Chula Med J Vol. 63 No. 3 July - September 2019; 137 - 142 DOI : 10.14456/clmj.3

Original article

Correlation between trans rectal ultrasound guided prostate biopsy and radical prostatectomy specimen and risk factors for upgraded Gleason score in prostate cancer

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Background: Gleason score is an important pathologic factor for risk stratification in prostate cancer. Upgraded Gleason score is not uncommon after radical prostatectomy.

Objectives: This study aimed to investigate the prevalence of upgraded Gleason scores between trans rectal ultrasound guided prostate biopsy (TRUS-biopsy) and radical prostatectomy (RP) specimen and to determine the predictive factors for increased Gleason scores.

Methods: We retrospectively reviewed the medical records of prostate cancer patients who underwent RP from June 2006 – June 2016 at King Chulalongkorn Memorial Hospital (KCMH). Gleason scores from TRUS-biopsy and RP were compared. Pre-operative clinical parameters were analyzed to determine the risk factors of upgraded Gleason scores between the group of patients with increased Gleason scores and those with no increased Gleason scores.

Results: In all, 33% (68/204) of patients had upgraded Gleason scores after RP. Patients with upgraded Gleason scores had significantly lower ages ($P = 0.02$), higher PSA levels ($P = 0.01$) and longer durations from TRUS-biopsy to RP ($P = 0.047$). Patients' age ≤ 65 years, PSA ≥ 10 ng/mL and duration from TRUS-biopsy to RP ≥ 6 months were statistically significant factors for increased Gleason scores in both univariate and multivariate analysis.

Conclusions: The prevalence of upgraded Gleason scores is 33%. Patients' age ≤ 65 years, PSA ≥ 10 ng/ml and duration from TRUS-biopsy to RP ≥ 6 months are predictors for upgrading Gleason scores after surgery. These results provide clinical implications for the treatment planning of patients with a risk of upgraded prostate cancer.

Keywords: Prostate cancer, Gleason score, upgraded, radical prostatectomy.

Prostate cancer has been the most common cancer in U.S. men since 1984. The incidence varies by race/ethnicity which is highest in African-American (138.6/100,000) and lowest in Asian-Americans and Pacific Islanders (75/10,000). [1] The diagnosis of prostate cancer is made by digital rectal examination, serum prostate-specific antigen (PSA) and trans rectal ultrasound guided prostate biopsy (TRUS-Biopsy). The biopsy results reported by Gleason scores indicate tumor grade. [2] The combination of Gleason score, PSA level and clinical stage are commonly used to classify the risk of disease recurrence after treatment, predict the prognosis and choose the modality of treatment including radical prostatectomy.

Radical prostatectomy (RP) is one of the treatment options of clinically localized prostate cancer. It gives accurate pathologic staging. Gleason score upgrading after prostatectomy (Gleason scores from RP are higher than Gleason scores from TRUS-Biopsy) has been related with poorer prognosis. From previous studies, the prevalence of Gleason scores discordant between TRUS-biopsy and RP ranged from 30% to 50% [3 - 5], with upgrading Gleason scores ranging from 24% to 49%. [3, 4, 6 - 10]

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Received: November 27, 2018
Revised: February 8, 2019
Accepted: February 11, 2019

Various clinical factors such as prostate volume, PSA density and pre-operative PSA were reported as associated factors with upgraded Gleason scores. [3 - 10] The aim of this study was to investigate the prevalence of patients with upgraded Gleason scores and analyze factors associated with upgraded Gleason scores after RP at King Chulalongkorn Memorial Hospital.

Materials and methods

After obtaining the approval of the Institutional Review Board for the study, we retrospectively reviewed all the medical records of the prostate cancer patients who underwent RP in all surgical approaches from June 2006 to June 2016 (10 - year period) at King Chulalongkorn Memorial Hospital. Patients who received neo-adjuvant androgen deprivation therapy, previous radiation therapy, atypical pathology, diagnosis by magnetic resonance imaging-ultrasonography fusion guided prostate biopsy and transurethral resection of prostate (TURP) were excluded from this study.

Analyzed clinical parameters included age, pre-operative PSA, prostate volume, total core of prostate biopsy, clinical staging, sum of Gleason scores from TRUS-biopsies, sum of Gleason scores from RP and duration from TRUS-biopsies to RP. The 2010 TNM staging system of the American Joint Committee on Cancer (AJCC) was used for clinical staging. [11] Gleason sums from TRUS-biopsies and RP specimen were compared. An upgraded Gleason score was defined as an elevation of Gleason sum after RP compared with TRUS-biopsy.

We divided the patients into 2 groups (Upgraded and Non-upgraded Gleason score) and analyzed factors associated with upgraded Gleason scores. Categorical data were reported as count (%) and continuous data were reported as mean ± standard deviation (SD) and median interquartile range (IQR). Statistical analysis was performed by Wilcoxon rank sum tests for continuous data and Chi-square test for categorical data. Univariate and multivariate logistic regression models were applied to evaluate the effect of clinical parameters on the risk of upgraded Gleason scores. Statistical analysis was performed by using STATA ver.13.1, with $P < 0.05$ considered significant.

Results

A total of 228 patients with clinical localized prostate cancer underwent radical prostatectomy at our hospital during the past 10 years. Twenty-four patients were excluded from the study because of diagnosed prostate cancer from TUR-P in 12 patients, received neo-adjuvant hormonal therapy in 7 patients, diagnosed from MRI-Ultrasonography fusion guided biopsy in 3 patients, prostatic sarcoma in 1 patient and prostatic basal cell carcinoma in 1 patient.

Patients' demographic data are shown in Table 1. The median age was 66 years (61 - 71), median PSA was 9.5 ng/mL (7 - 15.4) and median prostate volume was 32 mL (24.5 - 44). The mean and median total core of TRUS-biopsy cores were 15 and 12 (IQR 11-17). The median time from TRUS-biopsy to RP was 4 months. [4 - 7]

The Gleason score was upgraded in 33% of the patients (68/204). Patients' characteristics divided by groups and comparison are presented in Table 2. There were 141 patients in clinical stage T1 (69.1%), 30 patients in clinical stage T2 (14.7%) and 33 patients in clinical stage T3 (16.2%). The upgraded group had significantly lower patient's age ($P = 0.02$), higher PSA level ($P = 0.01$) and a longer duration time from TRUS biopsy to RP ($P = 0.047$).

Table 1. Demographic data of prostate cancer patients (n = 204).

	Mean ± SD	Median (IQR)
Age (years)	65.4 ± 6.5	66 (61 – 71)
PSA (ng/mL)	13.6 ± 12.2	9.5 (7 – 15.4)
Prostatic volume (mL)	36.0 ± 16.7	32 (24.5 - 44)
Total core of biopsy	15.1 ± 7.3	12 (11 – 17)
Duration from TRUS biopsy to RP (month)	4.8 ± 3.5	4 (3 - 6)

PSA: prostate specific antigen; TRUS: trans rectal ultrasound; RP: radical prostatectomy

Table 2. Comparison between non-upgraded and upgraded group (compared by median).

	Non-upgraded (n = 136)	Upgraded (n = 68)	*P* - value
Median age (IQR), (year)	67 (62 - 71)	64 (60 - 70)	0.02*
Median PSA (IQR), (ng/mL)	8.9 (6.7 - 14)	11.3 (8.3 - 20)	0.01*
Median prostate volume (IQR), (mL)	34 (25 - 45.4)	30.9 (24 - 42)	0.38
Median total biopsy cores (IQR)	12 (11 - 17)	13 (11 - 17)	0.96
Median time from TRUS biopsy to RP (IQR), (month)	4 (3 - 5)	5 (3 - 7)	0.047*
Clinical T staging (%)			
T1	96 (70.6)	45 (66.2)	
T2	20 (14.7)	10 (14.7)	0.56
T3	20 (14.7)	13 (19.1)	

PSA: prostate specific antigen; TRUS: trans rectal ultrasound; RP: radical prostatectomy
*$P < 0.05$ considered statistically significant

As for the upgraded group, we divided the patients into 2 groups for each clinical factor. The number of patients and prevalence in each subgroup are summarized in Table 3. Patients with an age of ≤ 65 years ($P = 0.004$), PSA level ≥ 10 ng/mL ($P = 0.03$) and a time from TRUS-biopsy to RP ≥ 6 months ($P = 0.003$) were significant contributors to the upgraded Gleason scores.

In univariate logistic regression analysis of potential clinical factors of upgraded Gleason scores from TRUS biopsy to RP, age ≤ 65 years ($P = 0.004$), PSA ≥ 10 ng/mL ($P = 0.03$) and duration from TRUS biopsies to RP ≥ 6 months ($P = 0.004$) were statistically significant contributors to upgraded Gleason scores with an odds ratio of 2.38 (95% CI 1.31 - 4.31), 1.9 (95% CI 1.05 - 3.45) and 2.56 (95% CI 1.35 - 4.83), respectively.

In multivariate logistic regression analysis, clinical factors that had a *P* - value < 0.1 from univariate analysis were selected for analysis in order to minimize the confounding factors. Patient's age ≤ 65 years ($P = 0.005$), PSA ≥ 10 ng/mL ($P = 0.03$) and a duration from TRUS biopsy to RP ≥ 6 months ($P = 0.006$) were significantly contributors to upgraded Gleason scores with an odds ratio of 2.52 (95% CI 1.32 - 4.82), 2.08 (95% CI 1.09 - 3.97), 2.54 (95% CI 1.31 - 4.94), respectively. (Table 4)

Table 3. Prevalence of subgroup in patient with upgraded Gleason scores.

	n	n of upgraded	Prevalence	95% CI	*P* - value
Total	204	68	33%	26.9 - 40.3	
Age					0.004*
≤ 65 years	94	41	43.6%	33.4 - 54.2	
> 65 years	110	27	24.5%	16.8 - 33.7	
PSA					0.03*
<10 ng/mL	103	27	26.2%	18.4 - 36.5	
≥ 10 ng/mL	101	41	40.6%	31.3 - 51.3	
Time from TRUS biopsy to RP					
< 6 months	143	39	27.3%	18.9 - 34.2	0.003*
≥ 6 months	61	29	47.5%	34.3 - 60.9	
Prostate volume					0.13
> 45 mL	46	11	23.9%	4.4 - 33	
≤ 45 mL	158	57	36.1%	24.1 - 42.3	
Total biopsy cores					0.73
≤ 12 cores	104	34	32.7%	20.8 - 42.9	
> 12 cores	100	34	34%	23 - 46	

PSA: prostate specific antigen; TRUS: trans rectal ultrasound; RP: radical prostatectomy
*$P < 0.05$ considered statistically significant

Table 4. Predictive factors for upgraded Gleason scores.

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	***P* - value**	**OR**	**95%CI**	***P* - *value***
Age ≤ 65 years	2.38	1.31 - 4.31	0.004*	2.52	1.32 - 4.82	0.005*
PSA ≥ 10 ng/mL	1.90	1.05 - 3.45	0.03*	2.08	1.09 - 3.97	0.03*
Prostate vol. ≤ 45 mL	2.11	0.79 - 5.57	0.13			
Total biopsy core	0.88	0.44 - 1.77	0.73			
Duration from TRUS biopsy to RP ≥ 6 months	2.56	1.35 - 4.83	0.004*	2.54	1.31 - 4.94	0.006*
Clinical T-stage						
T1	1	-				
T2	1.12	0.48 - 2.61	0.79			
T3	1.54	0.69 - 3.42	0.29			

PSA: prostate specific antigen; TRUS: trans rectal ultrasound; RP: radical prostatectomy; OR: odd ratio, *$P < 0.05$ considered statistical significant

Variables with **P*-value of < 0.1 in the univariate analysis were selected and evaluated by multivariate logistic regression models.

Discussion

In clinically localized prostate cancer, there are many standard treatment options including watchful waiting, active surveillance, radiotherapy, thermal ablative therapy and radical prostatectomy (RP). The proper treatment should be considered individually based on the patient's risk. D'Amico [12] stratified prostate cancer patients into three risk groups by using the PSA level, clinical stage and Gleason score. Patients with PSA < 10 ng/mL and Gleason score ≤ 6 and clinical stage T1-T2a were classified into the low risk group. Those with PSA 10 - 20 ng/mL or Gleason score 7 or clinical stage T2b were classified into the intermediate risk group and those with PSA > 20 ng/mL or Gleason score 8 - 10 or clinical ≥ T2c were classified into the high-risk group.

Active surveillance has been recommended only for patients in the low - risk group. However, the prevalence of Gleason scores discordant from TRUS-biopsy and RP specimen range from 30 - 50% [3 - 5], with 24 - 49% upgraded Gleason scores. [3, 4, 6 - 10] This incorrectly grouped patients and affected the decision making for treatment options. Various clinical factors were reported as risks for upgrading Gleason scores such as prostate volume, TRUS-biopsies Gleason scores, PSA density, and pre-operative PSA level. [3 - 10]

In the present study, 33% of the patients had upgraded Gleason scores after RP which were consistent with the results from previous studies. We found the patient's age, pre-operative PSA and duration from TRUS biopsy to RP were significant factors with upgrading in both univariate and multivariate analysis.

The effect of age on increased Gleason scores was studied by Gershman B, *et al*. Among 1,836 patients with Gleason scores 6 disease, age ≥ 60 years was associated with increased risk of upgrading Gleason scores. [6] Moreover, Richstone L, *et al*. reported patients of ≥ 70 years old had a higher prevalence of Gleason scores upgraded compared with age < 70 years. [13] However, our study showed young age increased the risk of upgraded Gleason scores. We found the prevalence of upgraded Gleason scores was significantly higher in patients ≤ 65 years. This could be explained by prostate cancer in young men having a more aggressive biology than in older patients. [14]

Pre-operative PSA has been associated with upgraded Gleason scores in many recent studies. Dong F, *et al.* [15] reported a PSA level > 5 ng/mL was associated with upgraded Gleason scores. Gershman B, *et al*. [6] and Tilki D, *et al.* [9] also reported that highs a PSA level was associated with upgraded Gleason scores. In this study, we determined the cut-off PSA level greater than 10 ng/mL was a significant contributors to upgraded with odd ratio = 2.08. In contrast, Moon SJ, *et al*. [4] and Nayyar R, *et al.* [16] reported that upgraded of Gleason score was not associated with high preoperative PSA level.

Our findings supported the relation between the duration from TRUS biopsies to RP and upgraded Gleason scores. This finding was consistent with the results from previous studies. [17 - 19] The conflicting results could be due to disease progression during the waiting time.

Dong F, *et al.* [15] found that prostate volume < 60 gm was associated with an increased risk of upgrading. Gershman B, *et al*. [6] reported that prostate size had an inverse relation to risk of being upgraded. It may be related to the increase of high-grade tumor in small prostates. However, in this study, the prostate volume was not a predictive factor of upgraded Gleason scores. This could be from the narrow range of prostate volume in our patients.

The limitation in our study was its retrospective design. Gleason scores were interpreted from multiple pathologists. However, we excluded all patients who had risk that may affect the interpretation of prostate tissue. Patients diagnosed with MRI-USG fusion guided biopsy, which is the modern technology of prostate biopsy, also were excluded from this study. Further studies on the clinical outcomes of upgraded Gleason scores are needed.

Conclusions

The prevalence of upgraded Gleason scores is 33%. Patient's age ≤ 65 years, PSA ≥ 10 ng/mL and a duration from TRUS biopsy to RP ≥ 6 months are predictors for increased Gleason scores after surgery. These results provide clinical implications for the treatment planning of patients with risk of upgraded prostate cancer.

Conflict of interest

The authors, hereby, declare no conflict of interest.

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