Urological Oncology

Differences in Postoperative Pathological Outcomes between Prostate Cancers Diagnosed at Initial and Repeat Biopsy

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Purpose: We evaluated the differences in pathological outcomes between prostate cancers (PCas) diagnosed at initial and repeat biopsy.

Materials and Methods: We retrospectively reviewed the medical records of 287 patients who underwent radical retropubic prostatectomy from 2005 to 2010. We investigated preoperative factors, such as age, serum prostate-specific antigen (PSA), prostate volume (PV), digital rectal examination (DRE) results, biopsy schema, clinical stage, and number of prior biopsies, and postoperative pathological outcomes, including specimen volume, percent tumor volume, Gleason score (GS), tumor bilaterality, pathological stage, positive surgical margin (PSM), lymphovascular invasion (LVI), and perineural invasion (PNI). Patients were then classified into two groups by the number of prior biopsies (initial biopsy vs. repeat biopsy). We compared preoperative factors and postoperative pathological outcomes between the two groups.

Results: Of the 287 patients, 246 (85.7%) were diagnosed with cancer at the initial biopsy and 41 (14.3%) at the repeat biopsy. The repeat biopsy group was older (p=0.048), had a larger PV (p=0.009), had a significantly different biopsy schema (p < 0.001), and had a lower (< 10%) percentage tumor volume (p=0.016). In the multivariate analysis (after adjustment for biopsy schema, age, serum PSA, PV, and DRE), repeat biopsy was not an independent predictor of GS, tumor bilaterality, pathological stage, PSM, LVI, or PNI (p=0.212, 0.456, 0.459, 0.917, 0.991 and 0.827, respectively), but repeat biopsy could predict lower percentage tumor volume (p=0.037).

Conclusions: The pathological outcomes of PCas detected at repeat biopsy were not significantly different from those of PCas detected at initial biopsy except for a lower (< 10%) percentage tumor volume.

Key Words: Biopsy; Prostatectomy; Prostatic neoplasms; Tumor burden

INTRODUCTION

Globally, prostate cancer (PCA) is one of the most prevalent forms of malignancy diagnosed in elderly men; moreover, it is the most common cancer and the second most common cause of cancer death in the United States and the United Kingdom [1]. In Korea the incidence of PCAs was 26.1 per 100,000 men during 2008 and had increased annually by 13.7% from 1999 to 2008 [2].

Most PCAs are diagnosed by transrectal ultrasound (TRUS)-guided prostate needle biopsy, which is indicated in men with an elevated serum prostate-specific antigen (PSA) level, abnormal digital rectal examination (DRE) finding, or hypoechoic lesions in TRUS. However, not all PCAs are diagnosed at the initial biopsy. Therefore, in men with a negative initial biopsy result and persistent clinical suspicion of prostate cancer, a repeat biopsy is indicated [3].

Previous studies have shown that PCAs diagnosed at repeat biopsy are smaller and are less likely to be high grade as shown by examination of the prostate needle biopsy specimen [4] and are related to better pathological outcomes after radical retropubic prostatectomy (RRP) [5-7].
Furthermore, repeat prostate biopsy patients are more likely to harbor clinically insignificant PCa or indolent cancer [5,8-10]. With regard to the nature of PCa diagnosed at repeat biopsy, controversies remain because some of the literature has reported that the Gleason score (GS), stage, and tumor volume of PCas detected on initial and repeat biopsy are similar [11].

However, there are few published data on the characteristics of PCa detected on repeat biopsy in Korea. In our study, we analyzed the differences in pathological outcomes in the RRP specimens on the basis of whether PCa was detected at the initial or repeat biopsy.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 287 PCa patients who underwent RRP from January 2005 to December 2010 and did not have a history of prior radiotherapy or hormonal therapy.

We collected preoperative clinical factors including age, serum PSA level, prostate volume (PV) on TRUS, DRE findings, biopsy schema (number of cores taken), clinical stage (2002 American Joint Committee for Cancer tumor-node-metastasis staging system), and number of prior prostate biopsy procedures. In addition, postoperative pathological outcomes such as specimen volume, percentage tumor volume, GS, tumor bilaterality, pathological stage, and presence of positive surgical margin (PSM)/lymphovascular invasion (LVI)/perineural invasion (PNI) were investigated.

A repeat biopsy was performed in patients with an abnormal DRE result, persistently increased or increasing (PSA velocity greater than 0.75 ng/ml/yr) PSA level, low free PSA, or prior atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia. However, each of us had a different indication for repeat biopsy.

With regard to biopsy schema, TRUS-guided sextant biopsy cores were taken until 2007; after that, 10- to 12-core biopsy was performed. In all repeat biopsy cases, however, a 10- to 12-core biopsy schema was used.

RRP specimens were reviewed by a single experienced pathologist. After the seminal vesicles were removed, fresh specimens were weighed and the fresh weight was regarded as specimen volume (actual prostate weight). Prostate specimens were then entirely embedded and serially sectioned at 3-mm intervals. On all slides involved with tumor, the tumor area was marked and the percentage tumor volume (tumor percentage for the entire prostate) was calculated. Percentage tumor volume was determined by the average of the sum of the results from all slides involved with tumor.

Patients were divided into two groups by the number of biopsies before diagnosis (initial biopsy vs repeat biopsy: at least two biopsies). We then compared preoperative clinical factors and postoperative pathological outcomes between the two groups. The Mann-Whitney U test was used for comparisons of continuous variables and the chi-square test was used for categorical variables. Multivariate logistic and linear regression analyses were used to assess the correlation between repeat biopsy and postoperative pathological outcomes. Statistical analysis was performed with SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA) and statistical significance was defined as a p < 0.05.

RESULTS

Of the 287 patients, 246 (85.7%) were diagnosed with PCa at the initial biopsy and 41 (14.3%) at the repeat biopsy. In the repeat biopsy group (41 patients), 26 patients (9.1%), 10 patients (3.5%), and 5 patients (1.7%) were diagnosed with PCa at the second, third, and fourth biopsy, respectively. The preoperative characteristics of the 287 patients stratified by the number of prior prostate biopsy procedures are summarized in Table 1. Patients with PCa diagnosed at a repeat biopsy were significantly older (70.0

### Table 1. Preoperative characteristics of 287 patients who underwent radical prostatectomy

| Factor                        | Initial biopsy (n=246) | Repeat biopsy (n=41) | p-value |
|-------------------------------|-----------------------|----------------------|---------|
| Age (yr)                      | 67.8 (56-81)          | 70.0 (57-79)         | 0.048   |
| PSA (ng/ml)                   | 9.8 (6.8-11.1)        | 9.7 (6.8-12.6)       | 0.331   |
| Prostate volume (cm³)         | 35.2 (14.3-121.1)     | 42.1 (16.3-90.0)     | 0.009   |
| No. of positive DRE, n (%)    | 71 (28.9)             | 6 (14.6)             | 0.059   |
| Biopsy schema, n (%)          |                       | < 0.001              |         |
| 6 cores                       | 106 (43.1)            | 0 (0)                |         |
| 10-12 cores                   | 140 (56.9)            | 41 (100.0)           |         |
| No. of clinical stage, n (%)  |                       |                      | 0.400   |
| T1c-T2b                       | 157 (63.8)            | 31 (75.6)            |         |
| T2c                           | 65 (26.4)             | 8 (19.5)             |         |
| T3                            | 24 (9.8)              | 2 (4.9)              |         |

PSA, prostate-specific antigen; DRE, digital rectal examination.

⁎Mean (range), ⁎⁎Mean (95% confidence interval for mean).

Serum PSA values of 269 patients (group of initial biopsy 236, group of repeat biopsy 33) were collected and analyzed because the data formen medicated with 5α-reductase inhibitors were excluded.
TABLE 2. Pathological outcomes in patients who underwent radical prostatectomy

| Factor                        | Initial biopsy | Repeat biopsy | p-value |
|-------------------------------|----------------|---------------|---------|
| Specimen volumea (g)          | 40.1 (19.0-122.0) | 44.6 (14.0-95.7) | 0.216   |
| Percent tumor volumeb (%)     | 15.0 (12.9-17.2) | 9.2 (5.7-12.6)  | 0.016c  |
| < 10, n (%)                   | 126/244 (51.6)  | 29/40 (72.5)   |         |
| ≥ 10, n (%)                   | 118/244 (48.4)  | 11/40 (27.5)   |         |
| Gleason score, n (%)          |                |               | 0.082   |
| 6 or less                     | 74/245 (30.2)   | 19/40 (47.5)   |         |
| 7                             | 148/245 (60.4)  | 17/40 (42.5)   |         |
| 8 or more                     | 23/245 (9.4)    | 4/40 (10.0)    |         |
| Tumor bilaterality, n (%)     | 140/233 (60.1)  | 18/38 (47.6)   | 0.158   |
| Pathological stage, n (%)     |                |               | 0.106   |
| T1c-T2b                       | 52/245 (21.2)   | 15/41 (36.6)   |         |
| T2c                           | 120/245 (49.0)  | 15/41 (36.6)   |         |
| T3                            | 73/245 (29.8)   | 11/41 (26.8)   |         |
| Positive surgical margin, n (%)| 141/245 (57.6) | 25/41 (61.0)   | 0.735   |
| Lymphovascular invasion, n (%)| 48/244 (19.7)   | 7/40 (17.5)    | 0.832   |
| Perineural invasion, n (%)    | 152/244 (62.3)  | 24/40 (60.0)   | 0.861   |

a: Mean (range), b: Mean (95% confidence interval for mean), c: This p-value was calculated by chi-square test for categorical variables (< 10 or ≥ 10%).

TABLE 3. Univariate and multivariate logistic and linear regression analyses for repeat prostate biopsy as a factor predicting pathological results

|                     | Univariate analysis | Multivariate analysisa |
|---------------------|---------------------|------------------------|
|                     | OR (95% CI for mean) | β±SE | p-value | OR (95% CI for mean) | β±SE | p-value |
| Logistic regression |                     |     |         |                     |     |         |
| Percent tumor volumeb | 0.41 (0.19-0.85) | 0.016 |         | 0.31 (0.10-0.93) | 0.037 |         |
| Tumor bilaterality  | 0.60 (0.30-1.19) | 0.143 |         | 0.74 (0.33-1.64) | 0.456 |         |
| Positive surgical margin | 0.87 (0.44-1.71) | 0.681 |         | 0.96 (0.41-2.24) | 0.917 |         |
| Lymphovascular invasion | 0.87 (0.36-2.08) | 0.747 |         | 0.99 (0.31-3.15) | 0.991 |         |
| Perineural invasion  | 0.91 (0.46-1.80) | 0.782 |         | 1.10 (0.48-2.50) | 0.827 |         |
| Linear regression   |                     |     |         |                     |     |         |
| Gleason score       | -0.17±0.10          | 0.107 |         | -0.15±0.12          | 0.212 |         |
| Pathological stage  | -0.18±0.12          | 0.135 |         | -0.10±0.13          | 0.459 |         |

OR, odds ratio; CI, confidence interval; β, correlation coefficient; SE, standard error.

a: Adjusted for biopsy schema, age, prostate-specific antigen, prostate volume, and digital rectal examination. b: This dependent factor was analyzed as a categorical variable (< 10 or ≥ 10%).

vs. 67.8, p=0.048) and had a larger PV (42.1 cm³ vs. 35.2 cm³, p=0.009) than did patients with PCa diagnosed at the initial biopsy and had a significantly different biopsy schema (p < 0.001). No significant differences were noted between the two groups in serum PSA level, DRE findings, or clinical stage.

Table 2 presents the univariate analysis of pathological outcomes in patients according to the number of prostate biopsies. There were no significant differences in specimen volume, GS, tumor bilaterality, pathological stage, or status of PSM/LVI/PNI. Regarding GS, the incidence of a GS of 6 or less, a GS of 7, and a GS of 8 or more was 47.5%, 42.5%, and 10.0%, respectively, in the repeat biopsy group compared with 30.2%, 60.4%, and 9.4%, respectively, in the initial biopsy group, reflecting a trend toward low GS disease in the repeat biopsy group. However, this trend did not reach statistical significance (p=0.082). Concerning percentage tumor volume, 72.5% of the repeat biopsy group had a percentage tumor volume < 10% compared with 51.6% of the initial biopsy group, and 27.5% of the repeat biopsy group had a percentage tumor volume ≥ 10% compared with 48.4% of the initial biopsy group. Thus, the repeat biopsy group had a lower (< 10%) percentage tumor volume (p=0.016).

The multivariate analysis (after adjustment for biopsy schema, age, serum PSA, PV, and DRE) showed that repeat biopsy was an independent predictive factor of lower (< 10%) percentage tumor volume (p=0.037). However, repeat biopsy was not an independent predictor of GS, tumor bilaterality, pathological stage, PSM, LVI, or PNI (p=
0.212, 0.456, 0.459, 0.917, 0.991, and 0.827, respectively) (Table 3).

DISCUSSION

According to recent studies, 20 to 30% of patients are diagnosed with prostate cancer at the initial biopsy. Because a negative initial biopsy does not mean that patients have no PCa, repeat biopsy has been a major concern for urologists and patients. Although there is no definitive guideline on repeat biopsy in men with an initial negative biopsy result, a repeat biopsy is usually indicated in men with a persistently increased PSA level, PSA velocity greater than 0.75 ng/ml/yr, low free PSA, abnormal DRE, or previous pathological findings related to an increased risk of cancer, such as atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia.

The published studies on PCa patients who have undergone RRP have reported that 72.6 to 92.5% of PCas are detected at the initial biopsy, and the remainder are diagnosed at a subsequent biopsy. In our study, of the 287 PCa patients, 246 patients (85.7%) were diagnosed with cancer at the initial biopsy and 41 patients (14.3%) at the repeat biopsy. This result shows that our diagnostic yield of prostate biopsy is comparable with that of previously published studies.

In our study, the repeat biopsy group had a significantly larger PV than did the initial biopsy group and showed no significant difference in biopsy schema. In many previous studies, PV was significantly higher in the repeat biopsy group and the biopsy schema was not identical during the time period. For these reasons, we adjusted for PV and biopsy schema in the multivariate analysis.

There is some controversy about the characteristics of PCa detected at repeat biopsy, although favorable outcomes have prevailed. In 2006 Lopez-Corona et al. studied 1,357 patients treated with RRP. Patients with 2 or greater biopsies had a higher rate of clinical T1c stage cancer and larger prostates than did patients with only 1 biopsy (each p < 0.0001). After RRP, patients with 1 biopsy had a lower rate of organ-confined tumors (61% vs. 75%, p < 0.0001) and a higher rate of extracapsular extension, seminal vesicle invasion, lymph node metastases, and a GS of 7 or greater than did other patients. Indolent cancer was found in 10% of patients with 1 biopsy and 18% of those with 2 or more biopsies (p = 0.018). Those authors concluded that PCa diagnosed after repeat biopsy has a favorable pathological outcome.

In conclusion, although the above-mentioned limitations existed in our study, we found that postoperative pathological outcomes of PCas detected at repeat biopsy were not significantly different from those of PCAs detected at the initial biopsy except that the percentage tumor vol-
ume was lower (<10%) in PCas diagnosed at repeat biopsy.

CONCLUSIONS

Other than in a few studies, most previous studies demonstrated that patients diagnosed with PCas at a repeat biopsy had more favorable pathological outcomes than did patients with PCas diagnosed at the initial biopsy. However, we found no significant differences in specimen volume, GS, tumor bilaterality, pathological stage, or PSM/LVI/PNI status between the initial and repeat biopsy groups, except that the percentage tumor volume was lower (<10%) in the patients diagnosed with prostate cancer at a repeat biopsy.

Further investigation including the evaluation of tumor volume itself and an analysis of the survival benefit of percentage tumor volume should be performed.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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