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PSA and Gleason: keys to understanding prostate cancer staging

PSA e Gleason: chaves para compreender o estadiamento do câncer de próstata

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ABSTRACT

Introduction: Prostate cancer is the most common neoplasm in men in Brazil, except for non-melanoma skin cancer. Prostate-specific antigen (PSA), although useful, can be elevated in benign conditions. Therefore, biopsy and Gleason score (GS) are essential for diagnosis, risk stratification, and understanding the relationship with factors such as body mass index.

Objective: To evaluate the correlation between PSA and GS, and to compare the GS obtained by biopsy with that of the surgical specimen (SC).

Method: This is an epidemiological, cross-sectional, retrospective study carried out by collecting data from the medical records of patients diagnosed with prostate cancer treated at a tertiary hospital, cataloging clinical data, laboratory tests, and anatomopathological findings. The sample consisted of 109 men.

Result: The mean age was 67 years. The most common stage of PSA was 7 (70.64%), with 40.36% corresponding to the sum of 3 + 4 and 30.27% to 4 + 3. When comparing age variables with PSA, there was no significant difference between the groups by age group. When comparing the PSA results from the biopsy with that from the surgical specimen, it was found that 13.76% were understaged and 30.27% were overstaged. There was no statistical significance in the comparison between PSA values and PSA results from the surgical specimen.

Conclusion: Discrepancies were observed between the PSA results from the biopsy and the PSA results from the surgical specimen, demonstrating difficulties in staging patients, which may impact treatment choice and prognosis in prostate cancer.

KEYWORDS: Prostate specific antigen. Neoplasm grading. Prostatic neoplasms.

Central Message

Prostate cancer is the most common neoplasm in men in Brazil. Prostate-specific antigen (PSA), while useful, can be elevated in benign conditions as well. Thus, biopsy and Gleason score are fundamental for diagnosis, risk stratification, and understanding of the relationship with various factors such as body mass index

Perspective

The discrepancies between the results of the Gleason score of the biopsy and those of the surgical specimen demonstrate difficulties in the staging of patients, which can impact the choice of treatment and prognosis in prostate cancer.

RESUMO

Introdução: O câncer de próstata é a neoplasia mais comum em homens no Brasil, exceto pele não melanoma. O antígeno prostático específico (PSA), embora útil, pode elevar-se em condições benignas. Assim, a biópsia e o escore de Gleason (EG) são fundamentais para diagnóstico, estratificação de risco e compreensão da relação com fatores como índice de massa corpórea.

Objetivo: Avaliar a correlação entre o PSA e o EG, e comparar o EG obtido pela biópsia e o da peça cirúrgica.

Método: Trata-se de estudo epidemiológico, transversal e retrospectivo realizado a partir da coleta dos dados de prontuários de pacientes diagnosticados com câncer de próstata atendidos em hospital terciário, catalogando dados clínicos, exames laboratoriais e anatomopatológicos. A amostra foi composta por 109 homens.

Resultado: A média de idade foi de 67 anos. EG mais observado foi o 7 (70,64%), sendo 40,36% correspondente à soma 3 + 4 e 30,27% a 4 + 3. Ao cruzar as variáveis de idade com o EG, não houve diferença significativa entre os grupos por faixa etária. Ao comparar o EG da biópsia com o da peça cirúrgica, constatou-se que 13,76% foram subestadiados e 30,27% super. Não houve significância estatística na comparação entre os valores de PSA e o EG da peça cirúrgica.

Conclusão: Foi possível observar discrepâncias entre o resultado do EG da biópsia e da peça cirúrgica, demonstrando dificuldade no estadiamento dos pacientes, o que pode impactar na escolha do tratamento e no prognóstico no câncer de próstata.

PALAVRAS-CHAVE: Antígeno prostático específico. Gradação de tumores. Adenocarcinoma prostático.

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INTRODUCTION

Prostate cancer (PC) represents an important public health problem on a global scale, with a higher incidence in developed countries. It is characterized by the uncontrolled growth of prostate cells, significantly affecting the health of individuals. According to estimates by the National Cancer Institute (INCA), for the 2023–2025 triennium, about 72 thousand new cases are expected per year in Brazil, corresponding to 10.2% of the total number of neoplasms diagnosed in the period. When non-melanoma skin cancer is excluded, PC is the most common malignant neoplasm among Brazilian men.[1]

Predominant in individuals with advanced age, PC is rare in patients younger than 50 years, with a mean age at diagnosis of 68 years.[2] The introduction of prostate-specific antigen (PSA) as a biomarker helped in the early detection of the disease, contributing to the reduction of advanced cases and the increase in diagnoses of localized tumors.[2,3] However, it has important limitations, such as low specificity and sensitivity. High levels can be associated with benign conditions, such as benign prostatic hyperplasia, chronic prostatitis, and even factors such as prostatic manipulation and recent ejaculation.[4,5] The positive predictive value of PSA is estimated at only 25%, which results in a significant number of unnecessary biopsies.[6]

The Gleason score (EG) is the main histopathological tool used for the classification and prognosis of PC. This system evaluates the degree of cell differentiation and is represented by the sum of 2 predominant histological patterns, ranging from 2 to 10, with higher scores indicating more aggressive neoplasms.[7] In order to improve its clinical applicability, the International Society of Urologic Pathology (ISUP) proposed alternative gradation, aiming at standardization and better prognostic stratification.[8,9]

Although widely used, ultrasound-guided transrectal prostate biopsy — the gold standard for initial diagnosis — has limitations, with false-negative rates ranging from 21-28%, in addition to histological underestimation in up to 17% of cases.[10] Studies have shown a significant discrepancy between the EG obtained in the biopsy and that determined in the surgical specimen after radical prostatectomy, with underestimation rates of up to 74.6% and overestimation in about 11% of the cases.[11-13]

In view of these diagnostic limitations, it is relevant to investigate the accuracy of the histopathological staging of PC by comparing the Gleason scores obtained by biopsy and surgery, as well as to explore the correlation between PSA levels and tumor aggressiveness. Such analyses can contribute to a more accurate staging, helping to define the prognosis and the most appropriate therapeutic choice.

METHOD

This study was approved by the Human Research Ethics Committee of the Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil – CAAE:71607223.9.0000.0103

This is a retrospective, cross-sectional, observational, and quantitative study. The population was restricted to patients classified by the International Classification of Diseases (ICD-10) as malignant neoplasm of the prostate (C61) between November 1, 2019 and April 17, 2023 who entered the Urology Service and Mackenzie Evangelical Hospital in Paraná, totaling an initial number of 269 (n=269). In addition, demographic data were collected on age considering the number of completed years at the time of the operation, pre- and postoperative PSA levels, and pre- and postoperative EG.

Of these, those who had already undergone previous radiotherapy, hormone therapy, any previous manipulation of the prostate, and had other tumors of the male genitourinary tract were excluded. Risk stratification was performed according to the criteria of the European Association of Urology using PSA and ISUP values; however, due to the lack of detailed data, digital prostate examination was not used as a criterion. In addition, patients with incomplete and duplicate medical records were excluded, resulting in 109 patients (n=109).

Statistical analysis

The collected data were compiled on the Excel platform. For the statistical analysis, the chi-square test, the Kruskal-Wallis test and Pearson's correlation test were used, and values of $p<0.05$ were considered statistically significant.

RESULT

After selection according to the eligibility criteria, 109 patient records were included for analysis during the stipulated period. The mean and median ages were 67 years, with 95.41% between 50 and 79 years. The standard deviation was 7.14.

The most observed EG was 7, totaling 70.64%. In the distribution by ISUP prognostic group, there was a higher frequency of ISUP 2 (40.36%) compared to ISUP 3 (30.27%). When comparing the EG of the biopsy with the EG of the surgical specimen, the ISUP biopsy with the ISUP specimen, and the risk stratification using the chi-square test, a statistically significant difference was found between the values obtained in the biopsy and in the surgical specimen ($p<0.01$). When analyzing these data, it was found that, of the 109 patients, 13.76% were overclassified and 30.27% were underclassified (Table 1).

TABLE 1 — Overall and subgroup agreement rate

	Total	6	7	8	9	10
n patients	109	26	60	13	8	2
Overclassification	15(13.7%)	0	3(5%)	6(46.2%)	4(50%)	2(100%)
Concordant classification	61 (56%)	5 (19.2%)	80.00%	4(30.7%)	4(50%)	0
Subclassing	33(30.3%)	21(80.8%)	9(15%)	3(23.1%)	0	0

The correlation between the EG of the biopsy and that of the surgical specimen was performed, and a moderate and statistically significant correlation was identified

(R=0.43; p<0.01). When comparing age with EG and with the ISUP, there was no significant difference between the groups, but there was a trend towards statistical significance when comparing age with risk stratification (Table 2).

TABLE 2 — Comparison of age (y-axis) with the patient's risk stratification (x-axis, n=109, p=0.077191)

	Low	Medium	High	Total
40-49	0	2	0	2
50-59	2	10	4	16
60-69	2	33	15	50
70-79	0	20	18	38
80+	1	1	1	3
Grand total	5	66	38	109

When performing specific analysis by age groups, comparing the EG of the biopsy with the EG of the surgical specimen, the ISUP biopsy with the ISUP specimen, and the risk stratification (RE) before the operation with the postoperative one, only the 70-79 year group showed a statistically significant difference in the comparisons between the pre- and postoperative findings (p<0.05, Table 3). Data on patients under 40 years of age were excluded from this comparison due to the low sample representation.

TABLE 3 — Disagreement of biopsy and preoperative RE findings with PC and post-RE findings by age group

	EG biopsy vs EG PO	ISUP biopsy vs ISUP PO	ER pre x ER PO
50-59	0.8732	0.9469	0.49874
60-69	0.0692	0.1444	0.00388
70-79	0.0111	0.0097	0.00349
80+	1	1	1

EG = Gleason score; PO=post-surgery; ER=Risk stratification; ISUP=International Society of Urological Pathology

It is noteworthy that we chose to use preoperative PSA values, as they better reflect the disease status at the time of the operation, and there was a need to eliminate outlier values, resulting in n=104 for the statistical analysis. Using the Kruskal-Wallis test, p=0.46856 was obtained, indicating that there is no statistical significance in the comparison between groups. The preoperative PSA value was also compared with the ISUP as well as with the risk stratification of the surgical specimen, resulting in p=0.36345 and p=0.23414, respectively, without statistical significance.

When relating PSA values as suggested by the guidelines of the European Association of Urology with EG, ISUP and risk stratification, no significant difference was found between the groups.

DISCUSSION

Gleason, age, and risk stratification

The high incidence of PC in Brazil requires special public health attention.[1] It is crucial to understand in depth the epidemiological profile of affected men, including histopathology, and risk stratification. With this knowledge, authorities can promote early diagnosis, develop effective treatment strategies targeted at specific groups, and increase patient survival.

Thus, the comparison of the data collected and analyzed with the national and international literature makes it possible to identify relevant characteristics. Regarding epidemiology, 83.49% of the patients were 60 years of age or older, and there were no patients under 40 years of age, which is in accordance with the international literature, which reports a significant increase in risk with age.[14-16]

In the sample, it was observed that 7.33% patients had EG 6, 70.64% had EG 7 and 21% had the sum of EG 8 and 9, which conflicts with the data available in the international literature, which indicate a more balanced distribution, with around 41% EG 6, 36% EG 7 and 15.2% EG 8-10.[17] This can be explained by the exclusion of data from patients who did not undergo RP, leading to an increase in the mean EG.

In the data collected in this study, no significant correlation was identified between older ages with EG and UPSI, but there was a trend towards significance in the correlation between higher age and risk stratification, which is in line with the international literature, which indicates this relationship.[18-20] This result indicates the need for further studies, with larger samples, so that the data presented are more reliable for the Brazilian population.

Gleason super and subclassification

In the sample analyzed, a significant number of underclassifications (13.76%) and overclassifications (30.27%) were observed, with a significant difference according to the statistical analysis. In the literature, discrepancy rates of up to 51% between the EG of the biopsy and the surgical specimen are also being observed, and this leads to questions about the accuracy of the chosen treatment and the need for further evaluation of patients, reinforcing that treatments for PC should not be based exclusively on EG.[21-23]

King in 2000[24] suggested that, given the clinical implications of EG, staging of organ-confined PC should include the likelihood of histological update when EG are used in the following settings: stratification of patients for clinical trials; comparison of outcomes for specific therapies based on biopsy classification; the use of tables or formulas to predict update risks; and for the recommendation of radical therapy.

It is worth noting that in the 70-79 age group, there were significant disagreements between the pre- and post-surgical data. The target population of PC is an older population and is characterized by tumor heterogeneity. This leads to increased discordance between biopsy and PC, especially at older ages.[25] In addition, PC upgrading is also more likely to occur in older patients,26 which may be due to physicians tending to offer less aggressive treatments to elderly patients.[27]

Because the tumor volume of older patients is larger, and because the biopsy targets small samples, the result may not reproduce reality. The true staging is established only with the PC, which will have the total volume of the tumor for analysis.

PSA and histological grade

The data found did not demonstrate a significant

correlation between higher PSA values with higher EG, and there was also no statistical significance when comparing it with the risk stratification of PSA, according to the EAU, disagreeing with data in the international literature.[19] However, it is not possible to affirm this in this study, and further research is needed to establish a larger sample of the Brazilian population.

In the literature, there are studies that emphasize that the extremes of PSA are not linearity in relation to the degree of the neoplasm; levels below 3.5 ng/ml tend to cause tumors in a more advanced stage in relation to those with PSA between 3.5 and 10 ng/ml.[28] In PSA above 70 ng/ml, the prognosis worsens, but ends up plateauing.[29] Such facts may affect an attempt at direct correlation even with the removal of outlier values.

The analysis revealed important limitations, such as the absence or incompleteness of data on the Gleason score of the surgical specimen in part of the sample, which impacted the statistical consistency of the results. Despite this, the study was conducted with methodological rigor and offers relevant contributions on PC in the population treated by a university hospital, serving as a basis for future more comprehensive investigations.

CONCLUSION

The study identified the importance of screening in higher-risk groups. The significant rate of over- and underestimation of EG in biopsies indicates that this parameter should not be used in isolation for therapeutic decisions. The absence of correlation between high PSA and high EG reinforces the limitations of PSA as a predictor of aggressiveness. Thus, the need for a multiparametric approach for the staging and appropriate management of prostate cancer is highlighted.

Authors' contributions
João Arthur Motta dos Santos – Conceptualization, Formal Analysis
Pedro Henrique Duarte Carvalho – Methodology, Research
Paulo Eduardo Dietrich Jaworski – Supervision, Writing (proofreading and editing)
Samya Hamad Mehanna - Project Management

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