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Relative Contribution of Sampling and Grading to the Quality of Prostate Biopsy: Results from a Single High-volume Institution

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Abstract

Background: The quality of prostate biopsy is affected by sampling (does the urologist take cores from the right place?) and the histological evaluation (does the pathologist grade correctly?).

Objective: To evaluate the relative contribution of sampling and histological evaluation to the reliability of prostate biopsy in terms of concordance with grading of the surgical specimen.

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Design, setting, and participants: We identified 848 prostate cancer patients who underwent radical prostatectomy between 2015 and 2017 at our institution with external or internal biopsies. Since 2016, a dedicated uropathologist has reviewed all the biopsies sampled externally.

Outcome measurements and statistical analysis: We considered the discordance between biopsy and final pathology as a proxy for the quality of prostate biopsy, and calculated the corresponding discordance rate for each biopsy setting.

Results and limitations: We observed the highest rate of grade discordance for patients who had an external biopsy without internal review (66%). Biopsies both sampled and reviewed internally had the lowest discrepancy rate (39%; $p < 0.0001$ compared to external biopsies). Biopsies sampled outside our institution and reviewed internally had an intermediate discordance rate (51%; $p = 0.003$).

Conclusions: The quality of prostate biopsy is influenced by both sampling and evaluation. Highly experienced pathological evaluation of needle biopsies is crucial, but biopsy quality also strongly depends on the quality of the sampled material. Future studies should investigate the mechanism underlying discordance in sampling. Consideration should be given to regionalization of prostate biopsy.

Patient summary: The quality of prostate biopsy varies between specialist and community centers. We found that this variation is affected by both sampling (does the urologist take cores from the right place?) and histological evaluation (does the pathologist grade correctly?).

Keywords

Prostate cancer; Prostate biopsy; Histological review; Technical sampling; Specialist pathologist; Pathological concordance; Radical prostatectomy

1. Introduction

Prostate biopsy is a highly skilled procedure. It is therefore likely that the quality of biopsy varies according to expertise, both in terms of sampling by the urologist and evaluation of tissue by the pathologist.

The second of these points has been subject to considerable attention. Interobserver and intraobserver variability are well known drawbacks of histological grading [1,2]. Previous studies have demonstrated wide discrepancies in grading between general and specialist pathologists, and the latter seems to be crucial for standardizing and improving the quality of grading [3]. Concerns about variations in grading are behind routine calls for centralized pathology review in prostate cancer studies.

Somewhat less attention has been paid to the issue of variation in sampling. Although there have been studies on the relationship between the number of cores and the cancer detection rate [4,5], many factors other than total tissue retrieved might affect biopsy quality, in particular the location and spacing of cores. For instance, a tumor focus may be missed if a biopsy needle is placed too close to the prior needle track and too far from the subsequent needle track, rather than equidistantly. Similarly, cancer can be missed if a needle is placed such that it samples tissue from outside the prostate. Even the most

experienced uropathologist will be unable to accurately grade a cancer if the prostate was not sampled appropriately.

Patients with newly diagnosed, clinically localized prostate cancer treated surgically at our institution, a tertiary care center, may have biopsies conducted either internally or may have a biopsy at an external site and then be referred to us for treatment. Furthermore, since November 2016, external samples have been reviewed internally by an expert uropathologist as a standard protocol before surgery. Hence, biopsy data derived from three different settings, according to where they have been sampled and evaluated, are available. In our study, we used biopsies performed internally in a specialist prostate cancer unit as a reference, on the assumption that this setting is optimal for sampling and evaluation. This allowed us to evaluate each factor separately: comparing external biopsies with and without internal review is informative on the importance of pathological evaluation; comparing external biopsies with internal review to biopsies conducted and evaluated internally is informative on the importance of sampling. We use pathology of the surgical specimen as the gold standard to define biopsy quality. Accordingly, here we sought to determine the relative contribution of sampling and pathological evaluation to the final accuracy of prostate biopsy.

2. Patients and methods

We evaluated 848 men who underwent radical prostatectomy at our institution between 2015 and 2017 for clinically localized prostate cancer diagnosed by transrectal ultrasound-guided (TRUS) prostate biopsy. Since 2016, internal biopsy review has been performed: up until November 2016, the indication for histological review of external biopsies was given by each treating physician on the basis of disease profile; after November 2016, all external biopsies were internally reviewed as a standard procedure after obtaining the original samples on request. At our institution, patients underwent at least 12-core, 18G-caliber needle biopsy with site-specific submission (two cores per anatomic site: apex, middle, and base on the left and right sides) performed by experienced (>200 previous biopsies) urologists, as recommended by the European Association of Urology (EAU) guidelines. A greater number of cores were taken if determined appropriate by the treating physician according to individual risk assessment. International Society of Urological Pathology (ISUP) grade was reported according to each anatomic sampling site. A small number of internal biopsies were conducted with magnetic resonance imaging guidance; these were excluded from our cohort. Patients were divided into three groups according to biopsy features: men who underwent TRUS prostate biopsy at our institution (n = 401; 47%); men who underwent biopsy at another institution but whose biopsies were prospectively reviewed at our institution by our expert uropathologists (n = 313; 37%); and men who underwent biopsy at another institution and received surgery without internal biopsy review (n = 134; 16%).

All the patients received surgery as their primary treatment as none of them received any neoadjuvant treatment. Radical prostatectomy was performed using a conventional surgical approach as previously described [6]. Two high-volume uropathologists examined both the internal biopsy and surgical specimens. For internal grading and staging purposes, the most

up-to-date ISUP grading system [7] and TNM classification at the time of evaluation were used [8]; moreover, a global ISUP grade, taking into account all cores positive for cancer, was assigned.

Histological data consisted of the number of cores taken, number of positive cores, and biopsy ISUP grade. The following data on the pathological specimen were documented: prostate and tumor volume, ISUP grade, pathological stage, extraprostatic extension, seminal vesicle involvement, lymph node involvement, perineural invasion, and surgical margin status. We also documented patient age, preoperative prostate-specific antigen (PSA), clinical stage, and D'Amico risk group [9]. Discordance was defined as a diagnostic prostate biopsy showing a different ISUP grade when compared with the corresponding surgical specimen. Undergrading was defined as a lower grade in biopsy than in surgical specimens, and overgrading as the opposite. For the purposes of this study, we decided to report our results using the ISUP grade groups, as it has been demonstrated that these are the most reliable prognostic tool for histological grading of prostate cancer [10].

The primary endpoint of the study was to assess the impact of biopsy sampling and uropathologist review on the diagnostic accuracy of prostate biopsy. To address this issue, we evaluated grading discordance rates between biopsy and final pathology according to different biopsy settings.

Our statistical analysis involved four steps. First, we tested the association between different biopsy settings (external, internal, and external with internal biopsy review) and the ISUP grade group discordance rate using univariable analysis. Second, we hypothesized that despite better accuracy given the highly experienced pathological review, other sampling-related factors might influence histological reliability. Therefore, we tested the same outcome in a multivariable setting. The covariates identified were age (continuous), preoperative PSA (continuous), pathological stage (T2 vs T3a vs T3b), pathologic ISUP grade group (1 vs 2–3 vs ≥3), and biopsy setting (internal vs external vs external reviewed). Since there is evidence that the weight of the gland is a reasonable surrogate for prostate volume [11], we included pathological prostate weight (continuous) in the multivariable model. Furthermore, since internal review was performed according to physician decision up until November 2016, we tested the hypothesis that external sampling was prone to selection bias by repeating the analysis and including the original ISUP grade (before internal review) in the model for patients with external biopsies. Third, we tested the hypothesis that the number of cores taken and positive for prostate cancer might affect the agreement between biopsy and surgical pathology. Specifically, our null hypothesis was that the accuracy of any given biopsy setting would not be influenced by the number of cores sampled or involved by tumor. Finally, not all grading discrepancies are equally important. For instance, a change between ISUP grade groups 1 and 2 would probably influence treatment decision-making, whereas a change between groups 3 and 4 would have less influence. Hence, we defined a clinically relevant discrepancy as any change between groups 1 and 2, downgrading from group 3, or any two-group discrepancy (eg, group 3 to group 5). We repeated all analyses for this new endpoint.

Statistical analyses were performed using Stata v.15.0 (StataCorp LP, College Station, TX, USA). All tests were two-sided with a significance level of 0.05.

3. Results

The preoperative characteristics and pathologic results for our cohort are reported in Table 1. Overall, the ISUP grade was significantly different among biopsy groups both for initial biopsy ($p < 0.0001$) and final pathology ($p = 0.03$), with internal patients generally having more aggressive disease, probably as a result of trends to treat higher-risk disease surgically. The number of cores retrieved differed according to biopsy setting, while the number of positive cores did not.

Results for grade discordance rates according to biopsy setting are listed in Table 2. Among patients who had an external biopsy without pathological review, the discordance rate was 66%, and a greater number were undergraded rather than overgraded. On the contrary, biopsies performed internally had the lowest rate of both discordance (39%; $p < 0.0001$) and undergrading ($p = 0.01$). Finally, among patients with external sampling and subsequent internal review, the discordance rate between the original biopsy and final pathology was 70%, and histological review lowered this rate to 51%. However, it is interesting that the discrepancy rate was still significantly higher than that for internal biopsies, while undergrading and overgrading rates remained similar.

On multivariable analysis, the probability of discordance was significantly higher for external biopsies without internal review than for internal biopsies (odds ratio [OR] 3.27, 95% confidence interval [CI] 2.12–5.05; $p < 0.0001$). External biopsies reviewed internally also had a higher rate of discordance (OR 1.62, 95% CI 1.18–2.23; $p = 0.003$; Table 3). Next, we hypothesized that the association between biopsy setting and biopsy quality would vary according to the number of cores or number of positive cores. However, all interaction tests were nonsignificant ($p > 0.1$), providing no evidence that differences in sampling or evaluation depend on the number of cores. Given that the indication for biopsy review was not standardized for the entire study period, it is possible that biopsies selected for review were different from those not selected. We compared the results for patients with external review and external sampling to those for patients with external sampling and internal review, but used the original grade before review for the latter group. We found no significant difference between the two groups in both univariable ($p = 0.5$) and multivariable analyses ($p = 0.7$).

Our final analysis was based on our definition of clinically significant grade discordance, found for 320 biopsies (38%). The results were similar to those for the main analysis, with external biopsies strongly related to the likelihood of discrepancy on univariable analysis ($p < 0.0001$ for both groups). On multivariable analysis, the OR for nonreviewed biopsies (OR 4.57, 95% CI 2.96–7.06; $p < 0.0001$) was higher than in our primary analysis; results for biopsies reviewed internally were similar (OR 1.61, 95% CI 1.15–2.25; $p = 0.005$; Table 4).

4. Discussion

We found that both sampling and pathological evaluation influence final concordance between the initial biopsy and final pathology, a marker of the quality of prostate biopsy. In particular, our findings suggest that the contribution of sampling is critical, importantly affecting the difference between internal and external biopsies.

Many studies have examined the impact of expertise on the quality of histological reports among pathologists. When the same biopsies were analyzed by general and specialist pathologists, the results reported by the latter were more accurate and reproducible [12,13]. Similarly, there is extensive evidence that in-house second opinions on biopsies by uropathologists predict final pathology better than the original reports did [3,14–17]. For example, in a series of 100 community biopsies, Truesdale et al [15] observed that internal review improved concordance between the highest grade at biopsy and the pathological report. Similarly, Barqawi et al [16] compared concordance rates with respect to the surgical specimens between external and reviewed biopsies and demonstrated that the internal Gleason scoring was significantly more accurate (52% vs 41%) than the outside reports. These findings are similar to ours, as we found that the concordance rate for external biopsies was significantly higher after internal review (49% vs 31%). However, the aforementioned series were published before the introduction of the 2014 ISUP guidelines for histological report and thus are not totally comparable to our contemporary cohort. Moreover, our lower rate of concordance among external biopsies may reflect a different level of experience for pathologists in our community compared with that in American series.

Although the literature makes a strong argument in favor of expert pathological evaluation, there is less evidence as to the relationship between accuracy and sampling. To the best of our knowledge, this is the first study that has addressed this issue directly. Prior studies investigated only single technical aspects. For example, previous investigations reported higher detection rates as the number of cores taken increased [5,18–20]. However, it is questionable whether the number of cores is sufficient. Not only are data on the number of cores equivocal [21,22] but other factors can also be hypothesized. For instance, the core length sampled may affect the amount of material available for the pathologist [18,23,24]. Furthermore, the sampling site may influence the final accuracy given that two cores too close together will not be of added value and may lead to insufficient sampling of other areas of the prostate.

Our study has several limitations that reflect the retrospective nature of our data. First, biopsy review was not standardized for the whole study period. However, it is unlikely that different prostate cancer characteristics among external biopsies would explain our findings, since a sensitivity analysis that incorporated the original ISUP grade group (before internal review) for patients with external biopsy did not affect our results. Baseline characteristics for these patients were similar and therefore the subsequent improvement in accuracy can be attributed to the internal review. Moreover, we consider as a potential bias the fact that in-house uropathologists reported on both the internal biopsies and surgical specimens, which has previously been described as “innate bias” [25]. However, we found that patients

with external sampling and internal review had worse concordance rates than patients whose biopsies were sampled and reported internally, even though they would have been subject to identical levels of this type of bias.

Second, our study lacked specific parameters such as total tissue sampled and single core length. We found a lower number of cores taken in the external biopsies, but we could not assert that this reflects a lower amount of sampled tissue. Furthermore, our results showed no interaction between the numbers of total and positive cores and histological accuracy. It can be postulated that the accuracy provided by well-sampled cores may be greater than that for a higher number of cores. However, further confirmatory studies would be needed to evaluate the accuracy of prostate biopsy after accounting for the amount of tissue sampled and single core length. Finally, we did not have information on biopsies conducted externally, for example, whether the original institution was academic or community-based, case-load volume, or details on sampling and reporting protocols. Moreover, no data on the expertise of the external pathologists were available. A certain level of variation is reasonable, as some institutions may have a uropathology department or urologists who specifically focus on prostate cancer care, even in a community setting. Conversely, some biopsies may be sampled or evaluated by inexperienced operators, with subsequently worse results. Accordingly, given the lack of such details, we assumed that our findings reflect the average quality of our community for both urologists and pathologists.

There are three implications for clinical practice. First, biopsies evaluated by community pathologists should be reviewed by expert uropathologists. Second, community biopsies are prone to sampling errors and thus may not be reliable for treatment choices. Accordingly, candidates for active surveillance whose biopsy was taken in a community setting should have a confirmatory biopsy, as recommended by the EAU guidelines [26]. Third, regionalization of prostate biopsy to high-volume centers should be considered.

5. Conclusions

We found that biopsies performed according to recommended protocols have a higher concordance with final pathology. Therefore, our results suggest a clear need to improve the quality of technical sampling through a standardized approach. Specific parameters such as the minimum amount of sampled tissue and single core length should be properly investigated as possible determinants of concordance with the final pathology [27]. Future studies should focus on the exact contribution of these parameters to the quality of prostate biopsies and provide a detailed, highly informative guide for operators. Similarly, future research should examine whether other factors (ie, imaging-guided techniques) could improve the quality of biopsy sampling in the community setting. It is plausible that the introduction of such approaches would be helpful for community urologists. However, it is also possible that the diffusion of fusion biopsies may be greater in high-volume centers, further widening the gap between external and internal biopsies. Thus, we cannot draw definite conclusions on this point. In conclusion, our results suggest that more serious attention should be paid to the issue of technical sampling for prostate biopsy. The diffusion of an evidence-based, standardized approach will provide higher-quality biopsies and thus better clinical care.

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Table 1 –

Demographic, biopsy and pathological data for the study cohort according to biopsy setting [a]

	External	External + review	Internal	*p* value
Patients, *n* (%)	134 (16)	313 (37)	401 (47)	
Age (yr)	65.1 (57.8–68.7)	63.2 (57.6–68.3)	66.4 (61.9–70.9)	<0.0001
Preoperative PSA (ng/ml)	7.1 (5.4–10.4)	6.4 (4.7–9.0)	6.9 (4.8–10.0)	0.046
Clinical stage				
cT1	76 (57)	167 (53)	255 (64)	
cT2	41 (30)	110 (35)	110 (27)	0.077
cT3	17 (13)	36 (12)	36 (9)	
D'Amico risk group				
Low	30 (22)	37 (12)	21 (5)	
Intermediate	76 (57)	199 (64)	257 (64)	<0.0001
High	28 (21)	77 (24)	123 (31)	
Biopsy Gleason score				
≤6	48 (36)	62 (20)	37 (9)	
7	75 (56)	196 (63)	265 (66)	<0.0001
>7	11 (8)	55 (17)	99 (25)	
Biopsy ISUP grade				
1	48 (36)	62 (20)	37 (9)	
2	45 (34)	128 (41)	166 (41)	
3	30 (22)	69 (22)	99 (25)	<0.0001
4	7 (5)	33 (11)	47 (12)	
5	4 (3)	21 (6)	52 (13)	
Number of cores (*n*)	12 (12–16)	12 (12–16)	14 (12–16)	<0.0001
Positive cores (*n*)	5 (2–8)	5 (3–7)	5 (3–7)	0.086
Positive core rate (%)	35.7 (20.0–59.3)	37.5 (21.1–53.8)	36.4 (21.4–50.0)	0.9
Pathological ISUP grade				
1	5 (4)	10 (3)	9 (2)	0.034
2	51 (38)	132 (42)	151 (38)	
3	52 (39)	115 (37)	125 (31)	
4	7 (5)	11 (4)	35 (9)	
5	19 (14)	45 (14)	81 (20)	
pT stage				
pT2	59 (44)	153 (49)	179 (44)	0.5
pT3a	58 (43)	127 (40)	163 (41)	
pT3b	17 (13)	33 (11)	59 (15)	
Extraprostatic extension				
No	59 (44)	153 (49)	179 (45)	0.5
Yes	75 (56)	160 (51)	222 (55)	
Seminal vesicle invasion				

	External	External + review	Internal	*p* value
No	117 (87)	280 (89)	342 (85)	0.3
Yes	17 (13)	33 (11)	59 (15)	
Perineural invasion				
No	128 (96)	302 (96)	372 (93)	0.082
Yes	6 (4)	11 (4)	29 (7)	
Positive surgical margins				
No	84 (63)	219 (70)	294 (73)	0.064
Yes	50 (37)	94 (30)	107 (27)	
pN stage				
pN0	101 (75)	201 (64)	269 (67)	0.020
pN1	16 (12)	35 (11)	60 (15)	
pNx	17 (13)	77 (25)	72 (18)	
Pathological prostate weight (g)	50 (38–62)	52 (43–62)	52 (43–65)	0.07
Pathological tumor volume (cm^3)	4.3 (2.0–7.9)	5 (2.5–9.0)	5.2 (2.9–10.0)	0.02

PSA = prostate-specific antigen; ISUP = International Society of Urological Pathology.

[a]Data are presented as median (interquartile range) for continuous variables and as *n* (%) for categorical variables.

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Table 2 –

Discordance rates according to biopsy group [a]

	External (*n* = 134)	External + review (*n* = 313)		Internal (*n* = 401)
		Before review	After review	
Discordant, *n* (%)	89 (66)	218 (70)	161 (51)	157 (39)
Overgrading, *n* (%)	7 (5)	36 (11)	29 (9)	36 (9)
Undergrading, *n* (%)	82 (61)	182 (59)	132 (42)	121 (30)

[a]Undergrading is defined as a lower grade in the biopsies and overgrading as a higher grade in the biopsies as compared to the surgical specimen grade.

Table 3 –

Multivariable analysis to predict discordance between biopsy and pathological grading ($n = 822$) with internal biopsies considered as the reference group

Variable	OR (95% CI)	*p* value
External sampling and internal review	1.62 (1.18–2.23)	0.003
External sampling and no internal review	3.27 (2.12–5.05)	<0.0001
Age	0.99 (0.97–1.01)	0.2
Preoperative prostate-specific antigen	0.99 (0.98–1.01)	0.3
Pathological stage		
T2	Reference	
T3a	1.52 (1.10–2.09)	0.011
T3b	1.37 (0.80– 2.34)	0.3
Pathological ISUP grade		
1	Reference	
2–3	10.58 (2.40–46.67)	0.002
4–5	14.79 (3.19–68.61)	0.001
Prostate weight	1.00 (0.99–1.01)	0.8

OR = odds ratio; CI = confidence interval; ISUP = International Society of Urological Pathology.

Table 4 –

Multivariable analysis to predict discordance between biopsy and pathological grading ($n = 822$) in a clinically significant scenario with internal biopsies considered as the reference group

Variable	OR (95% CI)	*p* value
External sampling and internal review	1.61(1.15–2.25)	0.005
External sampling and no internal review	4.57 (2.96–7.06)	<0.0001
Age	0.98 (0.96–1.01)	0.2
Preoperative prostate-specific antigen	0.99 (0.98–1.01)	0.5
Pathological stage		
T2	Reference	
T3a	1.30 (0.93–1.81)	0.1
T3b	1.11 (0.62–1.99)	0.7
Pathological ISUP grade		
1	Reference	
2–3	9.99 (2.23–44.79)	0.003
4–5	4.94 (1.04–23.49)	0.044
Prostate weight	1.00 (0.99–1.01)	0.8

OR = odds ratio; CI = confidence interval; ISUP = International Society of Urological Pathology.