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Multiparametric MRI for prostate cancer improves Gleason score assessment in favorable risk prostate cancer

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Abstract

Purpose—MRI-guidance may improve the accuracy of Gleason score (GS) determination by directing the biopsy to regions of interest (ROI) likely to harbor high-grade prostate cancer (CaP). The aim of this study was to determine the frequency and predictors of GS upgrading when a subsequent MRI-guided biopsy is performed on patients with a diagnosis of GS 6 disease on the basis of conventional, transrectal ultrasound (TRUS)-guided biopsy.

Methods—A consecutive series of 245 men with a diagnosis of low-risk CaP (i.e., cT1c, GS 6, PSA<10) based on TRUS-guided biopsy was enrolled in an active surveillance protocol that used subsequent MRI-guided biopsy for confirmation of GS. ROIs were categorized on a scale of 1 to 5. The Artemis ultrasound-MRI fusion device was used to perform targeted biopsies of ROIs, as well as systematic biopsies from a software-based 12-point map. Predictors of GS upgrading were analyzed using univariate and multivariate analyses.

Results—Fusion biopsy resulted in 26% of patients having GS upgrading (GS 3+4 in 18%, 4+3 in 5%, and 8–9 in 3%). Of the 72% of patients with ROIs appropriate for targeting, targeted cores upgraded the GS in 18%, while systematic cores upgraded the GS in 24%. In patients without targeted biopsy, GS upgrading was seen in 14%. On multivariate analysis, a category 5 ROI was the most significant predictor of GS upgrading with an odds ratio of 10.56 ($p<0.01$).

Conclusion—Nearly 25% of men with GS 6 CaP diagnosed by standard TRUS biopsy may experience GS upgrading when a subsequent MRI-ultrasound fusion biopsy is performed. The most important single predictor of upgrading is a category 5 ROI on mpMRI. GS upgrading may

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influence treatment decisions. Therefore, MRI-guided biopsy should be considered prior to formulating a management strategy in patients whose conventional biopsy reveals low-risk CaP.

Keywords

prostate cancer; multiparametric MRI; targeted biopsy

INTRODUCTION

Accurate Gleason score (GS) determination is critical for risk stratification and management decisions for patients with prostate cancer (CaP) (1). For patients undergoing radiotherapy, accurate GS determination is challenging since the actual highest GS will not be ultimately confirmed on a prostatectomy specimen. Conventional transrectal ultrasound (TRUS) guided biopsies may underestimate the whole-organ GS in 30–36% of cases (2). To ensure appropriate treatment recommendations, methods to improve the accuracy of biopsy are needed. Strategies have included extended core, saturation, and targeted biopsies of regions of interest (ROIs) found on multiparametric MRI (mpMRI) (3–11). Targeted biopsies of these ROIs have been shown to upgrade GS in 17–32% of patients (7, 12–14). This relatively high rate of upgrading suggests a role for mpMRI in the evaluation of patients with CaP.

A program was initiated at our institution in 2009 wherein all patients enrolled in active surveillance undergo confirmatory biopsy using mpMR-US fusion. In the fusion biopsy, both 12-point systematic samples and targeted samples of MRI-identified ROIs are obtained using the Artemis MRI-ultrasound fusion system (5, 7). We sought to identify the frequency and predictors of GS upgrading beyond GS 6, following confirmatory biopsy with the fusion system.

MATERIALS AND METHODS

Patient Selection

The study population consisted of 245 men with a prior diagnosis of GS 6 CaP, on the basis of a conventional TRUS biopsy, who were referred for enrollment in an active surveillance protocol between July 2009 and March 2014. In order to be eligible for this protocol, all men were required to have had at least 10 cores assessed on systematic, TRUS biopsy. A preliminary study of 113 men from the UCLA active surveillance cohort, examining the role of confirmatory mpMRI-ultrasound fusion biopsy, was reported previously (15). Those patients are included in this report.

Multiparametric MRI and Lesion Scoring

As part of our active surveillance protocol, all patients underwent an mpMRI followed by an mpMRI-ultrasound fusion biopsy as described previously (7, 16). mpMRI was performed with a 3.0 T Siemens Magnetom Trio with body coil and included T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging. mpMRI was performed one to eight weeks prior to fusion biopsy and reviewed on an Invivo DynaCAD or iCAD VersaVue

workstation by a single uroradiologist with nine years of prostate MRI experience (YY). mpMRI was performed at least three months after any prior biopsy.

T2-weighted imaging provides the best tissue contrast for detection of CaP, but can be inflammation and prostatic hyperplasia can be false positives. Because the free motion of water is restricted in cancerous tissue, diffusion-weighted imaging (DWI) can improve the specificity of CaP detection (17). Finally, dynamic contrast enhancement (DCE) imaging utilizes a T1-contrast enhanced sequence, and the enhanced contrast arrival ("wash-in") and dispersion ("wash-out") in tumors is sensitive and specific for CaP(18).

Suspicious ROIs were assessed on a scale between 1–5, with higher categories indicative of higher suspicion for CaP. This scale has been described previously and is similar to the PI-RADS scoring system (19). Briefly, an image-grade is assigned to each of the three sequences, with double-weighting given to DWI sequencing based on the apparent diffusion co-efficient. The criteria for each grade are shown in Table 1. An average of the image-grade for each parameter is taken to create an overall image grade. For example, if a region of interest was moderately dark on T2-weight imaging (i.e., a grade of 3), had an apparent diffusion coefficient value of 0.7 mm^2/s (i.e., a grade of 4), and had a dynamic-contrast enhancing sequencing that showed moderately abnormal enhancement (i.e., a grade of 3), the overall category would be (3+4+4+3)/4, or 3.5. The category is rounded up if the region of interest is in the peripheral zone, in this case giving it an overall category of 4, and rounded down if the region is in the transition zone, in this case giving it an overall category of 3 (19). All reporting was adherent to the Standards of Reporting for MRI Targeted biopsy studies (START) criteria (20).

mpMRI-Ultrasound Fusion Biopsy

The fusion biopsy protocol has been described previously (7). Biopsies were performed transrectally, under local anesthesia, and in an outpatient setting by a single urologist (ZZ). The MRI was loaded via CD into the Artemis device (Eigen, Grass Valley, CA). A TRUS (Hitachi Hi-Vision 5500) was performed, and a 3D prostate reconstruction was generated by the device, utilizing an algorithm incorporating both rigid and elastic registration.

A 12-point systematic mapping biopsy plan (bilateral medial/lateral, apex/mid/base), was scaled onto the 3D prostate reconstruction by the device, along with any ROIs. Targeted biopsy cores were obtained, followed by systematic biopsy cores. Targets were biopsied at 3 mm intervals based on prior work on registration accuracy with the device (5).

Statistical Analysis

Standard descriptive statistics were used to evaluate variables in various subsets. The primary method of analysis was logistic regression using GS ≥7 as the main outcome variable. A secondary analysis used primary Gleason grade ≥4 or more as the outcome variable. Several logistic models were evaluated and compared using stepwise procedures as well as models designed to test specific hypothesis. Goodness of fit was evaluated using the Hosmer-Lemeshow statistic and the area under the receiver operator characteristic (ROC) curve was used as a quantified measure of the strength of associations.

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 2. The mean age at diagnosis was 64 years old and the median PSA was 4.8 ng/ml (interquartile range, 2.9–6.7). Mean time from diagnosis to mpMRI-ultrasound fusion biopsy ranged from three to 125 months (average, 15.5 months). On average, each patient had 1.5 MRI based targets and the mean ROI category for identified targets was 2.3. The average total number of cores taken was 15 (12 systematic and 3.6 targeted).

Biopsy Results

Results of the mpMRI-ultrasound fusion biopsies are shown in Table 3. A sample MRI from a patient found to have a category 5 ROI is shown in Figure 1. In 182 patients (74%) of cases, the combination of targeted and systematic biopsies yielded a diagnosis of GS 6 disease. In 18% of cases the combination of targeted and systematic biopsies yielded GS 3+4=7 disease and in another 5% the GS was upgraded to 4+3=7. Three percent of patients were upgraded to having GS 8 or 9 disease.

69/245 (28%) patients did not have an ROI that could be targeted by biopsy (all of these were category ≤ 3) and thus only underwent mapping biopsy. For 14% of these patients, mapping biopsy upgraded the GS. Among patients for whom targeted biopsies were done (n=176), the targeted cores upgraded the GS in 18% while the mapping cores upgraded the GS in 24% of cases.

Predictors of Upgrading

In order to evaluate predictors of GS upgrading we analyzed the rate of upgrading by ROI category. Eighty (32.6%), 97 (39.6%), 57 (23.3%) and 11 (4.5%) patients had categories 1–2, 3, 4, and 5 ROIs, respectively. A GS upgrade was found in 73% of men with a category 5 ROI, 30% of men with a category 4 ROI, and 25% of men with a category 3 ROI.

Given the strong influence of ROI category on GS upgrading, univariate analysis was performed excluding patients with ROI categoriess of 5 or <3. The univariate analysis included PSA, ROI categories 3 or 4, prostate volume (on MRI), maximum tumor diameter (on MRI), total number of cores (targeted plus systematic), total number of systematic cores, total number of targeted cores, time from diagnosis to mpMRI-ultrasound fusion biopsy, and number of previous biopsies. The results of the univariate analysis are presented in Table 4 and demonstrate MRI ROI category, PSA, prostate volume, and total number of targeted cores are statistically significant in predicting the probability of a GS upgrade. The time between diagnosis and repeat biopsy was not associated with upgrading.

For the multivariate analysis we included the variables PSA at diagnosis, MRI prostate volume, and highest ROI category (3, 4, or 5). The results are shown in Table 4. PSA at diagnosis and having an ROI category 5 target were significant positive predictors of upgrading (odds ratios (ORs) of 1.24 and 10.56, respectively), while prostate volume was a significant negative predictor of upgrading (odds ratio of 0.96). No interaction effect was

seen between ROI category and any other parameter. The logistic model created on the basis of these data has a goodness-of-fit chi-squared value of 0.5249 and the area under the ROC curve is 0.7671, suggesting this is a valid and fair model. Since the ORs for GS upgrading with having a highest ROI categories of 3 or 4 were similar, we repeated our analyses with the variable “highest ROI categories 3 or 4” included along with PSA, prostate volume, and highest ROI category of 5. The ORs were 1.99 for highest ROI category of 3 or 4, and were unchanged for the other variables.

Based on the first multivariate model, we created four example patients all with the same initial PSA of 5 ng/mL but with varying prostate volumes and ROI categories (Table 5). Per this model, patient #1, with a PSA of 5, a gland volume of 45, and a category 5 ROI has a 67% chance of having his GS upgraded. With a category 4 ROI, this chance drops to 28%.

DISCUSSION

Biopsy-derived GS drives risk stratification and treatment recommendations for patients undergoing radiation therapy; however, conventional TRUS-guided biopsies frequently underestimate the true GS. By directly sampling ROIs corresponding to the regions at highest risk of harboring high-grade disease, mpMRI-ultrasound fusion biopsies can improve diagnostic accuracy and thus potentially alter treatment planning.

In the present study, we found that 25% of patients with a diagnosis of GS 6 disease based on conventional TRUS biopsies were upgraded to GS ≥7 disease on subsequent mpMRI-ultrasound fusion biopsies. This rate of upgrading is consistent with other studies, which have reported upgrading rates of 17–32% (7, 12–14). A recent meta-analysis demonstrated that MRI-guided targeted biopsies had a relative sensitivity of 120% compared with TRUS biopsies for the detection of significant CaP (21). Knowing the true GS can influence radiotherapy recommendations (i.e. androgen deprivation therapy and/or pelvic nodal treatment), particularly with recent data suggesting the importance of sub-stratifying intermediate risk CaP based on, among other factors, the primary Gleason grade (22). Further, while active surveillance protocols have yielded excellent long term results in carefully selected patients, over a third of patients at 10 years are no longer on active surveillance (23).

While the National Comprehensive Cancer Network (NCCN) does not currently recommend mpMRI in the evaluation of GS 6 CaP, our data suggest an important role for mpMRI in identifying patients who would benefit from GS upgrading on an mpMRI-ultrasound fusion biopsy. For example, our model predicts that a patient with a prostate volume of 45 cc, PSA of 5 ng/ml, and a category 5 ROI has a 67% risk of a GS upgrade. The predictive value of ROI category is consistent with our prior published experience in patients meeting the Epstein criteria for very low risk CaP, in which the OR for GS upgrading was 3.2 for patients with category 4 or 5 ROIs (15). Another study of patients eligible for active surveillance similarly identified lesion suspicion, in addition to number of lesions and lesion density, as predictive factors for GS upgrading (14). A recent prospective study found that the identification of highly suspicious lesions with mpMRI (i.e., score of 4 or 5 using the Prostate Imaging Reporting and Data System (PI-RADS) score) in patients on active

surveillance had a sensitivity of 92% for detecting primary Gleason grade 4 or 5 disease; conversely, the identification of PI-RADS 1 or 2 lesions had a negative predictive value of 84% for detecting any CaP (24). Finally, a recent randomized trial found that, among men suspected to have CaP on the basis of signs and/or symptoms, mpMRI had an accuracy of 97% for the diagnosis of CaP and identified more patients with clinically significant CaP than TRUS-guided biopsy (25).

PSA had little predictive effect on GS upgrading (OR 1.24), while gland volume had a small but significant negative effect (OR 0.96). The minimal PSA effect may be related to its nonspecific nature and the relatively low PSA values in this cohort of patients (average 5.4 ng/ml). The negative predictive effect of prostate gland volume likely reflects that fact that a small focus of high grade cancer in a large prostate may prove evasive, even with a systematic biopsy. Second, the patients with large prostates may have lower PSA density values and may therefore have very low risk CaP.

Our study has several limitations. First, the time interval from diagnosis to mpMRI-ultrasound fusion biopsy is large, ranging from 3 to 125 months. While our model did not identify the length of this interval as a positive predictor of upgrading, the series may not have had significant power to detect an effect. Additionally, our conclusion that a category 5 ROI is a significant predictor of GS upgrading is based on the small subset of 11 patients who had category 5 ROIs. This raises the possibility of a type I error, wherein the significance of this finding is the result of statistical chance. It is worth noting that category 4 ROIs showed a trend towards significance for predicting GS upgrading, which does suggest a relationship between risk of upgrading and category of ROI. In clinical practice, the identification of a category 5 ROI should prompt a targeted biopsy, while the presence of category 4 ROIs should prompt consideration for one. Another limitation is that a single fellowship-trained genitourinary radiologist categorized the ROIs, and thus lesion grading may not be generalizable to a clinical practice with a less experienced radiologist. Additionally, ROIs were categorized on the basis of an institution specific grading scale (Table 1) (16). In fact, one of the barriers to the widespread introduction of mpMRI for CaP is the lack of consensus guidelines for scoring findings (26). The aforementioned PI-RADS scoring system has recently emerged as a standard scoring system for mpMR; the results of a recent meta-analysis suggest that this scoring system, when used correctly, can have a sensitivity of up to 82% for the detection of CaP (27, 28). Our scoring system does differ from the PI-RADS system, as we assign points on the basis of absolute apparent diffusion coefficient values, and assign points for dynamic contrast enhancing MRI appearance qualitatively rather than on the basis of kinetic curves. Another limitation is that the Artemis system allows one to plan out and view the biopsy tract trajectory of the 12 core systematic biopsies. Doing this allows for a more even sampling distribution, which may improve cancer detection rates compared to a non-Artemis based approach (29). This makes it difficult to determine whether it is the systematic or the targeted biopsies that were more important in leading to GS upgrades. In our practice, we view the systematic and targeted biopsies as complementary to one another and perform both of them on all patients with grade ≥3 ROIs. Lastly, this analysis does not include final GS data from patients who underwent radical prostatectomy; thus the true GS may still under-graded, at least for some patients (16).

CONCLUSIONS

Our results show that nearly 25% of men with GS 6 CaP as diagnosed by standard TRUS biopsies may experience GS upgrading when a subsequent mpMRI-ultrasound fusion biopsy is performed. The most significant predictor of upgrading is having a category 5 ROI on mpMRI. Further investigation into using mpMRI and targeted biopsies in the evaluation of patients is warranted to avoid under-treatment in patients presumed to have low risk CaP.

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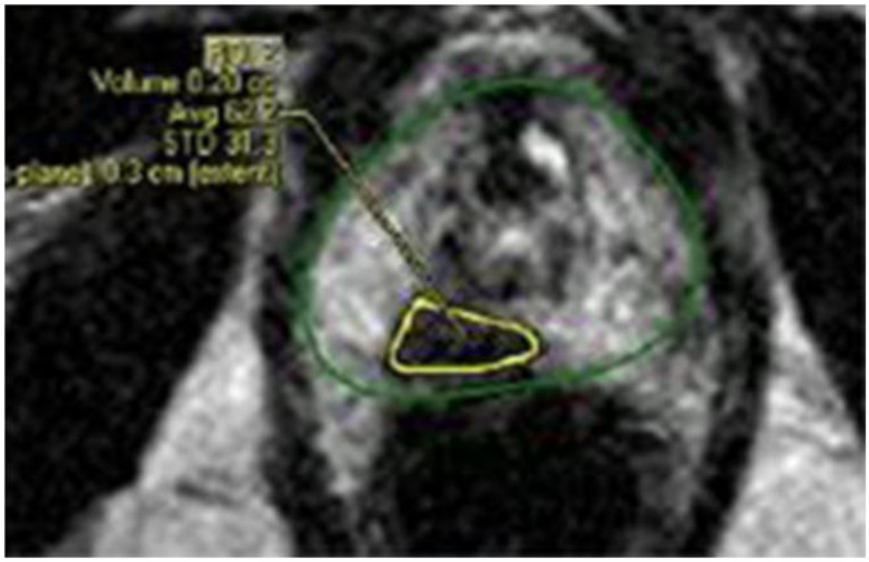

FIGURE 1.

mpMRI from a 76 year-old-man with 1/12 cores on TRUS biopsy showing GS 6 CaP. This T2-weighted image demonstrates a category 5 ROI in the right peripheral apex (green, prostate; yellow, ROI). mpMRI-ultrasound fusion biopsy found 3/5 targeted cores in this area to contain GS 3+4 CaP. He ultimately underwent definitive radiotherapy.

Table 1

UCLA scoring system for assigning level of suspicion to regions of interest on multi-parametric MRI

Image Grade	T2WI	ADC (mm^2/s)	DCE
1	Normal	>1400	Progressive (type I)
2	Indistinct, wedge-shaped, highly heterogeneous, or encapsulated border (transitional zone)	1200–1400	Early with plateau (type II) or progressive but intense (>200%)
3	Masslike but faint or slightly heterogeneous	1000–1200	Early with washout (type III) or early/plateau and intense
4	Blurred borders or uniform low signal with distinct borders	800–1000	Early and intense with washout (type III and >200%)
5	Invasion into capsule or other compartment	<800	Early & intense with immediate washout

T2WI, T2-weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced imaging

Table 2

Patient characteristics

n	**245**
Mean age at diagnosis (SD)	64 (7.4)
Median PSA (ng/mL) (SD; Interquartile Range)	4.8 (3.65; 2.9–6.7)
Months from diagnosis to ARTEMIS biopsy (SD)	15.5 (18.1)
Mean MRI prostate volume (cc) (SD)	50 (23)
Mean # of MRI based targets (SD)	1.5 (0.6)
Mean # of total cores (SD)	15 (3.1)
Outside systematic (SD)	12.4 (3.0)
Artemis Systematic (SD)	12 (1.5)
Artemis Targeted (SD)	3.6 (2.9)
Mean maximum tumor diameter (mm)	3.5 (3.6)
Mean number of previous biopsies	1.5 (0.9)
Mean MRI score	2.3 (1.7)

Table 3

Gleason scores based off of ARTEMIS targeted and systematic biopsies

GS	Maximum GS of targeted biopsy	Maximum GS of ARTEMIS systematic biopsy	Maximum GS of targeted or systematic
No Cancer	112 (46%)	109 (45%)	92 (38%)
6	33 (13%)	84 (34%)	90 (37%)
3+4	22 (9%)	38 (16%)	44 (18%)
4+3	5 (2%)	8 (3%)	11 (5%)
8 or 9	4 (2%)	6 (2%)	8 (3%)
Total # of pts	176*	245	245

* 69 patients did not have any targets on mpMRI and so did not have targeted biopsies Percentages are based n=245

Table 4

Univariate and multivariate logistic regression analysis for predictors of GS upgrading

Variable	Odds Ratio (95% confidence interval)	p-value
PSA	1.15 (1.06–1.26)	0.0008
MRI prostate volume	0.98 (0.96–0.99)	0.002
ROI category 3 or 4	1.93 (0.96–3.86)	0.05
MRI maximum tumor diameter	1.06 (0.98–1.14)	0.11
Total number of cores (targeted + systematic)	1.03 (0.93–1.15)	0.50
Number of systematic cores	0.82 (0.63–1.07)	0.11
Number of targeted cores	1.12 (1.01–1.25)	0.03
Time from diagnosis to Artemis biopsy	1.00 (1.02–0.48)	0.67
Number of previous biopsies	0.97 (0.71–1.24)	0.89

Multivariate Analysis		
Variable	**Odds Ratio (95% confidence interval)**	**p-value**
PSA	1.24 (1.12–1.37)	<0.001
Prostate Volume	0.96 (0.94–0.98)	<0.001
ROI category 3	1.91 (0.83–4.35)	0.128
ROI category 4	2.15 (0.87–5.35)	0.098
ROI category 5	10.56 (2.05–54.22)	0.005

This model excluded the n=11 patients with category 5 ROIs

This model includes patients with category 5 ROIs

Table 5

Probability of upgrading based off of patient parameters

Patient	PSA	MRI Prostate Volume (cc)	ROI MRI score	Probability of GS upgrading
1	5	45	5	0.6739
2	5	45	3/4	0.2806
3	5	55	5	0.584
4	5	55	3/4	0.2095

ROI = Region of interest

GS = Gleason score