



## Impact of Multiple Prostate Biopsies: Risk of Perioperative Complications and Biochemical Recurrence After Radical Prostatectomy

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## Impact of Multiple Prostate Biopsies: Risk of Perioperative Complications and Biochemical Recurrence After Radical Prostatectomy

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**Purpose:** The aim of this study was to analyze the perioperative complications and oncological outcomes of radical prostatectomy (RP) in patients who underwent multiple prostate biopsies.

**Materials and Methods:** A total of 1,112 patients who underwent RP between January 2009 and April 2016 at 4 different centers were included in this study. We divided these patients into 2 groups: patients who underwent only 1st biopsy, and those who underwent 2nd or more repeated biopsies. The association between the number of prior biopsies and perioperative complications and biochemical recurrence (BCR) was analyzed.

**Results:** Of 1,112 patients, 1,046 patients (94.1%) underwent only 1st biopsy, and 66 (5.9%) underwent 2nd or more repeated biopsies. There were no significant differences in preoperative prostate-specific antigen levels, operation times, blood loss volumes, or hospital stay durations (all  $p > 0.05$ ). Patients who underwent multiple prostate biopsies presented with a localized tumor significantly more often ( $p < 0.05$ ). The Gleason score and rate of positive surgical margins were significantly lower in patients with multiple biopsies (all  $p < 0.05$ ). The Cox proportional hazards model analysis indicated that there was no association between the number of prior prostate biopsies and BCR ( $p > 0.05$ ). Kaplan-Meier curve analysis indicated that BCR-free survival rates between the 2 groups were similar ( $p > 0.05$ ).

**Conclusions:** Multiple prostate biopsies are not associated with an increased risk of perioperative complications, adverse pathological outcomes, or higher rates of BCR in patients who have undergone RP. (Korean J Urol Oncol 2020;18:24-31)

**Key Words:** Prostate cancer • Radical prostatectomy • Multiple prostate biopsy • Perioperative complication • Biochemical recurrence

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### INTRODUCTION

Prostate cancer (PCa) is the most common solid malignancy, ranking third in cancer in 2017 with approximately 161,360 new diagnoses and 26,730 deaths in the United



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States.<sup>1</sup> The incidence of PCa has increased gradually in several Asian countries, and PCa has consistently become one of the main cancers of Asian people.<sup>2</sup> Likewise, in Korea, patients of PCa has steadily increased over the last 10 years.<sup>3</sup>

Prostate-specific antigen (PSA) is the most valuable serum marker used for the early detection and management of PCa.<sup>4</sup> It is a noted fact that elevation of serum PSA levels and/or abnormal digital rectal examination findings are indications for prostate biopsy.<sup>5</sup> Prostate biopsy is the reliable standard method to diagnose PCa.<sup>6</sup> However, in many cases, an initial prostate biopsy is negative.<sup>7</sup> Approximately more than 20% of patients are diagnosed with PCa upon a first biopsy; however, the remaining patients are followed clinically via regular of sampling serum PSA or performing a second prostate biopsy.<sup>8</sup> Because the volume of prostate obtained during a biopsy is considerably little, these patients may have PCa, in spite of presenting negative results at the initial biopsy.<sup>9</sup>

There are no clear guidelines concerning to repeat prostate biopsy in men with negative results upon an initial biopsy. Indications for a second prostate biopsy includes consistently rising and/or stationary high PSA serum levels, abnormal digital rectal examination findings,<sup>6</sup> atypical small acinar proliferation or prostatic intraepithelial neoplasia revealed upon initial prostate biopsy,<sup>5</sup> or treatment strategies such as active surveillance of PCa.<sup>10</sup> However, there are no fixed guidelines on when or whether to repeat prostate biopsies in patients with negative findings in the initial biopsy.<sup>11</sup>

The preceding studies demonstrated when repeating a prostate biopsy, the diagnosed PCa is less seem to be of high grade.<sup>12,13</sup> Furthermore, other studies have suggested that a patient who undergoes radical prostatectomy after repeat biopsy harbors PCa which is associated with better pathological outcomes.<sup>14,15</sup> However, to date, there have been few studies concerning the relationship between the number of prostate biopsies and perioperative complications or biochemical recurrence (BCR) after radical prostatectomy.

Therefore, we analyzed whether repeated prostate biopsies before radical prostatectomy were related to different perioperative complications or oncologic and pathological outcomes. In particular, we presumed that 2nd or more repeated prostate biopsies would be related to better oncologic and pathological outcomes, but perioperative outcomes were

worse.

## MATERIALS AND METHODS

### 1. Patients Selection and Study Design

From January 2009 to April 2016, 4 centers gathered the patients who were diagnosed as PCa and underwent radical prostatectomy. We excluded patients who did not undergo regular follow-up, who received neoadjuvant or adjuvant hormone/radiation therapy, and who presented with malignant solid tumors other than in the prostate. Finally, 1,112 patients met these criteria and we divided 2 groups. "1st biopsy" group and "2nd or more repeated biopsies" group. We retrospectively reviewed the medical records of the patients and analyzed whether there were any associations between the number of prior biopsies and BCR (defined as 2 consecutive measurements of PSA levels  $\geq 0.2$  ng/mL) or perioperative complications.

### 2. Statistical Analysis

Patient characteristics were analyzed using the chi-square test (pathologic T stage, Gleason score, surgical technique, lymphovascular invasion, surgical margin status, BCR) and Fisher exact test (D'Amico classification, Clavien-Dindo complications). The Student t-test was used for age, body mass index (BMI) scores, preoperative PSA levels, estimated blood loss volumes, operation times, hospital stay durations, time to removal of urethral catheter, and follow-up periods. In addition, multivariable Cox regression was used for the analysis of the impact of the number of prostate biopsies on BCR, and Kaplan-Meier curves via a log-rank test were used for the analysis of BCR-free survival. In addition, propensity-matching scores were calculated for each patient by chi-square test using the age, BMI, PSA, D'Amico classification. Statistical analysis was performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA), and  $p < 0.05$  was considered statistically significant.

This study was approved by the Ethics Committee of the Kyungpook National University School of Medicine (IRB number: KNUH 2017-06-011).

## RESULTS

Among 1,112 patients, 1,046 patients (94.1%) did 1st bi-

opsy and only 66 (5.9%) did 2nd or more repeated biopsies. Perioperative characteristics and pathologic outcomes according to the number of prior biopsies are shown in Table 1.

The mean age was  $66.6 \pm 6.3$  years, and the mean BMI was  $24.2 \pm 2.8$  kg/m<sup>2</sup>; there were no significant differences between the 2 groups ( $p=0.144$  and  $p=0.897$ , respectively).

**Table 1.** Perioperative characteristics and pathologic outcomes according to number of prior biopsies

Variable	Overall	No. of biopsy sessions		p-value
		1	≥2	
No. of patients	1,112 (100)	1,046 (94.1)	66 (5.9)	-
Age (yr)	$66.6 \pm 6.3$	$66.5 \pm 6.3$	$67.7 \pm 5.8$	0.144
Body mass index (kg/m <sup>2</sup> )	$24.2 \pm 2.8$	$24.2 \pm 2.8$	$24.2 \pm 2.9$	0.897
Preoperative PSA (ng/mL)	$11.8 \pm 10.5$	$11.8 \pm 10.7$	$12.0 \pm 7.5$	0.883
D'Amico classification				0.058*
Low	81 (7.3)	71 (6.8)	10 (15.2)	
Intermediate	619 (55.7)	585 (55.9)	34 (51.5)	
High	412 (37.1)	390 (37.3)	22 (33.3)	
Pathologic T stage				0.003
T2	651 (58.5)	599 (57.3)	52 (78.8)	
T3a	313 (28.1)	304 (29.1)	9 (13.6)	
≥T3b	148 (13.3)	143 (13.7)	5 (7.6)	
Gleason score				0.002
6	126 (11.3)	109 (10.4)	17 (25.8)	
7	700 (62.9)	664 (63.5)	36 (54.5)	
8	146 (13.1)	139 (13.3)	7 (10.6)	
≥9	140 (12.6)	134 (12.8)	6 (9.1)	
Surgical technique				0.451
Open	223 (20.1)	211 (20.2)	12 (18.2)	
Laparoscopic	146 (13.1)	134 (12.8)	12 (18.2)	
Robot-assisted	743 (66.8)	701 (67.0)	42 (63.6)	
Lymphovascular invasion				0.614
No	990 (89.0)	930 (88.9)	60 (90.9)	
Yes	122 (11.0)	116 (11.1)	6 (9.1)	
Surgical margin status				0.001
Negative	564 (50.7)	518 (49.5)	46 (69.7)	
Positive	548 (49.3)	528 (50.5)	20 (30.3)	
Estimated blood loss (mL)	$265.8 \pm 149.1$	$267.3 \pm 150.4$	$242.6 \pm 125.1$	0.129
Operation time (min)	$226.4 \pm 60.4$	$226.8 \pm 61.2$	$221.6 \pm 47.1$	0.399
Hospital stay (day)	$9.1 \pm 2.8$	$9.1 \pm 2.9$	$8.7 \pm 2.6$	0.280
Time to removal of urethral catheter (day)	$7.5 \pm 2.0$	$7.5 \pm 2.0$	$7.6 \pm 1.0$	0.414
Clavien-Dindo complication				0.881*
None	923 (83.0)	869 (83.1)	54 (81.8)	
I	33 (3.0)	31 (3.0)	2 (3.0)	
II	104 (9.4)	98 (9.4)	6 (9.1)	
IIIa	38 (3.4)	35 (3.3)	3 (4.5)	
IIIb	14 (1.3)	13 (1.2)	1 (1.5)	
≥IV	0 (0)	0 (0)	0 (0)	
Biochemical recurrence				0.414
No	901 (81.0)	845 (80.8)	56 (84.8)	
Yes	211 (19.0)	201 (19.2)	10 (15.2)	
Follow-up period (mo)	$43.2 \pm 18.6$	$43.2 \pm 19.1$	$43.5 \pm 7.6$	0.792

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

PSA: prostate-specific antigen.

\*Fisher exact test.

Preoperative PSA levels in the “1st biopsy” group were  $11.8 \pm 10.7$  ng/mL, and in the “2nd or more repeated biopsies” group was  $12.0 \pm 7.5$  ng/mL, but there was no significant difference ( $p=0.883$ ). There were no significant differences in the D’Amico classification (low versus intermediate versus high), surgical technique (open versus laparoscopic versus robot-assisted), or presence of lymphovascular invasion (LVI) between the 2 groups ( $p=0.058$ ,  $p=0.451$ , and  $p=0.614$ , respectively). However, the “2nd or more repeated biopsies” group exhibited more localized pathologic T stage cancers and this was statistically significant ( $p=0.003$ ). Furthermore, the “2nd or more repeated biopsies” group exhibited lower Gleason scores and lower rates of positive surgical margins, both being statistically significant ( $p=0.002$  and  $p=0.001$ , respectively).

There were no significant differences in estimated blood loss volumes, operation times, hospital stays, and time to removal of urethral catheter between the 2 groups (all  $p >$

0.05). There were no significant differences in the rates of Clavien-Dindo complications between the 2 groups ( $p > 0.05$ ). The mean follow-up period (at least more than 12 months) was  $43.2 \pm 18.6$  months and overall BCR rate was 19.0%. There were no significant differences in BCR rates between the 2 groups (19.2% vs. 15.2%,  $p=0.414$ ) according to univariate analysis.

According to multivariable Cox regression analyses, the significant risk factors for predicting BCR after radical prostatectomy were pathologic T stage, Gleason score, presence of LVI, and positive surgical margins (all  $p < 0.05$ ) (Table 2). However, the Cox proportional hazards model indicated that there was no association between the number of prior prostate biopsies and BCR ( $p=0.210$ ).

To minimize confounding, positive surgical margin (PSM) analysis was performed to compare the 1st biopsy and 2nd or more repeated biopsies groups in 66 matched pairs. Likewise, there were no significant differences in esti-

**Table 2.** Multivariable Cox regression analyses (MVAs) predicting biochemical recurrence in patients according to number of prior biopsies

Variable	MVA including use of 1 biopsy versus 2 or more biopsies	
	HR (95% CI)	p-value
Age	1.02 (0.99–1.04)	0.159
Prostate-specific antigen	1.00 (0.98–1.01)	0.499
Pathologic T stage		
T2	1.00 (Reference)	
T3a	1.70 (1.19–2.42)	0.004
$\geq T3b$	1.58 (1.02–2.47)	0.043
Gleason score		
6	1.00 (Reference)	
7	2.58 (1.04–6.40)	0.041
8	3.67 (1.42–9.46)	0.007
$\geq 9$	5.06 (1.95–13.17)	0.001
Lymphovascular invasion		
No	1.00 (Reference)	
Yes	1.48 (1.05–2.10)	0.026
Surgical margin status		
Negative	1.00 (Reference)	
Positive	1.41 (1.02–1.95)	0.036
Surgical technique		
Robot-assisted	1.00 (Reference)	
Laparoscopic	1.03 (0.64–1.64)	0.914
Open	0.78 (0.54–1.15)	0.212
No. of prior biopsies		
1	1.00 (Reference)	
2	1.52 (0.79–2.94)	0.210

HR: hazard ratio, CI: confidence interval.

mated blood loss volumes, operation times, hospital stays, and time to removal of urethral catheter between the 2 groups after PSM analysis (all  $p > 0.05$ ) (Table 3).

Kaplan-Meier curve analysis indicated that BCR-free sur-

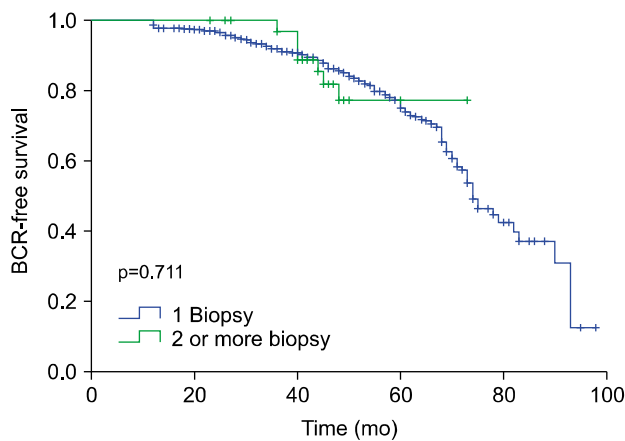
vival rates between the 2 groups were similar ( $p=0.711$ ) (Fig. 1).

**Table 3.** Perioperative characteristics and pathologic outcomes according to number of prior biopsies after propensity score matching adjustment

Variable	No. of biopsy sessions		p-value
	1	$\geq 2$	
No. of patients	264 (80)	66 (20)	-
Age (yr)	67.7 $\pm$ 5.8	67.65 $\pm$ 5.82	0.199
Body mass index (kg/m <sup>2</sup> )	24.5 $\pm$ 2.9	24.17 $\pm$ 2.93	0.474
Preoperative PSA (ng/mL)	11.6 $\pm$ 9.7	12.01 $\pm$ 7.52	0.756
D'Amico classification			0.030
Low	15 (5.7)	10 (15.2)	
Intermediate	135 (51.1)	34 (51.5)	
High	114 (43.2)	22 (33.3)	
Pathologic T stage			<0.001
T2	125 (47.3)	52 (78.8)	
T3a	92 (34.8)	9 (13.6)	
$\geq$ T3b	47 (17.8)	5 (7.6)	
Gleason score			0.005
6	26 (9.8)	17 (25.8)	
7	159 (60.2)	36 (54.5)	
8	34 (12.9)	7 (10.6)	
$\geq$ 9	45 (17.0)	6 (9.1)	
Surgical technique			0.462
Open	34 (12.9)	12 (18.2)	
Laparoscopic	43 (16.3)	12 (18.2)	
Robot-assisted	187 (70.8)	42 (63.6)	
Lymphovascular invasion			0.412
No	229 (86.7)	60 (90.9)	
Yes	35 (13.3)	6 (9.1)	
Surgical margin status			<0.001
Negative	115 (43.6)	46 (69.7)	
Positive	149 (56.4)	20 (30.3)	
Estimated blood loss (mL)	273.5 $\pm$ 160.2	242.6 $\pm$ 125.1	0.145
Operation time (min)	228.2 $\pm$ 62.3	221.59 $\pm$ 47.06	0.419
Hospital stay (day)	9.1 $\pm$ 2.7	8.7 $\pm$ 2.6	0.432
Time to removal of urethral catheter (day)	7.5 $\pm$ 1.8	7.6 $\pm$ 1.0	0.651
Clavien-Dindo complication			0.980
None	219 (83.0)	54 (81.8)	
I	9 (3.4)	2 (3.0)	
II	24 (9.1)	6 (9.1)	
IIIa	8 (3.0)	3 (4.5)	
IIIb	4 (1.5)	1 (1.5)	
$\geq$ IV	0 (0)	0 (0)	
Biochemical recurrence			0.183
No	203 (76.9)	56 (84.8)	
Yes	61 (23.1)	10 (15.2)	

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

PSA: prostate-specific antigen.



**Fig. 1.** Probability estimates of biochemical recurrence (BCR)-free survival in all patients stratified by number of prior biopsies using Kaplan-Meier curve.

## DISCUSSION

In the United States, more than 160,000 transrectal ultrasound (TRUS) guided prostate biopsies are performed each year.<sup>16</sup> Prostate biopsy is uncomfortable, invasive for patients, and there are many related complications, including very low percent ratio of sepsis.<sup>17</sup> Standard procedure, TRUS guided biopsy is not lesion-targeted and cause frequent false-negative results with samples less than 1% of the prostate gland.<sup>18</sup> Although the application of a randomized prostate biopsy as a standard method of the biopsy for PCa significantly improves the accuracy of diagnosis, but just 20–30% of PCa lesions are detected during an initial biopsy; the rest is clinically followed and may require repeated biopsies.<sup>8,19</sup> It is not easily understood why an initial prostate biopsy results may be negative for prostate with cancer, but several factors such as unskillful urologist to target the prostate and the spatial distribution, multifocal and size of carcinoma foci may provide some explanation.<sup>20</sup>

To date, there are no definite guidelines about when or whether performing a second prostate biopsy in suspected patients to harbor PCa clinically, but who present negative findings upon an initial biopsy. Therefore, it is important to understand the clinical significance of PCa detected upon repeat biopsy when counseling patients who were not diagnosed with cancer upon the initial prostate biopsy.

In 2016, Elshafei et al.<sup>21</sup> demonstrated a lower risk of pathological outcome after radical prostatectomy in men diagnosed with a favorable risk PCa when repeating a prostate

biopsy than men who were diagnosed with initial prostate biopsy. They divided 422 patients who met the National Comprehensive Cancer Network's "very low-risk" (n=199) and "low-risk" (n=223) PCa definitions and who underwent radical prostatectomy. They found that compared with repeating prostate biopsies, patient diagnosed with an initial prostate biopsy displayed higher Gleason scores ( $\geq 7$ ) (57.7% vs. 42.1%,  $p=0.005$ ) and extraprostatic extension (14.1% vs. 5.4%,  $p=0.01$ ). However, they did not analyze whether there were any associations between biopsy session and perioperative complications.

More recently, in 2017, Rosenbaum et al.<sup>6</sup> retrospectively analyzed the medical records about 12,624 patients who had radical prostatectomy from 2007 to 2013. According to this study, 10.8% underwent 2nd or more repeated sessions of prostate biopsy. With a median follow-up of 36.6 months, multiple prostate biopsy groups more often presented with organ-confined tumors and more favorable perioperative complication rates ( $p<0.05$ ). Gleason scores and status of surgical margin were not different. They concluded that the overall BCR rate was 18.9% and it could be comparable among the groups. There is no association between the number of prostate biopsies and BCR.

In our study, 2nd or more repeated prostate biopsies were not related to adverse pathologic results in Korean patients and the number of biopsy sessions did not reveal any negative effects on BCR or perioperative complications. In 2001, Djavan et al.<sup>12</sup> demonstrated that patients undergoing repeated biopsies more tend to have organ-confined disease during radical prostatectomy. At least 10% of patients with negative prostate biopsy were diagnosed with PCa during repeated biopsies. Although there were differences in location and multifocality, they concluded that the pathological and biochemical characteristics of cancers detected upon initial and repeated biopsies were similar, suggesting similar biological behaviors; thus, advocating repeated prostate biopsies in cases of negative findings upon an initial biopsy. A comparable study was also reported in 2006. Lopez-Corona et al.<sup>14</sup> retrospectively reviewed 1,357 patients performed with retropubic radical prostatectomy between 1983 and 2001. PCa was diagnosed in 1,042 patients (77%) during the first biopsy, in 227 (17%) upon second biopsy, in 59 (4%) upon third biopsy, and in 29 (2%) upon fourth or later biopsy. Patients who underwent 2nd or more repeated



biopsies revealed a higher proportion of clinical T1c-stage cancer ( $p < 0.0001$ ). They found that despite these more favorable pathological results, there were no differences in BCR rates. Other 2 similar studies exist that support these results.<sup>15,22</sup> In 2012, Kopp et al.<sup>15</sup> retrospectively analyzed 2,739 men with PCa who underwent radical prostatectomy enrolled in the SEARCH database. Multiple prostate biopsies are not associated with BCR. Another study performed by Park et al.<sup>22</sup> in 2012, patients diagnosed as PCa after repeat biopsy showed more favorable pathologic outcomes after radical prostatectomy (initial biopsy group [ $n=637$ ] vs. repeat biopsy group [ $n=63$ ]).

The present study has some limitations. First, it is a retrospective design. Second, the number of patients who underwent 2nd or more repeated biopsies is too small a number ( $n=66$ ). Heterogeneous groups of patients, no single surgeon and variable surgical techniques are also limitation. Third, this study did not evaluate whether the gap between the biopsy and the radical prostatectomy affected the perioperative results. In 2014, Park et al.<sup>23</sup> showed that biopsy-to-surgery interval did not affect positive surgical margin status, operative time, or estimated blood loss in radical prostatectomy. Fourth, we could not gather the exact number of prostate biopsy cores from the other centers. In 2017, Carneiro et al.<sup>24</sup> demonstrated that a greater number of transrectal ultrasound-guided prostate biopsy cores were shown to be related to higher blood loss volumes and perioperative complications during radical prostatectomy. They included a total of 1,042 patients in group 1 ( $\leq 12$  cores) and 1,012 patients in group 2 ( $> 12$  cores). The incidence of perioperative complications increased with the number of biopsies (group 1, 6.4% vs. group 2, 8.5%;  $p=0.03$ ). Multivariable logistic regression analysis indicated that group 2 presented with a 39% higher rate of experiencing perioperative complications during robot-assisted radical prostatectomy. In our study, it was impossible to analyze whether the number of biopsy cores influenced perioperative complications. It is the same for mean prostate volume and tumor volume, for which we could not collect the pathologic reports from other centers. Therefore, large-scale, prospective studies are needed in the future.

## CONCLUSIONS

Repeated prostate biopsies are not related to a rising risk of perioperative complications, adverse outcomes of pathology, or higher rates of BCR in men who have undergone radical prostatectomy.

## CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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