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Current Practices in Prostate Pathology Reporting: Results from a Survey of Genitourinary and General Pathologists

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Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Ethics Statement
(i) Informed, written consent considered obtained by accepting to fill out the survey
(ii) Studies were performed according to the Declaration of Helsinki;
(iii) The procedures were approved by the University of California Institutional Review Board, Protocol 3807, 11/6/2023.

Keywords: prostate, survey, reporting, prostate cancer

This study was presented at the USCAP 2023 Annual Meeting in New Orleans.

Abstract

Aims

Standardizing pathology reporting protocols through peer consensus review is critical for best quality of care metrics. Reporting heterogeneity due to discrepancies among professional societies and practice patterns may lead to heterogeneous management and treatment approaches. This issue prompted a multi-institutional survey of pathologists to address potential similarities or differences in trends and practice patterns in prostate pathology reporting worldwide.

Methods and Results

A REDCap survey was distributed among 175 pathologists worldwide, recruited through invitations and social media. The response rate among invited pathologists was 83%. The practice locations were as follows: North America (USA, Canada, and Mexico, 62%), Europe (17.0%), Australia/New Zealand (3%), Central/South America (2%), Asia (13%), Africa (2%). Most pathologists practiced for <5 years (28.0%). A genitourinary (GU) pathology fellowship was completed by 36.6%, 58.3% practiced in a subspecialized setting, and 43.4% in academia. Reporting includes (63.4%) or subtracts (36.6%) intervening benign tissue. Both Gleason score and Grade Groups (GG)s are reported by 96%; 94.3% report percent pattern 4 (%4). Aggregate

grading and volume estimation in undesignated cores with different grades in the same jar are reported by 73.1% and 53.7% for systematic biopsies, and 83.4% and 62.3% for targeted biopsies, respectively. Cribriform morphology is reported by 81.1%. For presumed intraductal carcinoma (IDC), 89.1% use basal cell markers when isolated (iIDC), 82.3% with GG1 cancer, and 36.6% with ≥GG2. iIDC or IDC associated with GG1 or with ≥GG2 is not graded by 89.7%, 77.7%, and 69.7%, respectively. In radical prostatectomies, 89.8% report %4, but only 53.5% report it if the overall grade is ≥7. A tumor with Gleason 3+3=6 and < 5% pattern 4 is graded as GG2 by 63.7%. A <5% cut-off for defining tertiary pattern is used by 73.9%, and 79.6% report >5% pattern 4 or 5 as a secondary pattern. Grading is assigned based on the dominant nodule by 58.6%. Finally, reporting practices were significantly associated with demographic characteristics.

Conclusions

Although most issues are agreed upon, significant discordance is identified among societies and pathologists in different practice settings. We hope this survey will serve as the basis for future studies and new collaborative approaches to more standardized reporting practices.

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Introduction

Consensus recommendations on grading and reporting of prostatic adenocarcinoma have been published by the International Society of Urological Pathology (ISUP) and the Genitourinary Pathology Society (GUPS) [1, 2]. Although the societies' position papers are in overall agreement, a few differences remain on important issues, which may impact patient management. Additional in-depth discussions of detailed differences between the two societies have been addressed in several excellent reviews[3-6] and will not be further discussed herein. Moreover, including specific histologic findings in the report can vary based on prevailing practice patterns. These variables could affect clinical decisions and treatment protocols. Given the clinical impact of such diverging approaches, in 2021, the College of American Pathologists opted to specifically address potential grading discrepancies by adding a single-select core question about whether IDC-P is incorporated into the grade within the prostate cancer protocol template [7-10].

The resulting practice standards among genitourinary (GU) pathologists worldwide have not been evaluated. The existing gap prompted this survey to delineate both areas of consensus and divergence among GU and general pathologists across various practice settings and to highlight areas requiring standardization. The current study aims to describe the spectrum of reporting practices in prostatic pathology by surveying GU and general pathologists with interest/expertise

in GU pathology. We aimed to highlight emerging areas of agreement and disagreement, identify areas needing further standardization, and support a unified reporting approach vision.

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Material and Methods

This cross-sectional study used a web-based survey querying grading and reporting practices in prostate pathology. The online survey, administered in September 2022, was prepared by two of the authors (GAG and SRW) and included 36 multiple-choice questions circulated among 175 pathologists worldwide recruited in two groups: Group 1 included 61 invited academic GU pathologists, selected based on demonstrated interest in prostate pathology; Group 2 included 114 pathologists recruited on social media (Twitter and Facebook). Invited pathologists were given the option of authorship. Study data were collected and managed using Research Electronic Data Capture (REDCap) [11, 12]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Responses were collected as anonymized data. Respondents were asked to choose the best possible answer based on their practice. Analyses of the survey responses was carried out using R (version 4.2.1) [13] and Stata (Version 18, StataCorp LLC, College Station, TX). The response differences for each question between groups (years of practice, GU fellowship, practice type, practice setting, and geographic location of practice) were compared using the Pearson's chi-squared test. Statistically significant comparisons were further analyzed using pairwise comparisons with p-values

adjusted by the Bonferroni multiple comparisons method. A *P*-value of 0.05 was considered significant for all statistical analyses.

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Results

The response rate among invited GU pathologists was 83% (61 of 73). An additional 114 pathologists were recruited on social media, for a total of 175 respondents. The analysis excluded incomplete surveys containing only responses to demographic questions. Of the total 175 surveys, 20 had only partial responses to questions related to pathology. Furthermore, the final radical prostatectomy survey page was not completed by 18 respondents, resulting in a total of 157 complete responses for this chapter. These responses were included in the analysis. The demographic characteristics of the participants are shown in Table 1. One participant self-defined as practicing in "Other" country without further specification and was not included in the comparisons for geographic location of practice. Details of reporting practices for prostate biopsies and radical prostatectomies are shown in Tables 2 and 3, respectively.

Association between demographic characteristics and biopsy reporting practices

The response differences for each reporting practice question were compared between groups of demographic characteristics (years of practice, GU fellowship, practice type, practice setting, and geographic location of practice). These comparisons are illustrated in Supplemental Tables 1 and 2.

Post-hoc analysis of the association between demographic characteristics and biopsy reporting practices

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Additional post-hoc analysis of significant comparisons was performed, and selected results of interest are discussed below.

Years of practice

Post-hoc analysis of comparisons between demographic characteristics and biopsy reporting practices showed that most respondents consistently measure the percent volume out of total cancer as opposed to the length of pattern 4 divided by total cancer length (P= 0.037) in all practice years groups.

GU fellowship

Participants with a GU fellowship are significantly less likely to report percent pattern 4 (%4) in cores with a score >7 (GU fellowship, 31% vs. no GU fellowship, 54%, P=0.016); and more likely to diagnose atypical intraductal proliferation (AIP) on biopsy (84% vs. 64%, P= 0.01). Prostate biopsies may be reported at either a specimen or case level, or both [14]. When a single core is received in a site-specific labeled specimen, core reporting is applicable. When multiple undesignated cores are received in a single specimen container, specimen-level reporting is generated for the entire tissue contained within the container. Case-level reporting provides a single, overall Gleason score for the entire case, which is either the highest Gleason score or a combined global Gleason score summary for the entire case. In the current survey, for systematic prostate biopsies, all pathologists are similarly significantly more likely to grade at a specimen level (*GU fellowship*-specimen level, 80% vs. case level, 0, P<0.01; specimen level, 80% vs. both, 20%, P<0.01- *No GU fellowship*, 68% vs. 13%, P<0.01; 68% vs. 19%, P<0.01), rather than case level with no difference in reporting based on presence or absence of fellowship.

Practice type

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Participants in both subspecialized (*subspecialized* – specimen level, 73% vs. case level, 4%, P<0.01; specimen level, 73% vs. both, 24%, P<0.01) and general (73% vs. 14%, P<0.01; 73% vs. 14%, P<0.01) practices are more likely to grade at a specimen than case level or specimen vs. both with no difference in reporting based on practice type.

Both subspecialized (88% vs 12%, P < 0.01) and general (77% vs 23%, P < 0.01) practices are more likely to assign a global score in targeted biopsies than to grade each core individually when multiple cores are present in the same jar.

When presented with a scenario of a loosely cribriform lesion with basal cells lacking marked atypia or necrosis, and in the absence of invasive cancer, subspecialized practices diagnose AIP more frequently than cribriform high-grade prostatic intraepithelial neoplasia (HGPIN) and IDC (AIP, 73% vs. HGPIN, 18%, P<0.01; AIP, 73% vs. IDC, 10%, P<0.01; HGPIN, 18% vs. IDC, 10%, P=1.0). In contrast, general practices diagnose AIP and HGPIN with equal frequency (AIP, 51% vs. 38%, p = 1.0), but identify more AIP cases than IDC (51% vs. 11%, p < 0.01) and more HGPIN cases than IDC (38% vs. 11%, p < 0.01). Nevertheless, subspecialized practices report more AIP diagnoses than general practices (73% vs. 51%, P = 0.049), while general practices report more cribriform HGPIN diagnoses (38% vs. 18%, P = 0.042).

Both subspecialized and general practices perform immunohistochemistry (IHC) for basal cell markers with isolated (in absence of invasive carcinoma) intraductal carcinoma (iIDC) (*subspecialized,* perform IHC, 94% vs. do not perform IHC, 6%, P<0.01; *general,* perform IHC, 82% vs. do not perform IHC, 18%, P<0.01) or associated with Gleason pattern 3 cancer (*subspecialized*, perform IHC, 88% vs. do not perform IHC, 12%, P<0.01; *general*, perform IHC, 74% vs. do not perform IHC, 25%, P<0.01). Finally, subspecialized practices are less likely to perform basal cell markers (do not perform IHC, 71% vs. perform IHC, 29%, P<0.01) with

presumed (hereafter, the word "presumed" is used to identify a cribriform proliferation where the differential diagnosis includes IDC and cribriform invasive pattern 4 carcinoma) IDC associated with Gleason score ≥7 , whereas general practices similarly do and do not perform basal cell markers (do not perform IHC, 53%, vs. perform IHC, 47%, P=1.00).

Geographic location of practice

Estimating %4 using volume, as opposed to measuring length in millimeters, was significantly more frequent in North America, Europe, and Asia. No significant difference emerged in Africa, likely due to the small sample size of responders. Responses from Central/South (C/S) America and Australia/New Zealand (NZ) were not estimable.

Compared to responders within North America, Australia/NZ, and Africa, where reporting responses were not significantly different, respondents from Asian countries and C/S America are more likely to report percent pattern 5 (%5) in cores with Gleason score >7 (*Asia*, report, 83%; do not report 17%; P=0.014; *C/S America*, report, 100%; do not report, 0, P=comparison not estimable).

Specimen-level grading is most common in North America (specimen level: 85% vs. case level, 3%, P<0.001; specimen level vs. both, 12%, P<0.001). Europe, Asia, Australia/NZ, C/S America, and Africa show no significant reporting differences.

For multiple targeted cores contained in the same jar, both North American (assign a global grade, 86% vs. grade separately each core, 14%, P<0.001) and European respondents (93% vs. 7%, P<0.001) are significantly more likely to assign a global grade. Responses from Australia/NZ, Asia, and Africa were not statistically different, while data from C/S America (100% vs. 0%) were not estimable.

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When faced with a loosely cribriform lesion with basal cells lacking marked atypia and necrosis, North American pathologists are more likely to diagnose AIP than cribriform HGPIN or IDC (AIP, 69% vs HGPIN, 26%, P<0.001; AIP vs. IDC, 6% P<0.001; HGPIN vs IDC, P=0.012). European pathologists also favor an AIP diagnosis (AIP, 67% vs. HGPIN, 27%, P=1.00; HGPIN vs. IDC, 7%, P=1.00; AIP vs. IDC, P<0.001). Diagnoses were not significantly different in other tested continents.

When questioned whether they entertained an AIP as a diagnosis on biopsy, most North American pathologists responded positively (yes, 80% vs. no, 20%, P < 0.001). Trends were similar for Europe (yes, 70% vs. no, 30%, P=1.00), Australia/NZ (yes, 100% vs. no, 0%, not estimable). In contrast, they were split for C/S America. Asian and African pathologists tend not to make this diagnosis (*Asia* - yes, 35% vs. no, 65%, P=1.00; *Africa* - yes, 33% vs. no, 67%, P=1.00).

Practice setting

Reporting %4 in cores with score >7 is significantly less likely in an academic setting (no, 68%, vs. yes 32%, P=0.031). Grading at a specimen level is more likely in academic (specimen level, 84%; case level, 3%; both, 13%; specimen vs. case, P<0.01; specimen vs. both, P<0.01) and private practice (specimen level, 72%; case level, 6%, both, 22%; specimen vs. case, P<0.01) compared to case level or both. Similar trends were seen in all other practice settings.

Association between demographic characteristics and radical prostatectomy reporting practices

GU fellowship

GU fellowship-trained pathologists are more likely to diagnose a tumor with Gleason 3+3=6 and a <5% pattern 4 component as GG2 (GG1, 25% vs. GG2, 75%, P<0.01) as opposed to GG1. The

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proportions differed for non-GU fellowship-trained pathologists (GG1, 44% vs. GG2, 56%, P<0.01).

Practice type

%4 is reported by both general (yes, 83% vs. no, 17%, P<0.01) and subspecialized practices (yes, 94% vs. no, 6%, P<0.01). In subspecialized practices, GG2 with a minor (< 5%) pattern 4 is the most likely diagnosis for a tumor with predominant Gleason 3+3=6 and a minor (< 5%) pattern 4 rather than GG1 (70% vs. 30%; P<0.01), whereas general practices equally diagnose GG2 and GG1.

General practices are more likely to report %5 (yes, 83% vs. no, 17%, P<0.01) (subspecialized, yes, 63% vs. no, 37%, P=0.57). General practices similarly define tertiary ("minor") pattern as <5% and any amount less than the primary and secondary pattern (<5%, 62% vs. 38%, P=0.39) compared to subspecialized practices, which more likely use a <5% cutoff (81% vs. 19%, P<0.01). Subspecialized practices are more likely to assign a grade based on the dominant nodule compared to aggregating the grade of multiple nodules (68% vs. 32%, P<0.01), with no difference in general practices (43% vs. 57%, P=1.00). Both subspecialized and general practices similarly more likely assign a secondary pattern to a tertiary ("minor") pattern >5% (subspecialized: secondary, 87% vs. minor, 14%, P<0.01; general, secondary, 68% vs. minor, 32%, P=0.016).

Both subspecialized (report, 94%; do not report, 6%) and general practices (report, 83%; do not report, 17%) report % 4 significantly more frequently.

Geographic location of practice

North American, Australian/NZ, and African responders were significantly more likely to define "tertiary pattern" as a <5% higher grade pattern compared to any amount less than the primary

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pattern. In contrast, Asian and European responders used both definitions similarly. C/S American and African responses were not estimable due to the small specimen size.

Discussion

Cancer extent

Cancer extent is known to have prognostic significance and clinical implications for active surveillance in prostate biopsies. Cancer extent in biopsies can be estimated as: 1) discontinuous tumor foci as a single tumor in and out of the plane of the section, including intervening benign glands [15]; or, by adding each focus, excluding intervening benign glands [16]. While the former method is predictive of stage and margin status, subtracting intervening benign tissue more closely predicts cancer extent in prostatectomy specimens [15, 17-19]. Currently, there is no consensus on the optimal measurement methods. These two methods can produce significantly different tumor volume estimations, which may affect clinical management. For example, a threshold of 50% is one of the criteria for excluding patients from active surveillance in some protocols [20]. Therefore, two small cancer foci at opposite ends of the biopsy could be interpreted as either 20% or 90%. In current practice, there may be a shift toward accepting any amount of GG1 and even some GG2 cancer for surveillance; however, this likely varies significantly among practices. In our survey, 63.4% of respondents include intervening benign tissue in the estimation. Practice type, geography, years of practice, and practice setting did not affect tumor quantitation.

Grading

Utilizing the proposed 5-tier GG system by the group at Johns Hopkins, followed by a multi-institutional validation study [21, 22], the 2014 International Society of Urological Pathology

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Conference recommended that the GG system be incorporated into pathology reports in conjunction with the Gleason score system (GS) [23]. In our survey, 96% of respondents include both GG and GS in their reports, and only 3.4% report only the GS, irrespective of years of practice, type of training, practice setting, and practice location. These findings are similar to those of the recent GUPS and ISUP surveys [1, 2].

Reporting Pattern 4 in Grade Groups 2 to 5

Reporting %4 in core biopsies with GG2 and GG3 is recommended by the GUPS, the ISUP, the College of American Pathologists, and the WHO Tumor Classification [1, 2, 24]. This recommendation has a strong clinical rationale. Intermediate-risk patients with low-volume pattern 4 (GG2) disease can be selected for active surveillance [20]. Increasing %4 on biopsy correlates with increasing rates of adverse pathology in radical prostatectomies [25, 26]. In intermediate-risk patients undergoing radiation therapy, %4 may have profound implications on clinical decision-making [20].

There is no established value in reporting %4 in patients with GG2 and GG3 with concurrent GG4 and GG5, as these are NCCN high-risk patients [20]. However, approximately half of patients with Gleason score 4+4=8 as the highest score on biopsy are downgraded to a lower Gleason Score [27-29], supporting the utility of risk stratification based on %4 in other cores with GG2 and GG3.

In our survey, 94.3% of respondents report %4 in biopsies. However, only 45.7% of respondents report %4 in cores with Gleason score >7. Reporting %4 in this setting was significantly more common among general pathologists than GU fellowship-trained pathologists.

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The rationale for reporting %4 in radical prostatectomy is less compelling, and the value of reporting %4 in GG2 and GG3 patients is conflicting. Some studies have demonstrated that %4 may impact the 5-year biochemical risk-free survival, whereas others have implicated minimal impact in predicting biochemical recurrence after radical prostatectomy [30-34].

Approaches for reporting %4 include continuous measurement (e.g., 13%), 5% or 10% increments, and quartile increments (<25%, 25%-49%, 50%-74%, and >75%). The quartile approach may limit interobserver variability but may impact precise risk stratification by lumping patients with variable risks into one group (for example, patients with <5% versus patients with 20% pattern 4). Further studies are required to address the best method of reporting %4. In our survey, 46.1% of responders use a 5% increment, 40.6% a 10% increment, and a minority use quartile increments (4.8%) or continuous measurement (8.5%).

Another practice pattern investigated was grading of systematic and targeted biopsy cores if multiple undesignated cores are submitted in the same jar. The GUPS recommends that "for systematic biopsies with multiple undesignated cores with cancer in one container, the current standard is to provide an overall grade for the cores in the specimen container. Following this practice, and until more studies are available to clarify the issue, we recommend reporting the same approach for grading when multiple cores are taken from a single MRI-targeted lesion" [2]. The ISUP similarly recommends reporting a separate score for individual biopsy sites for systematic biopsies, and a global score for each suspicious MRI lesion [1]. Aggregate Gleason score better predicted tumor volume and extraprostatic extension in targeted biopsies, but was inconclusive in predicting grade at radical prostatectomy [35]. More recently, targeted biopsy global GG showed slightly better agreement with the GG on radical prostatectomy than the highest GG and largest volume/linear length GG [36].

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In our survey, for systematic cores, 73.1% of respondents assign a global GG for all cores included in the same specimen jar versus 26.9% grading each core individually, and with even more disagreement with 46.3% assigning tumor volume per core and 53.7% reporting the aggregate volume from all cores. There was no difference based on years of practice, practice type, GU fellowship training, or practice location. Similarly, for targeted cores, 83.4% report a global GG compared to 16.6% grading each core separately, and 37.7% quantify tumor extent per core compared to 62.3% reporting the aggregate volume from all cores. Both subspecialized and general practices are significantly more likely to give a global GG to all targeted cores included in the same jar. North America and Europe were significantly more likely to assign a global grade. There was no significant association with years of practice, GU fellowship, practice type, and setting. However, some of the authors of this manuscript have experienced that the information conveyed by aggregating grade and volume may be misleading for patient management. For example, a targeted specimen containing eight cores involved by tumor, of which seven involved by Gleason score 3+3=6 (GG1) and one involved by Gleason score 3+4=7 (GG2, <5% pattern 4), would be reported by aggregating grade and volume as "prostatic adenocarcinoma, Gleason Grade 3+4=7 (GG2, <5% pattern 4), involving 8/8 cores", requiring a separate note explaining the presence of limited pattern 4 in only one of the total 8 cores. In our personal experience, this note prompted direct discussion with the urologist and reconsideration of surgical treatment towards active surveillance. Therefore, additional data followed by unified society consensus guidelines may be required to establish a unified approach to tumor grading and volume quantification in both systematic and targeted biopsies when more than one core is included in the same jar.

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Cribriform Pattern (Cribriform Invasive Adenocarcinoma, Intraductal Carcinoma and Atypical Intraductal Proliferation)

Invasive carcinoma with cribriform architecture on biopsy is strongly associated with upgrading and upstaging at radical prostatectomy, higher risk of biochemical recurrence, and lower disease-specific survival after radical prostatectomy or radiation [37-41]. In radical prostatectomy specimens with Gleason score of 7, cribriform architecture is associated with decreased 5-year biochemical-free survival [31, 42]. GUPS and ISUP recommend reporting cribriform morphology in biopsies and radical prostatectomies. In our survey, 81.1% and 84.1% of respondents report cribriform pattern in biopsy and prostatectomy specimens, respectively, irrespective of years of practice, practice setting, location, and training. These results differ from the 2019 GUPS survey, where only 49% of participants reported cribriform morphology on biopsies [2]. In contrast, 97% and 84% of the ISUP survey respondents agreed that invasive cribriform cancer should be commented on in GS7 and GS8 cases, respectively [1].

Large cribriform pattern may be associated with a worse clinical outcome compared with small cribriform pattern [42]. However, data are still conflicting [43, 44] due to varied defining criteria. Large cribriform glands have been defined as an area exceeding the size of an average benign gland [45], diameter of at least twice the size of adjacent benign glands [42], more than 12 luminal spaces [46], and size >0.25 mm [47]. GUPS and ISUP do not recommend reporting cribriform gland size without well-defined criteria and clinical significance. Our survey shows that over 87% of participants do not distinguish small and large cribriform glands on biopsy or radical prostatectomy. Among those who do, more than 12 luminal spaces and size >0.25 mm are the two most common criteria used to define large cribriform glands on biopsy, and cribriform

glands exceeding the size of an average benign gland as a criterion on prostatectomies. In our survey, all practice settings were significantly less likely to report size of cribriform glands. However, since the survey was conducted, additional data have emerged arguing the importance of large cribriform glands [44, 48].

Differential diagnosis of cribriform lesions also includes IDC and AIP. IDC is considered an extension of high-grade prostatic adenocarcinoma into prostatic duct and acini with at least focal preservation of basal cells. Morphologic criteria have been established to render IDC diagnosis more reproducible [49]. AIP has less stringent diagnostic criteria. Regardless of architecture, any growth within a duct with significant nuclear atypia or pleomorphism beyond HGPIN but falling short of diagnostic criteria for IDC, falls into the AIP category [50]. The distinction between cribriform HGPIN and AIP is problematic, and no reproducible criteria exist to separate these two entities. Therefore, GUPS recommends not diagnosing cribriform HGPIN on biopsy and using AIP instead [2]. Available data on the significance of AIP are limited. However, AIP is considered potentially unsampled IDC in biopsies [51].

In prostatectomies, IDC correlates with high Gleason score, large cancer volume, extraprostatic extension, seminal vesicle involvement, and lymph node metastasis [52-56]. In biopsies, IDC is associated with high-grade, high-volume prostate cancer in subsequent radical prostatectomy, higher risk of early biochemical recurrence, and cancer-specific survival [30, 57]. There is consensus that IDC should be reported in both biopsies and radical prostatectomies. However, there is considerable controversy surrounding the inclusion of IDC in the Gleason score. Although both societies agree that iIDC without invasive cancer should not be graded, GUPS recommends against grading when associated with invasive cancer. In contrast, ISUP favors factoring IDC

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into the Gleason score (as pattern 4 or 5) [1, 2]. This discrepancy has the potential to drive significant differences in Gleason scoring. For example, IDC associated with GG1 cancer could be reported as either Gleason score 3+3=6 with IDC or Gleason score 3+4=7 or 4+3=7 (if IDC with cribriform pattern) or Gleason score 3+5=8 or 5+3=8 (If IDC with solid pattern or comedonecrosis), depending on the grading method used. Our survey revealed diagnostic differences for AIP, IDC, and cribriform HGPIN across subspecialized and geographic settings. Regarding basal cell markers, ISUP advises against their use and recommends grading cribriform IDC as Gleason pattern 4 and solid IDC with/without comedonecrosis as Gleason pattern 5 [1]. According to GUPS, basal cell markers are unnecessary if they do not impact the overall GG, but they may be used with iIDC or with IDC associated with low-grade Gleason score 6 cancer. In our survey, 89.1% and 82.3% of respondents use basal cell markers with presumed IDC, either iIDC or IDC with GG1 cancer, respectively. However, only 36.6% use basal cell markers when presumed IDC is associated with a Gleason score of 7 or higher. On post-hoc analysis, both subspecialized and general practices were similarly more likely to perform IHC for basal cell markers with presumed iIDC or with Gleason pattern 3. This number dropped with a Gleason score of 7 or higher for subspecialized practices, whereas general practices were equally split. Only 10.3% of respondents grade IDC without any invasive carcinoma on biopsy. Post-hoc analysis of the statistically significant comparison between IDC grading and years of practice revealed that pathologists with all levels of experience were significantly more likely not to grade IDC without invasive carcinoma.

"Tertiary"/minor high-grade patterns

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Conventionally, a "tertiary"/minor high-grade pattern in radical prostatectomy specimens refers to the third most common pattern if: 1) it is the highest grade pattern; 2) it comprises 5% or less of a dominant tumor nodule [58-60]. The definition of "the third most common pattern" regardless of its grade and extent, has been used in some studies [61-64].

The clinical outcome of patients with "tertiary"/minor pattern 5 on biopsy is similar to that of patients with secondary Gleason pattern 5. Thus, incorporating a minor tertiary pattern into the Gleason score as the secondary pattern better predicts the pathology at radical prostatectomy [65]. Therefore, GUPS and ISUP recommend against reporting "tertiary"/minor pattern in biopsy and TURP and instead incorporating it into the Gleason score as the secondary pattern [1, 2]. In prostatectomy specimens, however, reporting minor patterns is more controversial. ISUP recommends that a minor (<5%) pattern 4 or 5 be reported as a "tertiary"/minor pattern and not included in the Gleason score, whereas 5% or more Gleason pattern 4 or 5 be included in the score as a secondary pattern. GUPS recommends that minor (<5%) tertiary pattern 5 only be used in radical prostatectomy showing GG2 or GG3 and that in prostatectomy specimens with Gleason score of 3+3 or 4+4, a minor tertiary pattern 4 or 5 be incorporated into the secondary pattern and reported as Gleason score 3+4=7 and 4+5=9, respectively, with a note mentioning that Gleason pattern 4 or 5 is minor (<5%) [1, 2]. In our survey, 73.9% of the respondents used <5% as a cut-off, and 79.6% report > 5% pattern 5 as a secondary pattern. Finally, for tumors with predominant Gleason 3+3 and a minor (< 5%) pattern 4, 63.7% report this tumor as GG2 with <5% pattern 4 instead of GG1.

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GU fellowship-trained pathologists are more likely to diagnose a tumor with Gleason 3+3=6 and a <5% pattern 4 component as GG2, as opposed to GG1. In contrast, non-GU fellowship-trained pathologists were evenly split between GG1 and GG2. An identical significant trend was also seen for subspecialized compared to general practices.

The definition of tertiary pattern was significantly differently reported, with subspecialized practices more likely to define it as <5% and more likely to report tertiary component >5% as a secondary pattern, whereas general practices are similarly likely to define tertiary pattern as <5% as well as any amount less than the primary and secondary pattern. Similarly, when grading multiple nodules, subspecialized practices are more likely to grade the case based on the dominant tumor. In contrast, general practices equally graded the dominant nodule and aggregated the grade of multiple nodules. Finally, both subspecialized and general practices similarly assigned a secondary or tertiary pattern to a “tertiary”/”minor" pattern 4 or 5 >5%.

Limitations

The study's limitations include a non-random recruitment sample, which could potentially introduce a selection bias, and a small sample size for certain countries. Notably, 56% of respondents practiced in the US, with more homogeneous grading rules expected within than between countries, which may have potentially skewed the data towards current US practice. Another potential bias is that the GUPS founding members are US GU pathologists, which may have also inherently led to skewing towards GUPS’ practice recommendations. The concept of a structured fellowship is unique to US and Canadian pathology training, making it inapplicable to approximately half of the survey participants.

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Finally, inherent limitations of *post-hoc* multiple comparison procedures are that they may not have enough statistical power to confirm the observed relationships.

Conclusions

This survey conducted among a heterogeneous cohort of pathologists worldwide describes the current status of reporting practice in prostate pathology. Main reporting practices in biopsies and radical prostatectomies are addressed, including reporting and quantifying pattern 4, methods of cancer volume quantification, case versus specimen-level grading, systematic versus multiparametric MRI-targeted grading, reporting of IDC, use of IHC, and reporting of minor tertiary pattern 5. The survey highlights a general agreement on major issues. However, several gray areas with significant discordance among GU pathology societies and pathologists in different practice settings, such as academic versus nonacademic and/or subspecialized versus general practices, as well as geographic differences, are shown. These differences affect generalization and applicability of research approaches to the general population and impact routine prostate cancer management. We hope this survey will pose the basis for future studies and new collaborative approaches to more standardized reporting practices.

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Table 1. Epidemiological characteristics of the participants' cohort.

Variable	Total Respondents (N)	Respondents (N)	%
Number of years in practice	175		
< 5		49	28.0
5 -10		30	17.1
11-15		49	19.4
16 - 20		29	16.6
>20		33	18.9
Did you complete a genitourinary pathology fellowship?	175		
Yes		64	36.6
No		111	63.4
Practice type	175		
Subspecialized		102	58.3
General		73	41.7
Geographic location of practice*	175		
North America		108	62.0
Europe		30	17.0
Australia/New Zealand		6	3.4
Central/South America		4	2.3
Asia		23	13.0
Africa		3	2.0
Other		1	0
Practice setting	175		
Academic		76	43.4
University-affiliated		24	13.7
Private Practice		32	18.3
Community Hospital		29	16.6
Government Hospital		14	8.0

Legend: N=175.

* One participant self-defined as practicing in "Other" country without further specification and was not included in the comparisons involving geographic location of practice (N=174).

Table 2. Grading and reporting patterns in prostate biopsies.

PROSTATE BIOPSY	Total Respondents (N)	Respondents (N)	%
Methods of tumor volume quantification	175		

Including intervening benign glands		111	63.4
Subtracting intervening benign glands		64	36.6
Reporting of cancer grading	175		
Gleason score only		6	3.4
Grade Group only		1	0.6
Both Gleason score and Grade Groups		168	96.0
Reporting percent pattern 4	175		
Yes		165	94.3
No		10	5.7
Estimating percent pattern 4	165		
Estimate the volume occupied by pattern 4 out of the total cancer area		151	91.5
Measure the length of pattern 4 in millimeters divided by total length of cancer		14	8.5
Methods of reporting percent pattern 4	165		
5% increments		76	46.1
10% increments		67	40.6
Quartile increments (e.g., < 25%, 25%-49%, 50%-74%, >75%0		8	4.8
Continuous measurements (e.g., 13%)		14	8.5
Reporting percent pattern 4 if higher grades are present in other specimen parts	175		
Yes		109	62.3
No		66	37.7
Reporting percent pattern 4 in cores with score >7	175		
Yes		80	45.7
No		95	54.3
Reporting percent pattern 5 in cores with score >7	175		
Yes		88	50.3
No		87	49.7
Grading systematic prostate biopsies if more than one core with different grade is submitted in the same jar?	175		
Grade separately each core		47	26.9
Give a global grade for all cores included in the specimen jar		128	73.1
Tumor volume quantification in systematic prostate biopsies if more than one core with different grade is submitted in the same jar	175		
Report volume per core (e.g., 20% of core)		81	46.3
Report the aggregate volume from all cores (e.g., 20% of the entire specimen)		94	53.7
Reporting grade in systematic prostate biopsies	175		
At a specimen level (e.g., assign an individual grade to each specimen)		127	72.6

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At a case level (e.g., assign a global grade to the entire case)		14	8.0
At both a specimen and case level		34	19.4
FOR CASE LEVEL ONLY			
Grading methodology at a case level for systematic biopsies	14		
The highest score		4	28.6
The composite score (e.g., the contiguous topographic location of positive sites representing the presumed dominant nodule)		1	7.1
The global score (e.g., all positive sites regardless of topography)		9	64.3
Grading at a case level in prostate biopsies with both systematic and targeted specimens	14		
A separate case level score for the systematic specimens and for the targeted specimens		4	28.6
A combined (global) case level score including both systematic and targeted specimens		10	71.4
Grading targeted prostate biopsies (target lesion) if more than one core with different grade is submitted in the same jar	175		
Grade separately each core		29	16.6
Give a global grade for all cores included in the specimen		146	83.4
For tumor volume quantification, which of the following do you apply to targeted prostate biopsies (target lesion) if more than one core per specimen is submitted in the same jar?	175		
Report volume per core (e.g., 20% of core)		66	37.7
Report aggregate volume from all cores (e.g., 20% of the entire specimen)		109	62.3
Cribriform morphology in prostate biopsies	175		
Yes		142	81.1
No		33	18.9
Diagnosis of cribriform HGPIN on biopsy	175		
Yes		57	32.6
No		118	67.4
Diagnosis of loosely cribriform lesion (< 50% cell density) surrounded by basal cells without marked atypia, necrosis without invasive cancer	175		
Cribriform HGPIN		46	26.3
Atypical intraductal proliferation		111	63.4
Intraductal carcinoma		18	10.3
Diagnose atypical intraductal proliferation on biopsy	175		
Yes		125	71.4

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No		50	28.6
Reporting large and small cribriform glands pattern 4 cribriform carcinoma?	175		
Yes		22	12.6
No		153	87.4
IF PREVIOUS ANSWER IS "YES"			
Criteria for diagnosis of small and large cribriform glands	22		
Having less or more than 12 luminal spaces		7	31.8
An area exceeding the size of an average benign gland		3	13.6
Diameter of at least twice the size of adjacent benign glands		5	22.7
Size of cribriform glands ≤0.25 mm vs. >0.25 mm		7	31.8
Immunohistochemistry for basal cell markers for cribriform glands without invasive carcinoma and with a differential diagnosis of intraductal carcinoma versus Gleason pattern 4 cancer?	175		
Yes		156	89.1
No		19	10.9
Immunohistochemistry for basal cell makers if Gleason 3+3=6 cancer and cribriform glands with a differential diagnosis of intraductal carcinoma versus Gleason pattern 4 cancer	175		
Yes		144	82.3
No		31	17.7
Immunohistochemistry for basal cell markers if Gleason score ≥7 and cribriform glands with a differential diagnosis of intraductal carcinoma versus Gleason pattern 4 cancer	175		
Yes		64	36.6
No		111	63.4
Grading intraductal carcinoma without invasive carcinoma?	175		
Yes		18	10.3
No		157	89.7
Grading intraductal carcinoma with Gleason 3+3=6 (Grade Group 1) carcinoma?	175		
Yes		39	22.3
No		136	77.7
Grading intraductal carcinoma with Gleason ≥ 7 (Grade Group ≥ 2) carcinoma?	175		
Yes		53	30.3
No		122	69.7

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Table 3. Grading and reporting patterns in radical prostatectomies.

RADICAL PROSTATECTOMY	Total Respondents (N)	Respondents (N)	%
Reporting percent pattern 4	157		
Yes		141	89.8
No		16	10.2
Grading Gleason 3+3=6 with <5% pattern 4	157		
Grade Group 1		57	36.3
Grade Group 2 with <5% pattern 4		100	63.7
Reporting percent pattern 4 if overall grade ≥7	157		
Yes		84	53.5
No		73	46.5
Reporting percent pattern 5	157		
Yes		111	70.7
No		46	29.3
Definition of tertiary ("minor") pattern	157		
<5%		116	73.9
Any amount less than the primary and secondary pattern		41	26.1
Reporting "minor" pattern 4 or 5 if >5%	157		
Report as secondary pattern		125	79.6
Report as tertiary pattern		32	20.4
Assigning grade when multiple and distinct nodules	157		
I assign the overall grade based on the dominant nodule		92	58.6
I combine the grade of all nodules to obtain a merged global grade		65	41.4
Reporting cribriform morphology	157		
Yes		132	84.1
No		25	15.9
Reporting large and small cribriform glands pattern 4 cribriform carcinoma?	157		
Yes		19	12.1
No		138	87.9
IF PREVIOUS ANSWER IS "YES"			
Criteria for diagnosis of small and large cribriform glands	19		
Having less or more than 12 luminal spaces		5	26.3
An area exceeding the size of an average benign gland		4	21.1
Diameter of at least twice the size of adjacent benign glands		7	36.8
		3	15.8

Immunohistochemistry for basal cell makers if Gleason 3+3=6 cancer and cribriform glands with a differential diagnosis of intraductal carcinoma versus Gleason pattern 4 cancer	96		
Yes		80	83.3
No		16	16.7
Immunohistochemistry for basal cell markers if Gleason score ≥7 and cribriform glands with a differential diagnosis of intraductal carcinoma versus Gleason pattern 4 cancer	156		
Yes		52	33.3
No		104	66.7
Grading intraductal carcinoma without invasive carcinoma?	157		
Yes		16	10.2
No		141	89.8
Grading intraductal carcinoma with Gleason 3+3=6 (Grade Group 1) carcinoma?	157		
Yes		38	24.2
No		119	75.8
Grading intraductal carcinoma with Gleason ≥ 7 (Grade Group ≥ 2) carcinoma?	157		
Yes		53	33.8
No		104	66.2

Graphical abstract text

This survey conducted among a heterogeneous cohort of pathologists worldwide describes the current status of reporting practice in prostate pathology. Main reporting practices in biopsies and radical prostatectomies are addressed, including reporting and quantifying pattern 4, methods of cancer volume quantification, case versus specimen-level grading, systematic versus multiparametric MRI-targeted grading, reporting of IDC, use of immunohistochemistry and reporting of minor tertiary pattern 5.

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