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ORIGINAL PAPER

The presence of chronic inflammation in positive prostate biopsy is associated with upgrading in radical prostatectomy

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Summary ***Objective: This study aimed to determine the predictive effect of the presence of chronic prostatitis associated with prostate cancer (PCa) in prostate biopsy on Gleason score upgrade (GSU) in radical prostatectomy (RP) specimens.***
Materials and methods: The data of 295 patients who underwent open or robotic RP with a diagnosis of localized PCa following biopsy were retrospectively analyzed. Patients were divided into two groups with and without GSU following RP. Predictive factors affecting GSU on biopsy were determined. The impact of chronic prostatitis associated with prostate cancer on GSU was examined via logistic regression analysis.
Results: Out of 224 patients with Gleason 3+3 scores on biopsy, 145 (64.7%) had Gleason upgrade, and 79 (35.2%) had no upgrade. Whilst comparing the two groups with and without Gleason upgrade in terms of patient age, prostate-specific antigen (PSA) value, PSA density (PSAD), prostate volume (PV), neutrophil/lymphocyte (N/L) ratio, number of positive cores, percentage of positive cores, and Prostate Imaging Reporting and Data System version 2 score, no statistically significant difference was detected. The presence of chronic prostatitis associated with PCa was higher in the patient cohort with GSU in contrast to the other group ($p < 0.001$). According to the univariate logistic regression analysis, the presence of chronic prostatitis was identified to be an independent marker for GSU.
Conclusions: Pathologists and urologists should be careful regarding the possibility of a more aggressive tumor in the presence of chronic inflammation associated with PCa because inflammation within PCa was revealed to be linked with GSU after RP.

KEY WORDS: *Prostate cancer; Prostate biopsy; Chronic prostatitis; Prostate inflammation.*

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INTRODUCTION

Inflammation may play a role in the development and progression of many cancers (1). In various epidemiologic studies, it is noted that ulcerative colitis, esophagitis, and hepatitis cause an increased risk for the development of malignant neoplasm and that chronic inflammation accompanies 17% of all cancers (2). After *Rudolf Virchow* identified the relationship between inflammation and cancer in 1863, several biological and epidemiological studies were conducted to demonstrate this. As a result of these studies, although contradictory opinions are present, it is stated that development of *prostate cancer* (PCa) is associated with chronic prostatitis (1, 3). Prostatitis, defined as inflammation of the prostate gland, is classified by the *National Institutes of Health* (NIH) as acute bacterial prostatitis, chronic bacterial prostatitis, inflammatory prostatitis, non-inflammatory prostatitis, and asymptomatic prostatitis (4). In a study of 68.675 male patients, the risk of developing PCa was found to be increased in patients with a history of prostatitis and prolonged prostatitis symptoms (5). These findings show that chronic inflammation plays an important role in PCa carcinogenesis (6). Via altering tumor microenvironment, interleukins (IL-8, IL-6) released as a result of inflammation may lead to an increase in angiogenesis, broadening of tumor size, build-up of invasive characteristics, progression of PCa, and cancer becoming more resistant to androgen blockade or chemotherapy (7, 8). There is no evidence that inflammation is related to tumor aggressive PCa. Because of the discrepancy between *Gleason score* (GS) detected in prostate biopsy and GS of *radical prostatectomy* (RP) specimen, it is difficult to predict tumor aggressiveness, and this may change the appropriate treatment options for patients. In the literature, advanced age, serum *prostate-specific antigen* (PSA) elevation, *PSA density* (PSAD), and *multi-parametric magnetic resonance imaging* (mp-MRI) have been reported to be predictors of *GS upgrade* (GSU) in various studies (9, 10).
The increase in tumor aggressiveness resulting from chronic inflammation suggests that it may be a predictor for GSU. In the published literature, no study has examined the relationship between the presence of chronic inflammation associated with PCa and GSU.
The aims of this study was to determine the predictive effect of coexisting chronic prostatitis in PCa diagnosed by prostate biopsy on GSU in RP specimen.

MATERIALS AND METHODS

Patient selection

After obtaining *Institutional Review Board* approval (2018/267)

No conflict of interest declared.

for the study, the data of 295 patients who underwent prostate biopsy due to high PSA levels after antibiotic therapy, PSA elevation together with suspicious *digital rectal examination* (DRE) or PSA elevation together with mpMRI findings and whose results showed prostate cancer and underwent radical prostatectomy from May 2012 to December 2018 were reviewed, retrospectively.
Patients receiving anti-androgen therapy, those with history of radiotherapy, patients with a previous biopsy history, those included in *active surveillance* (AS), patients with primary metastatic PCa, and subjects with incomplete data were excluded.
Transrectal ultrasound (TRUS)-guided (*GE Logic 9; General Electric, Milwaukee, WI, USA*) prostate biopsy (TRUS-Bx) was performed through an E8C 7.5-MHz transrectal linear array transducer placed in an automatic biopsy gun (*ACE-CUT; TAF, Tochigi, Japan*) equipped with an 18-gauge biopsy needle (*Magnum; Bard, Covington, GA, USA*). Regions suspicious for malignancy on mpMRI (targeted lesions) were sampled with two cores. This was followed by standard 10-core systemic biopsies that were taken from patients dependent on prostate volume. All MRI target TRUS-Bx and RP specimens were collected at our institution, and we obtained actual pathologic tissue slides for examination by two pathologists.
The clinical and pathologic data included preoperative PSA measured prior to DRE and TRUS, PSAD, prostate volume (assessed by TRUS), GS of TRUS-Bx and RP specimens, evidence of histologic chronic prostatitis on biopsy, number and percentages of positive cores in biopsy samples, the final (pathologic) GS of RP specimens, and *Prostate Imaging Reporting* and *Data System version 2* (PIRADS) scores in mpMRI.

Pathologic assessment

All pathology specimens were evaluated by two experienced uropathologists. TRUS-Bx specimens were analyzed in terms of the following: tumor type, GS, number of tumor localizations and positive core ratios, presence of perineural invasion, evidence of high-grade *prostatic intraepithelial neoplasia* (PIN) in tumor-free areas, presence of *atypical small acinar proliferation* (ASAP), evidence of atrophy, and presence of chronic or active prostatitis along with its extent. RP specimens were assessed more thoroughly; the factors taken into consideration in addition to the parameters described above for TRUS-Bx were as follows: intraductal component, predominant tumor localization and diameter, the status of surgical margins, seminal vesicle involvement, and bladder neck invasion.
Histopathologic diagnosis of chronic inflammation in the prostate was made by the presence of primarily lymphocytes (predominantly T lymphocytes) infiltrating the stromal and/or glandular component; neutrophils infiltrating the glands in some cases, even playing a role in development of luminal micro-abscesses or larger prostatic abscesses; macrophages to a lesser extent; plasma cells; and eosinophil leukocytes. The diagnosis of prostatitis was defined as chronic active prostatitis via the detection of neutrophils infiltrating the glandular epithelium within more than one gland and more than one core, or as chronic prostatitis in cases of uncertain neutrophilic infiltration by identification of increased number of lymphocytes (with or without histiocytes) forming aggregates in parenchyma, as well as infiltrating the glands.
In our study, GS in acinar adenocarcinoma were compared between TRUS-Bx and RP specimens for the same patient. In RP specimens, an increase in numerical value of GS or a change from a total score in TRUS-Bx of 3+4 = 7 to a score of 4+3 = 7, was acknowledged as GSU (11).

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Sciences version 21 software package (*IBM SPSS Statistics; IBM Corp., Armonk, NY*).
The Shapiro-Wilk test was used to determine whether distributions of continuous variables were normal.
The mean differences between two related groups of normally distributed data were compared by independent t-test, and the Mann-Whitney U test was used to compare non-normally distributed data. The effect of the presence of prostatitis on biopsy upon Gleason score upgrade was examined using logistic regression analysis. The *Chi-square* ($\chi 2$) test was used for comparison of qualitative independent variables within groups. A P value ≤ 0.05 was considered statistically significant.

Results

A total of 295 patients with complete clinical and pathologic data who underwent open or robotic RP with the diagnosis of localized PCa after biopsy were included in the study for analysis. Overall, the mean age, PSA, PSAD, and PV were respectively 61.4 ± 6 years, 9.5 ± 6 ng/mL, 23 ± 17.2 and 45.5 ± 17.3 cm^3. Histopathologic analysis following TRUS-Bx revealed 224 (75.9%) patients with GS 3+3, 52 (17.6%) patients with GS 3+4, 15 (5%) patients

Table 1.
Patient characteristics.

Age (years, mean ± SD)	61.4 ± 6.0
PSA value (ng/mL, mean ± SD)	9.5 (6.0)
PSA density (ng/mL^2, mean ± SD)	23.0 (17.2)
Prostate volume, n (%)	
≤ 35	83
35-65	173
≥ 65	39
Neutrophil/lymphocyte ratio (N/L) (mean ± SD)	5.2 (3.3)
Biopsy Gleason score, n (%)	
3+3	224 (75.9)
3+4	52 (17.6)
4+3	15 (5)
8	3 (1)
9-10	1 (0.3)
No. of positive cores, n (%)	3.73 (2.1)
Percentages of positive cores, n (%)	35.9 (21.5)
MR PI-RADS category, n (%)	
≤ 2	53 (17.9)
3	50 (16.9)
4	179 (60.6)
5	13 (4.4)
Prostatectomy Gleason score, n (%)	
3+3	79 (26.7)
3+4	131 (44.4)
4+3	47 (15.9)
8	21 (7.1)
9-10	17 (5.7)

Table 2.
Radical prostatectomy grades stratified by biopsy Gleason scores.

Biopsy GS	5-6	3+4	4+3	8	9-10	Total
Radical prostatectomy GS						
3+3	79	0	0	0	0	79
3+4	106	25	0	0	0	131
4+3	29	17	1	0	0	47
8	7	3	10	1	0	21
9-10	3	7	4	2	1	17
Total	224	52	15	3	1	295

Table 3.
Clinical and pathologic parameters with Gleason score (GS) group: upgrading from biopsy GS 5-6 to GS > 6 at radical prostatectomy.

Variables	Upgrade (n = 145)	No upgrade (n = 79)	P value
Age			0.099
Mean (SD)	61.5 (5.7)	60.3 (6.4)	
Median (range)	61.0 (46-78)	60.0 (47-74)	
PSA			0.902
Mean	9.8 (6.3)	9.0 (4.5)	
Median	8.0 (1.8-43.0)	7.5 (3.3-27.0)	
PSA density			0.285
Mean	22.3 (17.1)	22.2 (13.1)	
Median	16.0 (4.8-122.8)	19.6 (5.3-67.5)	
Prostate volume			0.282
≤ 35	31	26	
35-65	91	39	
≥ 65	23	14	
NL ratio			0.148
Mean	5.4 (3.4)	4.7 (2.7)	
Median	4.9 (1.1-20.8)	4.3 (1.1-15.0)	
No. of positive cores			0.141
Mean	3.75 (2.3)	3.1 (1.6)	
Median	3.0 (1-12)	3.0 (1-8)	
Percentages of positive cores			0.166
Mean	36.1 (22.5)	30.4 (16.8)	
Median	30.0 (6-100)	30.0 (8-83)	
MR PI-RADS category			0.729
≤ 2	34	15	
3	21	16	
≥ 4	90	48	
Bx result			< 0.001
PCa with chronic prostatitis	82	24	
Pure PCa	63	55	

with GS 4+3, 3 (1%) patients with a total GS of 8, and 1 (0.3%) patient with a total GS of 9-10. The median number of positive cores detected as cancer on biopsy was 3 (range, 1-12), and the mean percentage of positive cores was 30% (range, 6-100%). In mpMRI performed prior to biopsy, the results indicated the following: 53 (17.9%) patients with a PIRADS 2, 50 (16.9%) patients with a PIRADS 3, 179 (60.6%) patients with a PIRADS 4, and 13 (4.4%) patients with a PIRADS 5 lesion. On histopathologic examination of RP specimens, 79 (26.7%) patients had GS of 3+3, 131 (44.4%) patients had GS of 3+4, 47 (15.9%) patients had GS of 4+3, 21 (7.1%) patients had GS of 8, and 17 (5.7%) patients had GS of 9-10 (Table 1). Based on these findings, 145 (64.7%) of the total 224 patients with a GS of 3+3 on TRUS-Bx were identified as having GSU, and 79 (35.2%) had no upgrade (Table 2). There was no statistically significant difference observed between the two groups with and without GSU in terms of patient age, PSA value, PSAD, prostate volume, neutrophil/lymphocyte (N/L) ratio, number of positive cores, percentage of positive cores, and PIRADS score (Table 3). The presence of chronic prostatitis associated with PCa was higher in the GSU group in comparison with the other group ($p < 0.001$). According to the univariate logistic regression analysis, the presence of chronic prostatitis was found to be an independent predictor for GSU (OR: 2.98, 95% CI, $p < 0.001$) (Table 4).

Table 4.
Univariate logistic regression model to prediction of upgrading from biopsy GS 5-6 to GS > 6 at RP.

Variable	OR (95% CI)	p value
Bx result		
Pure PCa	ref	
PCa with chronic prostatitis	2.983 (1.668-5.333)	< 0.001

Discussion

Ethnic origin, age, and family history are amongst the known risk factors of PCa, yet there are many other probable risk factors currently being researched.

Epidemiologic, genetic, and experimental studies have suggested that chronic inflammation may be associated with PCa, though this is unclear (12). Although prostatitis is defined as inflammation of the prostate gland in terms of pathologic description, it has traditionally been used to express the clinical picture of urinary tract symptoms, inflammation, pain of prostate origin, and not fully understood etiopathogenesis. Pathologically, evidence of neutrophils, eosinophils, lymphocytes, macrophages, and plasma cells in the parenchyma is presented as prostatitis (13). The incidence of prostatitis in the male population is 4.5-9%; it is as common as ischemic heart disease and diabetes in the population (14, 15). Chronic asymptomatic inflammatory prostatitis is described as category IV according to the NIH classification and as the presence of inflammatory cells in biopsy specimens of asymptomatic patients with high PSA values (16). In patients with a PSA value of > 4 ng/mL, the incidence of chronic prostatitis is reported as 42% (17).

Although no verifiable infectious agent has been identified, an increase in PSA values may be present in cases where the rate of inflammation within the prostate is above 20% (18). Inflammatory infiltrates include T lymphocytes, macrophages, plasma cells, and eosinophils. The presence of CD-204 macrophages and CD-3 T lymphocytes play a role in tumor development. The pro-carcinogenic inflammatory process leads to cell transformation by activation of transcription factor NF-kB and a consequent increase of *tumor necrosis factor* (TNF)-α and IL-6 (19). In addition, IL-30 has been shown to take part in PCa stem-like cell regulation and is proven to be responsible for onset, vascularization, and increased tumor proliferation (20). In recent years, Vav3 oncogene has been documented to cause both chronic prostatitis and PCa (21). Studies in the literature indicate that the presence of chronic prostatitis increases the risk of PCa by

1.83-fold (22). Some authors state that the use of aspirin or *non-steroidal anti-inflammatory drugs* (NSAIDs) decreases the risk of PCa (23). Apart from the chemokines and cytokines produced in chronic prostatitis, inflammatory cells provide a microenvironment favorable to tumor progression by increasing production of oxygen species, which induce oxidative DNA damage, reducing DNA repair, stimulating tumor growth and angiogenesis (12). In patients with PCa not detected on the first biopsy, the incidence of PCa was found to be higher in patients with histologically demonstrated chronic inflammation after the 5-year follow-up in comparison with patients without chronic inflammation (20% *vs.* 6%) (24). Furthermore, evidence of chronic inflammation along with PCa results in patients having a more aggressive and advanced disease. Patients with high-grade inflammation surrounding malignant glands had significantly more advanced disease and higher postoperative *biochemical recurrence* (BCR) rates than patients with low-grade inflammation (25, 26). Considering the current studies, it is thought that co-occurrence of PCa and chronic inflammation might also be associated with the possibility of GSU, which is encountered in clinical practice with a 44% probability. In different studies, several markers such as higher PSA, older age, higher percentage of positive cores, lower prostate volume, PSAD, and mp-MRI findings have been identified as important indicators for upgrading and upstaging (9, 10). GSU may be associated with outcomes of RP including extra prostatic extension, positive surgical margin, and seminal vesicle invasion. This may lead us to be more selective in determining AS patients and may result in BCR during follow-up of these patients (9). In our study, factors described in previous studies for GSU were also reviewed, yet the presence of chronic prostatitis on biopsy accompanying PCa was the only significant marker for GSU according to logistic regression analysis. There are several studies in the literature in relation to the prediction of GSU using the N/L ratio prior to surgery. Although caution is advised regarding GSU in patients with N/L ≥ 3, some studies reveal no relationship between this finding and GSU (27). The N/L ratio was not classified as a predictive factor for GSU in our study. The intraobserver match was 41-43% in the histopathologic assessment of TRUS-Bx and RP specimens, but in our study, the possibility of misevaluation was eliminated via analysis of biopsy and RP specimens by two uropathologists. The point, as identified in our study, that the presence of chronic inflammation is a significant marker for GSU, is important for clinical practice and future studies. *Porcaro et al.* (28) showed that patients diagnosed with low-risk PCa in biopsy are a heterogeneous group, in fact, these patients may represent a higher disease than their PSA and positive cores.

On the other hand, *Gurel et al.* (29) found that men with more intraprostatic inflammation in patients with prostate cancer had a higher risk of poor outcomes. AS which is the first-line treatment plan for patients in the low risk group, is not a suitable treatment option in terms of GSU risk for patients with evidence of chronic inflammation. With the support of these studies in the future, we argue that one of the AS exclusion criteria should be the presence of prostatitis in the biopsy.

Our study has some limitations that should be taken into consideration. First, this was designed as a retrospective study. We did not quantify the extent of inflammation within each prostate specimen. They could not determine the relationship between the degree of inflammation and tumor aggressiveness. We did not report the presence of other prostatic lesions such as high grade PIN, post-atrophic hyperplasia or proliferative inflammatory atrophy. Due to the design of our study, it was not possible to assess the association of chronic inflammation presence with more aggressive outcomes. Our findings should be confirmed using more distant end points such as metastasis and survival.

Conclusions

The present study showed that inflammation within PCa was associated with GSU after RP. Hence, pathologists and urologists should be cautious about the possibility of a more aggressive tumor in the presence of chronic inflammation associated with PCa. This may be due to inflammatory mediators promoting development of aggressive PCa. Our study is the only study to demonstrate the relationship between chronic inflammation and GSU. However, prospective studies are required in order to examine clinical reflection and the long-term outcomes of our study.

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