Evaluation of Concordance between Gleason Scores of Transrectal Ultrasound Guided Biopsy and Radical Prostatectomy Samples in Prostate Cancer

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Abstract: *Objective*: In this study, we investigated the concordance between Gleason scores of transrectal ultrasound guided biopsy and radical prostatectomy specimens in patients diagnosed with prostate cancer via transrectal ultrasound guided biopsy and treated with radical prostatectomy in our clinic.

Material and Method: 115 patients were included in our study treated with radical prostatectomy for organ-confined prostate cancer between the dates of November 2011 and December 2014. Data of these patients are reviewed retrospectively.

Results: The average age of the patients was 61.8 ± 6.8 (43-76) years. The average body mass index of these patients were (BMI) 26.7 ± 3.34 (19.3 – 35.3) kg/m². Average PSA value was 6.6 ± 10.1 (1.4 – 80) ng/ml. Gleason scores of transrectal ultrasound guided biopsy and radical prostatectomy were observed concordant in 74 (64.3%) of 115 patients, while 41 (35.6%) were not concordant. Gleason score was decreased by 1 grade for 8.6% (10 patients) of patients, it was increased by 1 for 26.0% (30 patients) of patients and for 0.8% (1 patient) it was increased by 3.

Discussion: These findings indicate indicate that Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens may be discordant

Keywords: Gleason score, prostate biopsy, prostate cancer, PSA, radical prostatectomy.

1. INTRODUCTION

Prostate cancer, is in fifth place in the most common cancer types and is associated with age [1]. The current diagnostic methods for prostate cancer include; rectal touche (RT), serum prostate specific antigen (PSA) and active use of the combination of transrectal ultrasound (TRUS) done in conjunction with systematic biopsy [2]. Currently, the most commonly used prostate cancer grading system is the Gleason grading system [1]. In this system, a primary grade is given to the most commonly seen glandular shape and a secondary grade to the second most commonly seen glandular shape in the specimen. Grades range from 1 through 5. Gleason score is obtained by summation of primary and secondary grades. Gleason score of the prostate cancer is the most important information source about the biological behavior of cancer [3]. A high Gleason score is the indication of the aggressiveness of cancer [4]. Gleason score derived from prostatectomy specimen has proven to be a reliable data source for the prediction of the disease prognosis. Histological Gleason score of the biopsy material obtained from transrectal ultrasound guided biopsy is an important data for clinically determining the prognosis and evaluating the treatment options of the disease [4]. But the researches showed differences between Gleason scores obtained from transrectal ultrasound guided biopsy specimens and radical prostatectomy specimens. These differences can be both low and high Gleason scores. For this reason choosing the correct treatment strategy depends on reliability of Gleason score obtained with transrectal ultrasound guided biopsy.

The main purpose of this study is, investigation of concordance between Gleason scores of transrectal ultrasound guided biopsy and radical prostatectomy specimens in patients diagnosed with prostate cancer via transrectal ultrasound guided biopsy and treated with radical prostatectomy in our clinic.

2. MATERIAL AND METHODS

For the purpose of the study 115 sequential patients treated with RP for organ-confined prostate cancer between the dates of November 2011 and December 2014 were included in our study and their information was reviewed retrospectively.

Prostate biopsy in conjunction with transrectal ultrasound was applied to the cases suspected with prostate cancer in digital rectal examination and/or low serum PSA detected. Day before the biopsy, oral antibiotherapy was started and continued for five days

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after the biopsy. TRUS guided prostate biopsy, was done in lateral decubitus position with GE Healthcare LOQIC C2 ultrasonography device and biplanar multi-sector 6.5 Mhz transrectal ultrasound probe. Prostate biopsies were taken by 18 gauge 22 cm biopsy needle using biopsy gun working with spring system. Twelve biopsy samples were taken including two from each apex, median and base of both lobes of prostate. Eighteen or 24 biopsy samples were taken including transitional zone, and fixed with 10% formalin from patients with earlier biopsy pathologies showing ASAP.

Pathological examination of the samples was made by an experienced pathologist from Çukurova University Pathology Department. After the biopsy materials are passed through the routine process they are buried into paraffin blocks, 4 micron thick sections were taken and stained with Hematoxylin Eosin. Grading was reported according to Gleason system in the cases diagnosed with cancer by morphological evaluation of biopsy materials.

Clinical stage of cases diagnosed with prostate adenocarcinoma after prostate biopsy are identified by postero-anterior chest radiography, whole-body bone scintigraphy and whole abdominal radiological imaging (CT or MRI). For the cases evaluated as organ-confined prostate cancer by clinical staging, surgical treatment was indicated.

2.1. Pathological Examination

Surgical material examinations of patients performed with radical prostatectomy due to organ-confined prostate cancer are carried out by an experienced pathologist at Cukurova University Pathology Department. Surgical materials was fixed by 10% formaldehyde for at least 24 hours and in order to determine the surgical margins all of the outer surface was stained black with India ink. First, seminal vesicles were removed by the distal (apical) and proximal (bladder neck) margins. Distal surgical margins was separated from the apex through amputation of a 0.5-1 cm portion and taken into process by dissecting in the form of conization. Proximal surgical margins, as the distal surgical margins, was removed by finely skiving the surface and taped by placing on the stained facet. Seminal vesicles were taken to process as right and left, by preparing samples from the merging sites with the prostate. In the received tissues, seminal vesicle-prostate transition was observed. The remaining seminal vesicle tissues were put into processing. Later, the prostate was taken into whole sampling process. In whole sampling, distal and proximal margins and the base of seminal vesicle were taken into process. Prostate tissue was dissected with 3 mm intervals from apex (distal) through proximal (bladder neck). Each slice was evaluated individually in macroscopic manner. Coding from distal through proximal, each slice was taken into process by cuting in sizes to fit into the tapes. Preparations obtained by cutting the blocks dipped into the paraffin after the routine process as 4-5 micron thickness dissections are stained with Hemotoxylin-Eosin.

2.2. Statistical Analysis

SPSS 20 package program was used for the statistical analysis of the data. Categorical measurements were outlined as numbers and percentages, numerical measurements as the mean and standard deviation (as the median and minimum-maximum in required places). For the comparison of categorical measurements between the groups, Chi-square test was used. Whether the numerical measurements provide normal distribution assumption was tested with Kolmogrov Smirnov test. Between the groups in case of the the assumptions were verified when comparing numerical measurements T test was used, whereas if the assumptions were not verified Mann-Whitney-U test was used for independent groups. For general comparison of more than two groups containing numerical measurements without normal distribution Kruskal Wallis test was used. In these comparisons for situations found significant, Bonferroni corrected Mann-Whitney-U test was used in dual comparisons. Logistic regression was used to obtain odds ratio values of PSA values and tumor volume measurements in Gleason score concordance, surgical margins positivity and lymph node involvement. In all tests statistical significance level was accepted as 0.05.

3. RESULTS

This study was conducted on 115 cases with the average ages between 61,8 ± 6,8 (43-76), at Cukurova University Faculty of Medicine Department of Urology between the dates of November 2011 and December 2014. Average body mass index (BMI) of these patiens was 26,7 ± 3,34 (19,3-35,3) kg/m². Mean PSA value was 10.6 ± 10,1 (1,4-80) ng/ml. Four patiens underwent secondary TRUSB upon the arrival of ASAP as a result of first TRUSB.

Laparoscopic radical prostatectomy was performed in 9 of 115 patients, open retropubic radical

prostatectomy was performed in 106 patients. Average operation time was 239,5 ± 68,3 (150-510) minutes. The average amount of bleeding was 910 ± 250 (200-3,500) cc. Thirty-two patients had blood transfusions during the operation. Fourteen patients had blood transfusions after the operation. In one patient primary closure was performed after rectum injury during the operation. In one patient obturator nerve injury occurred during lymph node dissection. In three patients due to bleeding from drainage tube, and in one emergence of urinary catheter secondary operation and reanastomosis was performed after bleeding control. Average hospitalization duration was 106,7 ± 51,3 (68- 520) hours.

Surgical margins of 73 (63,4%) of the 115 patients was intact after radical prostatectomy. There was seminal vesicle invasion in 8 (6,9%) patients. At least one lymph node involvement was present in 10 (8,6%) patients. Antiandrogen treatment in 5 (4,3%) patients and antiandrogen treatment and radiotherapy in 8 (6,9%) patients was performed due to positive surgical margins and PSA increase.

It was observed that Gleason scores of TRUSB and radical prostatectomy specimens of 74 (64,3%) patients was concordant, in 41 (35,6%) patients they were not (Table **1**). Gleason score was decreased by 1 grade in 8.6% (10 patients) of patients, it was increased by 1 in 26.0% (30 patients) of patients and in 0.8% (1 patient) it was increased by 3. Discordance increases with the PSA values of patients although it is statistically insignificant (p=0,67) (Table **2**). Discordance in Gleason score increases with the tumor volume in radical prostatectomy specimen and it is statistically significant (p=0,01) (Table **3**). Discordance increases with the pathological stage of the patients (p =0,002). PSA values and tumor volumes of the patients show differences according to pathological stage (respectively p=0,003 ve p<0,001). As a result of multiple comparison analysis it was determined that PSA value and tumor volume differences are caused by the difference between Stage 2 patients (Stage 2a-2b-2c) and Stage 3 patients (Stage 3a-3b-3aN1-3bN1). PSA values and tumor volumes were found statistically significantly higher for more advanced ones between these stages. Gleason score discordance statistically significantly increases with surgical margins positivity (p=0.008). Odds ratio of Gleason score discordance of patients with positive surgical margins found 3.126 times (95% confidence interval 1,405-6,958) higher than those with negative surgical margins. Lymph node involvement increased Gleason score discordance statistically significant (p=0,03). No relationship was found between age and BMI with Gleason score discordance (respectively p=0.801 ve p= 0,940).

Table 1: Distribution of Gleason Score of TRUSB Specimens

Gleason Score of TRUSB specimens	Gleason Score				Total	
	Concordant		Discordant			
	n	%	n	%	n	%
6(3+3)	51	65,4%	27	34,6%	78	67,8%
7(3+4)	12	66,6%	6	33,3%	18	15,6%
7(4+3)	5	71,4%	2	28,5%	7	6,0%
8(4+4)	5	55,5%	4	44,4%	9	7,8%
9(5+4)	1	33,3%	2	66,6%	3	2,6%
Total	74	64,3%	41	35,7%	115	100%

Table 2: The Relationship between PSA and Gleason Score

PSA ng/ml	Gleason Score				Total	
	Concordant		Discordant			
	n	%	n	%	N	%
<4	5	83,3%	1	16,7%	6	5,2%
4 - 10	47	68,1%	22	31,9%	69	60%
10 – 20	19	57,6%	14	42,4%	33	28,6%
>20	3	42,9%	4	57,1%	7	6,0%
Total	74	64,3%	41	35,7%	115	100%

Table 3: The Relationship between Tumor Volume and Gleason Score

Tumor volume (cc)	Gleason Score				Total	
	Concordant		Discordant			
	n	%	n	%	N	%
<0,5	11	84,6%	2	15,4%	13	11,3%
0,5 – 1	17	81,0%	4	19,0%	21	18,2%
1 – 5	33	66,0%	17	34,0%	50	43,4%
5 – 10	9	40,9%	13	59,1%	21	18,2%
>10	4	44,4%	5	55,6%	9	7,8%
Total	74	64,3%	41	35,7%	115	100%

Significant relationship was observed between PSA increase and surgical margins involvement (p=0,013). Each unit increase in the value of PSA increases surgical risk of patient by 1.086 times (%95 CI 1.018-1.159). A statistically significant relationship was found between the increase in tumor volume and surgical margins involvement (p≤0,001). Each unit increase in tumor volume increases the risk of surgical margins involvement of the patient by 1.474 times (%95 CI 1.229-1.768). A significant relationship observed between PSA increase and lymph node involvement (p=0,02). Each unit increase in PSA value increases the risk of lymph node involvement for the patient by 1.053 times (%95 CI 1.006-1.102). A statistically significant relationship between the increase in tumor volumes and lymph node involvement (p<0,0001) was found. Each unit increase in tumor volume increases the risk of surgery for the patient by 1.205 times (%95 CI 1.090-1.332).

4. DISCUSSION

Prostate cancer is the fifth most common male malignity in the world [1]. In despite that it is among the second one in cancer-related cause of deaths it can be treated effectively when diagnosed in early stage [5]. With the identification of prostate spesific antigene (PSA), the increased common usage of imaging techniques like transtectal ultrasound (TRUS), patients can be diagnosed in earlier stages and they can be treated successively. In males with high PSA value and/or suspected with cancer in digital rectal examination, TRUS guided prostate biopsy for determining the histopathological diagnosis is a common, standard diagnosis method.

More than 95% of prostate cancers are adenocarcinomas. The other 4.5% are transient cell carcinomas and the remaining are neuroendocrine “small cell” carsinomas and sarcomas [2]. Histopathological grading is an important prognostic finding for prostate cancer. Gleason grading is the most commonly used one among many grading systems [6]. It is a system that is based on the glandular pattern recognized with low magnification under microscope, cytologic properties are ignored. These patterns are graded 1 being the best and 5 being the worst. Gleason pattern 1: rare and hard to be recognized. They are finely confined nodules formed by asini with uniform shape, size and distribution. Pattern 2 is very similar to pattern 1, certain amount of heterogeneity between shapes and size of asinii can be observed in it. Pattern 3 is the most commonly seen and its feature is that asini have different shape and size between each other and seperated by gaps. Characteristic feature of the pattern 4 is the fusion on the glands. While in pattern 5 there are solid cell layers are present without a glandular shape. Most commonly first and second structural patterns are identified and the summation of these two numbers gives the Gleason score. Gleason score is a value between 2-10. Grading is well differentiated between 2-4, medium differentiated between 5-7, between 8-10 poor differentiated prostate cancer. Gleason score is a parameter holding independent prognostic value [7]. Some changes have made to this classification, for example in 2005 it was updated by International Society of Urological Pathology (ISUP). Changes suggested at that committee were: 1. Gleason score 2-4 should not be used for transrectal ultrasound guided biopsy (TRUSB). 2. Poorly differentiated patterns should be reported as pattern 4 instead of 3. While use of tertiary pattern for TRUSB is approved, use for radical prostatectomy specimens is still contradictory. This modified classification system was revised by Epstein and published online.

However, presence of some differences between Gleason score of biopsy samples obtained with transrectal ultrasound and Gleason score after

prostatectomy was reported by some authors [8-11]. When publications are reviewed, it is seen that concordance between Gleason scores of transrectal ultrasound guided biopsy and radical prosatectomy specimens change between the range of 24% and 78% [12]. We evaluated whether there is a statistically significant concordance between Gleason scores of specimens obtained via transrectal ultrasound guided biopsy and Gleason scores of specimens of radical prostatectomy for patients diagnosed with prostate cancer in our clinic.

115 patients with clinically localized prostate cancer was included in the study conducted by Garnett *et al*. [13]. In this study, Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was detected same in 34 (29.5%) patients, there was difference by 1 in 49 patients (42.6%), 2 or more difference in 32 (27.8%) patients. In this study, when Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was compared, when transrectal ultrasound guided biopsy implemented to patients, Gleason scores of 37 (32.1%) of patients was detected higher, Gleason scores of 44 (38.2%) of the patiens was lower. As a result of this study, author comes into conclusion that post-prostatectomy tumor grade of diagnosis oriented biopsy specimens can be predicted correctly, although not for all, but for most of the patients.

In a study conducted by Spires *et al*. [14] 67 patients was included into study. In this study, Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was detected same in 39 (58.2%) patients, there was difference by 1 in 24 patients (35.8%), 2 or more difference in 4 (5.9%) patients. In this study, when Gleason scores of trans-rectal ultrasound guided biopsy and prostatectomy specimens was compared, when f transrectal ultra-sound guided biopsy was implemented to patients, Gleason scores of 10 (14.9%) of patients was detected higher, Gleason scores of 18 (26.8%) of the patiens was lower. In the end of study author comes into con-clusion that there is a good relation between Gleason scores of biopsy and prostatectomy specimens.

In the study conducted on a series of 316 patients by Bostwick *et al*. [15] Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was detected same in 35% of the patients, there was difference by 1 in 39%, difference by 2 in 26%. In this study, when Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was compared, Gleason scores with transrectal ultrasound guided biopsy for 25% of patients was detected higher, for 40% of the patiens it was lower.

According to the results of Thickmann *et al*.'s study [16] in which 124 patients were included, Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was detected same in 28% of the patients, there was difference by 1 in 34%, difference by 2 in 38%. In this study, when Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was compared, Gleason scores with transrectal ultrasound guided biopsy for 15% of patients was detected higher, for 57% of the patients it was lower. According to the kappa analysis results obtained in this study a weak concordance was detected between Gleason scores obtained from transrectal ultrasound guided biopsy and prostatectomy specimens (κ=0.31).

In the study conducted on a series of 226 patients by Cookson *et al*. [17] Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was detected same in 31% of the patients, there was difference by 1 in 43%, difference by 2 in 26%. In this study, when Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was compared, Gleason scores with transrectal ultrasound guided biopsy for 15% of patients was detected higher, for 54% of the patiens it was lower.

According to the results of Pourmand *et al*.'s study [18] in which 103 patietns were included, no changes were observed in Gleason score of 25 patients (48%), whereas 27 patients showed the difference in GS score (52%), with 19 patients marked as upgraded (36%) and 8 patients marked as downgraded (16%). The study showed 52% of discordance, which is very important for patients who are not indicated for aggressive treatments.

According to the results Khoddamİ *et al*.'s study in which 45 patients were included, The biopsy Gleason score was identical to the scores in prostatectomy specimens in 68.2% cases, while 31.8% were discrepant by 1 or 2 Gleason score. They had 9.1% downgrading and 22.7% cases upgraded after prostatectomy [19].

In our study, 115 patients was included in and Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens was detected same in

64.3% of the patients (74 patients), it was observed discordant in 35,7 % of the patients (41 patients). Gleason score was decreased by 1 grade in 8.6% (10 patients) of patients, it was increased by 1 in 26.0% (30 patients) of patients and in 0.8% (1 patient) it was increased by 3. In other studies rate of discordant is seen between %31.8-72 and rate of upgrading is higher than downgrading [13-19]. The results of our study are in this range and are consistent with other studies.

5. CONCLUSION

Gleason score is used for evaluation of tumor aggressiveness, prognosis and treatment modalities and these findings indicate that Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens may be discordant. There-fore we have to consider this in our treatment option. Also we needed new methods like Mr fusion biopsy to increase concordance of Gleason scores of transrectal ultrasound guided biopsy and prostatectomy specimens.

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