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Original Article

The factors predicting upgrading of prostate cancer by using International Society for Urological Pathology (ISUP) 2014 Gleason grading system

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ABSTRACT

Objective: To investigate the factors to predict Gleason score upgrading (GSU) of patients with prostate cancer who were evaluated by using the International Society for Urological Pathology (ISUP) 2014 Gleason grading system.

Material and methods: Between January 2008 and December 2015, we retrospectively investigated patients who had undergone radical prostatectomy and followed up in the uro-oncology outpatient clinic. The pathologic specimens of the patients were evaluated based on the ISUP 2014 classification system. The patients were divided into two groups with or without upgraded Gleason scores. Factors that could be effective in predicting upgrading such as age, prostate-specific antigen (PSA), prostate volume, D'Amico risk classification, PSA density, cancer of the prostate risk assessment (CAPRA) scores, biopsy tumor percentage, body mass index, and clinical stage parameters were compared between both groups.

Results: Of the 265 patients who could be evaluated and followed up regularly, Gleason score upgrades were observed in 110 (41.5%) patients. Advanced age (p=0.009), PSA >20 ng/mL (p=0.036), PSA density >0.35 (p=0.005), high CAPRA score (p=0.031), and high biopsy tumor percentage (p=0.009) were discovered to be correlated with Gleason score upgrade in univariate logistic regression analysis. Advanced age alone was a predictor for GSU in multivariate logistic regression analysis (p=0.002). Five-year biochemical recurrence-free survival rate was 86% in the non-GSU group and 55% in the GSU group (p<0.001).

Conclusion: GSU risk should be taken into consideration in making therapeutic decisions for older patients with prostate cancer, and precautions should be taken against development of aggressive disease.

Keywords: Gleason score; prostate biopsy; prostate cancer; radical prostatectomy.

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Introduction

Prostate cancer, one of the common cancer types, is one of the frequent reasons for cancer deaths.[1] The Gleason score is used for the histologic grading of prostate cancer, and it is one of the important markers in making treatment decisions.[2] The Gleason grading system was first defined in 1966 and updated in subsequent years, its last update being in 2014 by the International Society for Urological Pathology (ISUP).[3,4] There is a compliance problem between Gleason scores estimated for transrectal prostate biopsy and radical prostatectomy specimens up to 50% in the literature.[5,6] Having such different results for a parameter that is quite influential in therapeutic decision making creates a need for other markers in choosing the ideal treatment. Especially, it is difficult and risky to decide active surveillance.

We aimed to investigate factors that affected Gleason score upgrading (GSU) of the patients with prostate cancer who were evalu-

ated using the World Health Organization (WHO)/ISUP 2014 Gleason grading system.

Material and methods

Between January 2008 and December 2015, we retrospectively investigated patients who were under regularly surveillance in the uro-oncology outpatient clinic for at least one year after undergoing radical prostatectomy in Istanbul Medeniyet University Göztepe Training and Research Hospital. Ethics committee approval (2017/0336) was granted for collecting and analyzing data in our radical prostatectomy database. The pathological specimens of the patients were evaluated once more by the same experienced pathologist (BG) based on the WHO/ISUP 2014 classification system, and tumors were divided into 5 groups as follows: (Group 1: Gleason score 3+3=6/10; Group 2: Gleason score 3+4=7/10; Group 3: Gleason score 4+3=7/10; Group 4: Gleason total score 8 and Group 5: Gleason total score 9-10).
The patients were divided into two groups as those whose Gleason scores were upgraded (GSU) or not (Non-GSU) after comparing their biopsy and radical prostatectomy specimen Gleason scores. Preoperative and postoperative clinical characteristics and oncological follow-up results of the patients were recorded. Factors that could be effective in predicting GSU such as age, prostate-specific antigen (PSA), prostate volume, D'Amico risk classification, cancer of the prostate risk assessment (CAPRA) scores, biopsy tumor percentage, body mass index (BMI), and clinical stage parameters were compared between both groups.

During follow-up period, having at least two PSA values >0.2 ng/mL was considered as biochemical recurrence. Both groups were compared in terms of biochemical recurrence-free survival rates.

Statistical analysis

Parameters affecting GSU were analyzed using Student's t-test, Mann-Whitney U test, chi-square, and the multivariate logistic regression test in statistical analysis. Kaplan-Meier survival curve (log-rank) analysis was used to evaluate biochemical recurrence. The p-values <0.05 were considered statistically significant. Statistical analysis was performed using IBM Statistical Package for the Social Sciences version 21 (IBM SPSS Corp., Armonk, NY, USA).

Table 1. Clinical and histopathological predictive factors of all patients

	n=265
Age (year)	63.14±6.5 (44-76)
BMI (kg/m^2)	27.28±3.51 (17.9-42.51)
Prostate volume (cc)	42.68±20.82 (10-129)
PSA (ng/mL)	13±16.45 (2-125)
CAPRA score	
Low (0-2)	121 (45.6%)
Moderate (3-5)	107 (40.4%)
High (6-10)	37 (14%)
Mean follow-up time (mo)	46.08±23.84 (12-110)
Trus-Bx ISUP 2014	
1	149 (56.2%)
2	57 (21.5%)
3	18 (6.8%)
4	27 (10.2%)
5	14 (5.3%)
Pathologic stage	
T2a	47 (30.3%)
T2b	13 (8.4%)
T2c	58 (37.4%)
T3a	22 (14.2%)
T3b	13 (8.4%)
T4	2 (1.3%)
Biochemical recurrence	65 (24.5%)
RRP ISUP 2014	
1	97 (36.6%)
2	72 (27.2%)
3	33 (12.5%)
4	29 (10.9%)
5	34 (12.8%)
RRP tumor rate	35.48±26.32
pN Positive	12/90 (13.3%)

BMI: body mass index; PSA: prostate-specific antigen; CAPRA score: cancer of the prostate risk assessment score; RRP: radical retropubic prostatectomy; pN Positive: pathologic node positive

Results

Of the 265 patients who could be evaluated and followed up regularly, median age of the patients was 63.1 years (range, 44-76 years), median PSA (13 ng/mL: range, 2-125 ng/mL), BMI (27.2 kg/m^2) values and follow-up time (46.08 months: range, 12-110 months) were as indicated (Table 1). Gleason score upgrades were observed in 110 (41.5%) patients. A total of 22 patients had extraprostatic spread, and 13 patients had seminal vesicle invasion. Higher ISUP grades were estimated for radical prostatectomy specimens in respective number of patients in Groups 1 (n=97), 2 (n=72), 3 (n=33), 4 (n=29), and 5 (n=34). During the follow-up period 65

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(24.5%) patients in the whole series had biochemical recurrence. Advanced age (p=0.009), PSA >20 ng/mL (p=0.036), PSA density >0.35 (p=0.005), high CAPRA score (p=0.031), and high biopsy tumor percentage (p=0.009) were discovered to be correlated with Gleason score upgrade in univariate logistic regression analysis. However, GSU had no correlation with clinical stage, prostate volume, BMI, and D'Amico risk classification (p>0.05). However, advanced age alone was a predictor for GSU in multivariate logistic regression analysis (p=0.002) (Table 2).

Table 2. Analysis of factors that affect Gleason score upgrading

	No upgrade in Gleason score + decrease (n=155)	Upgrade in Gleason score (n=110)	Univariate p	Multivariate analysis (Logistic regression)
Age (years)				
<60	48 (31%)	22 (20%)	0.009*	0.002*
60-70	86 (55.5%)	58 (52.7%)		
>70	21 (13.5%)	30 (27.3%)		
BMI (kg/m^2)				
18.5-24.9	43 (27.7%)	37 (33.6%)	0.564	0.600
25-29.9	82 (52.9%)	52 (47.3%)		
>30	30 (19.4%)	21 (19.1%)		
Prostate volume (cc)	52 (33.5%)	36 (32.7%)	0.569	0.227
<30	72 (46.5%)	57 (51.8%)		
30-60	31 (20%)	17 (15.5%)		
>60				
D'Amico risk group				
Low	71 (45.8%)	38 (34.5%)	0.183	0.067
Moderate	52 (33.5%)	45 (40.9%)		
High	32 (20.6%)	27 (24.5%)		
Total PSA (ng/mL)				
0.1-10	107 (69%)	60 (54.5%)	0.036*	0.363
10.1-20	34 (21.9%)	31 (28.2%)		
>20	14 (9%)	19 (17.3%)		
PSA density				
<0.35	118 (76%)	66 (60%)	0.005*	0.323
>0.35	37 (24%)	44 (40%)		
CAPRA score				
0-2 low	80 (51.6%)	41 (37.3%)	0.031*	0.243
3-5 average	59 (38.1%)	48 (43.6%)		
6-10 high	16 (10.3%)	21 (19.1%)		
TRUS-biopsy tumor percentage	23.85±20.22	30.93±23.38	0.009*	0.234
Clinical stage				
T1c	89 (57.4%)	51 (46.4%)	0.180	0.828
T2	62 (40%)	54 (49.1%)		
T3	4 (2.6%)	5 (4.5%)		

BMI: body mass index; PSA: prostate specific antigen; CAPRA score: cancer of the prostate risk assessment score; TRUS: transrectal ultrasound

The five-year biochemical recurrence-free survival rate was 86% in the non-GSU group and 55% in the GSU group. There was a significant difference in the biochemical recurrence-free survival rates based on the Kaplan-Meier survival analysis (log-rank p<0.001) (Figure 1).

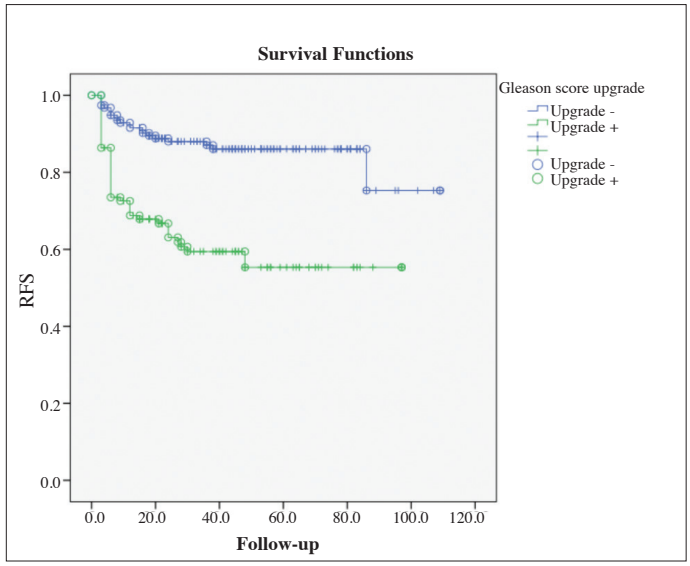

Figure 1. Biochemical recurrence-free survival

Discussion

The Gleason score is a highly effective parameter in making therapeutic decisions for prostate cancer. Identifying the Gleason score correctly helps physicians to decide on various treatment options such as active monitoring, radical prostatectomy, radiotherapy or adjuvant/salvage androgen deprivation therapy (ADT) with curative treatment accurately. Owing to the WHO/ISUP 2014 decision, patients who scored low can later on have higher scores. Additionally, grade grouping provided a more convenient use. In this study, we reevaluated the Gleason scores and discovered upgrades in 41% of the patients. Similar to previous studies, advanced age was found to have a correlation with increased upgrade risk in the multivariate analysis.[6-9] Decisions should be made more carefully for advanced-age groups due to their comorbidities, and despite popular belief, these patients have a higher risk for an aggressive disease. Moreover, patients undergoing radiotherapy (RT) and also active surveillance groups whose final Gleason scores cannot be found should be watched closely in order to prevent emergence of poor oncologic results.

Accurate evaluation of biopsy Gleason scores matters a great deal for the nomograms that aim to determine patients' pathologic stage in clinical practice.[10] Factors such as PSA, PSA density, prostate volume, BMI, CAPRA score, positive core percentage, low serum testosterone level, and prolonged time intervals between biopsy and surgery were found to be correlated with upgrades.[11-16] In our study, most of these factors were found to be effective in the univariate analysis but insignificant in the multivariate analysis. The reasoning behind this could be the fact that we used the new grading system.

In accordance with the literature, a relationship was detected between GSU and biochemical recurrence in the present study (p=0.001).[17,18] In a study by Santok et al.[19], the biochemical recurrence-free survival, cancer-specific survival, and overall survival rates were comparatively lower in patients who underwent robot-assisted radical prostatectomy (RARP) and had Gleason score upgrading (p≤0.001, p=0.003, and p=0.01). In order to demonstrate the relationship between GSU and the disease progression, the long-term monitoring was needed in our study.

Standard transrectal prostate biopsies and randomized sampling could make it difficult to determine the Gleason score accurately for multifocal prostate cancer. Magnetic resonance imaging (MRI) in prostate cancer allows the opportunity for disease staging and targeted biopsy.[20-22] Prostate biopsies performed with the aid of fusion-guided MRI/ultrasonography (US), detected 14.3% of prostate cancers that could not be detected using standard 12-core prostate biopsy. Diagnosis by using fusion biopsy, 86.7% of patients had clinically significant prostate cancer.[23] Lai et al.[24] reported that the results from MRI-targeted biopsies and findings from MRI could predict upgrade risk for patients with prostate cancer in the active surveillance group. Using MRI fusion biopsy, 26% of upgraded cases could be detected. The assumption that it is only possible to perform targeted biopsies from index lesions accurately and safely in special experienced centers based on the still-developing Prostate Imaging Reporting and Data System (PIRADS) classification precludes widespread use of MRI in the short term.

Genomic tests can provide valuable information on risks for radical prostatectomy performed after biochemical recurrence, metastasis, cancer-specific mortality or postoperative course of prostate cancer after RT.[25-28] Although genomic tests are included in current guidelines, there is still a need for a solution towards financial issues concerning its widespread clinical use.[29] Additionally, it was reported that the number of cancer-propagating cells found in prostate cancer (CPCs) correlated with GSU.[30] In order to provide patients with a safe and effective treatment plan, it would be ideal to acquire all final histopathological information. However, since the common choices in the current management of prostate cancer include options such as active surveillance and RT, current data will not be enough to overcome the problem of GSU. A model that combines MRI

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findings, genomic tests, and the patient's clinical characteristics could maximize the consistency of Gleason score.

The limitations of the present study included the need for long-term monitorization to evaluate cancer-specific survival and metastasis. The study was designed to be a retrospective trial and, the patients whose MRI information was not available were not included in the study. There is a gap in the field for prospective studies concerning MRI findings and genomic profiles.

Advanced age can be accepted as a predictive factor for GSU and, GSU risk should be taken into consideration in making therapeutic decisions for older patients with prostate cancer, and precautions should be taken to prevent development of aggressive disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul Medeniyet University School of Medicine (2017/0336).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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