A Comparative Analysis of Primary and Secondary Gleason Pattern Predictive Ability for Positive Surgical Margins after Radical Prostatectomy

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Abstract: To compare the predictive ability of primary and secondary Gleason pattern for positive surgical margins in patients with clinically localized prostate cancer and a preoperative Gleason score ≤6. A retrospective analysis of the medical records of patients undergone a radical prostatectomy between January 2005 and October 2010 was conducted. Patients' age, prostate volume, preoperative PSA, biopsy Gleason score, the 1st and 2nd Gleason pattern were entered a univariate and multivariate analysis. The 1st and 2nd pattern were tested for their ability to predict positive surgical margins using receiver operating characteristic curves. Positive surgical margins were noticed in 56 cases (38.1%) out of 147 studied patients. The 2nd pattern was significantly greater in those with positive surgical margins while the 1st pattern was not significantly different between the 2 groups of patients. ROC analysis revealed that area under the curve was 0.53 ($p=0.538$) for the 1st pattern and 0.60 ($p=0.048$) for the 2nd pattern. Concerning the cases with PSA <10 ng/ml, it was also found that only the 2nd pattern had a predictive ability ($p=0.050$). When multiple logistic regression analysis was conducted it was found that the 2nd pattern was the only independent predictor. The second Gleason pattern was found to be of higher value than the 1st one for the prediction of positive surgical margins in patients with preoperative Gleason score ≤6 and this should be considered especially when a neurovascular bundle sparing radical prostatectomy is planned, in order not to harm the oncological outcome.

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Introduction

Prostate cancer is the most common form of cancer and the second leading cause of cancer death among men. In 2010, an incidence of slightly less than 217,000 new cases and mortality of around 32,000 is expected in USA (Jemal et al., 2010).

Gleason grading system is widely accepted for evaluation of the prostate adenocarcinoma grade (Gleason and Mellinger, 1974). During pathological examination of cores, obtaining by prostate biopsy, the primary and second most prevalent architectural patterns are identified and assigned a grade from 1 to 5. Grade 1 is the most differentiated and 5 is the least. The addition of these 2 grades results in Gleason score (GS).

Radical prostatectomy (RP) is the treatment standard for patients with localized prostate cancer and a life expectancy more than 10 years. Positive surgical margins (PSM), as a result of artefacts induced by tissue processing, incising inadvertently into the prostate or incising into extraprostatic tumor that has extended beyond the limits of resection, increase the risk of biochemical and disease progression (Wieder and Soloway, 1998; Pfitzenmaier et al., 2008). Prostate specific antigen (PSA) or local recurrence rate and the development of distant metastasis are much higher in patients with PSM than in patients with negative margins.

Several pre-operative factors like patient's age, PSA, clinical stage and GS have been associated with PSM (Cheng et al., 2000; Liss et al., 2008; Ficarra et al., 2009). However, no available data is addressing the potential role of GS primary and secondary pattern separately for PSM prediction.

The aim of this study was to determine and compare the impact of each Gleason pattern for prediction of PSM in patients undergoing RP.

Material and Methods

In this retrospective study, we evaluated data from patients who underwent RP in our clinic from January 2005 until October 2010. All had preoperative GS ≤6. Patients with incomplete records and patients with prior therapy for prostate cancer or prior surgical therapy for benign prostate hypertrophy were excluded. All patients had clinically localized disease, determined by digital rectal examination and transrectal ultrasound, with negative staging examinations (abdominal and pelvic computer tomography, bone scan).

A prior operation prostate biopsy during a transrectal ultrasound was performed. Dominant, predominant and total GS of biopsy cores were analysed by experienced pathologists and information about the number of biopsy cores and percentage of positive for malignancy material obtained by the prostate biopsy were collected. The prostate size was calculated, by obtaining information according the maximum transverse diameter (D1), the maximum anteroposterior diameter (D2) and the maximum longitudinal diameter (D3) and by using the formula $D1 \times D2 \times D3 \times \pi/6$ based on the prostate ellipse dimension theory.

A retropubic RP by open or laparoscopic technique was performed in all patients. In those with preoperative clinical stage T1-T2a and intraoperative observation of non extraprostatic disease, an intrafascial or interfascial neurovascular bundle sparing procedure, bilateral (cT1 or unilateral (cT2a), was performed. The surgical specimen was fixed in neutral buffered 4% formaldehyde and was analysed by experienced pathologists in our institution. GS, tumor stage and grade were determined according to the 2002 TNM (tumor, node and metastasis) classification for prostate cancer. Statistical analyses were conducted using STATA statistical software (version 8.0). All p-values reported are two-tailed. Statistical significance was set at 0.05. Quantitative variables are presented with mean (standard deviation, SD) or median (interquartile range, IQR). Qualitative variables are presented with absolute and relative frequencies. For the comparisons of proportions the Fisher's exact test was used. If the normality assumption was satisfied for the comparison of means between two groups, Student's *t*-tests were used. Mann-Whitney test was used for the comparison of not normal variables between two groups. 1st and 2nd pattern were tested for their ability to predict PSM using receiver operating characteristic (ROC) curves. The overall performance of the ROC analysis was quantified by computing area under the curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was not different than chance. Using ROC analysis was determined the optimal sensitivity and specificity of using various cut-off values for the prediction of PSM. For the comparison of the predictive ability of different factors, logistic regression models were used in order to derive linear predictions and AUC for each model. The comparison of areas under the curve indicates which model is the best for the prediction of outcome measures. In order to find independent factors associated with PSM, multiple logistic regression analysis was performed. Adjusted odds ratios with 95% confidence intervals were computed from the results of the logistic regression analyses. Model diagnostics were evaluated using the Hosmer and Lemeshow statistic.

Results

Sample consisted of 147 patients with GS ≤6. Sample characteristics are presented in Table 1. The mean age of the patients was 66.1 years (SD = 6.4 years). PSM were found in 56 patients (38.1%). The median prostate volume was 40 ml (interquartile range: 30–60). Both the 1st and 2nd pattern had median value equal to 3 (interquartile range: 3–3). Table 2 describes the study variables for those with negative and positive surgical margins. Patients with PSM had significantly higher PSA and GS. The proportion of patients with PSA >10 ng/ml was greater in patients with PSM. Also, the 2nd pattern was significantly greater in those with PSM. The 1st pattern was not significantly different between the two groups of patients. Consistent with the aforementioned results ROC analysis showed that only the 2nd pattern had predictive ability for PSM. AUC was 0.53 (95% CI:

Table 1 – Sample characteris

Age (years), mean (SD)		66.1 (6.4)
Prostate volume (ml), median (IQR)		40.0 (30.0–60.0)
PSA (ng/ml), median (IQR)		8.2 (6.7–10.7)
PSA (ng/ml), n (%)	<4	3.0 (2.0)
	4–10	103.0 (70.1)
	>10	41.0 (27.9)
% of cancer in biopsy cores, mean (SD)		20.0 (10.0–34.1)
Gleason score, mean (SD)		6.0 (5.0–6.0)
Gleason score, n (%)	2	2.0 (1.4)
	3	9.0 (6.1)
	4	10.0 (6.8)
	5	26.0 (17.7)
	6	100.0 (68.0)
1st pattern, mean (SD)		3.0 (3.0–3.0)
1st pattern score, n (%)	1	2.0 (1.4)
	2	32.0 (21.8)
	3	113.0 (76.9)
2nd pattern, mean (SD)		3.0 (3.0–3.0)
2nd pattern score, n (%)	1	11.0 (7.5)
	2	25.0 (17.0)
	3	109.0 (74.1)
	4	2.0 (1.4)
Surgical margins, n (%)	negative	91.0 (61.9)
	positive	56.0 (38.1)

SD – standard deviation; IQR – interquartile range; PSA – prostate specific antigen; n – number of patients

Table 2 – Association of study variables with surgical margins

	Surgical margins		
	negative / median (IQR)	positive / median (IQR)	p Mann-Whitney
Age (years), mean (SD)	65.3 (6.5)	67.4 (6.1)	0.054*
Prostate volume (ml)	42.0 (30.0–65.0)	40.0 (30.0–57.5)	0.491
PSA (ng/ml)	8.0 (6.3–10.0)	8.8 (7.6–12.5)	0.014
PSA, n (%)			
<4	3.0 (3.3)	0.0 (0.0)	0.027**
4–10	69.0 (75.8)	34.0 (60.7)	
>10	19.0 (20.9)	22.0 (39.3)	
% of cancer in biopsy cores	20.0 (10.0–30.0)	22.3 (10.0–40.0)	0.320
Gleason score	6.0 (5.0–6.0)	6.0 (6.0–6.0)	0.029
1st pattern	3.0 (2.5–3.0)	3.0 (3.0–3.0)	0.400
2nd pattern	3.0 (2.0–3.0)	3.0 (3.0–3.0)	0.011

*Student's *t*-test; **Fisher's exact test; abbreviations like Table 1

0.46–0.60, p=0.538) for 1st pattern and 0.60 (95% CI: 0.53–0.66, p=0.048) for the 2nd pattern, as seen in Figure 1. ROC curve analysis showed that the optimal-cut off of the 2nd pattern for the prediction of PSM was 3 with sensitivity equal to 85.7%, specificity equal to 30.8, positive and negative predictive values equal to 33.9% and 60.9%, respectively. GS had also a good predictive ability with AUC equal to 0.59 (95% CI: 0.52–0.66, p=0.049). The predictive ability of GS was superior as compared with the correspondence ability of the 1st pattern (p=0.019), but similar as compared with the correspondence ability of the 2nd pattern (p=0.896). Concerning the cases with PSA <10 ng/ml (n=106) it was also found that only the 2nd pattern had a predictive ability for PSM. The AUCs were 0.56 (95% CI: 0.48–0.64, p=0.321) and 0.59 (95% CI: 0.51–0.67, p=0.050), for 1st and the 2nd pattern, respectively. When multiple logistic regression analysis was conducted with dependent the variable represents PSM (Table 3) it was found that the 2nd pattern was the only independent predictor. Adjusting for age, prostate volume, PSA, percentage of cancer in biopsy cores and the 1st pattern it was found that for one unit increase in the 2nd pattern the likelihood for positive surgical margins

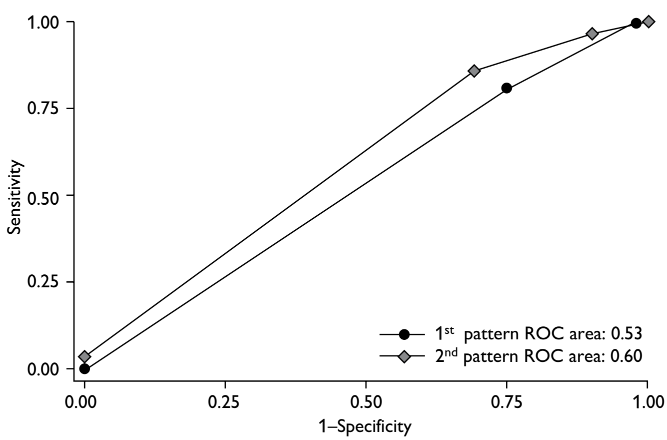

Figure 1 – ROC curve for the prediction of positive surgical margins from the 1st and 2nd Gleason pattern.

Table 3 – Odds ratios and 95% confidence intervals derived from multiple logistic regression analysis with dependent variable the surgical margins

	OR (95% CI)	P
Age (years)	1.05 (0.98–1.11)	0.149
Prostate volume (ml)	0.99 (0.98–1.01)	0.262
PSA (ng/ml)	1.02 (0.97–1.08)	0.493
% of cancer in biopsy cores	1.03 (0.97–1.09)	0.287
1st pattern	1.40 (0.64–3.07)	0.395
2nd pattern	2.01 (1.04–3.89)	0.038

OR – odds ratio; CI – confidence interval; PSA – prostate specific antigen increases 2.01 times. The results were similar when the 2nd pattern was included in the multiple analysis as binary variable using the cut-off provided by the ROC analysis. The adjusted odds ratio for the 2nd pattern more than 3 was 2.74 (95% CI: 1.02–7.37, p=0.045).

Discussion

The major oncologic principle of RP is the complete elimination of the malignant disease and it provides the best chance to cure localized prostate cancer. However, its accomplishment is challenging because of the close anatomic relationships of the organs within the pelvis. Despite advances in knowledge of pelvic anatomy with subsequent refinements in surgical techniques, on average, almost 30% of patients who undergo RP for clinically localized disease still have PSM (Watson et al., 1996; Wieder and Soloway, 1998). Cancer in the surgical margin has been shown to be a significant independent adverse factor associated with a greater risk of biochemical, local, and systemic progression (Catalona and Smith, 1994; Watson et al., 1996; Cheng et al., 1999).

In a series of 377 patients who had RP for localized prostate cancer, it was found that surgical margin status increased the risk of biochemical progression independently of extraprostatic extension and the 5-year progression-free survival was 90% and 78% for negative and positive surgical margins, respectively (Catalona and Smith, 1994). Another study reported a 10-year progression-free survival of 79% and 55% for patients with negative and positive surgical margins, respectively. This is a difference that remained statistically significant even when patients with seminal vesicle invasion were excluded (Epstein et al., 1993).

The above mentioned value of surgical margin status appeals clinically important in planning treatment especially for those patients being considered for a nerve-sparing procedure, a subgroup nowadays with a continuously increasing number. PSA-based prostate cancer screening has led to a significant downward stage migration. As a result, the significant majority of men present with well-differentiated cancers of low clinical stage and most are candidates for bilateral neurovascular bundle preservation (Etzioni et al., 2008). Furthermore, the recent American Urological Association guidelines recommend to start patients' screening at the age of 40 and to consider performing a prostate biopsy in patients with PSA >2.5 ng/ml (Greene et al., 2009). These trends may result in an increasing number of relatively young patients with small prostates and low-risk tumors presenting for RP performed with bilateral nerve preservation. In this low grade group of patients, in which more conservative means of treatment are in mind, it would be very useful if we could preoperatively predict the surgical margin status.

Reviewing the literature, several studies have tried to assess directly preoperative variables for prediction of surgical margins (Ackerman et al., 1993; Partin et al., 1993). GS, PSA level and clinical stage have been demonstrated to be the major factors directly related to the presence of a PSM. For instance, Ackerman et al. (1993) showed that the number of positive biopsies, preoperative serum PSA level, and PSA density were all significant predictors of margin status in univariate analysis. Additionally, biopsy GS were also associated with margin status. Multivariate analysis identified the number of positive cores obtained by the prostate biopsy as the most significant predictor of margin status. In our study, we also found that preoperative PSA level (p=0.014) and biopsy GS (p=0.029) were predictive of margin status in the univariate analysis. Furthermore, in other studies it has been suggested that age (Liss et al., 2008), the surgeon experience (Atug et al., 2006) and body mass index (Herman et al., 2007; Castle et al., 2008) should be considered when analyzing the incidence of PSM during RP. From these factors we found age being marginally associated with surgical margin status (p=0.054). Unilateral cancer on biopsy might be a valuable factor of negative surgical margins prediction. This was confirmed by the results of a contemporary study (Iczkowski et al., 2008), in which unilateral cancer status, based on the results of prostate biopsy, are among the strongest predictors of negative surgical margins after radical prostatectomy (OR, 2.53; positive predictive value, 82%).

Undoubtedly, biopsy GS has been one of the most well studied pre-operative factors associated with PSM. However, based in our knowledge there is a scientific gap in the literature so far concerning the individual role of each Gleason pattern in prediction of adverse pathology regarding cancer at the site of the surgical margins. Our analysis results demonstrate a statistically significant predictive role of the 2^{nd} Gleason pattern. In the multivariate analysis which conducted for the whole population of studied patients, the 2^{nd} Gleason pattern was the only independent predictive parameter that revealed significance among those which entered the analysis. Actually, its value was higher than the ones of PSA, prostate volume, percentage of cancer in biopsy material and patients' age. It was especially interesting and of high scientific value that 1^{st} Gleason pattern was unable to reach significance, as well (p=0.395).

Concerning the cases with preoperative PSA <10 ng/ml, the 2^{nd} Gleason pattern found to have a significant predictive role (p=0.050) for PSM in contrast to 1^{st} Gleason pattern which showed no significance (p=0.321). These specific results are of great value, since a large number of patients who undergone RP have been diagnosed with PSA values <10 ng/ml.

Several limitations to our study should be mentioned. Our study used the results of pathological analysis of biopsy cores made by different anatomists. Therefore, we believe that inter-observer variability in obtaining tumor grade might be built into the study results and allows these results to be generalized. The assessment of preoperative Gleason score was determined according to the older fashion grading system. The results of the present study, even significant, might alter if the conclusions of the ISUP 2005 conference (Epstein et al., 2005) are used. For this reason, design of new studies, assessing the impact of primary and secondary Gleason pattern in prediction of PSM, by using the modern grading classification system is mandatory for confirming or capsizing the present results. Furthermore, we should mention that we are aware about the statistical results, since they are a little less powerful than the standard.

Nowadays, neurovascular bundle spare during RP is the standard operative differentiation for patients previously potent that have low risk disease (PSA <10 ng/ml, GS ≤6 and clinical stage T1c-T2a) and are interested in preserving sexual function after surgery. However, since the goal of RP is primarily the eradication of the malignant disease, predictors that can preoperatively estimate the possibility for PSM are of great concern in order not to harm the oncological outcome. This is the first study to reveal the significant role of 2nd Gleason pattern in PSM prediction and these data should be considered when a nerve sparing RP is planned.

Conclusion

Results of the present study demonstrate higher predictive significance of the 2nd Gleason pattern in comparison with the primary one in patients with GS ≤6. It was confirmed in patients with varying PSA values and in patients with preoperative PSA ≤10 ng/ml. It can be of great concern especially in our days, where the trends in prostate cancer diagnosis have resulted an increase in the number of patients with small prostates and low risk tumors presenting for RP with neurovascular bundle preservation.

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