Analysis of Prostate Adenocarcinoma Histopathological Types in Relation to Tumor Grade

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ABSTRACT: Prostate adenocarcinomas are some of the most common malignancies diagnosed in men, and the evaluation of tumor growth patterns is the basis for establishing the aggressiveness of the lesions. The study included 283 cases of prostate adenocarcinomas for which histopathological type and tumor grade were analyzed. The results indicated the association of ductal, sarcomatoid and signet ring-like cell types with aggressive growth patterns and high scores, atrophic and pseudohyperplastic types with mild growth patterns and low scores, foamy gland type presented intermediate growth patterns/scores, while conventional and colloid types had variable aspects. The grading systems used may be considered consistent with the histological types of prostate adenocarcinomas.

KEYWORDS: Prostate adenocarcinoma, histological type, Gleason score.

Introduction

Prostate adenocarcinomas are common lesions in men's oncological pathology, ranking second after bronchopulmonary carcinoma [1].

Although the mortality rate from prostate cancer is relatively low compared to other malignancies, the aspect can only be discussed in the case of localized disease in which 5-year survival is about 100% and decreases to 30% in extensive and metastatic lesion [2].

In this context, prostate adenocarcinoma is expected to become the main malignant lesion of men in the coming years, with an incidence rate of 21%, compared to lung cancer with a rate of around 13% [2,3]. On the contrary, there are other studies projecting a decrease in the incidence of prostate cancer, especially due to the relatively wide access to screening programs on PSA (prostate-specific antigen) serum assessment, a decrease that could be affected due to population aging and increased incidence in patients under 50 years of age [4].

Thus, there is a permanent concern for improving the histopathological criteria for reporting prostate adenocarcinomas, which include the parameters of aggression of the lesions being directly related to the prognosis and therapeutic attitude, including tumor type, grade and stage. Although the grading systems of prostate adenocarcinomas have improved in the last 50 years, there are still some problems related to reproducibility, the reporting of tumor heterogeneity or the prognostic significance of growth sub-patterns [5-9].

In this study, the histopathological type of prostate adenocarcinomas was analyzed in relation to the grading systems of the lesions.

Material and Methods

This study included 283 prostate adenocarcinomas diagnosed during five years (2016-2020) in the Pathology Department of the Emergency County Hospital of Craiova. The biological material was represented by fragments of prostate biopsy (186 cases) and fragments of tumor transurethral resection (TURp) (97 cases) from patients who were first admitted to the Urology Clinic of the same hospital. The tumor fragments were fixed in 10% buffered neutral formalin and routinely processed for classical paraffin embedding and Hematoxylin-Eosin staining. All tumors analyzed were classified and graded according to indications of the WHO (World Health Organization) working group for tumors of the urinary system and male genital organs [10].

The inclusion criteria in the study were the diagnosis of prostate adenocarcinoma in patients who had no history of urological pathology or oncological history of any kind.

The statistical analysis used the chi square ($\chi^2$) comparison tests within SPSS 10 software. For images acquisition was used the Nikon Eclipse E600 microscope equipped with Lucia 5 software. The study was approved by the Ethical Committee of The University of Medicine and Pharmacy of Craiova, and all patients gave a written informed consent regarding the publication of these data.
Results

The study included 283 patients with prostate adenocarcinoma with a mean diagnostic age of 72.6±10.2 years. Analysis of the tumor histological type indicated the net predominance of conventional acinar carcinomas diagnosed in 200 cases, which represented 70.7% of the casuistry. Depending on the degree of differentiation, the tumor architecture was glandular, cribriform or solid.

Figure 1. Prostate adenocarcinoma, HE staining, x200. A. Conventional type; B. Atrophic type; C. Pseudohyperplastic type; D. Foamy cell type; E. Colloid type; F. Signet-ring like cells type; G. Sarcomatoid type; H. Ductal type.
In general, the tumor glands were small/medium, irregular, infiltrative, with rigid lumen, lined with atypical cuboidal-columnar cells and the absence of the basal layer, separated by a variable amount of stroma, sometimes with glandular fusions and accentuated pleomorphism (Figure 1A).

Atrophic and pseudohyperlastic acinar adenocarcinomas were identified in 6 cases, each representing 2.1% of the analyzed group. The atrophic type was usually mixed with conventional areas, with well-represented glands, some dilated and lined with flattened epithelia, while the pseudohyperplastic type showed a papillary glandular pattern with back-to-back pattern, with a distorted and anastomized appearance (Figures 1, B-C).

Foamy gland adenocarcinoma was identified in 31 cases, being second in frequency and representing 11%, tumor cells presenting abundant clear vacuolated cytoplasm, sometimes with acidophilic granules (Figure 1D).

The colloid type (mucinous) was present in 13 cases (4.6%), in which we found accumulations of extracellular mucinous secretion in over 25% of the tumor volume (Figure 1E).

The tumor type signet ring-like cells consisted in the presence of tumor cells with vacuolated cytoplasm and peripheral nucleus, an aspect observed in 4 cases (1.4%), while the sarcomatoid type consisted in the presence of slightly elongated tumor cells arranged fasciculately in a desmoplastic stroma, aspect identified in 6 cases (2.1%) (Figure 1F-G).

In the case of ductal adenocarcinoma identified in 17 cases (6%) the tumor areas were solid, papillary or cribriform, sometimes with central comedo necrosis (Figure 1H).

The analysis of tumor growth patterns indicated the predominance of mixed patterns present in 108 cases (38.2% of cases), followed by pattern 3 in 95 cases (33.6%), pattern 4 in 29 cases (10.2%) and pattern 5 in 51 cases (18%). The pure growth pattern 3 was characterized by the presence of groups of individualized infiltrative glands with malignant characters, the pure pattern 4 by the presence of fused glands, sometimes with compact or cribriform appearance, while the pure pattern 5 presented solid architecture or infiltrative cell cords (Figures 2, A-D).

In the mixed tumor growth, pattern 3 was present in 83 cases, pattern 4 in 82 cases and pattern 5 in 51 cases.

Figure 2. Prostate adenocarcinoma, HE staining, x100.
A. Growth pattern 3; B. Growth pattern 4; C. Growth pattern 5; D. Mixed pattern.
The analysis of growth patterns in relation to tumor type indicated statistically significant association of conventional, atrophic, hypertrophic and foamy gland types with pattern 3, ductal type with pattern 4 and colloid, signet ring-like cells and sarcomatoid types with pattern 5 (p<0.001, \(\chi^2\) test) (Table 1, Figure 3A).

Table 1. Distribution of cases depending on histologic type and tumoral growth pattern.

<table>
<thead>
<tr>
<th>Histologic type/Growth pattern</th>
<th>Pattern 3</th>
<th>Pattern 4</th>
<th>Pattern 5</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>63</td>
<td>20</td>
<td>35</td>
<td>82</td>
</tr>
<tr>
<td>Atrophic</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Foamy gland</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Colloid</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Signet ring-like cells</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Ductal</td>
<td>-</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Analysis of Gleason scores indicated the predominance of score 6 (95 cases, 33.6%), followed by the frequency of score 7 (57 cases, 20.2%), score 8 (55 cases, 19.4%), score 10 (51 cases, 18%) and score 9 (25 cases, 8.7%). In relation to the histological type, scores 6-8 were associated with the conventional type, score 6 with atrophic and pseudohyperplastic types, score 6-7 with foamy gland type, scores 9-10 with sarcomatoid and signet ring-like cells, aspects that were statistically significant (p<0.001, \(\chi^2\) test) (Table 2, Figure 3B).

Table 2. Distribution of cases depending on histologic type and classic Gleason score.

<table>
<thead>
<tr>
<th>Histologic type/Classic Gleason score</th>
<th>Gleason 6</th>
<th>Gleason 7</th>
<th>Gleason 8</th>
<th>Gleason 9</th>
<th>Gleason 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>63</td>
<td>44</td>
<td>44</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Atrophic</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Foamy gland</td>
<td>20</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colloid</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Signet ring-like cells</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Ductal</td>
<td>-</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

At the same time we found the association of atrophic and pseudohyperplastic types with simplified grade group 1, of the foamy gland type with groups 1-2 and of the ductal, sarcomatoid and signet ring-like cells types with groups 4-5, statistically significant aspects (p<0.001, \(\chi^2\) test) (Table 3, Figure 3C).

Table 3. Distribution of cases depending on histologic type and simplified grading groups.

<table>
<thead>
<tr>
<th>Histologic type/Simplified Gleason score</th>
<th>Grade group 1</th>
<th>Grade group 2</th>
<th>Grade group 3</th>
<th>Grade group 4</th>
<th>Grade group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>63</td>
<td>27</td>
<td>17</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>Atrophic</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Foamy gland</td>
<td>20</td>
<td>6</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colloid</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Signet ring-like cells</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Ductal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure 3. Distribution of cases depending on histopathological type of prostate adenocarcinoma and growth pattern (A), classic Gleason score (B) and simplifies grading groups (C).
Statistical analysis of histopathological types of prostate adenocarcinomas in relation to the degree of tumor differentiation indicated the concordance of tumor growth pattern with classic Gleason score and simplified grading scores and indicated a well differentiated appearance of atrophic and pseudohyperplastic types, predominantly moderately differentiated for foamy gland type, and predominantly poorly differentiated for ductal, sarcomatoid, and signet ring-like cell types, while conventional and colloidal types revealed varying degrees of differentiation.

Discussions
Histological variants of prostate adenocarcinomas have prognostic and therapeutic significance.

There are studies that have shown an excellent prognosis for the atrophic, pseudohyperplastic, foamy glands and microcystic types, while the signet ring-like cell, pleomorphic, sarcomatoid types are associated with a reserved prognosis [11].

Invasive ductal carcinoma is frequently associated with conventional types, accounting for approximately 5% of prostate carcinomas.

The atrophic type is most often graded as pattern 3 and can be identified sporadically after hormonal treatments or radiotherapy, while the pseudohyperplastic type can simulate papillary hyperplasia being classified with the same pattern [11,12].

Foamy gland type is in almost 20% of cases being mixed with conventional areas and is graded with pattern 3 or 4 although there may be higher Gleason scores [11,12].

Colloid adenocarcinoma is characterized by Gleason scores frequently ranging from 6-8, this type not being as aggressive as indicated in the past [13].

Signet ring-like cell type is designated as having pattern 5, and sarcomatoid type (carcinosarcoma) is a biphasic tumor in patients with a history of radiation therapy or hormone therapy [11,12].

The results obtained in our study are largely consistent with those in the literature and even if for some types gradation is not indicated, the appearance was reported on account of the associated conventional tumor areas.

The most common types were conventional adenocarcinomas (70.7%), followed by foamy gland type (11%), colloid type (4.6%), atrophic/pseudohyperplastic and sarcomatoid types (2.1%), signet ring-like cell type (1.4%) while the ductal type was identified in 6% of cases.

The Gleason grading system is one of the oldest and most effective pathological and clinical tools successfully in clinical practice and in relation to patient prognosis [9].

The grading systems of prostate adenocarcinomas have been in a permanent dynamic which has led to some changes over time, so that they can be directly associated with the prognosis, be reproducible and be representative of the entire tumor volume even if the degree is set on biopsy fragments [8,9,14-17].

The grading system for prostate adenocarcinomas was introduced by Broders A in 1926 and had four grades, and later in 1966 Gleason DF introduced a grading system based on five growth patterns observed in tumors, which was later adopted worldwide [14,18,19].

The International Society of Urological Pathologists (ISUP) in 2005 made some changes to the original Gleason gradation, including poorly defined or large cribriform tumor glands assigned to grade 4, well-defined glands or small cribriform ones to grade 3, and in the case of biopsies to be including grades 4 and 5 even when the percentage was below 5% [8,16,17,20].

Subsequently, patterns 1 and 2 were removed from the Gleason score in the case of biopsies and TURP, being considered without prognostic importance [14,21].

At the same time, the specialized studies indicated prognostic differences of the reporting of the primary pattern 3 or 4 within the Gleason 7 score [22].

In addition, some issues remained after 2005 related to the reproducibility of the Gleason score which was unsatisfactory [5].

In 2013, five simplified (prognostic) grading groups are proposed, respectively group 1 (Gleason≤6), 2 (Gleason 7=3+4), 3 (Gleason 7=4+3), 4 (Gleason 8) and 5 (Gleason 9 and 10), which were subsequently recommended by the WHO and the American Joint Committee on Cancer (AJCC) [23,24].

Currently, the intraobserver reproducibility rate for the Gleason score varies up to 80%, while the interobserver rate has a maximum of 81% according to the new grading criteria [16].

In this study, the association of the histological type with both the growth pattern and the classic and simplified Gleason grading was analyzed.
The Gleason system is entirely based on tumor growth patterns. Individual growth patterns are not usually specified in pathological reports, although they appear to have an independent predictive value [25].

In our study, the conventional and colloid histological types were associated with variable Gleason scores/Gleason grade groups, atrophic and pseudohyperplastic types to low scores/groups, foamy gland type to intermediate scores/groups and signet ring-like cell, sarcomatoid and ductal types to high scores/groups. In addition to the advantages related to the reproducibility and superior prognostic concordance of the new grading system, there are still disadvantages.

Thus, in addition to the loss of tumor heterogeneity assessment, the Sehn JK et al. emphasizes in 2018 these aspects that refer to the fact that tertiary patterns were excluded and group grading cannot be applied in these cases, there is no limit of prognostic significance for the percentage of pattern 4 in score 7, the cribriform pattern seems more aggressive compared with the glomeruloid one or with glands fused within the score 8 and the fact that there are other histological criteria (fibroplasia, the percentage of paternal 5 in the score 8) which are associated with a worse prognosis and which are not taken into account during gradation [9].

However, nowadays the Gleason grading system is an important parameter for the prognosis and treatment of prostate adenocarcinomas, being associated with biochemical values, local recurrence, localized/metastatic disease and the type of therapeutic attitude [9,17].

Conclusions
The results indicated the prostate adenocarcinomas of ductal, sarcomatoid and signet ring-like cell types as associated with aggressive patterns and high scores, foamy cell type associated with intermediate categories and atrophic and pseudohyperplastic types with low categories, while for conventional and colloidal lesions the aspects were variable.

The study indicated the usefulness of tumor growth pattern and classical and simplified grading systems for assessing the aggressiveness of different histological types of prostate adenocarcinomas, in the context of the statistical concordance of these parameters.

Conflict of interests
None to declare.

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