Downgrading of Grade Group After Radical Prostatectomy: Comparison of Multiparametric Magnetic Resonance Imaging Guided Fusion Biopsy and Standard 12-Core Biopsy

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OBJECTIVE To analyze the factors associated with Grade group (GG) downgrading post-radical prostatectomy.

PATIENTS AND METHODS We performed a retrospective analysis of 536 patients who underwent robot-assisted laparoscopic radical prostatectomy from February 2014 to October 2015. We have analyzed the clinical, radiological, and pathologic factors associated with GG downgrading in final pathology. Downgrading was defined as those patients who downgraded from GG 3, 4, or 5 on biopsy to GG 1 or 2 on final pathology as well as patients who downgraded from GG 2 on biopsy to GG 1 on final pathology. Categorical values were compared with chi-square and Fischer's exact tests. Mann-Whitney U and Kruskal-Wallis were used for analysis of independent variables associated with GG downgrading.

RESULTS Ninety-three patients underwent fusion biopsy (FB) and 443 underwent the standard 12 core biopsy. Baseline clinical characteristics were similar between the 2 groups except for race (P = .009). Downgrading was observed in 76 patients (14.1%). Rate of downgrading was higher in the FB group (n = 22, 23.7% vs n = 54, 12.2%, P = .008). In multivariable logistic regression analysis, FB (OR:2.39, P = .004) and maximum percentage of core involvement (OR:1.01, P = .013) were associated with downgrading after robot-assisted laparoscopic radical prostatectomy. After 1:2 propensity score matching, FB was still associated with an increased rate of downgrading (P = .034). Downgrading had no significant effect on pathologic outcome.

CONCLUSION FB and maximum percentage of core involvement are the only factors associated with GG downgrading in final pathology. However, downgrading did not influence surgical outcome.
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The standard 12 core TRUS biopsy (SB) randomly samples approximately 0.04% of a 62.5 grams prostate.[1] Due to insufficient sampling and its nontargeted nature, SB is not a reliable tool for identifying the dominant cancerous lesion of prostate.[2] Failure to identify the dominant lesion results in inaccurate sampling, which can result in grade group (GG) discordance between SB and radical prostatectomy specimens. Up to half of GG1 patients have upgrading in radical prostatectomy (RP) specimens.[3] MRI-ultrasound fusion targeted biopsy (FB) addresses this phenomenon by targeting specific lesions highly suspicious for cancer, rather than random sampling of the gland.[4] Furthermore, FB has a better concordance with RP pathology compared to SB.[5]

The risk of upgrading at final pathology has been extensively examined, because treatment options are driven by risk categories, and conservative strategies, such as active surveillance, should only be offered to appropriate patients.[6] However, downgrading must also be addressed to highlight the need to prevent unnecessary surgical morbidity on low risk and even low volume intermediate risk prostate cancer patients.[7] Therefore, we sought to analyze the factors associated with downgrading in patients who underwent RP.

Conflict of Interest: *None.*

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PATIENTS AND METHODS

Study Population

From a single surgeon series, we have performed an Institutional Review Board approved retrospective analysis of 536 patients who underwent robot-assisted laparoscopic radical prostatectomy from February 2014 to October 2015. Patients who underwent previous radiotherapy and/or androgen deprivation therapy were excluded from analysis. Final analyses were performed on patients who had complete biopsy data (n = 537).

Imaging and Biopsy Protocol

Every patient who underwent biopsy at our institution underwent a prebiopsy multi-parametric 3-Tesla MRI (mpMRI). Multiparametric MRI included T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging. Endorectal coil was not routinely used. Lesions were graded based on the Prostate Imaging Reporting and Data System (PI-RADS) v1 by a genitourinary radiologist. All patients who had a lesion with PI-RADS 3 or higher were offered FB (Artemis, Eigen, Grass Valley, CA). All patients who received FB received a 12-core standard template, in addition to 2-4 samples from each target lesion. Patients without any visible lesions underwent a standard 12-core biopsy. In needle biopsy specimen, the Gleason score was assigned for each core (container), and the highest Gleason score determined the grade group. Biopsy and surgical specimens were evaluated by a single pathologist, expert in the genitourinary field. Every biopsy done outside our institution was reviewed by the same pathologist, in order to avoid inter-observer variability.

Pathology Specimen Processing

After obtaining the prostate specimen, the surgical margins were examined for histologic evidence of cancer at the margins during frozen section. The prostatectomy specimen was inked for anatomic; red ink for right anterior surface, green ink for right posterior, blue for left anterior, and black for left posterior surface. Bilateral posterolateral and apical margins were obtained for frozen section analysis of the margin. After separating the seminal vesicles, the entire gland was serially sectioned into approximately 3-mm slices. Alternate slices were submitted for histopathologic examination. Tissue sections of 4-6 μm thickness were made from each paraffin block, stained with hematoxylin and eosin, and reviewed. The slides were evaluated microscopically for tumor and the Gleason score was determined with the sum of the 2 most predominant patterns (primary and secondary) in terms of surface area. The grade group of the tumor was then determined. Where more than one separate tumor was clearly identified, the Gleason scores of individual tumors were recorded separately. For a radical prostatectomy specimen, the highest Gleason grade observed was considered the final grade. An indication of tertiary grade is made when a higher-grade pattern was noted in small percentage (<5%). In general, presence of tertiary pattern is associated with higher pathologic stage and higher rate of biochemical recurrence. When the 3rd most common histologic pattern was graded higher than the primary and secondary pattern, and occupied <5%, a tertiary pattern was acknowledged in a separate note.

Variables and Outcome

Demographic (age and race), clinical (PSA, cT stage, prostate volume on MRI, presence of extra-capsular extension on MRI, biopsy GG), and pathologic (pT stage, pN stage, surgical margin status, extra-prostatic extension, pathology GG characteristics) were all included in the analysis.

In previous studies, downgrading was defined as any decrease in the Grade group or any change in order of primary grade and secondary grade.[8,9] Considering the criteria for clinically significant disease,[10] we considered a modified criteria for downgrading. Downgrading was defined as those patients who downgraded from GG 3, 4, or 5 on biopsy to GG 1 or 2 on final pathology, as well as patients who downgraded from GG 2 on biopsy to GG 1 on final pathology.

Statistical Analysis

Our cohort was divided into 2 groups for analysis. Group 1 underwent FB plus 12 core biopsy and Group 2 underwent standard 12 core biopsy for initial diagnosis. Categorical variables were compared with chi-square and Fischer's exact tests. Mann-Whitney U and Kruskal-Wallis were used for analysis of independent variables associated with GG downgrading. Multivariable analysis was performed

Due to the uneven sample size in the 2 groups and the statistically significant differences in the race distribution, we ran 1:2 propensity score matching to reduce the imbalance of covariates. The propensity scores were used to match baseline characteristics in terms of age, race, and PSA.

In all analysis $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Fusion Biopsy Vs Standard Biopsy

Among the 536 patients included in the analysis, 93 patients underwent FB and 443 underwent SB. Baseline clinical characteristics were similar between the 2 groups except for race ($P = .009$). There was no significant difference between the FB and SB groups with regards to pathologic and radiological variables (Table 1).

Downgrading

Downgrading was documented in 76 patients (14.1%). Fifty-seven patients (10.6%) downgraded to GG 2 and 19 patients (3.5%) downgraded from GG2 to GG 1. In patients diagnosed with FB, prevalence of downgrading was higher compared to those diagnosed with SB (n = 22, 23.7% vs n = 54, 12.2%, $P = .008$) (Table 1).

On univariate analysis there was no significant association between age ($P = .125$), race ($P = .579$), PSA ($P = .520$), clinical stage ($P = .435$), number of positive cores ($P = .067$), MRI volume ($P = .883$), ECE on MRI ($P = .240$), pathologic stage ($P = .467$), extra-prostatic extension on pathology ($P = .367$), positive surgical margin status ($P = .454$), pN status ($P = .232$) and downgrading after RP. Maximum percentage of core involvement by tumor ($P = .004$) and biopsy method ($P = .008$) were shown to have significant associations with downgrading (Table 2).

On multivariable logistic regression analysis, those who had FB had 2.39 times the odds of downgrading compared to those who had standard biopsy performed after radical prostatectomy (95% CI: 1.33, 4.28, $P = .0035$), when adjusting for PSA, percentage of maximum core, ECE on MRI, and prostate volume (Table 3).

After 1:2 propensity score matching, there was no statistically significant association between the race distribution and the

Table 1. Demographic, clinical, radiologic, and pathologic characteristics among fusion biopsy and standard biopsy cohorts

Variable	Standard Biopsy (n = 443)	Fusion Biopsy (n = 93)	*P* Value
Age (years, median, IQR)	62 (56, 67)	63 (56, 67)	.404
Race (%)			**.009**
Caucasian	340 (76.8)	81 (87.1)	
African-American	72 (16.3)	5 (5.4)	
Asian	16 (3.6)	6 (6.5)	
Other	15 (3.4)	1 (1.1)	
PSA (ng/mL, median, IQR)	5.5 (4.4, 7.7)	5.3 (3.9,8.9)	.567
% max core (median, IQR)	50.0 (20.0, 80.0)	50.0 (25.0, 80.0)	.501
Number of positive cores (median, IQR)	4 (2, 6)	4 (2, 7)	.091
Clinical T stage (%)			.092
T1c	299 (67.5)	54 (58.1)	
T2	144 (32.5)	39 (41.9)	
Biopsy grade group			.198
1	138 (31.2)	25 (26.9)	
2	183 (41.3)	33 (35.5)	
3	72 (16.6)	18 (19.4)	
4	34 (7.7)	14 (15.1)	
5	16 (3.6)	3 (3.2)	
MRI prostate volume (mL, median, IQR)	38.0 (28.8, 52.0)	41.0 (30.0, 55.0)	.186
ECE on MRI (%)			.354
Absent	322 (74.4)	73 (79.4)	
Present	111 (25.6)	19(20.7)	
Tumor volume on final pathology (g, median, IQR)	4.6. (2.8, 7.6)	4.2 (2.9, 6.6)	.624
Pathologic stage (%)			.688
T1c-T2	337 (76.1)	73 (78.5)	
T3	106 (23.9)	20 (21.5)	
Final pathology grade group (%)			.089
1	53 (12.0)	19 (20.4)	
2	282 (63.7)	47 (50.5)	
3	78 (17.6)	22 (23.7)	
4	8 (1.8)	1 (1.1)	
5	22 (5.0)	4 (4.3)	
EPE on pathology (%)			.892
Absent	344 (78.2)	76 (80.0)	
Present	96 (21.8)	20 (20.0)	
Surgical margin (%)			.367
Negative	405 (93.1)	97 (95.7)	
Positive	30 (6.9)	4 (4.3)	
pN stage (%)			1.0
pN0	412 (97.4)	89 (97.8)	
pN1	11 (2.6)	2 (2.2)	
Seminal vesicle invasion (%)			.105
Absent	391 (93.1)	88 (97.8)	
Present	29 (6.9)	2 (2.2)	
Downgrading (%)			**.008**
Absent	389 (87.8)	71 (76.3)	
Present	54 (12.2)	22 (23.7)	
Upgrading (%)			.258
Absent	310 (70.0)	71 (76.3)	
Present	133 (30.0)	22 (23.7)	

Bold Indicate a Statistically Significant Difference at the $p < 0.05$ Level.
*Results for continuous variables are reported as the median with IQR and compared with Mann Whitney U test. Fisher's exact test was used to compare frequency distributions in contingency tables.

treatment groups ($P = .737$). The rate of downgrading in the matched treatment groups (n = 92 and 182) was once again significantly higher in fusion biopsy group as compared to SB group ($P = .034$) (Table 4).

Overall, 155 patients (28.9%) upgraded, indicating any patient with GG 1 on biopsy to GG > 1 on final pathology, or with GG 2 on biopsy to any GG > 2 on final pathology. In patients diagnosed with FB, prevalence of upgrading was lower compared to those diagnosed with SB (n = 19, 20.4% vs n = 119, 26.8%). Grade group remained the same in 60.9% of the SB group and 55.9% of the FB group (Supplemental Table 1).

Downgraded and upgraded patients were compared in terms of pathologic outcome. There was no significant difference between the 2 groups in terms of pT stage ($P = .508$), EPE ($P > .999$, surgical margin status ($P = .127$), and SVI invasion ($P = .617$) (Supplemental Table 2).

DISCUSSION

FB uses mpMRI to target the area of prostate under the highest risk of harboring clinically significant prostate

Table 2. Demographic, clinical, radiologic, and pathologic characteristics among downgrading vs no downgrading

Variable	No Downgrading (n = 460)	Downgrading (n = 76)	*P* Value
Age (years, median, IQR)	62.0 (56.0, 66.5)	62.0 (58.0, 68.0)	.125
Race (%)			.579
Caucasian	362 (78.7)	59 (77.6)	
African-American	66 (14.4)	11 (14.5)	
Asian	17 (3.7)	5 (6.6)	
Other	15 (3.3)	1 (1.3)	
PSA (ng/mL, median, IQR)	5.4 (4.3, 7.8)	5.8 (4.3, 8.6)	.520
% max core (median, IQR)	50.0 (20.0, 80.0)	70.0 (30.0, 80.0)	**.004**
Number of positive cores (median, IQR)	4 (2, 6)	4.5 (3, 7)	.067
Clinical T stage (%)			.435
T1c	306 (66.5)	47 (61.8)	
T2	154 (33.5)	29 (38.2)	
MRI prostate volume (mL, median, IQR)	38.0 (29.5, 53.0)	38.0 (29.0, 51.8)	.883
ECE on MRI (%)			.240
Absent	345 (76.2)	50 (69.4)	
Present	108 (23.8)	22 (30.6)	
Pathologic stage (%)			.467
T1c-T2	349 (75.9)	61 (80.3)	
T3	111 (24.1)	15 (19.7)	
Pathology EPE (%)			.367
Absent	358 (77.7)	63 (82.9)	
Present	103 (22.3)	13 (17.1)	
Surgical margin (%)			.454
Negative	429 (93.3)	73 (96.1)	
Positive	31 (6.7)	3 (3.9)	
pN stage (%)			.232
pN0	426 (97.0)	75 (100.0)	
pN1	13 (3.0)	0 (0.0)	
Seminal vesicle invasion (%)			.796
Absent	408 (94.0)	71 (93.4)	
Present	26 (6.0)	5 (6.6)	
Biopsy method (%)			**.008**
Standard biopsy	389 (84.6)	54 (71.1)	
Fusion biopsy	71 (15.4)	22 (28.9)	

*Results for continuous variables are reported as the median with IQR.

Table 3. Multivariable logistic regression to predict factors associated with downgrading

Variable	β Estimate	Odds Ratio (95% C.I.)	*P* Value
PSA (ng/mL)	-0.00673	0.993 (0.963, 1.024)	.6657
% max core	0.0111	1.011 (1.002, 1.020)	**.0127**
ECE on MRI	0.3075	1.360 (0.767, 2.412)	.2927
Prostate volume (mL)	−0.00071	0.999 (0.987, 1.011)	.9077
Targeted biopsy	0.8713	2.390 (1.333, 4.287)	**.0035**
Intercept	−2.6476		

Bold Indicate a Statistically Significant Difference at the $p < 0.05$ Level.

Table 4. Comparison between biopsy groups (standard 12-core biopsy (SB) vs fusion biopsy (FB) before and after matching by propensity scores

		Before Matching		After Matching	
Variable	Group	(n = 443 vs 93)	*P* Value	(n = 182 vs 92)	*P* Value
Propensity score	SB	0.1701	.029	0.1876	0.911
	FB	0.1897		0.1887	
Age (years, mean)	SB	61.2	.381	61.7	0.907
	FB	61.9		61.8	
Race (Caucasian, percent)	SB	76.75%	**.016**	89.01%	0.737
	FB	87.10%		88.04%	
PSA (ng/mL, mean)	SB	8.116	.566	6.761	0.909
	FB	6.795		6.823	
Downgrading (percent)	SB	12.19%	**.008**	12.09%	**0.034**
	FB	23.66%		22.83%	

Bold Indicate a Statistically Significant Difference at the $p < 0.05$ Level.

cancer. Such targeting allows sampling of the highest grade of a dominant lesion, which may result in reporting a higher-grade group at biopsy. Furthermore, sampling a tertiary high score location is possible. Our results confirm this rationale since use of FB and maximum percentage of core involved by tumor were the only factors associated with downgrading. None of the other clinical, pathologic or radiological factors were associated with downgrading. Downgrading, however, does not have any effect on the pathologic outcome. Thus, the implications of our study lie in patient selection for radical prostatectomy in low risk and low volume intermediate risk prostate cancer patients.

Inaccurate grading is mainly attributed to inter-observer difference and sampling error.[11] We were able to overcome the inter-observer difference by having the slides of every biopsy performed by an outside institution reread by one genitourinary pathologist who read biopsies performed at our institution as well. Sampling error however, is difficult to overcome in a referral center since the majority of our patients are diagnosed at outside institutions. Another factor that creates discordance between FB and RP specimens is the multi-focality and heterogeneity of organ-confined disease. It was shown that ≥2 tumor foci were seen in 87% of RP specimens.[12] Therefore, cancerous lesions must be identified prior to biopsy. Though we have seen a higher rate of downgrading, mpMRI is currently the best tool for findings index lesions; accurately sampling the index tumor results in higher accuracy in grade group prediction.[6,13] A meta-analysis of 16 studies and 1926 patients has shown that FB and SB do not differ in prostate cancer detection (85% vs 95% sensitivity, 95% CI 0.80 - 0.89). However, FB has a higher detection rate of clinically significant cancer (91% vs 76% sensitivity) and a lower detection rate of clinically insignificant cancer (44% vs 83%).[14] Based on our results, mpMRI cannot be used to prevent overtreatment by predicting downgrading. Regardless, FB is still a better diagnostic approach than SB and should be performed for every lesion visible on an mpMRI.[15]

Downgrading to GG1 represents a group of patients who might have been a candidate for AS.[16] In our cohort, downgrading to GG1 was observed in 2.7% of SB and 7.5% of FB patients. Despite the low rates, the difference is almost 3-fold. On the other hand, grade group is not the only criteria in patient selection for active surveillance. Therefore, we can say that overtreatment was not a significant problem in our cohort. With regards to AS, upstaging has been studied more intensively in literature to avoid offering AS to intermediate high-risk patients as a result of sampling error. The prognostic effect of upstaging has previously been reported by Tilki et al. In their single institution retrospective analysis of 684 patients, they have shown that upgraded patients were under higher risk for extracapsular extension (44% vs 15%, $P < .001$), seminal vesicle invasion (18% vs 5%, $P < .001$), positive surgical margins (30% vs 13%, $P < .001$) and lymph node involvement (10% vs 1.5%, $P < .001$).[17] We have not seen such differences in patients who downgraded vs those who did not.

Our study differs slightly from previous studies in the literature. In their retrospective analysis of 683 patients, Porpiglia et al reported a higher rate of upgrading (39.3% vs 7.8%, $P < .001$) and downgrading (6.8% vs 0.8%, $P < .001$) in their SB group vs their FB group.[11] A retrospective analysis of 135 FB patients by Baco et al reported that 16% of patients were upgraded and 14% were downgraded.[18] Crawford et al analyzed the results of 32 patients diagnosed by transrectal biopsy and consequent reevaluation with transperineal biopsy prior to RP. Upgrading was seen in 12% of patients and 16% downgraded to 3+3 or 3+4.[19] The heterogeneity in study design and surgical populations make it difficult to compare our results with the aforementioned studies.

According to our results, mpMRI variables were not predictive of downgrading, so it cannot be used as a tool to reduce radical prostatectomy indications. However, mpMRI evaluation in our study was done using PIRADS v1 version[20], as this cohort has been biopsied between 2014 and 2015. Since then, a new version of PI-RADS has been published[21], with a better ability to avoid unnecessary prostate biopsies in men with a low PSA level (4 to 10 ng/ml).[22] Using PI-RADS v2 on a grade group 2 cohort, Woo et al, demonstrated that PI-RADS v2 score was predictive of downgrading. Patients with downgrading had a lower mean PI-RADS score (3.8 vs 4.4, $P = .012$). It is possible that using PI-RADS v2 could have helped in reducing downgrading. However, this is speculative at best, since their study had a low sample size and only 10 events.[23]

The weakness of our study lies in the retrospective design and its inherent selection bias. Since our cohort is derived from a large tertiary referral center, the majority of our patients received their biopsy at outside institutions. This can create a bias in the selection criteria, as biopsies are likely done using different US and biopsy systems. Furthermore, experience and skill of the Urologists vary between institutions. This limitation is unavoidable in every retrospective analysis. Additionally, despite the respectable size of our cohort, the event rate was 76. Therefore, prospective, single-institution design with a larger sample size is needed to validate our results. Tumor volume is another important variable in tumor upstaging and clinical significance and therefore must be studied. However, it was not the focus of our study. Because of inconsistencies in recording the total number of cores taken during biopsy and reporting of fragmented cores in the majority of our cases, we did not address the relation of the number of cores with respect to downgrading. On the other hand, our cohort is a single surgeon series, which means that there is consistency with regards to patient selection. We have also eliminated the inter-observer difference by having pathology slides from outside institutions reread by the same pathologist who reviews final pathology.

CONCLUSION

FB resulted in a significantly higher rate of downgrading compared to SB. Downgrading must be addressed and efforts must be made to minimize this effect to prevent unnecessary surgical morbidity on patients with very low, low, and low volume intermediate risk prostate cancer.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.02.001.

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