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## Gleason Misclassification Rate Is Independent of Number of Biopsy Cores in Systematic Biopsy

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### Abstract

**OBJECTIVE**—To compare the utility of saturation core biopsy and 12-core biopsy in detecting true Gleason grades, using final pathology in prostatectomy specimens as outcome measures, with a particular interest in Gleason upgrading.

**PATIENTS AND METHODS**—We compared the concordance rates of Gleason grades diagnosed on biopsies and prostatectomy specimens in 375 consecutive patients, including 106 saturation biopsies (18-33 cores, median = 20 cores) and 269 12-core biopsies. Grading bias was addressed by a central rereview of all cases that had discordance in reporting high Gleason grades (Gleason grade  $\geq 4$ ) on biopsies and prostatectomy specimens.

**RESULTS**—For patients with high Gleason grades on final pathology, saturation and 12-core biopsy schemes had a comparable sensitivity, specificity, negative and positive predictive values (72.5% vs 69.5%, 91.9% vs 97.6%, 64.2% vs 58.4%, and 94.3% vs 98.5%, respectively) in detecting high Gleason grades. On multivariate analysis, prebiopsy serum prostate-specific antigen and clinical T stage independently predicted Gleason upgrading; saturation biopsy was not a significant predictor. Approximately one-third of cases where high Gleason grade was not present in the biopsy were attributed to the confinement of high-grade tumors to unusual anatomic locations such as anterior lobes, apex, bladder neck, and parasagittal zones.

**CONCLUSION**—Our study showed that Gleason misclassification rate is independent of the number of biopsy cores in systematic biopsy. One of the reasons for missing high Gleason grade tumors on systematic biopsy was unusual tumor location outside of the biopsy grid, supporting the need for improved detection technique such as magnetic resonance imaging-guided targeted biopsies.

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Active surveillance is an important approach to the management of patients with low-grade, low-volume prostate cancer (PCa). However, this management relies on an accurate diagnosis of Gleason grade on biopsy. Detection of high Gleason grade (Gleason grade  $\geq 4$ )

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tumors on biopsy generally triggers definitive treatment, given expected patient survival of 10 years. Recent data suggest that the Gleason misclassification rate utilizing the standard biopsy scheme of 10-12 cores is unacceptably high, with upgrade rates at radical prostatectomy (RP) ranging from 30% to 60%.<sup>1-5</sup> This suggests that a significant number of clinically significant PCAs are not identified using the current biopsy scheme. A saturation biopsy scheme of 18 cores has been shown to have advantages in cancer detection compared with the 12-core biopsy scheme.<sup>6-9</sup> However, whether saturation biopsy improves the detection of clinically significant tumors is unclear. In this study, we performed a retrospective analysis to determine if increasing the number of biopsy cores from 12 to 20 would improve detection of high Gleason grade tumors.

## PATIENTS AND METHODS

### Patient Population and Data Retrieval

We retrospectively reviewed clinical characteristics and pathology reports of patients who had undergone both core needle biopsy and subsequent RP at our hospital from January 1, 2003 to December 31, 2013. All patients had a clinical diagnosis of localized prostatic adenocarcinoma preoperatively. Patients who received neoadjuvant therapy prior to RP were excluded (n = 5). We defined saturation biopsy as 18 cores and standard biopsy = 12 cores. We identified a total of 106 consecutive patients who underwent saturation biopsy and 269 consecutive patients who underwent 12-core biopsy and received immediate RP. Saturation biopsy technique performed at our hospital has been previously described.<sup>10</sup> The number of cores in the saturation biopsy group ranged from 18 to 33, with a median of 20 and interquartile range (IQR) of 19 to 24. RP specimens were sampled following a gross examination protocol that was consistent with the guidelines recommended by the 2009 International Society of Urological Pathology consensus conference.<sup>11</sup> The biopsy and RP specimens were originally reported by multiple pathologists at our institution. Prostate volume was measured at the time of core needle biopsy by ultrasound. When ultrasound measurement was not available, volume by magnetic resonance imaging (MRI) was utilized. The study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center, under the protocol 2010-P-000254.

### Slide Review

A grading discordance was defined as a difference in reporting the presence of high grade (Gleason grade 4) tumors in biopsy and prostatectomy specimens. Bias was addressed by a central rereview of all discordant cases by two pathologists (LQ and HY) using the 2014 International Society of Urological Pathology consensus of modified Gleason grading criteria.<sup>12</sup> The central review changed the Gleason grades assigned in the original pathology reports in 22% of the biopsy cases and 4% of the RP cases. A Gleason upgrade was defined as the presence of high-grade tumors on RP specimens of patients who had G3 only on biopsy. A Gleason downgrade was defined as final pathology of G3 only on RP specimens of patients who had high-grade tumors diagnosed on biopsy. To classify anatomic locations of high Gleason grade component on RP specimens, we first determined whether the high Gleason grade tumor was confined to the anterior lobe. Next, for cases that had high Gleason grade tumors located outside of the anterior lobe, we determined whether the high Gleason

grade tumors were confined to the apex, bladder neck, or parasagittal zone. The parasagittal zone was defined as the mid third zone that flanks the prostatic urethra on standard transverse cross-sections.

### Statistical Analysis

Stata 12.1 (StataCorp, College Station, TX) was used for statistical analysis. Characteristics between groups were compared using Pearson chi-square and Fisher's exact tests for categorical variables, and Wilcoxon rank-sum test for nonparametric continuous and ordinal variables. Logistic regression was used to analyze candidate predictors for binary outcomes. A  $P < .05$  was considered statistically significant.

## RESULTS

Subjects in the 12-core biopsy group and the saturation biopsy group demonstrated similar pathologic findings on both biopsy and RP specimens. On RP specimens, the final Gleason scores ranged from  $3 + 3 = 6$  to  $5 + 4 = 9$ . A similar proportion of patients from the two groups had high Gleason grade tumors, with 65.1% in the saturation biopsy group and 69.5% in the 12-core biopsy group, respectively (Table 1). There were no statistically significant differences in pathological characteristics including tumor stage, nodal status, and margin status between groups. Although the saturation biopsy group had a higher median prostate weight and a slightly lower median tumor volume, the two groups of patients had homogeneous tumor characteristics (Table 1).

On core biopsy, the Gleason scores ranged from  $3 + 3 = 6$  to  $5 + 4 = 9$ . A similar proportion of patients had high Gleason grade cancer detected on saturation biopsy compared with 12-core biopsy (50.0% and 49.1%, respectively). Furthermore, the number of positive cores and the maximum percentage of core involvement by cancer were comparable between the two groups (Table 1). However, there was some difference in clinical characteristics. The saturation biopsy group had a lower frequency of African Americans, a lower prebiopsy serum prostate-specific antigen (PSA) level, a higher prostate volume, and lower likelihood of abnormal digital rectal examinations (cT2) compared to the 12-core biopsy group.

We evaluated the diagnostic accuracy of the 2 biopsy methods in the detection of high Gleason grade cancer by calculating the sensitivity, specificity, negative predictive value, and positive predictive value. For the detection of high Gleason grade, saturation and 12-core biopsy had a sensitivity of 72.5% and 69.5%, and a specificity of 91.9% and 97.6%, respectively. Saturation and 12-core biopsy had a negative predictive value of 64.2% and 58.4%, and a positive predictive value of 94.3% and 98.5%, respectively, in predicting high Gleason grade on RP specimens. There was no statistically significant difference in sensitivity, specificity, negative predictive value, and positive predictive value between two biopsy methods ( $P = .648, .173, .467, .143$ , respectively). Areas under the receiver operating characteristics curves for saturation and 12-core biopsy schemes were 0.82 and 0.84, respectively (Table 2).

Next, we compared the discordance rate of high Gleason grade detection in paired biopsy and RP specimens between the two groups. A Gleason upgrade was defined by the presence

of high Gleason grade tumors in the RP specimens of those patients whose biopsy showed G3 only. As shown in Table 2, 35.8% (19 of 53) of men who were diagnosed with pure G3 on saturation biopsy were found to have high Gleason grade in the final pathology. Of those who had pure G3 on 12-core biopsy, 41.6% (57 of 137) were found to have high Gleason grade on RP specimens. There was no statistical significance in Gleason upgrade rate between the two groups ( $P = .467$ ). Patients who had G4 cancer detected on saturation biopsies (5.7%, 3 of 53) had G3 only in their RP slides compared to men in the 12-core group (1.5%, 2 of 132) ( $P = .143$ ).

In patients who had pure G3 diagnosed on biopsy, we analyzed preoperative variables that were predictive of Gleason upgrade on final pathology. On univariate analysis, a higher prebiopsy serum PSA level and a higher maximum % of cores involved by cancer were associated with a higher risk of Gleason upgrade (odds ratio 1.097 and 1.011,  $P = .037$  and .049, respectively). Patient age, race, prostate volume, clinical stage, biopsy scheme, and number of positive cores showed no significant association with Gleason upgrade rate. On multivariable analysis, a higher prebiopsy serum PSA level and a clinical T2 stage (palpable tumors on digital rectal examination) predicted a higher and a lower risk of Gleason upgrade (odds ratio 1.157 and 0.322,  $P = .008$  and .040), respectively. Prostate biopsy scheme (12-core vs saturation) did not significantly affect the risk of Gleason upgrade after controlling for other covariates, nor did patient age, race, prostate volume, number of positive core, or maximum % of cores involved by cancer (Table 3).

Finally, we analyzed potential causal factors of missing high Gleason grade tumors on biopsy. Among a total of 76 patients who were upgraded from G3 on biopsy to having a high Gleason grade in RP specimens, 31.6% had the high-grade tumors confined to unusual anatomic locations such as anterior lobe, apex, bladder neck, and parasagittal zones. Anterior lobe, bladder neck, and parasagittal zones are typically not sampled on systematic biopsy grids. Moreover, we examined the extent of the high-grade component in the RP tumors of those 76 patients. For the upgraded saturation biopsy cases, the high-grade component in their RP tumors ranged from 3% to 85%, with a median of 5% and an IQR of 3%-13%. For the upgraded 12-core biopsy cases, the high-grade component in the RP tumors ranged from 3% to 25%, with a median of 7% and an IQR of 5%-15%. Overall, 75% of upgraded cases had 15% of G4 in their RP tumors. There were 30.3% found to have a very small G4 component that involved 5% of the tumor on final pathology. The two groups had a similar proportion of cases that an upgrade on biopsy could be attributed to either unusual locations of high Gleason grade tumors or minimal amount of G4 (Table 4).

## COMMENT

The Gleason score on biopsy is one of the most important criteria in determining definitive treatment (RP) vs active surveillance in patients with localized PCa. It is generally believed that patients whose biopsy show high Gleason grade (G 4) require definitive treatment for cure. However, a significant number of patients may not receive the appropriate treatment algorithm if these clinically significant tumors are missed. As such, it is important to examine whether saturation biopsy would improve the detection of higher Gleason grade

tumors. To address this question, we summarized our 10-year experience in adopting a saturation biopsy scheme at our institution.

Our central review changed the Gleason grades assigned in the original pathology reports in 22% of the biopsy cases and 4% of the RP cases. The change of grading reflects interobserver variation as well as the evolution of Gleason grading criteria since 2003.<sup>12-15</sup> It illustrated the importance of a central review in retrospective studies involving Gleason grading. Compared to the biopsy cases, only a few RP cases had Gleason grades reassigned after the central review. The high concordance of grading in RP cases can be explained by our observations that multiple G4 variants frequently coexist in high-grade tumors on RP specimens, whereas grading of several G4 variants including raggedly infiltrating, fused, and microacinar glands has remained the same since 1977.<sup>12-15</sup>

After the bias eliminated through central review, our data have demonstrated that with saturation biopsy there is no statistically significant improvement in the detection of high Gleason grade cancer preoperatively. The reasons for missing a high Gleason grade component on biopsy could be attributed to: (1) unusual anatomic locations of high Gleason grade tumors, including anterior lobe, bladder neck, and parasagittal zones that are out of the systematic biopsy grids, and apical tumors that are difficult to biopsy; (2) minimal G4 tumor present in the prostate glands; and (3) intrinsic limitation of biopsy due to sampling error. The distribution of causal factors is very similar between the two groups. The first causal factor supports the use of multiparametric MRI or MRI/ultrasound fusion-guided targeted biopsy, which has been shown to increase detection of high Gleason grade tumors.<sup>16-18</sup> For the tumors of Gleason score  $3 + 3 = 6$  with a tertiary grade of 4, two studies have shown that they behave similarly as the pure G3 tumors on post-RP follow-up.<sup>19,20</sup> Their data suggest that upgrading in those patients may not affect disease prognosis, although their findings need to be confirmed in additional independent cohorts.

In this study, there were 3 of 53 cases in the saturation biopsy group and 2 of 132 cases in the 12-core group that had G4 detected on biopsy but not on prostatectomy specimens. Gleason downgrade usually occurs when the high Gleason grade component is a very small fraction of the tumor, or is due to undersampling of the RP specimens. For the three downgraded saturation biopsy cases, one case had <5% G4 component in a single high-grade core and the prostate was entirely submitted; the second case had 5% G4 in a single high-grade core and the prostate was not entirely submitted; the third case had up to 40% G4 in five high-grade cores and the prostate was not entirely submitted. For the two downgraded 12-core biopsy cases, one case had <5% G4 component in a single high-grade core and the prostate was entirely submitted; the other case had up to 10% G4 in two high-grade cores and the prostate was not entirely submitted. In summary, only one case from each biopsy group had true Gleason downgrading according to the prostate being entirely submitted. The remaining three cases might have high grade tumors in the remaining prostatic tissue that was not sampled. Although subtotal submission is sufficient for staging and grading of RP specimens in most cases, our results suggest that it would be a good practice to submit the remaining prostate when in rare occasions a Gleason downgrading occurs.

Our study has several limitations. First, this is a study using data from a single tertiary-care academic hospital, in which patients with PCa were mostly treated by four urologists. Therefore, our study results may not be representative of other urological practices, particularly private practice and community hospitals. Second, the saturation biopsy approach was performed by a single urologist, whereas the 12-core biopsy approach was performed by multiple urologists. The operator factor could lead to differences in biopsy core quality.

## CONCLUSION

In summary, we have shown that increased number of core biopsies from 12 to 20 did not reduce the error rate of systematic biopsy. One of the main reasons of missing high Gleason grade tumors on systematic biopsy was unusual tumor location outside of the biopsy grids, which supports current effort to use imaging-guided targeted biopsy.

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**Table 1**

Clinicopathologic parameters of two biopsy methods

	<b>Saturation Biopsy (N = 106)</b>	<b>Twelve-core Biopsy (N = 269)</b>	<b>P Value</b>
Median age at diagnosis (IQR)	59 (56, 63)	60 (54-65)	.864
Race (%)			
African American	7 (6.6)	52 (19.3)	.002*
Other	94 (88.7)	201 (74.7)	
Unknown	5 (4.7)	16 (5.9)	
Median ng/mL prebiopsy PSA (IQR)	4.6 (3.1, 7.1)	5.4 (4.2, 8.3)	.017*
Median mL prostate volume (IQR)	42 (31, 57)	36 (28, 50)	.022*
No. of cT2 cases (%)	13 (12.3)	64 (26.6)	.003*
Biopsy			
No. of Gleason (%)			
G3 only	53 (50.0)	137 (50.9)	.871
G 4 detected	53 (50.0)	132 (49.1)	
No. of positive cores (IQR)	3 (2, 6)	3 (2, 5)	.143
Max cancer % of cores (IQR)	40 (17, 60)	40 (20, 70)	.254
RP			
Median g prostate weight (IQR)	54 (44, 66)	46 (38, 57)	<.001*
No. of Gleason (%)			
G3 only	37 (34.9)	82 (30.5)	.407
G 4 detected	69 (65.1)	187 (69.5)	
No. of pT stage (%)			
pT2	84 (79.2)	197 (73.2)	.226
pT3	22 (20.8)	72 (26.8)	
% Tumor volume (IQR)	10 (5, 20)	12 (5, 20)	.043*
No. of pN stage (%)			
pN1	1 (0.9)	2 (0.7)	.721
pN0	97 (91.5)	181 (67.3)	
pNx	8 (7.5)	86 (32.0)	
Margin status (%)			
Positive	22 (20.8)	75 (27.9)	.098
Negative	84 (79.2)	194 (72.1)	

IQR, interquartile range; RP, radical prostatectomy; PSA, prostate-specific antigen.

\*  $P < .05$  considered statistically significant.



**Table 2**

Statistical performance characteristics of two biopsy methods in G4 detection

Parameter	Saturation Biopsy (N = 106)		Twelve-core Biopsy (N = 269)		P Value
	Estimate	95% CI	Estimate	95% CI	
Sensitivity	0.725	0.604-0.825	0.695	0.624-0.760	.648
Specificity	0.919	0.781-0.983	0.976	0.915-0.997	.173
ROC area	0.82	0.75-0.89	0.84	0.80-0.87	
NPV	0.642	0.498-0.769	0.584	0.497-0.667	.467
PPV	0.943	0.843-0.988	0.985	0.946-0.998	.143
Upgrade rate (3 + 3 = 6 on biopsy that had G 4 on RP)	0.358 (19/53)		0.416 (57/137)		.467
Downgrade rate (G4 on biopsy that had 3 + 3 = 6 on RP)	0.057 (3/53)		0.015 (2/132)		.143

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; other abbreviation as in Table 1.

**Table 3**

Univariate and multivariate analysis of candidate predictors of Gleason upgrade

Variables	Univariate		Multivariate	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	0.986 (0.942, 1.032)	.539	0.975 (0.922, 1.030)	.363
Race	1.004 (0.461, 2.185)	.993	0.790 (0.323, 1.935)	.606
Prebiopsy PSA (ng/mL)	1.097 (1.005, 1.198)	.037*	1.157 (1.039, 1.290)	.008*
Prostate volume (mL)	0.995 (0.980, 1.010)	.492	0.993 (0.966, 1.022)	.639
Clinical stage (cT2 vs cT1)	0.393 (0.150, 1.029)	.057	0.322 (0.109, 0.949)	.040*
Number of biopsy cores (saturation vs 12-core)	0.784 (0.407, 1.512)	.468	0.760 (0.340, 1.700)	.505
No. of positive cores	1.144 (0.997, 1.313)	.055	1.100 (0.915, 1.322)	.313
Max cancer % of cores	1.011 (1.000, 1.023)	.049*	1.009 (0.993, 1.025)	.270

OR, odds ratio; other abbreviations as in Tables 1 and 2.

\*  $P < .05$  considered statistically significant.

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**Table 4**

Potential reasons for Gleason undergrading on biopsy

	Saturation Biopsy (N = 19)		Twelve-core Biopsy (N = 57)		Total (N = 76)	
Unusual locations	6	31.6%	18	31.6%	24	31.6%
Anterior only	4		6		10	
Apex only	1		3		4	
Bladder neck only	0		1		1	
Parasagittal only	1		8		9	
Minimal G4 (G4 = 5%)	6	31.6%	17	29.8%	23	30.3%
Remaining cases	7	36.8%	22	38.6%	29	38.2%