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Is histological prostate inflammation in an initial prostate biopsy a predictor of prostate cancer on repeat biopsy?

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Abstract
Purpose To investigate whether histological inflammation detected in an initial prostate biopsy can predict the risk of prostate cancer on a repeat biopsy.
Methods This was a retrospective study of 171 patients who underwent repeat prostate biopsy for persistently elevated prostate-specific antigen after an initial negative biopsy result. The enrolled patients were divided into two groups according to the results of the repeat biopsy: the noncancer group ($n = 126$) and the cancer group ($n = 45$). Multivariate regression analysis was used to determine the effect of inflammation grade, aggressiveness, and prostate-related parameters on the detection of prostate cancer at the repeat biopsy.
Results Prostate inflammation grade ($p = 0.005$) and aggressiveness ($p = 0.001$) in the initial biopsy were significantly different between the cancer and noncancer groups. Factors associated with the risk of prostate cancer at the repeat biopsy were age [odds ratio (OR) 1.08; 95 % confidence interval (CI) 1.03–1.14], prostate-specific antigen density (OR 24.30; 95 % CI 9.3–62.9), prostate-specific antigen velocity (OR 1.05; 95 % CI 1.01–1.09), and inflammation aggressiveness (OR 0.05; 95 % CI 0.01–0.27).
Conclusions A histological inflammatory finding at the initial prostate biopsy was negatively associated with prostate cancer detection in repeat biopsy. This result could be useful to determine the need for repeat prostate biopsy in patients with persistently elevated prostate-specific antigen.

Keywords Biopsy · Inflammation · Prostatic neoplasms

Introduction

Digital rectal examination (DRE) and serum prostate-specific antigen (PSA) testing are the most useful screening tests for the diagnosis of prostate cancer [1]. In patients showing abnormalities in a screening test, transrectal ultrasound-guided prostate biopsy is performed to confirm the diagnosis of prostate cancer [2]. Even if the result of the first prostate biopsy is negative, prostate cancer may be found in repeat biopsies performed more than twice [3]. However, it is not easy to perform repeat biopsies, because prostate biopsy is an invasive procedure that can result in serious complications such as hematuria, acute urinary retention, urinary tract infection, bacteremia and sepsis [4].

PSA is used in the early detection of prostate cancer, in pretreatment staging, and in the follow-up after treatment; however, it is an organ-specific marker rather than a cancer-specific marker [5]. Therefore, rising PSA values resulting from the destruction of the internal cellular architecture of the prostate can occur in diseases of the prostate, such as prostatitis and benign prostatic hyperplasia (BPH), as well as in prostate cancer. PSA can also be increased after prostate manipulation, such as a DRE or prostate biopsy, and after urinary retention [6].

Acute or chronic inflammation is commonly observed in prostate biopsy specimens and is thought to be one of the

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leading causes of increased serum PSA [7]. Asymptomatic chronic prostatitis, especially showing histological inflammation without clinical symptoms, can lead to unnecessary repeat prostate biopsy owing to a constantly increasing serum PSA value, even though prostate cancer is not diagnosed in an initial prostate biopsy [8].

To date, the data are insufficient on the association between histological prostate inflammation in an initial biopsy and prostate cancer detected in a repeat biopsy. Therefore, in this retrospective study, we evaluated whether prostate inflammation grade and aggressiveness at the initial biopsy could predict prostate cancer risk at a repeat biopsy.

Methods

Study population

Among 3105 patients who underwent a prostate biopsy for the first time at Chonnam National University Hospital from May 2004 to April 2011, prostate cancer was diagnosed in 1052 patients (33 %). Of the remaining 2053 patients, the medical records of 190 patients who underwent a repeat prostate biopsy for persistently elevated serum PSA were reviewed, and 171 patients who did not have symptoms or a history of prostatitis were analyzed. The indications for prostate biopsy were abnormal digital rectal examination findings and/or elevated serum prostate-specific antigen (PSA) level (>3.0 ng/mL). This study protocol was reviewed and approved by the institutional review board (IRB registration number: CNUHH-2015-030). Informed consent was waived by the board.

Data collection

Transrectal ultrasound-guided (GE Logic 9; General Electric, Milwaukee, WI, USA) prostate biopsy was performed with an E8C 7.5-MHz transrectal linear array transducer with an automatic biopsy gun (ACECUT; TSK, Tochigi, Japan) equipped with an 18-gauge biopsy needle (Magnum; Bard, Covington, GA, USA). Prostate volume was calculated by the formula of width × height × length × (π/6), for which the width and the height were obtained in maximum cross-sectional images and the length in maximum longitudinal images.

To investigate the predictors of prostate cancer at a repeat biopsy, we analyzed parameters including age of the patients, prostate volume, serum PSA, prostate-specific antigen density (PSAD), percentage of free PSA to total PSA (%fPSA), prostate-specific antigen velocity (PSAV; annual increase in serum PSA), and inflammation of the prostate tissue in the initial prostate biopsy specimens.

The biopsy specimens were graded on a four-point scale for inflammation and aggressiveness as proposed by Irani et al. [9]. Inflammation was graded as follows: 0, no inflammatory cells; 1, scattered inflammatory cell infiltrate within the stroma without lymphoid nodules; 2, nonconfluent lymphoid nodules; and 3, large inflammatory areas with confluence of infiltrate. Inflammation aggressiveness was graded as follows: 0, no contact between inflammatory cells and glandular epithelium; 1, contact between inflammatory cell infiltrate and glandular epithelium; 2, interstitial inflammatory infiltrate associated with a clear but limited glandular epithelium disruption on <25 % of the examined material; and 3, glandular epithelium disruption on more than 25 % of the examined material [9]. The histological prostate inflammation was confirmed by one uropathologist (C. Choi). The pathologist was blinded to the subsequent biopsy results during the assessment of inflammation in the initial biopsy.

Statistical analysis

SPSS Statistics version 20.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. Student's *t* test (two-tailed) was conducted to assess differences in clinical parameters between the cancer group and the noncancer group. The difference in frequency of prostate cancer on a repeat biopsy according to the histological inflammation in the initial prostate biopsy was analyzed by using the Chi-squared test (two-tailed). One-way ANOVA was conducted to compare the differences in the prostate-related factors according to the histological inflammation in the initial prostate biopsy. Multivariate logistic regression (stepwise forward procedure) was performed to determine predictive factors of prostate cancer on the repeat prostate biopsy. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Patient demographics

Of the 171 patients included in the analysis, the number of repeat biopsies was two in 131 patients (76.6 %), three in 36 patients (21.1 %), four in 3 patients (1.8 %), and six in 1 patient (0.6 %). A total of 45 patients (26.3 %) were diagnosed with prostate cancer in a repeat biopsy, and 126 patients (73.7 %) were diagnosed with benign disease such as BPH. Of the 45 patients diagnosed with prostate cancer, the number of repeat biopsies at the time of diagnosis was two in 31 patients (68.9 %), three in 12 patients (26.7 %), four in 1 patient (2.2 %), and six in 1 patient (2.2 %).

The period from initial to repeat biopsy did not differ significantly between the prostate cancer

Table 1 Patient characteristics

	Total	Repeat biopsy results		*p* value
		Noncancer ($n = 126$)	Cancer ($n = 45$)	
Age (years)	62.7 ± 10.3	61.7 ± 10.9	65.4 ± 7.7	0.036
Prostate volume (ml)				
Initial biopsy	40.9 ± 20.1	43.4 ± 20.7	34.0 ± 16.5	0.007
Repeat biopsy	42.5 ± 22.4	45.3 ± 23.9	34.7 ± 15.1	0.006
PSA (ng/ml)				
Initial biopsy	11.7 ± 24.0	11.2 ± 26.5	13.0 ± 14.9	0.567
Repeat biopsy	11.6 ± 13.3	8.7 ± 7.7	19.8 ± 20.6	0.001
PSAD (ng/ml/ml)				
Initial biopsy	0.32 ± 0.54	0.29 ± 0.56	0.41 ± 0.48	0.150
Repeat biopsy	0.35 ± 0.53	0.22 ± 0.16	0.71 ± 0.91	0.001
%fPSA (%)				
Initial biopsy	16.6 ± 8.4	17.1 ± 8.9	15.2 ± 7.1	0.170
Repeat biopsy	16.7 ± 7.7	17.1 ± 7.8	15.5 ± 7.7	0.218
PSAV (ng/ml/year)	0.47 ± 15.6	−1.49 ± 13.64	5.99 ± 19.3	0.006

Data presented as mean ± SD

PSA prostate-specific antigen, *PSAD* prostate-specific antigen density, *%fPSA* percentage of free PSA to total PSA, *PSAV* prostate-specific antigen velocity

(30.8 ± 18.0 months) and noncancer (27.0 ± 15.4 months) groups ($p = 0.206$). As shown in Table 1, the patients in the cancer group were significantly older (65.4 ± 7.7 years) than the patients in the noncancer group (61.7 ± 10.9 years; $p = 0.036$). Furthermore, prostate volume was significantly higher in the noncancer group than in the cancer group at both the initial ($p = 0.007$) and repeat ($p = 0.006$) biopsies. PSA did not differ significantly between the groups at the initial biopsy, but was significantly higher in the cancer group (19.8 ± 20.6 ng/ml) than in the noncancer group (8.7 ± 7.7 ng/ml) at the repeat biopsy ($p = 0.001$). Also, PSAD did not differ significantly between the groups at the initial biopsy but was significantly higher in the cancer group (0.71 ± 0.91 ng/ml/ml) than in the noncancer group (0.22 ± 0.16 ng/ml/ml) at the repeat biopsy ($p = 0.001$). %fPSA did not differ significantly between the groups at either the initial or the repeat biopsy. PSAV, however, did differ significantly between the groups ($p = 0.006$).

We compared the first histopathological diagnosis with the results of the repeat biopsy. Prostate cancer was diagnosed in a repeat biopsy in 42 of 165 patients initially diagnosed with BPH or prostatitis, in 1 patient with high-grade prostatic intraepithelial neoplasia, in 1 of 2 patients with atypical cells, and in 1 patient with squamous metaplasia in the initial biopsy.

Table 2 Association of repeat biopsy results with histological prostate inflammation on the initial biopsy

	Total	Repeat biopsy results		*p* value
		Noncancer ($n = 126$)	Cancer ($n = 45$)	
Inflammation grade				0.005
0	45 (26.3)	28 (22.2)	17 (37.8)	
1	81 (47.4)	57 (45.2)	24 (53.3)	
2 or 3	45 (26.3)	41 (32.5)	4 (8.9)	
Inflammation aggressiveness				0.001
0	94 (55.0)	58 (46.0)	36 (80.0)	
1	58 (33.9)	50 (39.7)	8 (17.8)	
2 or 3	19 (11.1)	18 (14.3)	1 (2.2)	

Data presented as *n* (%)

Association of repeat biopsy outcomes with histological prostate inflammation in the initial biopsy

Concerning the degree of histological inflammation of the initial biopsy, 45 of the total 171 patients (26.3 %) showed no infiltration of inflammatory cells, 81 patients (47.4 %) showed grade 1 inflammation, and 45 patients (26.3 %) showed grade 2 or 3 inflammation (Table 2). The aggressiveness of inflammation was grade 0 in 94 patients (55.0 %), grade 1 in 58 patients (33.9 %), and grade 2 or 3 in 19 patients (11.1 %). The incidence of prostate cancer in a repeat biopsy was associated with both the inflammation grade ($p = 0.005$) and aggressiveness ($p = 0.001$) shown in the initial biopsy specimens (Table 2). Both the inflammation grade and aggressiveness were lower in the cancer group than in the noncancer group (Table 2).

Association of prostate-related parameters with histological prostate inflammation in the initial biopsy

In the analysis of the differences in initial PSA, PSAD, and %fPSA according to inflammation grade and aggressiveness, no significant differences were found in PSA, PSAD, or %fPSA according to inflammation grade (Table 3). With respect to the aggressiveness of inflammation, however, PSA ($p = 0.001$) and PSAD ($p = 0.001$) were higher in patients with grade 2 or 3 inflammation than in those with grade 0 and grade 1 inflammation (Table 3).

Predictive factors of prostate cancer on repeat biopsy

Variables were selected for the multivariate analysis according to their significance in the univariate analysis. In the multivariate logistic regression analysis, age [odds ratio (OR) 1.09; 95 % confidence interval (CI)

Table 3 Association of prostate-related parameters with histological prostate inflammation on the initial biopsy

	Inflammation grade			*p* value
	0 ($n = 45$)	1 ($n = 81$)	2 or 3 ($n = 45$)	
PSA (ng/ml)	8.6 ± 12.0	10.0 ± 7.9	17.8 ± 43.8	0.134
PSAD (ng/ml/ml)	0.29 ± 0.45	0.28 ± 0.18	0.42 ± 0.92	0.352
%fPSA (%)	14.8 ± 5.3	17.0 ± 9.8	17.6 ± 8.3	0.237
	Inflammation aggressiveness			*p* value
	0 ($n = 94$)	1 ($n = 58$)	2 or 3 ($n = 19$)	
PSA (ng/ml)	8.1 ± 10.3	10.6 ± 5.8	32.3 ± 65.4	0.001*
PSAD (ng/ml/ml)	0.25 ± 0.33	0.28 ± 0.23	0.75 ± 1.35	0.001**
%fPSA (%)	16.8 ± 9.4	15.3 ± 6.6	19.3 ± 8.0	0.191

Data presented as mean ± SD

PSA prostate-specific antigen, *PSAD* prostate-specific antigen density, *%fPSA* percentage of free PSA to total PSA

* Post hoc analysis: 0 versus 2 or 3 ($p = 0.001$), 1 versus 2 or 3 ($p = 0.001$)

** Post hoc analysis: 0 versus 2 or 3 ($p = 0.001$), 1 versus 2 or 3 ($p = 0.003$)

Table 4 Logistic regression analysis for the predictors of malignancy on repeat biopsy

	Odds ratio (95 % CI)	*p* value
Age	1.09 (1.03–1.15)	0.001
Prostate volume	1.01 (0.98–1.04)	0.644
PSA	0.97 (0.82–1.15)	0.740
PSAD	24.3 (9.3–62.9)	0.001
PSAV	1.05 (1.03–1.09)	0.007
Inflammation		
Grade (0 vs. 1, 2, 3)	1.03 (0.36–2.94)	0.950
Aggressiveness (0 vs. 1, 2, 3)	0.05 (0.01–0.18)	0.001

PSA prostate-specific antigen, *PSAD* prostate-specific antigen density, *PSAV* prostate-specific antigen velocity

1.03–1.15; $p = 0.001$], PSAD (OR 24.3; 95 % CI 9.3–62.9; $p = 0.001$), PSAV (OR 1.05; 95 % CI 1.03–1.09; $p = 0.007$), and inflammation aggressiveness (OR 0.05; 95 % CI 0.01–0.18; $p = 0.001$) were independent factors associated with prostate cancer risk in a repeat biopsy (Table 4). The inflammation aggressiveness had an inverse relationship with prostate cancer in repeat biopsy.

Discussion

Although transrectal ultrasound-guided prostate biopsy is currently the most important diagnostic modality for prostate cancer, according to Fleshner et al. [10], only 30 % of patients are diagnosed with prostate cancer in the initial prostate biopsy and 23.8 % of patients with an initial negative biopsy result are diagnosed with prostate cancer in a repeat prostate biopsy. In the present study, 33 % of patients were diagnosed with prostate cancer in the initial biopsy and 26.3 % of the patients were diagnosed with prostate cancer after a repeat prostate biopsy. Because of the possibility of failure in the initial biopsy and the possibility of detection of prostate cancer in a repeat biopsy, repeat prostate biopsy is considered to be necessary for many patients [11, 12]. Indications for repeat prostate biopsy include rising or persistent PSA levels, suspicious DRE results, atypical small acinar proliferation, and extensive high-grade prostatic intraepithelial neoplasia (i.e., in multiple biopsy sites) [13]. To reduce the number of unnecessary repeat prostate biopsy procedures performed, many prostate-related parameters utilizing PSA, such as PSAD, %fPSA, and PSAV, have been developed and can provide some information for the detection of prostate cancer, although not enough to be clinically definitive [14–16].

Despite the relatively high prevalence of prostate cancer, only family history, ethnicity, and age are universally recognized as risk factors, none of which is modifiable [17]. In this context, the role of chronic inflammation remains debated [17]. Although epidemiological, histopathological, and molecular evidence suggests a robust relationship between prostatic inflammation and the pathogenesis and progression of benign prostatic enlargement [18], the role of inflammation in prostate carcinogenesis remains controversial.

Several studies have investigated a relation between prostate inflammation and serum PSA changes and prostate cancer prediction. With respect to how prostate inflammation increases serum PSA, Brawer et al. [19] documented the increase in PSA in cases of prostatitis as the result of a leak phenomenon, whereby inflammatory

cells induce destruction of the anatomical barrier between the prostate glandular epithelium and the systemic circulation. Irani et al. [9] analyzed 66 patients with exclusively benign prostatic tissue on prostate biopsies. Their results supported the hypothesis that inflammation significantly contributes to increased serum PSA, especially when the inflammation is associated with glandular epithelial disruption. Similar to Irani et al., Schatteman et al. [20] investigated whether subclinical inflammation can elevate PSA and PSAD. Those authors found that the extent of inflammation is not of importance, but the disruption of epithelial integrity caused by the inflammatory infiltrate is. Kandirali et al. [21] assessed the association of extent and aggressiveness of inflammation with PSA, PSAD, and %fPSA in asymptomatic patients. In that study, both extent and aggressiveness of inflammation were positively associated with the serum PSA level and PSAD and negatively associated with %fPSA. Kim et al. [22] evaluated patients who underwent transurethral resection of the prostate for BPH and found that the extent of chronic inflammation had a considerably greater relationship with increased PSAD than with PSA. However, Park et al. [23] explored the influence of chronic prostate inflammation on prostate cancer in asymptomatic patients, in both cancer and noncancer groups, and saw no significant changes in levels of prostate-related parameters (PSA, PSAD, %fPSA) according to extent or aggressiveness of inflammation. In the current study, PSA and PSAD significantly increased according to the histological findings of inflammation in the initial prostate biopsy, particularly in relation to the aggressiveness of inflammation. These results support the leak phenomenon by which prostatic inflammation induces apoptotic leaks of PSA in the glandular epithelium and increases vascularity and vascular permeability rather than PSA production [19]. This implies that the disruption of epithelial integrity rather than the extent of inflammation is more important for increasing serum PSA.

With respect to whether histological inflammation in a prostate biopsy is a predictive factor for the detection of prostate cancer, Terakawa et al. [24] compared prostate cancer and noncancer groups that had undergone initial needle biopsies of the prostate. PSAD and the presence of histological inflammation appeared to be independently associated with the detection of prostate cancer. In addition, Pepe and Aragona [25] found that an inflammatory pattern in the primary biopsy was not associated with a decrease in prostate cancer incidence at a repeat saturation prostate biopsy. Moreover, Gurel et al. [26] showed that men with inflammation on 1 or more biopsy cores were 1.78 times as likely to develop prostate cancer as were those who had no histological evidence of inflammation (OR 1.78; 95 % CI 1.04–3.06). This association was more pronounced for high-grade disease (OR 2.24; 95 % CI 1.06–4.71) than for low-grade disease (OR 1.57; 95 % CI 0.83–3.00) [26]. By contrast, Fujita et al. [27] explored whether histological findings or clinical indicators of inflammation in an initial biopsy could predict the outcome of a subsequent biopsy. In that study, age, PSAD, acute inflammation, and urinary pyuria were associated with benign disease at a repeat biopsy. Furthermore, the REDUCE study [28] and the Finnish prostate cancer screening trial [29] found that men without prostate cancer had a lower risk of developing prostate cancer if inflammation was detected in a negative biopsy sample. In REDUCE, both acute inflammation and chronic inflammation in a negative biopsy sample before trial entry were associated with a lower risk of prostate cancer on the 2-year biopsy (OR 0.745; 95 % CI 0.592–0.938 for acute inflammation; OR 0.651; 95 % CI 0.553–0.766 for chronic inflammation) [28]. Moreover, evaluation of prostatitis in autopsied prostates, chronic inflammation, was more common in glands with BPH compared to glands with no BPH or glands with cancer [30]. Even in glands with cancer and chronic inflammation, infiltrates of inflammation were not identified within or in periphery of tumor foci [30].

Along with these studies, we found that PSAD and PSAV were associated with an increased risk of prostate cancer. In addition, the aggressiveness of histological inflammation was an independent factor associated with reduced risk of prostate cancer in a repeat prostate biopsy. Because asymptomatic chronic prostatitis with highly infiltrated inflammation may be overlooked in the clinical situation but may cause a sustained increase in serum PSA and be correlated with a reduced risk of prostate cancer, histological confirmation of inflammation may be helpful for avoiding unnecessary repeat biopsy in the follow-up of patients with continuously elevated serum PSA levels after an initial negative biopsy result. However, the relationship of prostate inflammation to PSA, the presence or severity of inflammation in prostatic tissue, and prostate cancer risk is still controversial; therefore, a large population-based prospective study will be needed to prove an association between the presence or severity of inflammation and prostate cancer development.

This study had several limitations. Because of the retrospective nature of the study, we could not control for the number of biopsy cores having a significant impact on the diagnosis, and the small number of enrolled patients was not enough to perform subgroup analysis according to the number of biopsies. In addition, only a visual assessment of inflammation was performed. Quantitative image analysis of immunohistochemically stained inflammatory infiltrates using a panleukocyte marker, such as an anti-CD45 antibody [18], would provide a more accurate measure of inflammation.

In conclusion, inflammation aggressiveness as shown in the histological findings of the initial prostate biopsy specimen was a significant predictor for reduced risk of prostate cancer on a repeat biopsy, whereas advanced age, high PSAD, and PSAV were predictors for increased risk of prostate cancer on a repeat biopsy. Thus, the combination of the histological finding of highly infiltrated prostate inflammation in the initial biopsy and monitoring of PSAD and PSAV may be useful when considering whether repeat prostate biopsy is needed in patients with persistently elevated PSA after an initial negative biopsy result.

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

Ethical standards This study protocol was reviewed and approved by the institutional review board (IRB registration No.CNUHH-2015-030).

Informed consent Informed consent was waived by the board.

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