Accuracy of Grading Gleason Score 7 Prostatic Adenocarcinoma on Needle Biopsy: Influence of Percent Pattern 4 and Other Histological Factors

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BACKGROUND. Recognition of Gleason pattern 4 in prostatic needle biopsies is crucial for both prognosis and therapy. Recently, it has been recommended to record percent pattern 4 when Gleason score 7 cancer is the highest grade in a case.

METHODS. Four hundred and five prostate needle core biopsies received for a second opinion at our institution from February–June, 2015 were prospectively diagnosed with prostatic adenocarcinoma Gleason score 7 as the highest score on review by a consultant urological pathologist. Percentage of core involvement by cancer, percentage of Gleason pattern 4 per core, distribution of Gleason pattern 4 (clustered, scattered), morphology of pattern 4 (cribriform, non-cribriform), and whether the cancer was continuous or discontinuous were recorded.

RESULTS. Better agreement was noted between the consultant and referring pathologists when pattern 4 was clustered as opposed to dispersed in biopsies (P = 0.009). The percentage of core involvement by cancer, morphology of pattern 4, and continuity of cancer did not affect the agreement between the consultant and referring pathologists. There was a trend (P = 0.06) for better agreement based on the percent of pattern 4.

CONCLUSIONS. When pattern 4 is scattered amongst pattern 3 as opposed to being discrete foci, there is less interobserver reproducibility in grading Gleason score 7 cancer, and in this setting pathologists should consider obtaining second opinions either internally within their group or externally. Prostate © 2017 Wiley Periodicals, Inc.

KEY WORDS: prostate cancer; gleason grading; percent pattern 4; interobserver

INTRODUCTION

Gleason grading is widely used, and is the officially recommended histopathologic grading system for prostatic carcinoma in the United States [1–6]. Identification of Gleason pattern 4 in prostatic needle biopsies is fundamental both prognostically and therapeutically. The Gleason grading system has undergone several revisions in the last decade. Changes in the grading system that could affect the diagnosis of Gleason score 7 first occurred in 2005 and more recently in 2014 [3,4]. How the extent of pattern 4 and morphological variations of pattern 4 influence interobserver agreement in diagnosing Gleason 7 on needle core biopsies in the modern era has not been studied.

MATERIALS AND METHODS

Four hundred and five consecutive prostate needle core biopsies with prostatic adenocarcinoma Gleason score 7 as the highest grade received for a second opinion at our institution from February–June, 2015 were prospectively diagnosed with prostatic adenocarcinoma Gleason score 7 as the highest score on review by a consultant urological pathologist. Percentage of core involvement by cancer, percentage of Gleason pattern 4 per core, distribution of Gleason pattern 4 (clustered, scattered), morphology of pattern 4 (cribriform, non-cribriform), and whether the cancer was continuous or discontinuous were recorded.

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opinion at our institution from February–June, 2015 were studied. The agreement between an expert urological pathology consultant and general submitting pathologists was studied. The Gleason grades provided by the consultant pathologist was divided into two groups \( (3 + 4 = 7, \text{ Grade Group 2}) \) and \( (4 + 3 = 7, \text{ Grade Group 3}) \), and then each group was compared to general pathologists grading (under-grading, same grading, and over-grading). For each case, a set of the morphologic factors that could contribute and influence the level of concordance when assigning Gleason score 7 between urological pathologists and general pathologists were recorded. These included quantitative and qualitative factors present in the needle biopsy of the prostate such as percentage of core involvement by cancer, percentage of Gleason pattern 4 per core assessed by “eye-ball” estimate in 10% increments, distribution of Gleason pattern 4 (clustered, scattered), morphology of pattern 4 (cribriform, non-cribriform), and whether the cancer was continuous or discontinuous. Non-cribriform pattern 4 included both poorly-formed and fused glands. Statistics were performed using STATA (Stata-Corp, College Station, TX).

RESULTS

The overall percentage of tumor per core ranged from 5% to 100% with an average of 47% and the overall percentage of pattern 4 per core provided by the consultant ranged from 5% to 90% with an average of 34%. Two hundred and ninety biopsies (71.6%) were assigned Gleason score \( 3 + 4 = 7 \) (Grade Group 2) and 115 biopsies (28.4%) were assigned Gleason score \( 4 + 3 = 7 \) (Grade Group 3) on the consultant’s review. When the consultant assigned Gleason score \( 3 + 4 = 7 \) (Grade Group 2), there was agreement with the referring pathologists in 187 biopsies (64.5%), 79 biopsies (27.2%) were under-graded, and 24 biopsies (8.3%) were over-graded relative to the consultant. When the consultant assigned Gleason score \( 4 + 3 = 7 \) (Grade Group 3), there was agreement with the referring pathologists in 54 biopsies (47%), 50 biopsies (43.5%) were under-graded, and 11 biopsies (9.5%) were over-graded relative to the consultant.

Greater agreement was noted between the consultant and referring pathologists when pattern 4 was clustered \( (P = 0.009) \) in biopsies with Gleason scores \( 3 + 4 = 7 \) (Grade Group 2) and \( 4 + 3 = 7 \) (Grade Group 3) (Figs. 1–4). The percentage of core involvement by cancer, morphology of pattern 4, and continuity of cancer did not affect the agreement between the consultant and referring pathologists (Table I) (Fig. 5). One-way ANOVA test was conducted to explore the difference between the referring pathologists’ grading groups in terms of overall percentage of the tumor and percentage of pattern 4 provided by the consultant pathologist. The analysis was performed separately for samples graded as \( 3 + 4 \) (Grade Group 2) and \( 4 + 3 \) (Grade Group 3) by the consulting pathologist. There was a trend \( (P = 0.06) \) for better agreement based on the percent of pattern 4. When the consultant diagnosed Gleason \( 3 + 4 \) (Grade Group 2) and the contributors graded lower, in 80% of the cases there was <20% pattern 4. When the consultant diagnosed Gleason \( 4 + 3 \) (Grade Group 3) and the contributors graded lower, 70% of the cases...
DISCUSSION

Gleason score 7 prostatic carcinomas are traditionally subdivided into $3 + 4 = 7$ (Grade Group 2) and $4 + 3 = 7$ (Grade Group 3), depending whether pattern 4 is predominant. Published studies have shown that the greater the amount of Gleason pattern 4, the worse the prognosis [7–11]. Multiple studies have examined the inter-observer reproducibility of Gleason grading of prostatic adenocarcinoma both amongst urologic pathologists as well as between general pathologists. A consistent finding in studies that examined the inter-observer reproducibility of Gleason grading of prostatic carcinoma amongst urologic pathologists is the presence of substantial inter-observer agreement for Gleason score 7 [12–14]. On the other hand, other studies have demonstrated consistent under-grading of Gleason scores with Gleason score 7 being under-diagnosed by general pathologists [15–16]. A recent study examined the inter-observer reproducibility among urologic pathologists, addressing the impact of diagnosing “poorly formed glands” Gleason pattern 4 prostatic adenocarcinoma [17]. The study showed fair overall reproducibility among urologic pathologists for diagnosing “poorly formed glands” of Gleason pattern 4. McKenney et al. also has demonstrated that interobserver reproducibility for the histological distinction of tangentially sectioned Gleason pattern 3 from Gleason pattern 4 was only fair (Light’s % 0.27) [18].

In the present study, we assessed the agreement between a urologic pathologist and general pathologists when assigning Gleason score 7 on needle core biopsy. The most significant factor that we demonstrated to improve interobserver reproducibility was the presence of clustered distribution of pattern 4. It makes sense that it is easier to assess the percent of pattern 4 when the pattern 4 is localized as a cluster of either poorly formed, fused, or cribriform glands as opposed to scattered amongst well-formed glands of pattern 3 (Fig. 4). There was a trend for lower percentage of pattern 4 to result in an increased likelihood of undergrading. It is intuitive that cases of $3 + 4$ (Grade Group 2) with $<20\%$ pattern 4 would have an increased potential of being undergraded as Gleason $3 + 3$ (Grade Group 1). Similarly, Cases of $4 + 3 = 7$ (Grade Group 3) with $50–70\%$ of pattern 4 would have an increased potential of being undergraded as Gleason $3 + 4 = 7$ (Grade Group 2).

Although not included in the ISUP manuscript on the 2014 consensus conference, it was recommended at the meeting the percent pattern 4 be recorded for Gleason score 7 in both needle biopsy and radical prostatectomy specimens. The major advantage for recording the percent pattern 4 is in biopsy for men being considered for active surveillance (AS). For the appropriate patient, Gleason score $3 + 3 = 6$ (Grade Group 1) is accepted for men to undergo active surveillance. However, there may be some men, depending on age, co-morbidity, extent of cancer, imaging findings, patient desire, etc., who could be a candidate for active surveillance with Gleason score $3 + 4 = 7$ (Grade Group 2) if the pattern 4 is limited. The amount of pattern 4 is not only used for active surveillance but could be used for radiation therapy as well. Currently, there are different radiation therapy protocols for Gleason score $3 + 4 = 7$ (Grade Group 2) versus Gleason score $4 + 3 = 7$ (Grade Group 3). A case that is
borderline between these two grades would be apparent if the percent pattern 4 is recorded and then other factors (clinical stage, PSA, number of cores positive, etc.) could be used to decide therapy. By recording percent pattern 4 it would also explain cases, as seen in the current study, where there are discrepant diagnoses between pathologists with borderline amounts of pattern 4. This would apply to several scenarios: (i) one pathologist grades a tumor as 3 + 4 = 7 (Grade Group 1) and the other as 3 + 4 = 7 (Grade Group 2) with limited percent pattern 4; and (ii) one pathologist grades a tumor as 3 + 4 = 7 (Grade Group 2) and the other as 4 + 3 = 7 (Grade Group 3) with 50–70% pattern 4. Recording percent pattern would also help explain when one pathologist grades a tumor as 4 + 3 = 7 (Grade Group 3) and the other as 4 + 4 = 8 (Grade Group 4) with 80–90% pattern 4, data not studied in the current study.

In conclusion, including percent pattern 4 in reports on prostate adenocarcinoma on needle biopsy can help explain discrepant grading between pathologists in borderline cases, and improve patient care. Our study also demonstrates that when pattern 4 is scattered amongst pattern 3 as opposed to being discrete foci, there is less inter-observer reproducibility in grading Gleason score 7 cancer. In the setting of a core with scattered poorly-formed glands surrounded by well-formed glands, where the core represents the highest grade in the case, pathologists should consider obtaining second opinions either internally within their group or externally.

| TABLE I. Influence of Percent Gleason Pattern 4 and Other Histological Factors on Interobserver Reproducibility When the Consultant Assigns Gleason Score 3 + 4 = 7 and Gleason Score 4 + 3 = 7 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Gleason 3 + 4 = 7 assigned by the consultant (n = 290) | Gleason 4 + 3 = 7 assigned by the consultant (n = 115) |
|                 | Undergraded n = 79 (27%) | Agree n = 187 (65%) | Overgraded n = 24 (8%) | Undergraded n = 50 (43%) | Agree n = 54 (47%) | Overgraded n = 11 (10%) |
| Percent Pattern 4 | Mean 16% | Mean 19% | Mean 21% | Mean 72% | Mean 75% | Mean 71% |
| Percent cancer/core | Mean 56% | Mean 45% | Mean 44% | Mean 58% | Mean 48% | Mean 27% |
| Cribriform pattern 4 | 9 (11%) | 32 (17%) | 1 (4%) | 6 (12%) | 7 (13%) | 1 (9%) |
| Non-cribriform pattern 4 | 70 (89%) | 155 (83%) | 23 (96%) | 44 (88%) | 47 (87%) | 10 (91%) |
| Discontinuous cancer | 26 (33%) | 48 (26%) | 5 (21%) | 17 (34%) | 18 (33%) | 2 (18%) |
| Continuous cancer | 53 (67%) | 139 (74%) | 19 (79%) | 33 (66%) | 36 (67%) | 9 (82%) |

Fig. 5. Gleason score 3 + 4 = 7 (Grade Group 2) with well-formed discrete glands of Gleason pattern 3 (top) and cribriform gland of Gleason pattern 4 (bottom left).

Fig. 6. Agreement in grading between general pathologists and consultant uropathologist with Gleason score 7 cancer relative to extent of cancer.
REFERENCES


