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Original Article

Upgrading in prostate cancer: Clinical and pathological parameters that predict the Gleason score changes

Kaan Karamik[1], Mustafa Yuksel[1], Hakan Anil[1], Ekrem Islamoglu[1], Husnu Tokgoz[1], Basak Goktas[2], Murat Savas[1]
[1] *Department of Urology, Anatalya Training and Research Hospital, Antalya, Turkey*
[2] *Department of Public Health, Akdeniz University, Faculty of Medicine, Antalya, Turkey*

Abstract. Prostate cancer is the most common malignancy in men. Several studies have shown that the difference between biopsy and prostatectomy specimen Gleason score (GS) ranges from 28% to 58%. The aim of this study was to investigate equivalence of GS between biopsy and radical prostatectomy specimen. We also aimed to evaluate the clinical and pathological parameters that predict GS changes. We retrospectively reviewed data from 101 patients who underwent prostatectomy at our hospital. Prostate needle biopsies were performed under ultrasound guidance through the trans-rectal route after quinolone group antibiotic prophylaxis. At least 10 core biopsies were taken. Upgrading was defined as an increase in total GS or increase in initial GS. The mean age of patients was 63.15 and the mean prostate specific antigen (PSA) level was 12.25. The most common needle biopsy GS was 3+3 (79.2%) followed by 3+4 (11.9%). The most frequent pathological GS was 3+3 (52.5%) followed by 3+4 (28.7%). 38.6% of the patients received an upgrading on radical prostatectomy material. We evaluated the correlation s between the patients' ages, preoperative PSA, biopsy GS, number of tumor cores, number of cores with presence of high grade prostatic intraepithelial and/or atypical small acinar proliferation accompanying tumor, positive surgical margin status and upgrading. When multivariate logistic regression analysis was performed, in patients above the age of 65 (p=0.019) with higher PSA (p=0.024), an increase was observed in GS of prostatectomy material compared to needle biopsy. Patients who were upgraded were more likely to have positive surgical margins (p=0.022). Accurate staging is crucial in prostate cancer for optimal treatment planning. In our study upgrading was found to be correlated with age and PSA. We believe prospective studies involving larger patient series and more parameters will allow us to reach clearer judgments on this topic.

Keywords: Biopsy, Gleason score, upgrading, prostate

Introduction

Prostate cancer continues to be the most common cancer among men, supporting previous knowledge. [1] Diagnosis uses prostate needle biopsy after examinations of serum prostate specific antigen (PSA) levels and digital rectal examination. The Gleason staging system, defined by Donald F. Gleason in 1966, is accepted globally for prostate cancer staging and has been updated many times to evaluate histology results of prostate needle biopsy. The Gleason score (GS) shows the aggressiveness and progression of the tumor, in addition to being very important to choose appropriate treatment [2].

Apart from radical prostatectomy, correct Gleason scoring is important for prostate needle biopsy results for current treatment choices such as active surveillance, brachitherapy, radiotherapy and cryotherapy. This is because the decision for these treatment alternatives is histopathologically only made according to the prostate needle biopsy GS. At this point for patients to receive most appropriate treatment (for example, addition of lymph node dissection for a patient about to undergo radical prostatectomy or performing nerve-protecting surgery) GS is one of the most important determinants together with PSA. However, many studies have shown differences in the equivalence between needle biopsy GS and prostatectomy specimen GS [3, 4]. This study investigated compliance between biopsy and pathology GS and the factors affecting upgrading patients in this situation.

Materials and Methods

Retrospectively 101 patients who underwent needle biopsy followed by radical prostatectomy within 4 months from 2009 to 2016 were included in the study. Patients who were diagnosed with prostate cancer after transurethral prostate resection were excluded. Prostate needle biopsies were performed under ultrasound guidance through the transrectal route after quinolone-group antibiotic prophylaxis. As recommended at least 10 core biopsies were taken [5]. To ensure standardization, biopsy results from external centers were not included.

* Corresponding author: Kaan Karamık, M.D (kaankaramik@gmail.com).

TABLE 1
CHARASTERICTICS OF THE PATIENTS

Factor	No. (%)
Age (years)	
Mean	63.15
Range	46-81
PSA (ng/ml)	
Mean	12.25
Median	7.96
Range	3.1-87.5
Positive core	
Mean	3
Range	1-11
Age Groups	
<65	55 (54.5)
≥65	46 (45.5)
Presence of HPIN	
Positive	18 (17.8)
Negative	83 (82.2)
Presence of ASAP	
Positive	4 (4)
Negative	97 (96)
Biopsy Gleason score	
3+3	80 (79.2)
3+4	12 (11.9)
4+3	6 (5.9)
4+4	2 (2)
5+5	1 (1)
Operation type	
Robotic	68 (67.3)
Open	33 (32.7)
Pathological Gleason score	
3+3	53 (52.5)
3+4	29 (28.7)
3+5	1 (1)
4+3	5 (5)
4+4	4 (4)
4+5	6 (5.9)
5+4	2 (2)
5+5	1 (1)
Upgrading and upstaging	
Upgraded	39 (38.6)
No upgraded	62 (61.4)

HPIN, high grade prostatic intraepithelial; ASAP, atypical small acinar proliferation.

Both needle biopsy and prostatectomy specimens were examined by pathologists at our center. All patients had open retropubic radical prostatectomy (ORP) or robot-assisted radical prostatectomy (RARP) surgery. These surgeries were performed by 5 different surgeons. No patient received neoadjuvant treatment.

TABLE 2
ASSOCIATION OF CLINICAL AND PATHOLOGIC PARAMETERS WITH GLEASON SCORE

Factor	Non Upgrade No. (%)	Upgrade No. (%)	P value
Age (years)			
<65	40 (72.7)	15 (27.3)	0.019
≥65	22 (47.8)	24 (52.2)	
Presence of HPIN			
Positive	10 (55.6)	8 (44.4)	0.769
Negative	52 (62.7)	31 (37.3)	
Presence of ASAP			
Positive	4 (100)	0 (0)	0.157
Negative	58 (59.8)	39 (40.2)	
PSA (mean ± SD)	10.8 ± 11.4	14.4 ± 1.5	0.024
Surgical margin			
Positive	10 (40)	15 (60)	0.022
Negative	52 (68.4)	24 (31.6)	

HPIN, high grade prostatic intraepithelial; ASAP, atypical small acinar proliferation.

Statistical analysis included the patients' ages, preoperative PSA, biopsy GS, number of tumor cores, number of cores with presence of high grade prostatic intraepithelial (HPIN) and/or atypical small acinar proliferation (ASAP) accompanying tumor and prostatectomy specimen GS. PSA value was measured before digital rectal examination and transrectal ultrasound and biopsy. Upgrading was defined as an increase in total GS or increase in initial GS (e.g., GS: 3+3 to GS: 3+4 or GS: 3+4 to GS: 4+3). The inverse of this situation was defined as downgrading. For upgrading the Gleason tertiary scores were not included.

Continuous variables were evaluated using mean and standard deviation, according to their distribution. The association between upgrading and age, and presence of HPIN or ASAP were evaluated using the Chi-square test and Fisher's exact test, depending on their distribution. The association between upgrading and preoperative PSA level and number of tumor positive core samples were evaluated using the Mann Whitney U test, depending on their distribution. Statistical analyses were performed using SPSS software, version 16.0. Statistical significance was set at the level of $p=0.05$.

Results

The mean age of patients participating in the study was 63.15 years. Mean preoperative PSA value was 12.25 ± 13.2. Tumor positive core samples were between 1–11 samples. Mean positive core sample was 3 ± 2.43. Of the cases, 17.8% had accompanying HPIN while 4% had ASAP. Surgical margin positivity rate was 24.8%, while 67.3% of cases underwent ORP, and 23.7% had RARP. The distributions of descriptive characteristics of patients were shown in Table 1.

The most common needle biopsy GS was 3+3 (79.2%) followed by 3+4 (11.9%). For prostatectomy specimens,

the most common GS was 3+3 (52.5%) followed by 3+4 (28.7%). While only 1 patient had downgrading, 38.6% of patients had upgrading. As a result statistical analysis was studied as presence or absence of upgrading.

Table 2 shows the correlation between preoperative clinical and pathological variables and upgrading situation in detail. As patient age increased and if PSA value was high, more upgrading was observed. When multivariate logistic regression analysis was performed, in patients above the age of 65 (p=0.019) with higher PSA (p=0.024), an increase was observed in GS of prostatectomy material compared to needle biopsy. Patients who were upgraded were more likely to have positive surgical margins (p=0.022). Positive surgical margin rate in ORP was 26.5%, similarly this rate was 28% in RARP. There was no significant statistical difference for the other variables studied.

Discussion

Gleason score is the most reliable factor for identifying prostate cancer [6, 7]. With the increase in PSA screening, the probability of diagnosing prostate cancer in the early stages has increased and disease mortality has reduced. Patients with characteristics of clinical stage⩽T2a, PSA < 10 ng/ml and biopsy Gleason score⩽6 can benefit from conservative treatment (e.g., watchful waiting, active surveillance). To avoid unnecessary and aggressive treatments to patients with low clinical stage and prevent from leaving pathologically higher Gleason score cancers without definitive therapy, accurate Gleason scoring is critically important.

A large review has shown that the difference between biopsy and prostatectomy specimen GS ranges from 28% to 58% [8]. In our study, this rate was 38.6%. There are several studies performed to estimate factors affecting this situation. Among these factors, one of the most commonly assessed is PSA. PSA values, supporting our data (p=0.024), were often found to be predictive of upgrading [9-11]. In contrast to this, a few studies found no correlation between PSA and upgrading [4, 12].

The relationship with patient's age has been called into question and the largest series in the literature demonstrated that higher patient age correlated with upgrading [11]. According to our data, patient age was a significant predictor of upgrading in the group of patients aged over 65 (p=0.019). When the comorbidities of patients above 65 years of age are considered, the importance of appropriate treatment choice and upgrading becomes even more important.

Capitanio et al. [13] researched the relationship between number of positive core on biopsies and upgrading. In patients evaluated with 10-12 biopsies, the upgrading rate was 47.9%. The upgrading rate in the 13-18 core biopsy patients was 31.6% and for those with over 18 core biopsies the upgrading rate was 23.5%. As the number of biopsy cores increased, the probability of upgrading decreased and this was statistically significant. Similar to this study, other studies researching the correlation between core count and upgrading found that as the number of pieces taken for biopsy increased more accurate Gleason scores were obtained and upgrading rates reduced. [9, 14] In our study, all patients had 10-12 core biopsies so the correlation between biopsy core count and upgrading could not be examined. These studies show that higher numbers of samples taken from the prostate gland may be helpful in choosing a more appropriate treatment modality for patients.

Several studies have questioned the association between positive surgical margin and upgrading of GS [9, 10, 15]. In our study, supporting the previous these studies, upgraded patients were more likely to have positive surgical margins (p=0.022). In addition to this, the study by Freedland et al. showed that upgrading was highly associated with biochemical recurrence [9]. There is strong evidence that biochemical recurrence is more frequently observed during follow-up of patients with positive surgical margin [16, 17]. As more surgical margin positivity and biochemical recurrence is observed in upgrading patients, the importance of upgrading to avoid worse oncologic results is revealed once again.

There are studies researching the tertiary grade of the pathologic Gleason score. One study found the upgrading rate of patients with a Gleason score of 6 or less was 36.3% and of these 20% had tertiary pattern [11]. In our study the tertiary pattern of the Gleason score was not examined; if it had, higher upgrading rates may have been identified.

On biopsy results, there was no significant statistical difference identified between upgrading and the presence of HPIN (p=0.769) and/or ASAP (p=0.157) in addition to adenocarcinoma. Another study on upgrading and presence of HPIN did not find significant results [4].

Limitations of our study include its retrospective nature, the low number of patients and lack of discussion of oncologic results as patients were not monitored.

Conclusion

One of the largest obstacles to appropriate treatment choice for prostate cancer patients is accurate staging. In spite of developments in pathologic investigations, high upgrading rates are still encountered. In our study, upgrading was found to be correlated with age and PSA. We believe prospective studies involving larger patient series and more parameters will allow us to reach clearer judgements on this topic.

Conflict of Interest

The authors declare no conflicts of interest.

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