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Research Article

# Analysis of Functional Pattern Gleason 5 as Risk Factor for Biochemical Recurrence in Patients with Gleason Pattern 7 Group 2 E 3, Prostate Adenocarcinoma -

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## ABSTRACT

**Introduction:** Biochemical recurrence after radical prostatectomy has been associated with Gleason pattern 5(GP5) and Prostatic Specific Antigen (PSA) is a sensitive marker of relapse. Was analyzed the correlation between the Gleason score 7(group 2 e 3), pattern Gleason 5, biochemical recurrence and its correlation with other adverse histological findings.

**Material and Methods:** Historic cohort comprising 219 patients, subjected to score 7 radical prostatectomy with acinar adenocarcinoma and GP5 represents 5% or less of tumor size. Recurrence was determined as postoperative PSA less or equal 0.2/ ml in the second post-prostatectomy assessment. Were considered as significant value of $p <$ or equal to 0,005. All statistical analysis were conducted using the SPSS (SPSS Inc: released 2009, version 18.0, Chicago, IL, USA).

**Results:** Of Patients Gleason score 7 and follow-up PSA 25.9% showed GP5. These 38% had biochemical relapse and the five year survival was 77.8%. Of 74.1% that not showed GP5 24.2% biochemical relapse with the five survival of 91.7%. In the bivariate analysis, seminal vesicle invasion and preoperative PSA have statistical significance. In multiple cox regression GP5 was no longer significance with of $p$ 0. 57.

**Discussion:** Studies demonstrated risk of recurrence for patients with GP5. Identified correlation between biochemical relapse and seminal vesicle invasion and preoperative PSA. GP5 has no impact as an independent predictive factor in the multivariate analysis probably due to the size of the sample. The combination with others variables is necessary.


**Keywords:** Prostate adenocarcinoma; Gleason score; Biochemical recurrence

## INTRODUCTION

Prostatic adenocarcinoma is the sixth most common type of cancer in the world and second most prevalent in men. In Brazil the number of new cases estimed for 2018 is 68,200 (Instituto Nacional do Câncer) and the increased use of Prostatic Specific Antigen (PSA) significantly increases the number of cases detected [1,2].

One of the most clinical application of serum prostatic antigen is for detecting prostate cancer recurrence after radical prostatectomy. Studies have demonstrated recurrence of disease in 15-44% of patients [3].

In radical prostatectomy specimens, Gleason score 7 is among the most commonly assigned scores for prostate carcinoma accounting for 30%-50% of cases [4]. Nevertheless, Gleason score 7 tumors are heterogeneous and the Gleason Pattern 5 (GP5) is associated with biochemical relapse. The score of Gleason is especially important for recurrence biochemical and survival, and the GP5 less or equal a 5 represents a small component of a more aggressive grade presenting which is not included in the score but influence the disease prognoses. The amount of GP5 increasing the final score by one point more [5-7]. The International Society of Urological Pathology (ISUP 2016) recommended that biopsy Gleason score by adding GP5 to the primary grade [8].

The detection of PSA is a sensitive marks of biochemical relapse, having been associated with other predictive factors for recurrence: stage pathological, surgical margin, vesicles seminal invasion and preoperative PSA [9,10].

To determine the correlation between the Gleason score7, GP5 less or equal a 5 and biochemical relapse free survival was analyzed compared patients with GP5 and patients without GP5.

The aim of our study is to evaluate the importance of the tertiary Gleason 5 standard for the post radical prostatectomy prognosis, to determine the influence of pattern 5 on the patient's evolution by biochemical relapse and to characterize normograms with adverse histological parameters: extra-prostatic invasion, seminal vesicles and margins, and lymph node metastases.

## MATERIAL AND METHODS

The study comprised a retrospective cohort and was conducted at the Irmandade Santa Casa de Misericórdia de Porto Alegre Hospital Complex and the Faculdade de Ciências da Saude de Porto Alegre, RS, Brazil, in the period from January 2000 to December 2005. A total of 219 patients subjected to radical retropubic prostatectomy diagnose with Gleason score 7 (3+4 and 4+3) conventional acinar adenocarcinoma were reviewed. The presence of GP5 findings was estimated as a percentual less than 5% of the tumor volume, examined by two pathologists based on slides with hematoxilin-eosin at magnification at 20x-40x. The recurrence status was determined by the PSA test, considering the second dosing in the postoperative period.

Patients who were followed by serial serum PSA concentration was under the detection limit of a regular assay (less or equal 0.2 ng/ ml) in the post chirurgical. Relapse biochemical was assessed using cox regression with 95% confidence intervals and biochemical relapse-free survival by the Kaplan Meyer curve and Log Rank analysis.

Surgical time was defined as the time interval between the date of surgery and the last serum specimen collected in the study for PSA test or in the second post-prostatectomy assessment.

The categorical variables considered were surgical margins, extraprostatic extension, seminal vesicle invasion, Gleason score, preoperative PSA and GP5. Absolute and frequencies were used.

For the continuous variables such as age and PSA, men, median and interquartile deviation were used.

Were considered as significant value of $p <$ or equal to 0.005.

All statistical analysis were conducted using the SPSS (SPSS Inc: released 2009, version 18.0, Chicago, IL, USA).

This research was approved by the committee of ethics and research of the Federal University of Health Sciences of Porto Alegre under opinion number 1128/ 10; cadastro 635/ 10. Follow the guidelines for research on humans.

## RESULTS

The median age of the patients in the series was 65 years taking into account the date prostatectomy, with standard deviation of 8,4.

Among the 219 patients with Gleason score 7 and follow-up PSA, 42 (25.9%) showed Gleason pattern 5 and of these 38% had experienced biochemical relapse, and 120 (74.1%) not showed GP5 and these, 24.2% had biochemical relapse. Were excluded 57 patients after review of Gleason grade migration for 6 or 10.

A median PSA follow-up was 102 months.

Patients GP 5 was associated with biochemical relapse using the cox regression calculation with risk at a HR = 1.83 (95% CI: 0.99-3.38). Patients with GP5 had biochemical relapse in 32% dos cases and 20.3% showed extra prostatic and seminal vesicle invasion.

The median follow-up for PSA was 59 months.

For patients with Gleason 5 standard, five-year survival was 77.8% and, at 10 years, 43%, considering the Log Rank test with $p$ 0.004. Five-year survival in patients without GPT was 91.7% (figure 1).

In the bivariate analysis the categorical variables seminal vesicle invasion at ($p$ = .017) and Pre-operative PSA ($p$ = 0.053) were significant for biochemical relapse risk. The remaining variables in the group did not have any significance for biochemical relapse risk: Circumferential surgical margin ($p$ = .34), urethral surgical margin ($p$ = .41), extra prostatic extension ($p$ = .18).

In a multiple the cox regression a presence of a Gleason pattern 5 with $p$ 0.57 was limited and therefore we can not state in our research that it represents a predictive factor probably due to the size of the sample.

## DISCUSSION

The Gleason grading system introduced in the 1960 s is still used nowadays by pathologists for grading prostatic cancer. However due to tumor heterogeneity with variable degrees of differentiation and the presence of Gleason pattern 5 confers more aggressive tumor it has been associated with biochemical relapse [5,6].

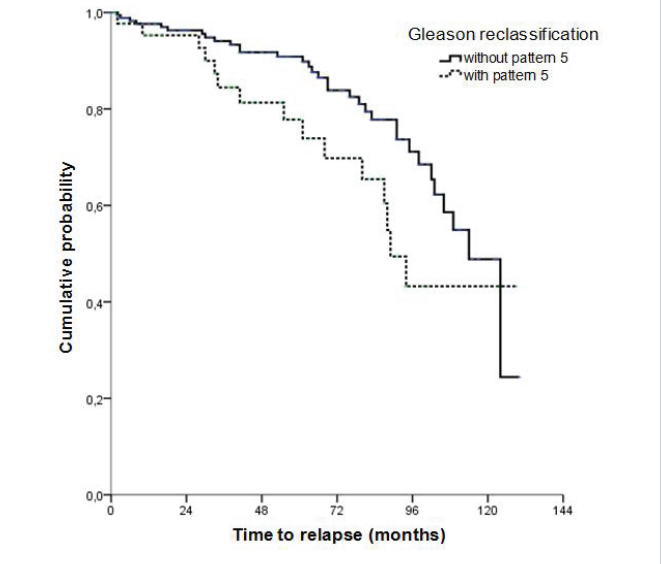


**Figure 1:** Graph showing the time to biochemical relapse (in months) in patients with and without tertiary Gleason pattern 5.

The PSA is a sensitive marker of occult prostatectomy cancer relapse. Because of tumor heterogeneity, a PSA relapse does not equal a clinical relapse or death from prostate cancer [11,12].

Many studies have been performed on specimens of prostatectomy and involving GP5 and PSA postoperative. Pan et al. demonstrated that finding Gleason 4 or 5 had a 5 year biochemical relapse-free survival of 19% while those without GP5 on survival rate of 70% [13]. Whittemore et al. [14] also demonstrated the existence of risk for biochemical relapse for patients with GP5 in 5-10 years.

Similary, Trock et al. [15] evaluated the cohort of 3230 patient's including 373 with GP 5 que was associated a greater risk for biochemical relapse.

Rasiah et al. [16] found that patients with Gleason 4+3 and GP5 had greater biochemical relapse in comparison with patients with 4+3 sem GP5. Sim et al. assessed 509 radical prostatectomies with Gleason score 7 and 66 patients with GP.GP4 or 5 was an independent predictive of biochemical failure [17,18].

To determine in our series the prognostic value of the Gleason score and correlation between GP5 in Gleason score 7 and biochemical relapse free survival was measured in series. In the bivariate analysis, seminal vesicle invasion and preoperative PSA showed statistical significance for biochemical recurrence. Based on the multivariate statistical analysis, it said that GP5 has no impact as an independent predictive factor and a combination with other variables is necessary.

Just like in other studies, it is important to list the limitations of this historic cohort. The small sample size influences the accuracy of the statistical analysis, in addition to retrospective study is susceptible to potential selection. On the other hand we had variable PSA follow-up time and difficulties in obtaining data: small sample size, especially for TGP5, retrospective cohort study to potential selection errors, variable PAS follow-up time and difficulties in obtaining data.

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