Gleason Score 6 – Prostate Cancer or Benign Variant?

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Summary
The leading motivation behind wanting to call a ‘malignant’ prostate lesion ‘benign’ is the evidence of indolent prostate cancer that is not associated with a fatal outcome and in part makes therapeutic measures such as surgery and radiotherapy appear like overtreatment for some or possibly the majority of such patients. This awareness has led to the strategy of active surveillance, i.e. monitoring the patient for progression of a low malignant tumor instead of imposing other therapeutic modalities, and repeating prostate biopsies based on clinical data. This approach is demanding for all disciplines involved. Not only does it require a thorough and detailed histomorphological diagnosis based on sufficient biopsy material, but it also demands adequate communication with the patient to allow proper guidance regarding the diagnosis. Thus, the idea and desire to call some of the tumors of the prostate benign is an inherent wish to avoid patient stigmatization and ease guidance of the patients.

The issue discussed here is not limited to prostate cancer. It will be examined based on pathological definitions needed by all clinicians to arrive at an unequivocal diagnosis.

Gleason Score and Gleason Score 6

Acinar prostate cancer is defined histologically by atypical glandular growth with a lack of basal cells and prominence of nucleoli in glandular epithelial cells as the 2 main features (fig. 1A and B). For this cancer, which is often found in variable patterns of atypical glandular structure and acinar as well as less frequent ductal differentiation, these findings prove cancer, and dubious cases are differentiated from benign and regenerative lesions by immunohistochemistry mostly applied as a panel of 2 basal cell markers (cytokeratin 5/6, cytokeratin34ßE12 or P63) [1] and often combined with alpha-methylacyl-CoA racemase (AMCAR) as a marker positive for prostate cancer [2]. Along with the unequivocal diagnosis of cancer, grading of tumors is mandatory. The internationally used Gleason score was developed and established by Donald Gleason and the Veterans Administration Cooperative Urologic Research group between 1966 and 1974 as a grading system for pattern recognition [3], and has replaced the standard 3-tiered grading system of the WHO still used for nearly all solid tumors. Changes to the original version (ISUP Modified Gleason System [4]) have been
made and have been proven to be valuable for biopsies by showing improved concordance of the grading to subsequent prostatectomy specimens [5, 6].

In 2005, it was decided that it is necessary to handle Gleason scoring of biopsy specimens differently from that of prostatectomy specimens. A biopsy includes the score of the highest amount of tumor found in the specimen, and the subdominant pattern as a second score unless there is a tertiary pattern of higher grade. Irrespective of amount, in these cases, the worst pattern is counted as the secondary pattern in the Gleason score of a biopsy. In contrast, in a prostatectomy specimen, we still count the most frequent pattern and the second most frequent pattern to define the Gleason score. In prostatectomy specimens, small amounts of higher Gleason grade are mentioned as tertiary patterns as part of the diagnosis. Also, grading in the biopsy is recommended and usually starts with a Gleason score of $3 + 3 = 6$ since lower Gleason scores cannot be defined in core biopsies [7]. The reason for this is insufficient amounts of tissue to show the complete acinar structure necessary to define Gleason scores 1 and 2.

From these historical cornerstones, the reader can derive that the material critical for the decision of the patient’s therapy gets a Gleason score of 6 as the best possible diagnosis for cancer. In contrast, the original numbering allowed numbers from 2 to 10 within this scoring system. While there is no doubt that we deal with malignancy, it is an indicator of a good prognosis. This has been shown abundantly, for example in a very recent large cohort study of prostatectomy specimens showing a 5-year biochemical recurrence-free survival of 96% with a confidence interval of 95% [7]. Well differentiated variants of cancer can still metastasize, and urologists are well aware that for example metastases of highly differentiated clear cell renal carcinoma can be found in various body sites; this is supported by molecular work which also shows that metastases of Gleason 6-graded prostate cancer can be detected [8].

Hence, it is important to delineate well differentiated or low-grade cancer from high-grade cancer based on molecular features in order to be more certain about therapeutic consequences. The distinction is especially necessary for active surveillance cases within the group of Gleason 6 cancer, since despite a gradual shift towards cancers with a good prognosis due to the change in grading, the individual patient needs reassurance that active surveillance is the correct choice. According to the National Cancer Network guidelines, approximately 20% of patients with very low-risk disease still have a worrying pathology [9]. While certain markers such as PTEN and Ki67 seem to play a diagnostic role [10], promising results have recently been achieved with 2 multigene expression profiling tests (Oncotype DX®, Genomic Health, Inc., Redwood City, CA, USA, and Prolaris®, Myriad Genetics, Inc., Salt Lake City, UT, USA) [11]. These tests represent either multigene panels with genes from representative cancer pathways (Oncotype DX) or a set of cell cycle-related genes (Prolaris). The expression profile in itself provides objective data; however, it should be kept in mind that the tissue subjected to the test is of vital importance, thus warranting tight quality assurance on the part of the diagnosing pathologist. While the tests lack prostate cancer specificity, they might still help to identify patients at higher risk for whom active surveillance may not be the right strategy. Costs have to be systematically weighed against the kind of answers that can be provided by so-called precision medicine. High resolution imaging (multiparametric magnetic resonance imaging) has a negative predictive value for Gleason scores larger than 6 of 80–90%. Comparably, molecular testing methods have been categorized as supportive methods adding precision to known clinical parameters by further refining and validating them.

In the case of prostate cancer, the most important issue with regard to molecular subgrading is that it is more heterogeneous than many other solid tumors. It is both multifocal and multiclonal [12]. Furthermore, it is known that the natural microenvironment within the prostate differs between the inner and peripheral zone, which has an impact on tumor growth in spite of morphologically identical pictures [13]. All of this has led to a high frequency of core biopsies as a basis for diagnosis, as well as the inclusion of additional clinical parameters such as prostate-specific antigen and prostate volume into the individual risk assessment.

In contrast to organs such as the bladder or the oral cavity with a high degree of visual access, tissue changes in the prostate cannot be directly visualized, and therefore much hope is placed into high resolution imaging techniques possibly allowing the distinction between low- and high-grade tumors (for review see [14]). This would give support to active surveillance strategies and provide options for focal therapy.

**Precancerous Lesions of the Prostate**

Since tumor biology does not allow a low-grade carcinoma to be called benign, it seems important to emphasize that there are well defined precursors to prostate cancer [15]. Prostatic intraepithelial

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**Fig. 1.** a Typical Gleason score 6 prostate cancer with lack of basal cells, prominent nucleoli, and either lack of or atypical secretion in the glandular lamina; b enlargement of a; hematoxylin-eosin staining.
neoplasia (PIN), low-grade (PIN LG) or and high-grade (PIN HG), is limited to intra-acinar or intraductal primary proliferation with maintenance of basal cells (fig. 2A and B), identical to e.g. ductal carcinoma in situ of the breast. Precancerous lesions are biologically different from intraductal spread of carcinoma and can be diagnosed earlier with the support of immunohistochemical staining of PTEN and ERG [16, 17]. PIN is one of the diagnoses accepted and demanded as part of the diagnostic workup on core needle biopsies (table 1). While a diagnosis of ductal carcinoma in situ of the breast leads to mandatory therapeutic measures such as surgery and/or radiation, the finding of PIN HG on biopsy is an indicator for possible emergence of carcinoma [18], and on its own results in mere closer observation of the patient.

**Gleason Score 6 as Cancer Diagnosis**

After admitting that Gleason 6 cancer cannot be called benign, and given the fact that the pathologist should strive to reach an unequivocal diagnosis whenever possible in order to provide meaningful support for clinical decisions, some help may come from the first results of a study by the Urology Department of the Johns Hopkins Hospital, Baltimore, testing a new grading system on a cohort of more than 800 men [7]. This paper contains the first clinical evaluation of an attempt to address the confusion arising from the Gleason scoring system by introducing 5 grades (i.e., 1–5). With the change in the Gleason scoring system resulting in Gleason score 6 as the best diagnosis in core biopsies (see above), the authors have suggested to call Gleason score 6 ‘grade group 1’ and use 5 grade groups to replace the Gleason scoring system (table 2). The data are currently limited to the evaluation of biochemical recurrence; however, they do confirm the high discriminatory value of the 5 grade groups in multivariate analyses for both cases with radical prostatectomy and those with mere radiation therapy. The psychological impact of calling low-grade cancer ‘grade 1’ is emphasized.

**Concluding Remark**

Precision medicine is representative of the constant endeavor of doctors to achieve better outcomes for their patients. In the case of prostate cancer, an extreme degree of tumor heterogeneity demands excellent work in an interdisciplinary setting. Use of unequivocal language will avoid misunderstandings. The determination to systematically explore new paths such as imaging and molecular diagnoses will be most helpful to a patient diagnosed with cancer independent of grade and stage.

**Disclosure Statement**

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References


