Original paper

Prostate volume effect on Gleason score upgrading in active surveillance appropriate patients

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__Summary__ *Introduction: Gleason Score (GS) upgrading rates in the literature are reported to be around 33-45%. The relationship between prostate volume and GS upgrading should be defined, aiming to reduce upgrading rates in patients with low risk groups who are eligible for active surveillance (AS) or minimally invasive treatment, by varying biopsy cores, or lengths of cores according to prostate volumes. In this regard, the aim of our study was to establish the relationship between prostate volume and GS upgrading.*
Materials and methods: We retrospectively analyzed the medical records of 78 patients, who were appropriate for AS between 2011-2016 at our hospital. Inclusion criteria were patient age under 65 years, PSA level under 10 ng/ml, GS (3 + 3) or (3 + 4), and 3 or less positive cores, clinical stages ≤ T2. GS increase in radical prostatectomy specimen was considered as 'upgrading' and in addition, score reported by biopsy as 3 + 4 but in surgical specimen as 4 + 3 were also considered as 'upgrading'. The effect of prostate volume on Gleason grade upgrading was examined by calculating upgrading rates separately for patients with prostate volume 30 ml or less, those with 30 to 60 ml, and those over 60 ml.
Results: As a result of the analysis of the data, upgrading was seen in 35 (44.8%) of 78 patients included in the study. In the cohort mean prostate volume was 49.8 (± 26.3) ml. Twenty-two patients (28.2%) had prostate volume 30 ml or less, 34 (43.6%) 30 to 60 ml, and 22 (28.2%) 60 ml or more. The patients were divided into two groups as those with and without GS upgrading. Between the groups prostate volume and prostate volume range (0-30/31-60/> 60) were not significantly different (p value > 0.05).
Conclusions: Gleason grade upgrading causes patients to be classified in a lower risk group than they actually are, and may lead to inappropriate treatment. This condition has a direct effect on the decision of active surveillance. Therefore, it is important to define the factors that can predict GS upgrading in active surveillance appropriate patients. In this study, we found that prostate volume has no significant effect on upgrading in active surveillance appropriate patients.

KEY WORDS: *Prostate cancer; Gleason score; Upgrading; Active surveillance.*

INTRODUCTION

Prostate cancer is the second most common cancer worldwide and the fifth most common cause of cancer-related deaths. Because of this reason, there are lots of studies on prostate cancer (1-2).
Active surveillance (AS) has been defined in the appropriate group of patients for low-risk prostate cancer. *Gleason Score* (GS) is the most important criteria for patient selection for AS and used in the nomograms. In most studies and nomograms (3+3) GS in the biopsy is used as an inclusion criterium. Recently, researchers have included some eligible patients with a biopsy GS 3 + 4 to their studies (3-6).
In patients, considered AS option, all pathological data, including GS are dependent on prostate needle biopsy. So that, the accuracy of the GS in needle biopsies is very important for this patient groups. However, there may be a significant difference between GSs in needle biopsies and radical prostatectomy specimens. If the score in prostatectomy specimen is higher than needle biopsy, that is defined as 'upgrading', if it is lower, 'downgrading' is mentioned. Upgrading rates in the literature are reported to be around 33-45% (7).
Because of upgrading, patients who are not actually suitable for AS can be recommended with inappropriate treatment options. The reason for this high pathological disruption seems to be that less than 1% of the prostate tissue can be sampled with needle biopsy. Assessment in such a small tissue volume can cause tumor tissue to be undetectable or even missed (8-9). This is supported by studies showing that rates of upgrading in needle biopsies of enlarged prostate are lower (10-14). In most of previous studies, an inverse correlation was found between prostate volume and upgrading rates (15-17). *Kulkarni et al.* have not found significant relationship between prostate volume and upgrading rates, in a retrospective study published in 2006 in which they reviewed 369 patients (18).
If the relationship between prostate volume and GS upgrading can be assessed, it may be aimed to reduce upgrading rates in patients with low risk groups who are

eligible for active follow-up or minimally invasive treatment, by varying biopsy cores, or lengths of cores according to their prostate volumes.

In this regard, the aim of our study is to establish the relationship between prostate volume and GS upgrading.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 78 patients, who are appropriate for AS between 2011-2016 at our Hospital (*Dr. Lütfi Kırdar Kartal Training and Research Hospital, Istanbul, Turkey*).

Age, *prostate-specific antigen* (PSA), prostate volume, total number of cores in the preoperative biopsy, cancer positive core number in the biopsy, GS in the biopsy report, clinical stage, GS in prostatectomy specimen, presence of *prostatic intraepithelial neoplasia* (PIN), *extracapsular extension* (ECE), vascular invasion, surgical margin status, perineural invasion (PNI), seminal vesicle involvement (SVI) were evaluated. Study protocol was approved by *Ethics Committee of Dr.Lütfi Kırdar Training and Research Hospital*. Inclusion criteria were patient age under 65 years, PSA level under 10 ng/ml, GS (3+3) or (3+4), and 3 or less positive cores, clinical stages ≤ T2. Prostate volumes were measured transrectally during biopsy, all biopsies were 12 cores and pathologic examination was performed by two experienced uro-pathologists in our hospital. GS, total cores, and cancer positive core numbers were noted in the biopsy specimens that detected adenocarcinoma. The length or percentage of the cancer positive tissue couldn't found in most reports. GS, PIN, surgical marginal status, PNI, SVI, ECE, presence of vascular invasion were registered. Biopsy and prostatectomy specimens were evaluated according to 2005 *International Society of Uro-pathologists* (ISUP) modified Gleason system. GS increase in radical prostatectomy specimen was assessed as 'upgrading' and in addition also cases in which the score reported by biopsy was 3 + 4 and the score found in the specimen was 4 + 3 were evaluated as 'upgrading'.

The effect of prostate volume on Gleason grade upgrading was examined. Patients initially were divided into GS upgrading or not. These groups were compared in terms of age, PSA value, prostate volume, number of total biopsy cores, number of positive cores, clinical stages, surgical margin status, and SVI, presence of ECE, PIN, PNI, and vascular invasion.

Upgrading rates were calculated separately for patients with prostate volume 30 ml or less, those with 30 to 60 ml, and those over 60 ml. In the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The distribution of the variables was measured with the Kolmogorov Simirnov test. Mann-Whitney U test was used for quantitative independent data analysis. Chi-square test was used for the analysis of qualitative independent data and SPSS 22.0 (*Statistical Package for the Social Sciences*) program was used in the analysis. P value below 0.05 were considered statistically significant ($p < 0.05$).

RESULTS

As a result of the analysis of the data, upgrading was seen in 35 (44.8%) of 78 patients included in the study.

The mean age of patients included in the study was 60.6 (± 4.4) years, and the mean PSA was 6.0 (± 2.2) ng/ml. According to needle biopsy reports, 65 patients (83.3%) had a GS of (3 + 3) and 13 patients (16.7%) had (3 + 4). In cohort mean prostate volume was 49.8 (± 26.3) ml. Twenty-two patients (28.2%) have prostate volume 30 ml or less, 34 (43.6%) 30 to 60 ml, and 22 (28.2%) 60 ml or more. The demographic and clinico-pathological

Table 1.
Demographics and clinico-pathological outcomes of the patients undergoing radical prostatectomy.

		Range	Median	Mean+/-SD
Age		46.0+/-65.0	61.5	60.6+/-4.4
PSA		2.3-10.0	5.7	6.0+/2.2
Prostate volume		14-135	43.0	49.8+/-26.3
Prostate volume	0-30	22		28.2%
	31-60	34		43.6%
	>60	22		28.2%
Gleason Score Biopsy	3+3	65		83.3%
	3+4	13		16.7%
Stage	T2c	26		33.3%
	T2	52		16.7%
N° positive cores	I	31		39.7%
	II	17		21.8%
	III	30		38.5%
Gleason Score Specimen	3+3	38		48.7%
	3+4	25		32.1%
	4+3	9		11.5%
	4+4	5		6.4%
	4+5	1		1.3%
Upgrade	(-)	43		44.8%
	(+)	35		55.1%

Table 2.
Comparison of the upgraded and non-upgraded groups.

		Upgrade (-)		Upgrade (+)		p
		Mean	**Median**	**Mean**	**Median**	
Age		59+/-4.8	61	61.4+/-3.8	62	0.183 m
PSA		5.8+/-2.2	5.4	6.2+/-2.2	5.9	0.529 m
Prostate volume		53.1+/-28	46	45.8+/-23.9	39	0.303 m
Prostate volume	0-30	12	27.9%	10	28.6%	0.604 x^2
	31-60	17	39.5%	17	48.6%	
	> 60	14	32.6%	8	22.9%	
GS biopsy	3+3	35	81.4%	30	85.7%	0.611 x^2
	3+4	8	18.6%	5	14.3%	
N° positive cores	I	18	41.9%	13	37.1%	0.747 x^2
	II	8	18.6%	9	25.7%	
	III	17	39.5%	13	37.1%	
GS specimen	3+4	5	11.6%	20	57.1%	0.000 x^2
	4+3	0	0	9	25.7%	
	4+4	0	0	5	14.3%	
	4+5	0	0	1	2.9%	

m: Mann-Whitney U test; x^2: Chi-Square test.

outcomes of the patients included in the study are summarized in the Table 1.

The patients were divided into two groups as those with and without GS upgrading. In the analysis, no significant difference was observed between these groups in terms of age, PSA values, biopsy GS, number of positive biopsy cores, clinical stage ($p > 0.05$).

GS (3 + 3) was significantly higher in non-upgrading group ($p > 0.05$) (Table 2).

Between the groups with different prostate volume (0-30/31-60/> 60) no significant difference was found (p value > 0.05) (Table 2).

DISCUSSION

Treatment options in prostate cancer differ according to defined risk groups. Low risk patients have better prognosis than middle and high risk group and lower biochemical recurrence rates after radical prostatectomy.

In these patients, active follow-up, brachytherapy and focal therapies are used in order to avoid the complications and side effects of radical prostatectomy or radiotherapy (17, 19-20).

PSA level, clinical stage and GS are used to determine these risk classification (21-22). GS is the most important prognostic factor of prostate cancer risk for classification and choice of treatment options (16, 22-23). Accurate determination of patient's risk group and GS at the time of diagnosis is important in order to choose the appropriate treatment options.

However, there are significant pathological differences between needle biopsies and radical prostatectomy specimens such as GS upgrading in 33-45%. This high rate led investigators to examine the factors that might be effective to predict upgrading.

PSA level, number of cores taken, number of positive cores are some of these factors. Also there are several studies on the effect of prostate volume on GS upgrading. (10, 15, 24-27).

In 2008 *Turley et al.* investigated 586 patients retrospectively. In this study, GS elevation rate was found to be increased as prostate volume decreased (28).

In a study that *Moon et al.* reviewed 107 patients retrospectively demonstrating that 12 or less number of cores in the biopsy and prostate volume of 36.5 ml or less were a predictive factor of GS upgrading (15, 29).

Davies et al. published a retrospective study on prostate volume effect on GS upgrading in 2011. In this large study, medical records of 1.251 low-risk patients were retrospectively investigated and it was found that risk of GS upgrading was more than fifty percent in subjects with prostate volume 36 cm^3 compared to those with 58 cm^3 (16).

Similarly, *Chung et al.*, in a retrospective study of 247 patients published in 2013, reported that patients with prostate volumes of 25 cm^3 or lower had a GS upgrading risk of 2.7 times more than patients with a prostate gland volume of 40 cm^3 or more (15).

However, in a retrospective study of 369 patients, *Kulkarni et al.* reported no significant relationship between prostate volume and GS upgrading (18).

Gleason grade elevation is most important in active sur-

veillance. However, a study that examined the effect of prostate volume on GS upgrading in active surveillance appropriate patients has not been previously mentioned in the literature.

In this study, 78 patients with active monitoring were included. Inclusion criteria were patient age under 65 years, PSA level under 10 ng/ml, GS 3+3 or 3+4 and 3 or less positive cores, clinical stage ≤ T2. Prostate volume effect on GS upgrading in active surveillance appropriate patients was examined, and patients with prostate volume of 30 ml or less, between 30 ml and 60 ml and greater than 60 ml were compared.

According to our results prostate volume found to have no significant effect on GS upgrading in patients who are eligible for active surveillance. Retrospective nature and small number size of this study, and the calculation of prostate dimensions by different clinicians were the limitations of our study.

CONCLUSIONS

Treatment alternatives in prostate cancer may differ according to risk groups. So that it is important to classify patients in the correct risk group.

Gleason grade upgrading causes patients to be classified in a lower risk group than they actually are, and may lead to inappropriate treatment. This situation has a direct effect on the decision of active surveillance. Therefore, it is important to define the factors that can predict GS upgrading in active surveillance appropriate patients. In this study, we found that prostate volume has no significant effect on upgrading in active surveillance appropriate patients.

COMPLIANCE WITH ETHICAL STANDARDS

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