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The Role of Magnetic Resonance Imaging in Delineating Clinically Significant Prostate Cancer

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Abstract

OBJECTIVE—To determine whether multiparametric magnetic resonance imaging might improve the identification of patients with higher risk disease at diagnosis and thereby reduce the incidence of undergrading or understaging.

METHODS—We retrospectively reviewed the clinical records of 115 patients who underwent multiparametric magnetic resonance imaging before radical prostatectomy. We used Epstein's criteria of insignificant disease with and without a magnetic resonance imaging (MRI) parameter (apparent diffusion coefficient) to calculate sensitivity, specificity, as well as negative and positive predictive values [NPV and PPV] across varying definitions of clinically significant cancer based on Gleason grade and tumor volume (0.2 mL, 0.5 mL, and 1.3 mL) on whole-mount prostate specimens. Logistic regression analysis was performed to determine the incremental benefit of MRI in delineating significant cancer.

RESULTS—The majority had a prostate-specific antigen from 4.1–10.0 (67%), normal rectal examinations (90%), biopsy Gleason score ≤6 (68%), and ≤2 cores positive (55%). Of the 58 patients pathologically staged with Gleason 7 or pT3 disease at prostatectomy, Epstein's criteria alone missed 12 patients (sensitivity of 79% and NPV of 68%). Addition of apparent diffusion coefficient improved the sensitivity and NPV for predicting significant disease at prostatectomy to 93% and 84%, respectively. MRI improved detection of large Gleason 6 (≥1.3 mL, $P = .006$) or Gleason ≥7 lesions of any size ($P < .001$).

CONCLUSION—Integration of MRI with existing clinical staging criteria helps identify patients with significant cancer. Clinicians should consider utilizing MRI in the decision-making process.

Against the backdrop of the United States Preventive Services Task Force's recommendation against prostate cancer screening, active surveillance has evolved as a viable alternative to definitive treatment for men with low-risk prostate cancer.[1] Ideally, newly diagnosed patients with indolent disease are advised to monitor their disease and

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undergo treatment only if the disease progresses over time. However, because of sampling bias, the ability of biopsy to identify men who have insignificant disease and are ideal candidates for active surveillance is limited even in expert hands and interpreted by renowned pathologists.[2] In response, multiparametric magnetic resonance imaging (mpMRI) has emerged as a potential adjunct to clinical staging and preoperative anatomical localization of disease.[3] Diffusion-weighted imaging (DWI), through the apparent diffusion coefficient (ADC), is the only functional imaging technique that is capable of quantifying molecular diffusion and biophysical properties of tissues.[4] We have previously reported on the value of DWI in discriminating patients with higher-grade tumors from those that are indolent.[5] Recently, investigators at the National Institutes of Health have shown that magnetic resonance (MR) fusion with real-time ultrasound can significantly improve the positive predictive value (PPV) of identifying for higher grade and larger tumors.[6,7]

In many cases, disease upgrading and upstaging while on active surveillance stems from missed diagnosis on initial biopsy rather than true biologic tumor progression. Given the ability of DWI to identify aggressive prostate cancer, we hypothesized that the addition of DWI to Epstein's biopsy criteria would better identify patients harboring aggressive prostate cancer. The purpose is to provide patients and providers the peace of mind required to commit to active surveillance when Epstein's criteria and MRI both demonstrate less significant disease.

MATERIALS AND METHODS

Study Population

After attaining institutional review board approval and informed consent from each patient, we conducted a retrospective study of 115 consecutive men who underwent preoperative prostate MRI at 3.0 T on a Siemens Magnetom TrioTim scanner using an endorectal coil followed by radical prostatectomy for biopsy-proven localized prostate cancer. mpMRI included T2-weighted imaging, DWI with ADC map, dynamic contrast-enhanced perfusion imaging using a k-space sharing technique, and 3-dimensional chemical shift spectroscopic imaging. All images were consensus reviewed by 2 fellowship-trained genitourinary radiologists (S.S.R. and D.J.A.M.) with at least 10 years of experience and who were blinded to clinical data. They identified the index tumor and any secondary tumor(s) for which the size and average ADC were recorded. Eleven men were excluded because of inadequate MRI related to hemorrhage, low B-values, or lack of dynamic contrast-enhanced images. Robot-assisted laparoscopic prostatectomy was performed by a single surgeon (R.E.R.). Whole-mount pathology was reviewed for surgical staging and grading by a single fellowship-trained genitourinary pathologist (J.H.) who was not aware of the imaging findings.

Predictor(s) and Pathologic Findings

We used Epstein's modified pretreatment criteria of clinically insignificant disease, Gleason score ≤6, prostate-specific antigen ≤10 ng/mL, <3 biopsy cores positive, and none with >50% involvement.[8] Based on an a priori association between DWI and higher Gleason scores (4 + 3),[5] we used an ADC value of $<0.85 \times 10$ mm^2/s (850 μm^2/s) in combination with Epstein's pretreatment criteria to determine the incremental benefit in identifying pathologically significant disease on whole-mount prostate sectioning. The definition of clinical significance on whole-mount incorporated Gleason grade and tumor volume and is represented in Table 1. We used tumor volume from prior reports of important disease—0.2 mL, 0.5 mL, and 1.3 mL.[8–10] We derived tumor volume using the spherical assumption of maximum tumor diameter ($4/3\pi r^3$) of the highest-grade lesion.

Statistical Analysis

Statistical analyses were performed to measure the incremental difference in sensitivity, specificity, negative predictive values (NPV), and PPV for Epstein's criteria with and without ADC. The dependent variable comprised a combination of Gleason score and tumor volume. Logistic regression analysis comparing the full model (Epstein's criteria with ADC) with the nested model (Epstein's criteria alone) is depicted. Model fit is represented with McFadden's r^2. We conducted all analyses with STATA software (College Station, TX). All statistical tests were 2-tailed, and the probability of a type I error was set at .05.

Study Design

Although some may question our premise of including patients with high grade or high volume disease on biopsy as potential candidates for active surveillance, we chose to include these patients in our analysis for a number of reasons. First, it helped eliminate selection bias because all patients were included in the analysis irrespective of biopsy findings. Second, the inclusion of high grade or high volume disease also helped quantify diagnostics (eg PPV) for Epstein's criteria. Third, some may argue that patients with high grade or high volume disease may still benefit from active surveillance if their life expectancy is not significant because of advanced age or significant comorbid conditions. Therefore, we found it important to validate the MR findings in those who we suspected to have high grade or high volume disease. Last, by excluding those with clinically significant disease based on Epstein's criteria, we would significantly underpower our study to detect any difference because our study would be comprised 37 patients, 12 of whom were upstaged or upgraded.

RESULTS

Cohort Characteristics

Mean age was 60.8 years, and median PSA was 5.6 ng/mL (Table 2). Most men had a PSA ranging from 4.1 to 10.0 (67%), normal digital rectal examination (90%), biopsy Gleason score ≤6 (68%), and ≤2 cores positive (55%). Ninety-three men (89.4%) had at least a 10-core biopsy of the prostate at the time of diagnosis. On prostatectomy pathology, most men had pT2 (67%), Gleason score 6 (48%), and a maximum tumor diameter of 1.0–1.9 cm (40%).

Epstein's Criteria Alone and Pathologic Significance

Sixty-seven (64.4%) men had clinically significant disease on biopsy based on Epstein's criteria (Gleason score of >6, PSA >10 ng/mL, ≥3 biopsy cores positive, or at least one biopsy core with >50% involvement). We then examined the sensitivity, specificity, PPV, and NPV of Epstein's criteria on biopsy in predicting the preset criteria of clinically significant disease on whole-mount prostatectomy (Table 1). Sensitivity is defined here as the proportion of men with significant disease on prostatectomy pathology by the a priori definitions in Table 1 that were found to have clinically significant disease on biopsy using Epstein's criteria. Therefore, the false negative rate is defined as the proportion of men who had pathologically significant disease but met Epstein's criteria of clinically insignificant disease on biopsy. If we define extraprostatic extension, or Gleason >6, or Gleason 6 with a tumor volume ≥1.3 mL as pathologically significant, then 24% of these men would have had the extent of their disease underestimated. If we define extraprostatic extension, or Gleason >6 of any size as pathologically significant, then 21% of them would have been underestimated as clinically insignificant disease. If we define extraprostatic extension, or Gleason ≥4 + 3, or Gleason 3 + 4 with a tumor volume ≥1.3 mL as pathologically significant, then 19% of these men would have been underestimated as having clinically insignificant disease.

The NPV is defined here as the proportion of men who had insignificant clinical parameters (Epstein's criteria) and pathologically insignificant disease. Therefore, 1-NPV, or probability of disease given a negative test, is described as the number of men who had insignificant clinical parameters on biopsy, but who in fact had pathologically significant disease as defined in Table 1. Among men who satisfy Epstein's criteria of clinically insignificant disease, 49% had extraprostatic extension or Gleason ≥6 with a tumor volume ≥1.3 mL, 32% had extraprostatic extension or Gleason ≥7 of any size, and 27% had extraprostatic extension or Gleason ≥7 with a tumor volume ≥1.3 mL.

Epstein's and MRI Criteria, and Pathologic Significance

Based on the a priori definitions in Table 1, we included an ADC value of 850 $\mu m^2/s$ to Epstein's criteria to quantify the incremental benefit in predicting severity of disease. First, we measured the false negative rate (1-sensitivity). If we define extraprostatic extension, or Gleason >6, or Gleason 6 with a tumor volume ≥1.3 mL as pathologically significant, then 13% of these men would have had the extent of their disease underestimated because they satisfied both Epstein's criteria and MR criteria of clinically insignificant disease (compared with 24% for Epstein's criteria alone). If we define extraprostatic extension, or Gleason >6 of any size as pathologically significant, then 7% of these men satisfied Epstein's and MR criteria of clinically insignificant disease (compared with 21% for Epstein's criteria alone). If we define extraprostatic extension, or Gleason ≥4 + 3, or Gleason 3 + 4 with a tumor volume ≥1.3 mL as pathologically significant, then 4% of these men satisfied Epstein's and MR criteria of clinically insignificant disease (compared with 19% for Epstein's criteria alone).

Next, we measured the probability of disease given a negative test (1-NPV) for Epstein's criteria with ADC. When compared with Epstein's criteria alone, the addition of an ADC value of 850 $\mu m^2/s$ decreased the number of men who were misclassified. For instance, among men who satisfy both Epstein's and MRI criteria of clinically insignificant disease, 40% had extraprostatic extension, or Gleason >6, or Gleason 6 with a tumor volume ≥1.3 mL (compared with 49% for Epstein's criteria alone); 16% had extraprostatic extension or Gleason >6 of any size (compared with 32% for Epstein's criteria alone); and 8% had extraprostatic extension, or Gleason ≥4 + 3, or Gleason 3 + 4 with a tumor volume ≥1.3 mL (compared with 27% for Epstein's criteria alone).

In Table 3, we have outlined 2-by-2 diagnostic tables for 2 different definitions of pathologic significance. The first is ≥pT3 or Gleason score >6 and the second is ≥pT3, or Gleason ≥4 + 3, or Gleason 3 + 4 that is ≥1.3 mL. Using Epstein's criteria alone, we would have "understaged" 12 men as having insignificant prostate cancer, when in fact they harbored more aggressive disease (≥pT3 or Gleason >6) and "overstaged" 21 men as having clinically significant disease, when in fact they had pathologically insignificant disease (pT2 and Gleason 6). With the addition of ADC, we would minimize the number of "understaging" to 4 men (compared with 12) at the expense of "overstaging" 25 men (compared with 21). If we define ≥pT3 or Gleason ≥4 + 3, or Gleason 3 + 4 that is ≥1.3 mL as pathologically significant, then Epstein's criteria alone would have "understaged" 10 men and "overstaged" 23 men. The addition of ADC above and beyond Epstein's criteria would minimize the number of "understaging" to 2 men (compared with 10) at the expense of "overstaging" 27 men (compared with 23).

Model Fit

To ascertain the incremental benefit of ADC in predicting pathologically significant prostate cancer, we generated nested logistic regression models with and without ADC (Table 4). An ADC of <850 $\mu m^2/s$ did not significantly improve model fit beyond Epstein's criteria alone

in identifying small volume (≥0.2 and ≥0.5 mL) Gleason 6 tumors (P = .09 and P = .11, respectively). However, for larger volume (≥1.3 mL) Gleason 6 disease or Gleason 7 of any size, the ADC value of <850 $\mu m^2/s$ significantly improved model fit (P = .006 and P <.001, respectively). The model fit for Epstein's criteria alone did not significantly differ irrespective of grade or size of disease (r^2 = 0.09–0.14). The addition of ADC to Epstein's criteria did not significantly improve model fit for smaller Gleason 6 tumors (r^2 = 0.08–0.14). However for large (≥1.3 mL) Gleason 6 tumors or Gleason 7 tumors of any size, the addition of ADC was found to significantly improve model fit (r^2 = 0.20–0.24).

COMMENT

Our study combining mpMRI with conventional clinical staging yielded four principal findings. First, the incremental benefit of DWI above and beyond Epstein's criteria is limited to recognition of higher grade (Gleason 7: 14% absolute improvement in sensitivity and 16% absolute improvement in NPV) and larger lesions (≥1.3 mL: 11% absolute improvement in sensitivity and 9% absolute improvement in NPV). Others have previously reported on the use of DWI in recognizing high-grade prostate cancer.[5,11,12] More recently, Turkbey et al compared the accuracy of mpMRI with that of clinical criteria (D'Amico, Epstein, and CAPRA) in discerning more aggressive prostate cancer (Any Gleason 4 or 5 pattern or tumor volume >0.5 mL).[13] The accuracy of D'Amico and CAPRA in appropriately discerning indolent from aggressive tumors was 70% and 59%, respectively. However, the accuracy of Epstein's criteria was 88%—not significantly different from 92% accuracy with mpMRI. Nevertheless, mpMRI did outperform Epstein's criteria in the case of sensitivity (93% vs 64%) and PPV (57% vs 45%). In our study, Epstein's criteria for insignificant disease did not perform as well—32% of patients satisfying Epstein's criteria harbored Gleason 7 disease, most of whom had high-volume disease (27%). This 32% coincides with the active surveillance failure rate (to active treatment) of 36%.[14–21] Addition of an objective MRI parameter (ADC <850 $\mu m^2/s$) to Epstein's criteria reduced the unexpected finding of any Gleason 7 at prostatectomy to 16% and that of large-volume Gleason 7% to 8%. Third, the incremental improvement in sensitivity and NPV was derived from a single objective and quantifiable MRI parameter. Although the inclusion of multiple MRI parameters will undoubtedly better characterize tumor biology, it does come at the expense of lack of generalizability. In essence, this objective finding transcends image-guided risk stratification from the "Aunt Minnie" effect in a few academic institutions to one that is quantifiable in community practices—where the bulk of urologic care is managed. Last, the insignificant benefit of DWI above and beyond Epstein's criteria to recognize small-volume (<1.3 mL), low-grade tumors (Gleason 6) speaks to the limitations of contemporary MRI rather than particular cut-offs. Although this may be problematic as a diagnostic modality (ie replacing a prostate biopsy), it does not detract from its use in identifying pathologically significant prostate cancer (large volume or higher grade).

Our study has several limitations. First, as a retrospective study, it is subject to selection and verification biases. The mere fact that patients were undergoing radical prostatectomy may suggest that our patients may not be representative of a population of men with less significant disease. If the proportion of men with clinically insignificant disease were augmented, then our probabilities and NPV may also be subject to bias. However, 69 patients (66%) in our series had D'Amico low-risk tumors, which is significantly higher than the national trends whereby 46% of all men diagnosed with prostate cancer,[22] and 10% of Medicare beneficiaries undergoing radical prostatectomy have these low-risk features.[23] At our institution, preoperative MRI is performed for staging purposes on all patients before undergoing prostatectomy, thereby eliminating the selection bias associated with the provision of MRI. Second, we assumed that tumor volume was derived from spherical dimensions of maximum tumor diameter. While this may have impacted the incremental use

of identifying larger lesions (≥1.3 mL), it would not have affected Gleason score. Third, some will contend that while ADC significantly improved the sensitivity (14%) and NPV (16%) of identifying Gleason 7 disease, it came at the modest cost of over-treating 8% of patients. However, our primary intent was to improve sensitivity and NPV so that patients may pursue active treatment early and avoid being lost to follow-up, and have progression of disease. Fourth, despite the similar protocols used, variation in ADC values may ensue, as scanners made by different manufacturers will yield different sequence parameters. However, there is evidence that inter-scanner variation is reasonable at least for ADC parameters (5%).[24] Fifth, our study was limited by the fact that we used a 3.0-T on a Siemens Magnetom TrioTim scanner and that all images were consensus reviewed by 2 fellowship-trained genitourinary radiologists with at least 10 years of experience. Although this clearly improves internal validity, it comes at the cost of external validity and generalizability. Hence, access to this infrastructure may only be limited to a few academic institutions. Sixth, some may argue that mpMRI is unnecessary in the hands of an experienced urologist and the added cost of performing an MRI on all patients before radical prostatectomy may not be cost-prohibitive, especially in this current era of budgetary austerity. However, there is significant variability in the number of cores removed and the quality of the prostate biopsy in the community, where the bulk of prostate cancer is diagnosed.[25] Therefore, the purpose of the mpMRI and the associated cost is to minimize variability of care and, facilitate generalizability for patients who have clinically insignificant prostate cancer and are considering active surveillance. Seventh, some may question the use of mpMRI in the era of genomic testing (eg Genomic Health, Myriad, and Bostwick Laboratories), whereby we may be better able to discern indolent tumors from more aggressive ones.[26] However, these genomic tests still rely on appropriate tissue sampling, and variance in the quality of prostate biopsies may undermine the use of these tests. We would anticipate that the use of these genomic tests may be augmented by the ability of mpMRI to help localize areas concerning for significant disease. Last, while template prostate mapping and saturation biopsies may be better at detecting or measuring the extent of disease than MRI,[27] it does come at the expense of morbidity and low-risk of sepsis.[28] Despite these limitations, the findings of the current study highlight the clinical implications of incorporating MRI into routine prostate cancer.

The diffusion and integration of MRI in the prostate cancer decision-making process has been slow at most academic centers, let alone community practices. Its slow dissemination is in part attributed to costs, clinical utility, and subjectivity in radiologic interpretation. Herein, we report that although MRI may still be imperfect at identifying small, low-grade tumors, a single quantifiable, objective parameter (ADC) shows promise at identifying larger or higher-grade tumors. As active surveillance proves to be a cost-effective approach that simultaneously preserves quality of life,[29,30] it is likely that active surveillance for men with indolent disease and the incidence of progression to active treatment will become a Patient Quality Reporting System quality measures. In this context, the clinical use of MRI will play an increasing salient role in delineating early on who will benefit from active surveillance vs treatment.

CONCLUSION

When compared with Epstein's criteria alone, the addition of an ADC value of 850 $\mu m^2/s$ decreased the number of men who were misclassified. Integration of MRI with existing clinical staging criteria helps identify patients with significant cancer.

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Table 1

Incremental benefit of apparent diffusion coefficient in delineating varying definitions of significant prostate cancer

		Epstein Alone				Epstein + ADC <850 μm^2/s			
Pathologic Findings	***N* (%)**	**Sens, %**	**Spec, %**	**PPV, %**	**NPV, %**	**Sens, %**	**Spec, %**	**PPV, %**	**NPV, %**
Gleason >6 Any Size or Gleason = 6 and Tumor Volume ≥0.2 mL	90 (87)	70	71	94	27	81	57	92	32
Gleason >6 Any Size or Gleason = 6 and Tumor Volume ≥0.5 mL	87 (84)	70	65	91	30	82	53	90	36
Gleason >6 Any Size or Gleason = 6 and Tumor Volume ≥1.3 mL	76 (73)	76	68	87	51	87	54	84	60
Gleason >6 and Any Size	58 (56)	79	54	69	68	93	46	68	84
Gleason >3 + 4 Any Size or Gleason = 7 and Tumor Volume ≥0.2 mL	58 (56)	79	54	69	68	93	46	68	84
Gleason >3 + 4 Any Size or Gleason = 7 and Tumor Volume ≥0.5 mL	58 (56)	79	54	69	68	93	46	68	84
Gleason >3 + 4 Any Size or Gleason = 7 and Tumor Volume ≥1.3 mL	54 (52)	81	54	66	73	96	46	66	92

ADC, apparent diffusion coefficient; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Table 2

Cohort characteristics

Variables	Distribution (%)
Age	
<55	20 (19)
55–64	53 (51)
≥65	31 (30)
Pretreatment PSA	
≤4.0	24 (23)
4.1–10.0	70 (67)
>10.0	10 (10)
Clinical Stage	
T1c	94 (90)
T2a	10 (10)
Biopsy Gleason Score	
≤6	71 (68)
3 + 4	19 (18)
4 + 3	8 (8)
8–10	6 (6)
Cores Positive	
≤2	57 (55)
3–6	35 (34)
≥7	12 (11)
Maximum Percent Per Core	
≤50	80 (77)
>50	24 (23)
Pathologic Stage	
pT2a	23 (22)
pT2b	6 (6)
pT2c	41 (39)
pT3a	23 (22)
pT3b	10 (10)
pT4	1 (1)
Pathologic Gleason Score	
≤6	50 (48)
3 + 4	34 (33)
4 + 3	13 (12)
8–10	7 (7)
Pathologic Maximum Tumor Diameter (cm)	
<1	18 (17)
1.0–1.9	42 (40)
2.0–2.9	29 (28)

Variables	Distribution (%)
≥3.0	15 (15)

PSA, prostate-specific antigen.

Table 3

Test diagnostics of sample definitions of pathologic significance

	Pathologic Findings (≥pT3 or Gleason >6 of Any Size)		
Epstein's Clinical Criteria Alone	Significant Disease	Insignificant Disease	
Significant Disease	46	21	PPV = 69%
Insignificant Disease	12	25	NPV = 68%
	Sensitivity = 79%	Specificity = 54%	
	Pathologic Findings (≥pT3 or Gleason >6 of Any Size)		
Epstein's Clinical Criteria or ADC<850 μm^2/sec	Significant Disease	Insignificant Disease	
Significant Disease	54	25	PPV = 68%
Insignificant Disease	4	21	NPV = 84%
	Sensitivity = 93%	Specificity = 46%	
	Pathologic Findings (≥pT3, or Gleason ≥4+3, or Gleason 3+4 and ≥1.3 mL)		
Epstein's Clinical Criteria Alone	Significant Disease	Insignificant Disease	
Significant Disease	44	23	PPV = 66%
Insignificant Disease	10	27	NPV = 73%
	Sensitivity = 82%	Specificity = 54%	
	Pathologic Findings (≥pT3, or Gleason ≥4+3, or Gleason 3+4 and ≥1.3 mL)		
Epstein's Clinical Criteria or ADC<850 μm^2/sec	Significant Disease	Insignificant Disease	
Significant Disease	52	27	PPV = 66%
Insignificant Disease	2	23	NPV = 92%
	Sensitivity = 96%	Specificity = 46%	

Abbreviations as in Table 1.

Table 4

Logistic regression analysis comparing model fit for Epstein's criteria with and without magnetic resonance imaging

Pathologic Findings	Epstein's Criteria	r^2	Epstein's Criteria	ADC <850 $\mu m^2/s$	r^2	*P* Value
Gleason ≥6 and Tumor Volume ≥0.2 mL	5.83 (1.68–20.24)	0.11	5.58 (1.58–19.66)	3.53 (0.71–17.43)	0.14	.09
Gleason ≥6 and Tumor Volume ≥0.5 mL	4.30 (1.44–12.86)	0.10	4.11 (1.36–12.46)	2.77 (0.72–10.72)	0.08	.11
Gleason ≥6 and Tumor Volume ≥1.3 mL	6.80 (2.62–17.65)	0.14	7.04 (2.59–19.13)	4.85 (1.41–16.64)	0.20	.006
Gleason ≥7 and Any Size	4.56 (1.93–10.79)	0.09	5.35 (1.99–14.39)	8.78 (2.95–26.13)	0.22	<.001
Gleason ≥7 and Tumor Volume ≥0.2 mL	4.56 (1.93–10.79)	0.09	5.35 (1.99–14.39)	8.78 (2.95–26.13)	0.22	<.001
Gleason ≥7 and Tumor Volume ≥0.5 mL	4.56 (1.93–10.79)	0.09	5.35 (1.99–14.39)	8.78 (2.95–26.13)	0.22	<.001
Gleason ≥7 and Tumor Volume ≥1.3 mL	5.16 (2.13–12.50)	0.10	6.46 (2.28–18.25)	9.35 (3.16–27.64)	0.24	<.001

Abbreviation as in Table 1.