighter counterparts (group 1), patients with heavier prostates (group 2) were older ($p < 0.001$) and had a higher PSA level ($p < 0.001$). No significant differences in biopsy Gleason score or clinical stage were detected between the two groups. Patients with a smaller prostate tended toward a shorter operative time (172.4 minutes vs. 182.1 minutes, $p=0.052$), but there was no significant association between estimated blood loss and prostate weight (855.2 ml vs. 907.0 ml, $p=0.248$).

The pathologic stage was T2 in 508 patients (61.2%), and in 311 (37.5%) it was T3. Of the total patient population, 307 patients (37.0%) had positive surgical margins, 213 (25.7%) had extraprostatic extension, and 27 (3.3%) had positive lymph nodes. In addition, 581 patients (70.0%) had a pathologic Gleason score of 7 or greater. In terms of pathologic outcomes, patients with small prostates had higher pathologic T stage, smaller tumor volume, and more positive surgical margins than did patients with large prostates (Table 2). No significant difference in pathologic Gleason score was detected between the groups.

Mean follow-up duration in groups 1 and 2 was 47.6 months (range, 13 to 87 months) and 43.0 months (range, 13 to 76 months), respectively. In the univariate analysis, the 5-year biochemical-recurrence-free survival was 62.3% for patients with prostates of ≤ 40 g and 73.2% for patients with prostates of > 40 g ($p=0.005$) (Fig. 1). In the multivariate analysis, small prostates of less than 40 g

TABLE 2. Pathologic outcomes according to prostate weight

	Group 1: Prostate ≤ 40 g (n=458)	Group 2: Prostate > 40 g (n=472)	p-value
Pathologic stage (%)			0.003
T2a	81 (17.7)	89 (23.9)	
T2b	5 (1.1)	0 (0)	
T2c	185 (40.4)	148 (39.8)	
T3a	135 (29.5)	78 (21.0)	
T3b	49 (10.7)	49 (13.2)	
T4	3 (0.7)	8 (2.2)	
Pathologic Gleason score (%)			0.261
≤ 6	126 (27.6)	121 (32.6)	
7	271 (59.3)	201 (54.2)	
≥ 8	60 (13.1)	49 (13.2)	
Tumor volume (ml)	4.9 (±5.1)	8.9 (±12.3)	< 0.001
(%)	16.4 (±16.2)	17.3 (±22.9)	< 0.001
Positive surgical margin (%)	184 (40.3)	123 (33.1)	0.019

Values are presented as number (%) or mean (±SD).

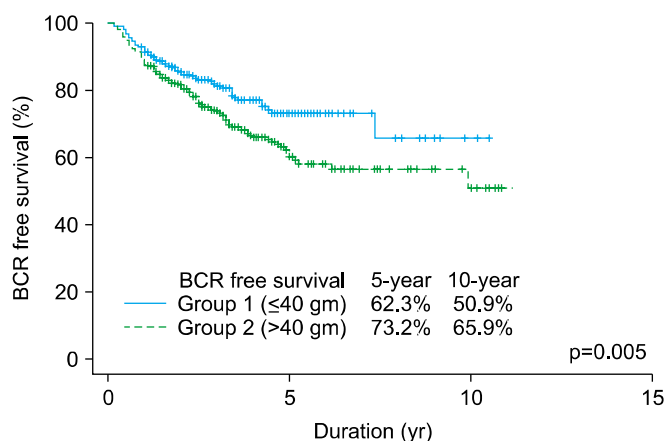


FIG. 1. Biochemical recurrence (BCR)-free survival according to prostate size.

(hazard ratio [HR], 1.378; 95% confidence interval [CI], 1.027 to 1.848; p=0.032), extraprostatic extension (HR, 1.592; 95% CI, 1.147 to 2.209; p=0.005), positive surgical margin (HR, 2.348; 95% CI, 1.701 to 3.242; p < 0.001), and pathologic Gleason score (7 vs. ≤ 6, HR, 1.507, 95% CI, 1.292 to 1.758, p < 0.001; ≥ 8 vs. ≤ 6, HR, 9.728, 95% CI, 2.732 to 62.320, p < 0.001) were identified as predictors of BCR (Table 3).

DISCUSSION

In our study, men with smaller prostates had more advanced disease at the time of radical prostatectomy and were at significantly higher risk of BCR.

Our results support several previous studies of the asso-

TABLE 3. Multivariate analysis for biochemical-recurrence-free survival

Variable	Hazard ratio	95% CI	p-value
Extracapsular extension	1.592	1.147-2.209	0.005
Positive surgical margin	2.348	1.701-3.242	< 0.001
pGleason score	1.507	1.292-1.758	< 0.001

CI, confidence interval.

ciation between smaller prostate size and more aggressive pathological features [11,12]. Briganti et al. [11] reported that small prostates were associated with a higher rate of high-grade prostate cancer at biopsy and at radical prostatectomy, with higher rates of extracapsular extension and seminal vesicle invasion and with larger tumor volume after adjustment for several parameters. Freedland et al. [12] also identified that prostate size was inversely associated with the outcomes of high-grade disease, positive surgical margins, extracapsular extension, and biochemical progression (comparing prostate weight < 20 vs. ≥ 100 g; relative risk, 8.43; 95% CI, 2.9 to 24.0; p < 0.001) [12].

The reasons for these findings remain unknown. However, several potential explanations exist. First, it has been suggested that men with smaller prostates may have lower levels of testosterone, which has been shown to correlate with more aggressive prostate cancer. Several studies have suggested that smaller prostate size may represent low androgenicity because androgen influences the growth and differentiation of the prostate [13-15]. Some studies have also suggested that lower pretreatment total androgen concentrations have been associated with poor response to treatment and survival [16-19]. Second, benign tissue in a large prostate might serve as a barrier to the growth of malignancy, thus eliminating the chance of malignant tissue to grow or acting as a physical buffer preventing local extension of malignant foci [20,21]. Many more normal cells and a thicker prostate capsule in a large prostate than in a small prostate play an important role in suppressing cancer progression [22]. Third, cancers might be detected earlier in men with larger prostates, because biopsies are taken earlier as a result of high PSA levels derived from enlarged glands.

There were some limitations to our study. The major limitation was the retrospective nature of the study design, which was therefore susceptible to all limitations and biases inherent in a retrospective design. However, we tried to control for many factors that could influence the results in our analysis; therefore, despite the limitations of our study, prostate size is certainly an important prognostic factor after radical prostatectomy in Korean men with prostate cancer. In addition, our study population was all Korean; thus, it is difficult to apply our data to the general population. However, the fact that such an association was observed among a Korean population should not be overlooked, considering the potential hormonal differences

that exist among different races [23].

CONCLUSIONS

The findings of our study suggest that smaller prostate size was associated with an increased risk of higher pT stage and positive surgical margin after radical prostatectomy. Also, with the use of prostate size as a categorical variable, smaller prostate size less than 40 g was an independent prognostic factor for BCR. Thus, we could conclude that small prostates have a constellation of worse prognostic indicators that may have an adverse impact on prognosis after radical prostatectomy.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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