Factors predicting Gleason score 6 upgrading after radical prostatectomy

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KEY WORDS

prostate cancer ◗ Gleason score ◗ biopsy ◗ prostatectomy ◗ upgrading

ABSTRACT

Objectives. Prostate cancer Gleason score 6 is the most common score detected on prostatic biopsy. We analyzed the clinical parameters that predict the likelihood of Gleason score upgrading after radical prostatectomy.
Methods. The study population consisted of 241 patients who underwent radical retropubic prostatectomy between Feb 2002 and Dec 2007 for Gleason score 6 adenocarcinoma. The influence of preoperative parameters on the probability of a Gleason score upgrading after surgery was evaluated using multivariate logistic regression and ROC curves.
Results. Gleason score upgrade was found in 92 of 241 patients (38.2%). Multivariate logistic regression analysis showed that only percentage of cancer in dominant lobe and prostate weight were significant predictors for Gleason score upgrading ($p = 0.043$ and $p = 0.006$, respectively). ROC curves showed that prostate weight and PSA density were only two independent significant parameters for prediction of upgrade (AUC – 0.634, $p < 0.0001$ and 0.604, $p = 0.006$, respectively). Gleason score upgrading was observed to be accompanied by significantly higher rates of extra prostatic extension ($p < 0.001$) and seminal vesicle invasion ($p = 0.002$).
Conclusions. Almost forty percent of tumors graded Gleason 6 at biopsy are Gleason 7 at surgery. Upgraded tumors significantly associated with adverse pathological features. The probability of Gleason score upgrade can be predicted using prostate weight and PSA density as independent parameters.

INTRODUCTION

Prostate cancer (PCa) grade detected at biopsy provides only pathological information when non-surgical treatment modality is chosen. Growing interest to active surveillance in cases of PCa is enforced by the need of identifying the right candidate for such treatment. Increasing number of patients with non palpable disease and low prostate specific antigen (PSA) level at PCa diagnosis shows that there is necessity for more powerful prognostic parameter for disease staging, grading, response and outcomes. Gleason score (GS) could be such prognostic tool because the grade of PCa is one of the most important factors when predicting post treatment biochemical recurrence or even developing metastasis. Attention should be paid to histological variations of PCa in gland. Gleason noted that final prostatectomy scores are often in concordance with biopsy one [1]. GS 6 detected in biopsy cores deserves special attention for some reasons - it is one of the low risk group parameters, and it has the highest likelihood for upgrading. In the study Chun et al. a GS upgrade was found in 37.6% of cases with biopsy score 6 but only in 2.3% with biopsy score 7 [2]. In most cases upgrading is more common and more clinically important than downgrading. Patients with biopsy GS 6 that is upgraded after surgery to GS 7 have worse outcomes [3, 4] and are more likely for extra prostatic extension or positive surgical margins compared to those with not upgraded tumor [5].

The risk of score upgrading varies from 70% to 20% in the last 20 years, and it depends on biopsy scheme and various clinical or pathological factors; however, there is no consensus which parameters are the most powerful for prediction of GS upgrading [6-9].

We describe the pathological and clinical factors which can be used for prediction of upgrading in patients with biopsy Gleason score 6 that underwent radical retropubic prostatectomy (RP). Detected significant parameters could be used when making decision about initial or subsequent PCa treatment.

MATERIAL AND METHODS

The study population included patients with biopsy GS 6 who underwent RRP between Feb 2002 and Dec 2007. The biopsy and surgery were performed in Hospital of Kaunas University of Medicine. All information was obtained retrospectively through database, clinical records and pathological reports presented by the Department of Urology. In most cases, laterally directed sextant prostate biopsy technique was used for initial diagnosis of cancer. Biopsy samples and specimens after RP were reviewed by one institutional uropathologist I.G.

Patients included into the study had complete sets of parameters available, including pre biopsy PSA, biopsy GS, total number of biopsy cores taken, number of biopsy cores with cancer, percentage of cancer in dominant involved prostate lobe, clinical and pathological stage, GS after surgery and prostate weight. Patients who received any neoadjuvant treatment were excluded. The study was approved by local ethical committee, and 241 patients with biopsy GS 6 were included in the study.

Patients who were upgraded postoperatively to GS 7 or higher were compared to those who were not upgraded. Categorical variables were compared using Pearson Chi-Square test and continuous one using Mann-Whitney test. Multivariate logistic regression was used for detecting significant predictors of upgrading. A curve of receiver operator characteristics (ROC) was used to demonstrate graphically predictive performance of significant parameters. Patient's age, pre biopsy PSA, clinical stage, number of total and positive cores, percentage of positive cores, percentage of cancer at

Table 1. Clinical variables in patients with and without Gleason score upgrade on final pathological evaluation

	Gleason score 6 N = 149	Gleason score ≥7 N = 92	p value
PSA (ng/ml) Mean (range)	7,82 (0.7-32.7)	8.86 (3.4-50.20)	N.S
Age (years) Mean (range)	64.32 (46-76)	64.7 (49-76)	N.S.
Prostate volume (ml) Mean (range)	58.39 (20.0-175.0)	48.83 (20.0-211)	<0.001
PSA density Mean (range)	0.153 (0.02-0.78)	0.205 (0.04-1.52)	0.006
No. of total biopsy cores 6 or less 7-8 cores 9-11	 126 (84.6%) 21 (14.1%) 2 (1.3)	 72 (78.3%) 19 (20.7%) 1 (1.1%)	N.S.
No. of cores with Ca 1 2 3 ≥4	 56 (37.6%) 49 (32.9%) 21 (14.1%) 23 (15.4%)	 31 (33.7%) 32 (34.8%) 13 (14.1%) 16 (17.4%)	N.S.
% of cores with Ca Mean (range)	34.99 (13-100)	37.47 (13-100)	N.S.
Disease bilaterality 1 lobe 2 lobes	 107 (71.8%) 42 (28.2%)	 60 (65.2%) 32 (34.8%)	N.S.
Ca % in dominant lobe Mean (range)	48.18 (5-100)	43.65 (5-100)	N.S.
Pathological stage T2 T3	 136 (91.3%) 13 (8.7%)	 63 (68.5%) 29 (31.5%)	<0.001
Clinical stage T1 T2	 128 (85.9%) 21 (14.1%)	 77 (83.7%) 15 (16.3%)	N.S.

dominant lobe, prostate weight, PSA density and disease bilaterality were used for statistical analysis as potential predictors. Statistical difference between upgraded and non-upgraded patient groups was considered significant at $p < 0.05$. Calculations were performed using SPSS version 14.0.

RESULTS

241 patients were included in to the study during 2002-2007. Median patient's age was 66.0 years (mean – 64.5, range (46-77)), median PSA was 6.7 ng/ml (mean – 8.2, range (0.7-50.2)), and median prostate surgical specimen's weight was 49.0gm (mean – 54.7, range (20-211)). Sextant laterally directed biopsies were performed in 198 (82.2%), 7-8 cores were taken in 40 (16.6%) and ≥8 in 3 (1.2%) of cases. One cancer positive biopsy core was detected in 87 (36.1%), 2 cores in 81 (33.6%), 3 cores in 34 (14.1%), ≥4 in 39 (16.2%), and mean positive cores number was 2.24.

Of the 241 patients with biopsy GS 6, postoperatively GS was 6 in 149 (61.8%), 7 in 87 (36.1%) and 8 in 5 (2.1%) of cases. Overall upgrading rate in the study population was 38.2% (92 of 241). No downgrading was observed in our study.

Table 1 shows contribution of investigated clinical parameters in the 92 (38.2%) patients when GS was upgraded after surgery and in 149 (61.8%) when it was not.

The upgraded and no upgraded patient groups were similar in age, PSA, clinical stage, taken biopsy cores number, biopsy cores with cancer number, percentage of biopsy cores with cancer, disease bilaterality and percentage of cancer in dominant lobe. However, the group of upgraded patients was different according prostate weight ($p < 0.001$), PSA density ($p = 0.006$) and pathological stage ($p < 0.001$). In upgraded patients, the prostate weight was significantly lower. Despite that PSA was similar in both groups, the PSA density was higher in upgraded patients. GS upgrading associated more significantly with extra capsular extension (T3) than with organ confined (T2) disease (Table 1).

Percentage of the cancer in dominant lobe had a tendency to be greater in not upgraded patients but did not reach significant level ($p = 0.099$). Other preoperative PCa volume indicators as well as positive cores number, percentage of positive cores or disease bilaterality did not provide any additional information about probability of GS upgrading.

Multivariate logistic regression analysis was done using all preoperative parameters as potential predictors for upgrading. Percentage of PCa in dominant lobe was a moderately significant predictor for GS upgrading (OR 0.989, $p = 0.043$, 95% CI 0.979-1.00). The strongest predictor for upgrading was prostate weight – OR 0.981, $p = 0.006$ (95% CI 0.981-0.968).

As for assessing the predictive role of observed predictors for upgrading, the ROC curves were constructed. Prostate weight and PSA density (AUC 0.634, $p < 0.0001$ and 0.604, $p = 0.006$ respectively) were only two significant parameters (Fig. 1). The cut-off level for significant parameters was 47.5 gr. (prostate weight) and 0.135 (PSA density) with 60% sensitivity and specificity.

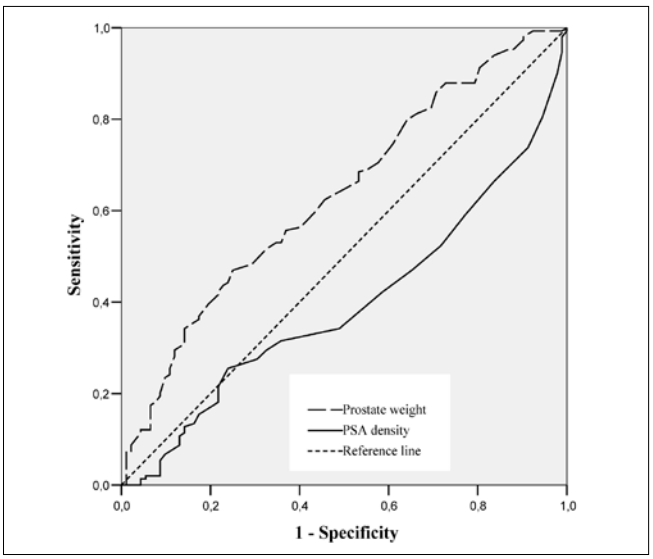

Fig. 1. Receiver operating characteristics (ROC) curves of prostate weight and PSA density for predicting Gleason score upgrading.

Among study population, 42 (17.4%) showed extra capsular extension at examination of specimens after RP. When comparing groups with and without GS upgrading after surgery, GS upgrading was observed to be accompanied by significantly higher rates of extra capsular extension ($p < 0.001$). In 9 patients (3.7%) seminal vesicle invasion and in all those T3b cases GS upgrading were detected (Chi square test 10.18, $p = 0.002$). Positive lymph nodes if dissection was performed were found in 4 (1.7%) cases – 3 in upgraded and 1 in not upgraded groups.

DISCUSSION

GS on transrectal ultrasound guided biopsy is an important parameter for some reasons. It is an independent outcome predictor for localized PCa [10]. Accordingly, biopsy GS patients are categorized to low or intermediate risk groups what is an important factor for making further less aggressive treatment decision, such as watchful waiting [11] or standard brachytherapy [12]. On the other hand, tumor grade 7 may trigger supplemental interventions, such as the addition of hormonal therapy to external beam radiation or a pelvic lymph node dissection at RP [13, 14]. We should agree that ability to predict GS accurately has been poor. It confirms high degree of discordance between the biopsy and surgery GS that was from 55% to 72%, as reported by King [15]. Recent studies show less discordance, but only a few of them reached upgrading lower than 30% [9]. In an effort to reduce discordance as well as improve the PCa detection rate, the standard sextant biopsy was recently changed to more extended scheme at most centers [16,17,18]. Some studies clearly show that accuracy of post operative GS detection is better using extended biopsy scheme [19, 20, 21]. In most cases (82.2%) of our study the laterally directed biopsy scheme was used, but concordance of GS was 61.8% which is similar to 68% reported by Mian B.M at extended biopsies [19]. The importance of additional sampling was also analyzed by Dong et al. [5]. The authors proved that using extended biopsy scheme the upgrading from GS 6 remained very high – 50% and study results did not support the fact that extended biopsies improve grading accuracy. The impact of extended biopsies on upgrading still causes some doubt if we look at positive cores number detected at sextant or extended biopsies that provide information about cancer volume. In our study population, the mean cores with PCa was 2.24 (2.16 in non upgraded group *vs.* 2.36 at upgraded one) and median 2.0. The same positive cores number was detected in studies using extended biopsies; however, in most studies such data are not presented [19]. Even 12 cores biopsy scheme study results presented by Hong et al. with low risk PCa patient's population showed the upgrading rate up to 40% and median positive cores number in upgraded patients was 2 [22]. It shows that extended biopsies do not always correlate with median positive cores number and with increasing concordance of GS. In our study positive cores number correlated significantly with prostate weight ($r = -0.139$, $p = 0.031$) but not with all cores number taken ($r = 0.104$, $p = 0.108$). We agree with findings of Dong et al. that the extended number of cores does not improve grading accuracy, and there are some more important indicators to predict the aggressiveness of PCa at biopsy [5].

Biopsy cancer volume has been proved to correlate with pathological stage and biochemical relapse following RP [23, 24]. Despite that the role of amount of cancer in predicting GS upgrading remains controversial. In some studies it is not a predictive parameter; however, the results of other recent studies confirm the predictive role of cancer volume on GS upgrading [5, 19, 22, 25-28]. Discrepancies in these results may be related to patient's characteristics or statistical power. In our study, only percentage of cancer in dominant lobe as well as prostate weight has significant power in multivariate logistic regression. As a single independent predictor, this parameter did not reach statistically significant level.

There are a few studies where the prostate volume or weight was detected as significant predictors for postoperative GS upgrading. Some studies show that small prostate gland size has been associated with biochemical progression after surgery or brachytherapy [29, 30]. Our study results show that prostate weight was different in upgraded and not upgraded groups, and this parameter was the most powerful for prediction of more aggressive PCa (Gleason ≥7, ≥T3a) at logistic regression analysis. Our results suggest that there is some biological difference between cancer in small and large prostates which points out that prostate weight should be taken into account before treatment modalities of cancer are chosen. The cut off level for significant probability to upgrade GS from 6 to 7 (with 62% sensitivity and 60% specificity) in our study was 47.5 gr.

The importance of PSA level on prediction of GS upgrading still remains controversial. In general high preoperative PSA has been correlated with upgrading, although the results of some studies do not support such findings [19, 25, 26]. In our study, we did not observe difference in PSA value between upgraded and not upgraded cases, but PSA density was one of a few characteristics that were significantly different in estimated groups. AUC for this parameter was 0.604 ($p = 0.006$) and cut off level was 0.135 (with 60% sensitivity and 60% specificity). Patients with larger prostates tend to have higher PSA level because of increased reproduction of benign hyperplastic cells. Increased PSA level in smaller glands suggests that PCa likely to be more aggressive. We believe that PSA remains one of the most important PCa predictors, but in prediction of GS upgrading the PSA density seems to be the most important one.

This study is limited by its retrospective design and its location at a single center but on the other hand, the biopsy and surgery at 1 institution minimize referral bias. Sextant biopsy in the temporary era of more extended biopsy schemes seems as study limitation, but detected positive cores number and percentage of upgrading 38.2 are comparable to literature data. Despite potential limitations, this study identifies risk parameters for upgrading of patients diagnosed with GS 6 prostate cancer. Patients at high risk for pathological upgrading may benefit from more extended RP because of increased likelihood of locally advanced disease. Patients with low risk for upgrading could be real candidates for less invasive treatment. Future studies with different biopsy schemes and long follow up after surgery would be needed to establish exact importance of detected significant parameters for upgrading.

CONCLUSIONS

Our results show that up to 40 percent of patients with GS 6 at biopsy may have upgrading following RP. PSA density and especially prostate weight may be useful predictors for identifying those patients with increased risk of GS upgrading which was observed to be significantly associated with adverse pathological features such as extra prostatic extension or seminal vesicle invasion.

REFERENCES

1. Gleason DF: *Histologic grading of prostate cancer: a perspective*. Hum Pathol 1992; 23: 273-279.
2. Chun FK, Briganti A, Graefen M, Montorsi F, et al: *Development and external validation of an extended 10-core biopsy nomogram.* Eur Urol 2007; 52: 436-444.
3. Sved PD, Gomez P, Manoharan M, et al: *Limitations of biopsy Gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer.* J Urol 2004; 172: 98-102.
4. Pinthus JH, Witkos M, Fleshner NE, et al: *Prostate cancers scored as Gleason 6 on prostate biopsy are frequently Gleason 7 tumors at radical prostatectomy: implication on outcome*. J Urol 2006; 176: 979-984.
5. Dong F, Jones JS, Stephenson AJ, et al: *Prostate volume at biopsy predicts clinically significant upgrading.* J Urol 2008; 179: 896-900.
6. Thickman D, Speers WC, Philpott PJ, Shapiro H: *Effect of the number of core biopsies of the prostate on predicting Gleason score of prostate cancer.* J Urol 1996; 156: 110-113.
7. Garnett JE, Oyasu R, Grayhack JT: *The accuracy of diagnostic biopsy specimens in predicting tumor grades by Gleason's classification of radical prostatectomy specimens.* J Urol 1984; 131: 690-693.
8. Cookson MS, Fleshner NE, Soloway SM, Fair WR: *Correlation between Gleason score of needle biopsy and radical prostatectomy specimen: accuracy and clinical implications.* J Urol 1997; 157: 559-62.
9. Gofrit ON, Zorn KC, Taxy JB, et al: *Predicting the risk of patients with biopsy Gleason score 6 to harbor a higher grade cancer.* J Urol 2007; 178: 1925-8.
10. Graefen M, Karakiewicz PI, Cagiannos I, et al: *International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy.* J Clin Oncol 2002; 20: 3206-3212.
11. Carter HB, Walsh PC, Landis P, Epstein JI: *Expectant management of nonpalpable prostate cancer with curative intent: preliminary results.* J Urol 2002; 167: 1231-1234.
12. D'Amico AV, Whittington R, Malkowicz SB: *Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer.* JAMA 1998; 280: 969-674.
13. D'Amico AV, Schultz D, Loffredo M et al: *Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for clinically localized prostate cancer.* JAMA 2000; 284: 1280-1283.
14. Conrad S, Graefen M, Pichlmeier U et al: *Prospective validation of an algorithm with systematic sextant biopsy to predict pelvic lymph node metastasis in patients with clinically localized prostatic carcinoma.* J Urol 2002; 167: 521-525.
15. King CR: *Patterns of prostate cancer biopsy grading: trends and clinical implications.* Int J Cancer 2000; 90: 305-311.
16. Mian BM, Naya Y, Okihara K, et al: *Predictors of cancer in repeat extended multisite prostate biopsy in men with previous negative extended multisite biopsy.* Urology 2002; 60: 836-840.
17. Babaian RJ, Toi A, Kamoi K, et al: *A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy.* J Urol 2000; 163: 152-157.
18. Gore JL, Shariat SF, Miles BJ, et al: *Optimal combinations of systematic sextant and laterally directed biopsies for the detection of prostate cancer.* J Urol 2001; 165: 1554-1559.
19. Mian BM, Lehr DJ, Moore CK, et al: *Role of prostate biopsy schemes in accurate prediction of Gleason scores.* Urology 2006; 67: 379-383.
20. Makhlouf AA, Krupski TL, Kunkle D, Theodorescu D: *The effect of sampling more cores on the predictive accuracy of pathological grade and tumour distribution in the prostate biopsy.* BJU Int 2004; 93: 271-274.
21. San Francisco IF, DeWolf WC, Rosen S, et al: *Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy.* J Urol 2003; 169: 136-140.
22. Hong SK, Han BK, Lee ST, et al: *Prediction of Gleason score upgrading in low-risk prostate cancers diagnosed via multi (> or = 12)-core prostate biopsy.* World J Urol 2009; 27: 271-276.
23. Freedland SJ, Aronson WJ, Terris MK et al: *SEARCH Database Study Group. Percent of prostate needle biopsy cores with cancer is significant independent predictor of prostate specific antigen recurrence following radical prostatectomy: results from SEARCH database.* J Urol 2003; 169: 2136-2141.
24. Sebo TJ, Bock BJ, Cheville JC, et al: *The percent of cores positive for cancer in prostate needle biopsy specimens is strongly predictive of tumor stage and volume at radical prostatectomy.* J Urol 2000; 163: 174-178.
25. Carlson GD, Calvanese CB, Kahane H, Epstein JI: *Accuracy of biopsy Gleason scores from a large uropathology laboratory: use of a diagnostic protocol to minimize observer variability.* Urology 1998; 51: 525-529.
26. Kojima M, Troncoso P, Babaian RJ: *Use of prostate-specific antigen and tumor volume in predicting needle biopsy grading error.* Urology 1995; 45: 807-12.
27. Freedland SJ, Kane CJ, Amling CL, et al: *SEARCH Database Study Group. Upgrading and downgrading of prostate needle biopsy specimens: risk factors and clinical implications.* Urology 2007; 69: 495-499.
28. Park HK, Choe G, Byun SS, et al: *Evaluation of concordance of Gleason score between prostatectomy and biopsies that show more than two different Gleason scores in positive cores.* Urology 2006; 67: 110-114.
29. Freedland SJ, Isaacs WB, Platz EA, et al: *Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: A search databased study.* J Clin Oncol 2005; 23: 7546-7554.
30. Quan AL, Ciezki JP, Reddy CA, et al: *Improved biochemical relapse-free survival for patients with large/wide glands treated with prostate seed implantation for localized adenocarcinoma of prostate.* Urology 2006; 68: 1237-1241.

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