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Predictive Factors of Prostate Cancer at Repeat Biopsy in Patients with an Initial Diagnosis of Atypical Small Acinar Proliferation of the Prostate

Jae Hyun Ryu, Yun Beom Kim, Jeong Ki Lee, Yoon Jung Kim[1], Tae Young Jung

Departments of Urology and [1]Pathology, Seoul Veterans Hospital, Seoul, Korea

Purpose: The factors that predict prostate cancer detection on repeat biopsy were evaluated in patients with atypical small acinar proliferation (ASAP) on the initial biopsy.
Materials and Methods: From 2003 to 2008, 3,130 men with suspected prostate cancer underwent a prostate needle biopsy, and 244 (7.8%) were diagnosed as having ASAP. One hundred seventy of 244 patients were rebiopsied at least once more. They were classified into a prostate cancer group and a noncancer group according to the final pathological diagnosis. The database of rebiopsied patients included age, initial prostate-specific antigen (PSA), PSA density (PSAD), PSA velocity (PSAV), total prostate volume (TPV), and transitional zone volume of the prostate (TZV). We compared differences in the aforementioned parameters between the 2 groups.
Results: A total of 57 patients (33.5%) with ASAP were ultimately shown to have prostate cancer. Univariate analysis showed that PSAD (p=0.002), PSAV (p=0.001), TPV (p=0.035), and TZV (p=0.005) differed significantly between the cancer and noncancer groups. The results of the multivariate analysis showed that PSAD (p=0.022), PSAV ($p < 0.001$), and TPV (p=0.037) had a statistically significant correlation with cancer detection.
Conclusions: PSAD, PSAV, and TPV are predictive factors of prostate cancer in patients with an initial diagnosis of ASAP of the prostate. Although repeat biopsy is mandatory irrespective of PSA values, the follow-up of PSA may help to estimate the probability of cancer in these men.

Key Words: *Diagnosis; Needle biopsy; Prostatic neoplasms*

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Corresponding Author:
Tae Young Jung
Department of Urology, Seoul Veterans Hospital, 6-2, Dunchon 2-dong, Gangdong-gu, Seoul 134-791, Korea
TEL: +82-2-2225-1739
FAX: +82-2-484-4604
E-mail: urodoct@hotmail.com

INTRODUCTION

Prostate cancer is usually diagnosed by means of transrectal ultrasound (TRUS)-guided needle biopsy. Tissue samples simply and clearly indicate the presence or absence of cancer, but may contain other histological aspects, such as nodular hyperplasia (so-called benign prostatic hyperplasia, or BPH), prostatitis, atrophy, adenosis, prostate intraepithelial neoplasia (PIN, which is distinguished as low-grade PIN, or LGPIN, and high-grade PIN, or HGPIN), and atypical small acinar proliferation (ASAP) [1,2]. ASAP is commonly regarded as atypical foci suspicious but not diagnostic of malignancy. Several studies have demonstrated that this diagnosis is predictive of malignancy in a subsequent biopsy specimen in 34% to 60% of cases [3,4]. Consequently, a repeat biopsy is recommended in cases of an initial ASAP diagnosis.

The evidence for predictors of prostate cancer after an initial diagnosis of ASAP is contradictory and uncertain. Some authors have reported that no clinical or pathological findings can increase the accuracy of prediction of cancer [5,6]. However, several studies have shown various parameters as predictive factors in prostate cancer detection [1,7-9]. Hence, we evaluated the clinical factors that pre-

dicted the detection of prostate cancer at rebiopsy.

MATERIALS AND METHODS

From January 2003 to December 2008, 3,130 men underwent a TRUS-guided (IU-22; Philips, Andover, MA, USA) prostate biopsy with an 18-gauge needle biopsy gun (Acecut; TSK Laboratory, Tochigi, Japan) at our institution, and 244 (7.8%) were diagnosed as having ASAP. We advised men with ASAP to undergo rebiopsy within 3 to 6 months, irrespective of follow-up prostate-specific antigen (PSA) values. Of 244 cases of ASAP, 170 patients had at least one more repeat biopsy; the other 74 had no further biopsy at our institution owing to patient preference, concurrent prostate cancer, concomitant morbidities, or loss to follow-up. Rebiopsied patients were classified into a prostate cancer group and a noncancer group according to final pathological diagnosis. We categorized one patient with ASAP as the final diagnosis (all results for 4 consecutive rebiopsies were ASAP) in the noncancer group. We retrospectively reviewed our database to obtain age, initial PSA, PSA density (PSAD), PSA velocity (PSAV), total prostate volume (TPV), and transitional zone volume of the prostate (TZV) in all 170 patients.

Prostate volume was calculated by the formula 0.523x transverse diameter x anteroposterior diameter x longitudinal diameter measured by TRUS. The number of needle biopsies was 6 cores in patients with TPV less than 30 ml and 12 cores in patients with TPV of 30 ml or more. Immunostains with high molecular weight cytokeratin (34βE12) and p63 were added to initial H&E stains. Each histologic slide was reviewed by a single experienced pathologist.

Univariate analysis (Mann-Whitney U test) was performed to compare the clinical patterns of cancer patients with those of the noncancer group at rebiopsy. Multivariate logistic regression analysis was used to identify any correlation between the detection rate of prostate cancer and the previously mentioned factors, with control for potentially confounding factors. A value of $p<0.05$ was considered statistically significant. All data analyses were performed by using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the 170 patients was 74.0 years (range, 58-85 years), the mean initial PSA value was 10.7 ng/ml (range, 1.4-89.9 ng/ml), the mean PSAD was 0.30 ng/ml/ml (range, 0.03-2.75 ng/ml/ml), the mean TPV was 39.6 ml (range, 12.6-133.8 ml), and the mean TZV was 19.6 ml (range, 4.2-99.0 ml). The PSAV was known for 155 of the total 170 patients; the mean PSAV of these 155 men was 2.8 ng/ml/year (range, −77.0-453.2 ng/ml/year) (Table 1).

A total of 57 patients (33.5%) with ASAP were ultimately diagnosed with prostate cancer. The cancer detection rates of the 1st, 2nd, 3rd, and 4th repeat biopsy were 24.1% (41/170), 34.1% (14/41), 18.2% (2/11), and 0% (0/2), respectively.

In 57 patients with a final diagnosis of prostate cancer, the mean age was 74.6 years, the mean initial PSA was 12.2 ng/ml, the mean PSAD was 0.36 ng/ml/ml, the mean PSAV was 12.7 ng/ml/year, the mean TPV was 35.7 ml, and the mean TZV was 16.0 ml. In 113 patients with no cancer, the mean age, mean initial PSA, mean PSAD, mean PSAV, mean TPV, and mean TZV were 73.7 years, 9.9 ng/ml, 0.27 ng/ml/ml, −2.2 ng/ml/year, 41.6 ml, and 21.5 ml, respectively (Table 2). Univariate analysis showed that PSAD (p=0.002), PSAV (p=0.001), TPV (p=0.035), and TZV (p=0.005) differed significantly between the prostate cancer and noncancer groups (Table 2). The results of the multivariate analysis showed that PSAD (p=0.022), PSAV ($p<0.001$), and TPV (p=0.037) had a statistically significant correlation with cancer detection (Table 3).

TABLE 1. Characteristics of rebiopsied patients (n=170)

	Mean (range)
Age (yr)	74.0 (58-85)
Initial PSA (ng/ml)	10.7 (1.4-89.9)
PSAD (ng/ml/ml)	0.30 (0.03-2.75)
PSAV (ng/ml/year)[a]	2.8 (−77.0-453.2)
TPV (ml)	39.6 (12.6-133.8)
TZV (ml)	19.6 (4.2-99.0)

PSA: prostate-specific antigen, PSAD: PSA density, PSAV: PSA velocity, TPV: total prostate volume, TZV: transitional zone volume of the prostate, [a]: PSAV was known for 155 of the total 170 patients.

TABLE 2. Several parameters in rebiopsied patients (with results of Mann-Whitney U test)

Variables	Mean (95% CI for mean)		p-value
	Noncancer group (n=113)	Cancer group (n=57)	
Age (yr)	73.7 (72.5-75.0)	74.6 (73.0-76.3)	0.478
Initial PSA (ng/ml)	9.9 (7.9-11.9)	12.2 (8.7-15.7)	0.159
PSAD (ng/ml/ml)	0.27 (0.21-0.33)	0.36 (0.28-0.44)	0.002
PSAV (ng/ml/year)[a]	−2.2 (−4.3-0.0)	12.7 (−5.0-30.3)	0.001
TPV (ml)	41.6 (37.6-45.5)	35.7 (32.2-39.1)	0.035
TZV (ml)	21.5 (18.2-24.7)	16.0 (13.0-19.1)	0.005

CI: confidence interval, PSA: prostate-specific antigen, PSAD: PSA density, PSAV: PSA velocity, TPV: total prostate volume, TZV: transitional zone volume of the prostate, [a]: PSAV was known for 155 of the total 170 patients.

TABLE 3. Results of the multivariate logistic regression analysis[a]

Variables	p-value
Age	0.165
Initial PSA	0.133
PSAD	0.022
PSAV	< 0.001
TPV	0.037
TZV	0.066

PSA: prostate-specific antigen, PSAD: PSA density, PSAV: PSA velocity, TPV: total prostate volume, TZV: transitional zone volume of the prostate, [a]: multivariate analysis was performed for 155 patients because PSAV was known for only 155 of the total 170 men.

DISCUSSION

ASAP has been described by several terms, but today, pathologists commonly adopt ASAP or 'atypical foci suspicious but not diagnostic of malignancy' to define a diagnostic category including a broad group of entities [1]. ASAP is not a single entity, but rather encompasses a diverse array of lesions such as benign crowded glands, basal cell hyperplasia, adenosis, reactive atypia, and atypical glandular proliferations suspicious for carcinoma, which cannot be accurately diagnosed for various reasons such as insufficient amount of specimen or biopsy-induced mechanical distortion [10,11]. Iczkowski mentioned that biopsy cores meriting an ASAP diagnosis fall into 2 broad categories: (i) Qualitatively inadequate cytoarchitectural features. A focus may contain about a dozen acini showing such features as probable loss of the basal cell layer and infiltrative pattern but with a continuum of cytologic features that fall short of the cytologic and histologic criteria for cancer. (ii) Quantitatively minute linear extent or very few acini. The acini in the focus display cytoarchitectural findings compatible with cancer but the size of the focus is the major limitation [12].

Iczkowski reported that the incidence of ASAP on the basis of their most recent study was 197 (3.3%) of 6,026 men undergoing prostate biopsy [12]; previous studies reported incidences of 1.5% to 9.0% [13,14]. Several studies have demonstrated that this diagnosis is predictive of malignancy in a subsequent biopsy specimen in 34% to 60% of cases [3,4]. Consequently, a repeat biopsy is recommended in cases of initial ASAP diagnosis.

ASAP has been subclassified according to degree of suspicion for prostate cancer by several investigators. Chan and Epstein found cancer in 61% of patients with atypical biopsy favoring a cancer versus 33% of patients with atypical biopsy favoring a benign process [15]. However, Scattoni et al suggested that the subclassification of lesions into ASAP highly suspicious for cancer and ASAP favoring a benign diagnosis was not clinically useful, and they mentioned that the stratification scheme is too subjective to be reproducible, even among expert diagnosticians [7].

Immunostains with 34βE12 and p63 can aid in the investigation of ASAP, but immunohistochemically negative patterns are not diagnostic of prostate cancer (false-negative staining) [16]. Therefore, a positive marker such as alpha-methylacyl coenzyme A racemase (AMACR/P504S) has also been used. AMACR is strongly and diffusely positive in 97% to 100% of prostate cancers and can convert atypical foci to cancer in approximately 10% of cases [17-19]. However, staining with AMACR is not an error-free method because of positivity in 8% of 12% of benign glands [20,21].

The evidence for predictors of prostate cancer after an initial diagnosis of ASAP is contradictory and uncertain. Iczkowski et al found that neither age, serum PSA, digital rectal examination (DRE), number of positive foci, nor histological findings was predictive of cancer [5]. Ebstein and Herawi also reported that no clinical or pathological features contributed to or predicted prostate cancer [6]. However, Park et al reported that DRE and patient age were independent predictors of cancer in patients with 'atypia' [9]. Borboroglu et al showed that PSAV was the only significant predictor of positive repeat biopsy [8], whereas Scattoni et al claimed prostate volume and HGPIN together with ASAP were the only predictive factors in prostate cancer detection [7]. Mearini et al commented that the free/total PSA ratio and prostate volume seemed to be independent predictors of prostate cancer at rebiopsy and that the clinical value of PSAD in the larger prostate gland is altered by the BPH component, which prevails over the tumor [1]. Scattoni et al and Ficarra et al suggested that the lower rate of prostate cancer in larger prostate glands could be due to sampling error [7,22]. In our study, PSAD, PSAV, and TPV were significant variables predicting cancer detection in patients with ASAP in the multivariate analysis, even though TZV was also a significant factor in the univariate analysis.

Brausi et al found that 100% of 25 patients with isolated ASAP who underwent radical prostatectomy had cancer. Those authors suggested that immediate radical prostatectomy may be the treatment of choice for young patients with ASAP [23]. However, performing radical prostatectomy in patients diagnosed as having ASAP is not acceptable clinical practice in most countries. Ebstein and Herawi, Scardino recommend that all men with ASAP undergo rebiopsy within 3 to 6 months, irrespective of follow-up PSA values [6,24].

However, the most useful rebiopsy strategy is controversial. Allen et al reported that prostate cancer was detected in 84.8% of cases at either the same sextant site as the previous biopsy, at adjacent ipsilateral sites, or at adjacent contralateral sites (47.8% of the cancer was detected in the same sextant site) and recommended that 3 cores should be sampled from the site of the initial atypical site, 3 cores from the adjacent ipsilateral and adjacent contralateral sites, and 1 core from other sextant sites [25]. On the other hand, Scattoni et al found a precise spatial concordance between ASAP and cancer in only 33% of the cases

in a multisite scheme study, which was not statistically different from the probability of finding cancer in adjacent sites or in nonadjacent sites. They reported that 12 cores might not be sufficient to correctly sample prostate glands larger than 50 ml in which ASAP is present [7]. According to our study, the TPV of the cancer group was smaller than that of the noncancer group. Therefore, we suggest that patients diagnosed as having ASAP should undergo more extended repeat biopsy with increasing biopsy cores in patients with large prostate volumes.

Several limitations to our study exist. (i) Immunohistochemical stains with high molecular weight cytokeratin (34βE12) and p63 were performed in our institution, but stain with AMACR could not be performed for all patients because it was introduced in the middle of our investigation period. (ii) A special protocol for repeat biopsy could not be established because our investigation was a retrospective study. At the repeat biopsy, the number of needle biopsy cores (6 cores in patients with prostate volume less than 30 ml and 12 cores in patients with prostate volume of 30 ml or more) was not different from that of the initial biopsy cores, although extended biopsy with additional biopsy is appropriate in initial ASAP patients. Although we did not intend this, these biopsy strategies reinforced our argument of more extended repeat biopsy in patients with a large prostate volume, because men with large volumes showed a lower incidence of cancer detection despite these strategies. (iii) Although some authors have suggested that the free/total PSA ratio and prostate volume seem to be independent predictors of prostate cancer at rebiopsy [1], we excluded the free/total PSA ratio from the clinical factors in our study because free PSA was not routinely examined for all patients.

CONCLUSIONS

PSAD, PSAV, and TPV were significant predictive factors of a diagnosis of prostate cancer at a repeat biopsy in men with an initial diagnosis of ASAP. PSAD and PSAV were higher and TPV was smaller in the cancer group than in the noncancer group. Although repeat biopsy is necessary within 3 to 6 months, irrespective of PSA values, the follow-up of PSA may help to estimate the probability of cancer.

Conflicts of Interest

The authors have nothing to disclose.

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