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Integrating Tertiary Gleason 5 Patterns into Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens

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Article info

Abstract

Background: Presence of small (tertiary) Gleason 5 pattern is linked to a higher risk of biochemical recurrence in prostate cancer. It is unclear, however, how to integrate small Gleason 5 elements into clinically relevant Gleason grade groups.
Objective: To analyze the prognostic impact of Gleason 5 patterns in prostate cancer and to develop a method for integrating tertiary Gleason 5 patterns into a quantitative Gleason grading system.
Design, setting, and participants: Prostatectomy specimens from 13 261 consecutive patients and of 3295 matched preoperative biopsies were available. Percentages of Gleason 3, 4, and 5 had been recorded for each cancer.
Outcome measurements and statistical analysis:
Results and limitations: Our data demonstrate that minimal Gleason 5 areas have strong prognostic impact in Gleason 7 carcinomas, while further expansion of the Gleason 5 pattern population has less impact. We thus defined an integrated quantitative Gleason score (IQ-Gleason) by adding a lump score of 10 to the percentage of *unfavorable Gleason pattern (Gleason 4/5)* if any Gleason 5 was present and by adding another 7.5 points in case of a Gleason 5 fraction >20%. There was a continuous increase of the risk of prostate-specific antigen recurrence with increasing IQ-Gleason. This was also true for subgroups with identical Cancer of the Prostate Risk Assessment Postsurgical scores ($p < 0.0001$) or Gleason grade groups ($p < 0.0001$).
Conclusions: The IQ-Gleason represents a simple and efficient approach for combining both quantitative Gleason grading and tertiary Gleason grades in one highly prognostic numerical variable.

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Patient summary: Prostatectomy specimens (13 261) were analyzed to estimate the relevance of small Gleason 5 elements in prostate cancers. Even the smallest Gleason 5 areas markedly increased the risk of prostate-specific antigen recurrence after surgery. Larger fractions of Gleason 5 patterns had less further impact on prognosis. Based on this, a numerical Gleason score (integrated quantitative Gleason score) was defined by the percentages of Gleason 4 and 5 patterns, enabling a refined estimate of patient prognosis.
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1.   Introduction

In radical prostatectomies, the Gleason score is defined by the most and the second-most frequent architectural pattern, while an additional third pattern is added as a tertiary Gleason grade if it is worse than the primary and secondary grade. The presence of a tertiary Gleason grade is significantly linked to unfavorable tumor features [1–4]. It is unclear, however, what minimal fraction of Gleason 5 patterns is needed to exert a prognostic role and how the tertiary Gleason pattern could optimally be included into a *summary Gleason grade* [1,5,6]. Considering the lack of convincing data in this area, the recent consensus paper on Gleason Grading by the International Society of Urologic Pathology (ISUP) postponed suggestions on the integration of a tertiary Gleason 5 pattern [7]. It is thus not surprising that many urologists have difficulties in interpreting the clinical impact of tertiary Gleason patterns and may even disregard this important additional grading information [8].

At our institution, we have analyzed more than 20 000 radical prostatectomy specimens between 2005 and 2015. For all these patients, we had recorded the relative quantities of Gleason patterns present in their tumors. Using the percentage of Gleason 4 patterns as a classifier we had earlier shown that the risk of prostate-specific antigen (PSA) recurrence continuously increases with a rising percentage of Gleason 4 patterns [9]. While this *quantitative Gleason grading* enables a finer prognostic discrimination within Gleason 7 score prostate cancers than traditional grade grouping, it does not further classify cancers with a tertiary Gleason grade. In this present study, we thus investigated the relative role of the percentage of Gleason 4 and 5 patterns in a cohort of 13 261 patients with complete follow-up data and developed a method for integrating both patterns into one continuous numerical score.

2.   Material and methods

2.1.   Patients

Prostatectomy specimens from 13 261 consecutive patients operated between 2005 and 2015 at the University Medical Center Hamburg-Eppendorf had complete follow-up data. Preoperative biopsies from at least eight locations were available from 3295 patients. For each cylinder the length of the cancer was recorded as well as the percentages of Gleason 3, 4, and 5 patterns. For details see the Supplementary data.

2.2.   Integrated quantitative Gleason score

The integrated quantitative Gleason score (IQ-Gleason) combines all Gleason pattern data of a prostate cancer in one continuous numerical

value. It ranges from 0 to 117.5 and is calculated as follows: percentage of unfavorable Gleason pattern (Gleason 4 + Gleason 5) + 10 score points if any Gleason 5 pattern was seen + another 7.5 score points in case of Gleason 5 quantities of >20%. For example, the IQ-Gleason of a Gleason 3 + 4 = 7 cancer with 40% Gleason 4 is *40*, the IQ-Gleason of a Gleason 3 + 4 = 7/tertiary grade (TG) 5 cancer with 40% Gleason 4 and 5% Gleason 5 is $40 + 5 + 10 = 55$. This represents the *basis value* (percentage of unfavorable Gleason pattern = 45) plus 10 score points because there is ≤20% Gleason 5 pattern. The IQ-Gleason of a (Gleason 4 + 5 = 9) cancer with 60% Gleason 4 and 40% Gleason 5 is $60 + 40 + 10 + 7.5 = 117.5$. For details see Supplementary data.

2.3.   Cancer of the Prostate Risk Assessment, Postsurgical score

The Cancer of the Prostate Risk Assessment, Postsurgical score (CAPRA-S; including preoperative PSA, Gleason score, surgical margin status, extracapsular extension, seminal vesicle invasion, and lymph node invasion) was calculated for a subset of 12 992 cancers as described [10].

2.4.   Statistics

See Supplementary data.

3.   Results

3.1.   Gleason Grade and tumor phenotype

The relationship of classical Gleason categories with other clinical and pathological parameters is shown in Table 1. Gleason 5 pattern occurred in 2883 (22%) of our patients including 1967 (19%) patients with Gleason 3 + 4 or 4 + 3 cancers where the Gleason 5 component was small enough to result in a tertiary pattern.

3.2.   Prognostic impact of the fractions of Gleason 4 and 5 patterns in Gleason 3 + 4 cancers with a tertiary Gleason 5 grade

The separate analysis of the percentage of Gleason 4 (Fig. 1A) and Gleason 5 patterns (Fig. 1B) within the subgroup of 742 Gleason 3 + 4/TG 5 cancers revealed a fundamental difference in their prognostic impact. For the fraction of Gleason 4 patterns, there was a continuous increase of the risk of PSA recurrence with increasing percentage of Gleason 4 patterns (Fig. 1A). In contrast, prognosis deteriorated sharply in the presence of minimal amounts of Gleason 5 patterns and only worsened slightly with increasing Gleason 5 percentage.

3.3.   Prognostic impact of the fractions of Gleason 4 and 5 patterns in Gleason 4 + 3 cancers with a tertiary Gleason 5 grade

A similar analysis for the subgroup of 1225 Gleason 4 + 3 = 7/TG 5 cancers revealed a continuous increase of