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Authors

Liss, Michael A
Newcomb, Lisa F
Zheng, Yingye
et al.

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Magnetic Resonance Imaging for the Detection of High-Grade Cancer in the Canary Prostate Active Surveillance Study

Michael A. Liss,
University of Texas Health Science Center San Antonio

Lisa F. Newcomb,
Fred Hutchinson Cancer Research Center, University of Washington

Yingye Zheng,
Fred Hutchinson Cancer Research Center

Michael P. Garcia,
Fred Hutchinson Cancer Research Center

Christopher P. Filson,
Emory University School of Medicine

Hilary Boyer,
Fred Hutchinson Cancer Research Center, University of Washington

James D. Brooks,
Stanford University

Peter R. Carroll,
University of California at San Francisco

Matthew R. Cooperberg,
University of California at San Francisco

William J. Ellis,
Fred Hutchinson Cancer Research Center, University of Washington

Martin E. Gleave,
University of British Columbia

Frances M. Martin,
Eastern Virginia Medical School

Todd Morgan,
University of Michigan

Peter S. Nelson,
Fred Hutchinson Cancer Research Center, University of Washington

Corresponding Author: Michael A. Liss, MD, MAS. Department of Urology, UTHSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78229, liss@uthscsa.edu, Phone: 210-567-5676 / Fax: 210-567-6868.

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Andrew A. Wagner,
Beth Israel Deaconess

Ian M. Thompson Jr.,
University of Texas Health Science Center San Antonio

CHRISTUS Santa Rosa Medical Center, San Antonio

Daniel W. Lin
Fred Hutchinson Cancer Research Center, University of Washington

Abstract

Purpose: We investigated the ability of prostate MRI to detect Gleason Grade Group (GG) ≥2 cancer in a standardized, multi-institutional active surveillance cohort.

Material and Methods: We evaluated men enrolled in Canary Prostate Active Surveillance Study (PASS) with GG<2 and who underwent a biopsy within 12 months of a multiparametric MRI. Our primary outcome was biopsy reclassification to GG2 or greater. We evaluated the performance of MRI PIRADS score and clinical factors. Multivariable logistic regression models were fit with MRI and clinical factors and used to perform receiver operating curve analyses.

Results: There were 361 participants with 395 prostate MRIs with a median follow-up of 4.1 (IQR: 2.0–7.6) years. Overall, 108/395 (27%) biopsies showed reclassification. Defining positive MRI as PIRADS 3–5, the NPV and PPV for detecting GG ≥2 cancer was 83% (95% CI: 76–90%) and 31% (95% CI: 26–37%), respectively. PIRADS was significantly associated with reclassification (PIRADS 5 versus 1 and 2: OR = 2.71; 95% CI: 1.21–6.17, p = 0.016) in a multivariable model but did not improve upon a model with only clinical factors (AUC 0.768 versus 0.762). In 194 fusion biopsies, higher grade cancer was found in targeted cores in 21 (11%) instances, while 25 (13%) had higher grade cancer found in the systematic cores.

Conclusions: This study adds the largest cohort data to the body of literature for MRI in active surveillance, recommending systematic biopsy in patients with a negative MRI and the inclusion of systematic biopsy in patients with a positive MRI.

Introduction

Active surveillance (AS) for low-risk prostate cancer is considered the preferred initial management strategy by national guidelines.[1–3] Providers and patients remain concerned that apparent low-grade prostate cancer may harbor occult higher grade disease that would warrant treatment, and that the delay in primary curative therapy may introduce unnecessary risk of cancer progression.[4] Furthermore, active surveillance involves prostate biopsies which are costly and invasive, with risks of significant pain, bleeding, infection, and anxiety.[5] Tools that improve outcomes of active surveillance would have great benefit.

MRI has been promoted for the initial diagnostic workup for elevated PSA, particularly in men with previous negative biopsies.[6, 7] Multiple studies have reported that MRI targeted biopsies increase detection of clinically significant prostate cancer and can reduce unnecessary biopsies and over detection of indolent cancers.[8, 9] Widespread adoption of MRI has been hampered by variations in scan performance characteristics, high

interobserver variability, and cost.[10, 11] Most active surveillance studies investigating MRI are small, single-institution case series reporting variable sensitivity/specificity, even in tertiary care centers of excellence.[12–14] One notable randomized clinical trial of MRI in active surveillance reported that the addition of MRI with targeted biopsies to systematic biopsies did not significantly increase the upgrading rate compared with systematic biopsy alone.[15]

Against this background, we report the operating characteristics of multiparametric MRI (mpMRI) in a cohort of men with low-grade prostate cancer who are participants in a prospective, multi-institutional active surveillance clinical study. We specifically examined the association of mpMRI lesions with disease reclassification at protocol-directed surveillance biopsies. We further studied the utility of MRI fusion biopsy techniques when compared to systematic biopsies alone.

Methods

Study sample and analytic cohort:

The Canary Prostate Cancer Active Surveillance Study (PASS) is an IRB approved multicenter prospective study (clinicaltrials.gov NCT00756665) of men who elected AS for prostate cancer management and has been described in detail.[16, 17] Briefly, follow-up included quarterly PSA measures, semi-annual digital rectal examinations, and surveillance prostate biopsies at one and two years after initial diagnosis and then every two years. Use of prostate MRI as a component of surveillance was not mandated by this protocol and left to each clinician's discretion. For this analysis we captured clinical data up through February 2019 on participants from a central database. We excluded men if they had no MRI, an MRI before initial diagnosis, MRI with no subsequent biopsy within 12 months, or Gleason Grade Group (GG) > 1 before MRI. Details are depicted in Supplemental Figure 1. In this analysis, data were included from 9 of the 10 PASS sites.

Exposures and outcomes of interest:

Images were from July 2010 to January 2019, IQR: November 2015 – August 2017. Images were interpreted according to the procedure at each site, and all were graded based on PIRADS, with approximately 80% using PIRADS v2.0. We defined MRIs as "normal" if no lesions were noted, or if suspicious regions were graded as PIRADS 1/2. If no lesion was found, for analysis the MRI was treated as a negative MRI and assigned as PIRADS 1. There was no standard protocol in terms of magnet strength (1.5T vs 3T) or use of endorectal coil, although the large majority of images were obtained with 3T magnets, with the exception of early images at 2 sites (<10% of images) that were obtained with 1.5T magnet using endorectal coil. Our primary outcome of interest was biopsy reclassification defined as any upgrade to Gleason GG ≥ 2 on the post-MRI biopsy. Biopsies were performed at the discretion of the clinician, including cognitive or MR-US fusion-image guidance, as well as the amount of systematic sampling added to targeted biopsy cores.

Statistical Analysis:

For our assessment of the diagnostic performance of prostate MRI, we considered an MRI as "negative" if no lesion or a PIRADS 1/2 lesion was present. A separate analysis was performed in which PIRADS 1–3 were grouped together in the definition of negative MRI. Biopsy results were considered the gold standard result, with presence of GG2 and greater cancer considered a positive result. Negative and positive predictive values (NPV and PPV), true and false positive rates (TPR and FPR) were calculated at the MRI-level to evaluate the accuracy of MRI (positive versus negative) for classifying reclassification status.

We then fit multivariable logistic regression models based on previously established models using available clinical information to estimate the odds of our outcome of interest. A base model, consistent with previous studies[18], included age, body mass index (BMI), number of negative biopsies after diagnosis, percent of total biopsy cores containing cancer from the previous biopsy, log-transformed prostate size, and log-transformed serum PSA. We then added PIRADS score (categorical) to a second model. We then used receiver operating curve (ROC) analyses to calculate the areas under the curve (AUC) for both models to assess the discriminatory capacity for separating patients with and without biopsy reclassification.

In a separate analysis, we compared targeted versus systematic biopsy approaches for detection of high-grade cancer in the subset of men who had concurrent systematic and targeted MR/ultrasound fusion biopsy. All analyses were conducted using R version 3.1.1 (http://www.r-project.org/).

Results

Of the 361 AS patients who had an MRI and biopsy, 306 (85%) were Caucasian, 25 (7%) African American, and 30 (8%) other race (Table 1). The median PSA at the time of MRI was 5.6 ng/ml (IQR: 3.9–8.2), the median prostate size was 43.8 cm^3 (IQR: 32.1–60.3), and the median percent of total biopsy cores with cancer was 8.3 (IQR: 7.1–17.4). Participant characteristics were very similar between participants in the PASS cohort who did and did not receive a prostate MRI (Supplemental Table 1). The median follow-up time for participants in the analysis who did not upgrade at biopsy was 4.1 years (IQR: 2.0–7.6). There were 395 MRI studies performed at a median of 25 (IQR: 7.4 – 57) months from diagnosis; 186 (47%) of MRI's were obtained prior to the first surveillance biopsy after initial diagnosis, 77 (20%) before the second surveillance biopsy, 67 (17%) before the third surveillance biopsy, and 65 (16%) before later biopsies.

The 361 participants had a total of 395 MRI's performed, 111 (28%) of which were negative (PIRADS 1–2), and 284 were positive, 87 (22%) of which were PIRADS 3, 145 (37%) PIRADS 4, and 52 (13%) PIRADS 5 (Table 2). In the biopsies following MRI, 287 (73%) had either no cancer or GG 1 detected, and 108 (27%) had reclassification to GG ≥ 2. Of the negative MRI studies, 17% (19/111) upgraded or reclassified to GG2 prostate cancer. The NPV of a negative MRI (PIRADS 1–2) was 83% (95% CI: 76–90%), and the PPV of a positive MRI was 31% (95% CI: 26–37%).The FPR and TPR were 68% (95% CI: 63–73%) and 82% (95% CI: 75–89%) respectively. If a negative MRI was defined as PIRADS 1–3, the NPV was 82% (Supplemental Table 2).

When PIRADS was included in a base multivariable model of clinically available data, MRI remained a significant predictor of upgrading (PIRADS 5 versus PIRADS 1 and 2: OR = 2.71; 95% CI: 1.21–6.17, p = 0.016; Table 3). In ROC analysis for prediction of biopsy upgrading, the AUC for a model including PIRADS was minimally larger than for a base clinical model without PIRADS (0.768 and 0.762 respectively; Figure 1).

In 194 MR/ultrasound fusion biopsies with concurrent targeted and systematic biopsy cores, 148 (76%) had either no high grade or the same grade cancer found in both targeted and systematic cores (Table 4). There were 21 (11%) biopsies that had higher grade cancer found in the targeted cores relative to the systematic cores, and 25 (13%) that had higher grade cancer found in the systematic cores.

Discussion

For 361 patients who underwent a mpMRI and subsequent biopsy while on AS, a negative MRI was associated with a lower risk of upgrading on subsequent surveillance biopsy. We identified mpMRI is associated with an NPV of 83%, [6, 15, 19] suggesting that a negative MRI will still miss a substantial proportion of patients with GG≥2 disease. In addition, systematic biopsies detected a similar number of unique GG≥2 cancer as targeted MRI cores. Thus, if the goal of surveillance biopsy is to identify higher-grade disease, both systematic and targeted biopsies should be obtained for men with a region of interest (ROI) identified on MRI. Furthermore, we also found that while PIRADS 5 lesions were significantly associated with upgrading or reclassification when compared to PIRADS 1 and 2, models including PIRADS scores were only minimally improved over models that contain clinical variables alone.

While there appears to be consensus that MRI is associated with improved diagnoses of high-grade cancers and with fewer low-grade cancers upon screening prostate biopsy, there are no robust data to guide clinical practice in the active surveillance setting. For example, multiple guideline statements do not support the routine use of MRI in prostate cancer active surveillance.[15, 20, 21] Our findings are consistent with studies showing that targeted biopsies in the active surveillance population may add little in terms of predicting upgrading or reclassification.[15, 22–24] The translation of MRI performance in the diagnostic setting to the surveillance population is likely hampered for several reasons. Patients in AS often have had multiple biopsy sessions with more extensive gland sampling, making them less likely to have large, high grade cancers that are more likely to be evident on mpMRI.

Our findings should be considered in the context of several limitations. First, there was no standard imaging incorporated within our multi-institutional protocol, and the decision to obtain an MRI was based on physician judgment and local practice standards. Furthermore, there was no central review of imaging or biopsy results or other accounting for known inter-observer variation.[25–27] Nonetheless, both of these limitations reflect real-world practice as there are no guideline-based recommendations for the frequency or need for MRI imaging during surveillance, and central radiology review is challenging in the setting of this observational cohort study. Additionally, the results of this study include data from the early adoption of MRI with the associated learning curve of MRI interpretation and evolution of

the PIRADS scoring system. It is possible that contemporary interpretation and performance of MRI could lead to better performance, as could future improvements in computer-aided and artificial intelligence systems-based analyses, although artificial intelligence would require major allocation of resources for well-curated data.[28–30] Finally, although a substantial proportion of the MRI's were obtained at the time of the first surveillance biopsy, we report on all the MRI tests obtained during the course of AS in our cohort. Thus, the risk of upgrading is likely variable, depending on the time point of the imaging in relation to the initial diagnosis, which consequently affects the pre-test probability of upgrading and/or finding a clinically significant MRI lesion, although the variable performance of MRI due to cancer prevalence has been previously reported.[6]

Despite these limitations, our data have significant implications on the practice of AS and the use of MRI. First, we found an NPV of 83% suggesting that a negative MRI does not ensure a lack of tumor upgrading in a patient on active surveillance. Second, if an MRI is abnormal, both targeted and systematic biopsies should be performed. The practice of limited sampling, such as performed with in-gantry MRI-directed strategies, will likely miss GG≥2 cancers and have implication for clinical-decision making. While higher PIRADS scores are associated with a greater risk of a clinically significant cancer, several other clinical factors are associated with upgrading including volume/number of biopsy cores with cancer, prostate size or PSA density, and patient age. MRI has little improvement over these factors for predicting upgrading and the clinical factors should be considered when assessing risk during active surveillance.

This study adds the largest cohort data to the body of literature for MRI in active surveillance, providing awareness of the utility and shortcomings of MRI in surveillance, recommending systematic biopsy in patients with a negative MRI and the inclusion of systematic biopsy in patients with a positive MRI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AS	Active Surveillance
PSA	Prostate Specific Antigen
MRI	Magnetic Resonance Imaging
mpMRI	Multi-parametric Magnetic Resonance Imaging

PASS	Prostate Cancer Active Surveillance Study
GG	Gleason Group
PIRADS	Prostate Imaging-Reporting and Data System
MR-US	Magnetic Resonance Imaging – Ultrasound
ROC	Receiver operator curve
AUC	Area under the curve
IQR	Interquartile Range
FPR	False Positive Rate
TPR	True positive rate
NPV	Negative predictive value

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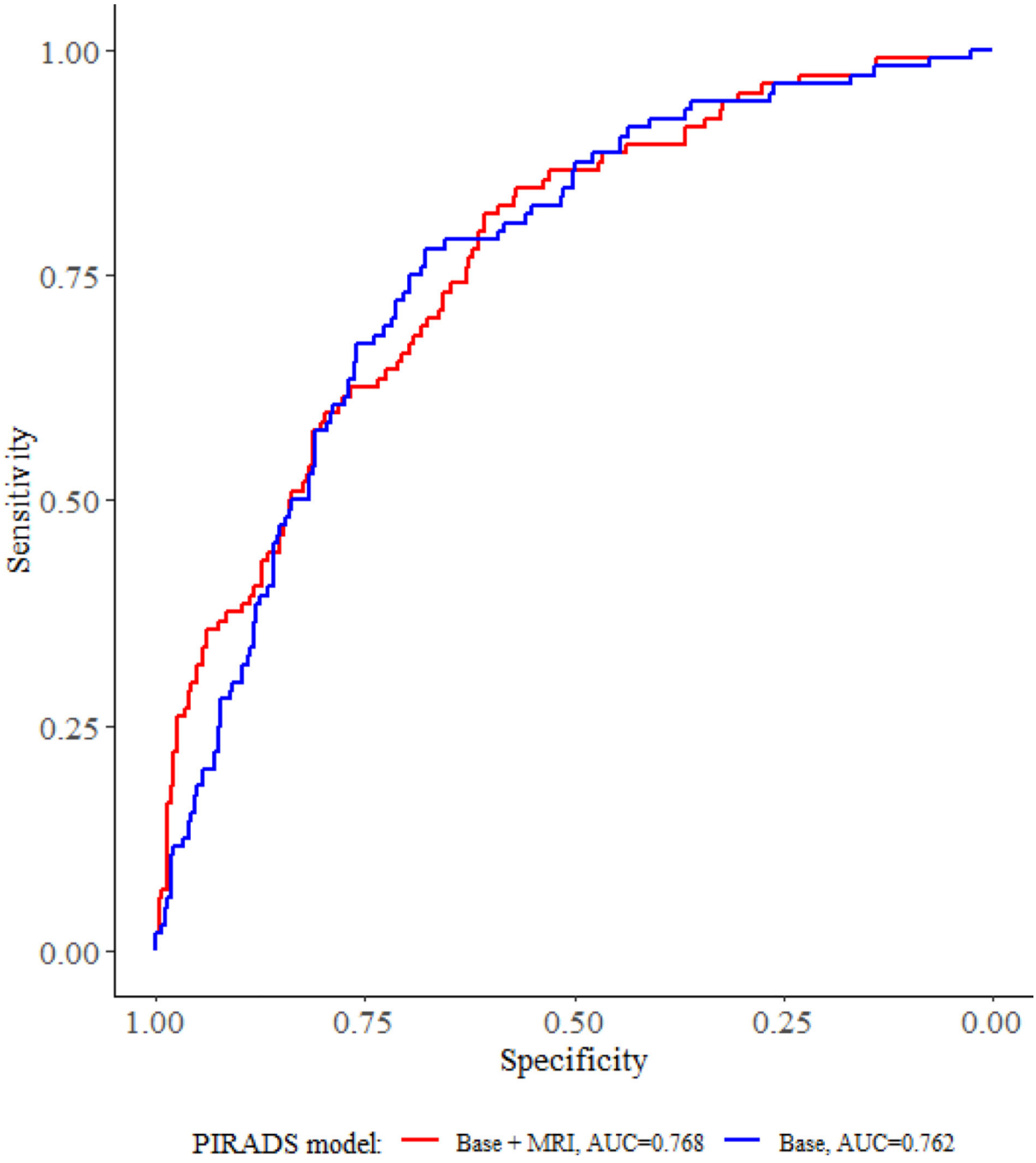

Figure 1.
Receiver Operating Characteristic curves for prediction of reclassification.

Table 1.

Participant characteristics at time of first MRI (N = 361).

Characteristic	N (%) or Median (IQR)
Race	
Caucasian	306 (85%)
African American	25 (7%)
Other	30 (8%)
Age (yrs)	65 (59–69)
BMI (kg/m^2)	27.3 (25.1–30.4)
PSA (ng/ml)	5.6 (3.9–8.2)
Prostate Size (cm^3)	43.8 (32.1–60.3)
PSA Density	0.12 (0.08–0.16)
% positive cores	8.3 (7.1–17.4)

Table 2.

MRI PIRADS association with Gleason upgrading. Results are shown A) categorically by PIRADS and GG, and B) dichotomous in a 2×2 table used to calculate NPV, PPV, FPR and TPR.

A.

PIRADS	Gleason Grade Group						Total (%)
	No cancer	1	2	3	4	5	
1	23	29	8	1	0	0	61 (15)
2	21	19	7	1	1	1	50 (13)
3	29	42	15	0	0	1	87 (22)
4	23	75	32	10	3	2	145 (37)
5	6	20	17	6	2	1	52 (13)
Total (%)	102 (26)	185 (47)	79 (20)	18 (5)	6 (1)	5 (1)	395

B.

	No Gleason pattern 4	Gleason pattern ≥4	Total
MRI Negative	92	19	111
MRI Positive	195	89	284
Total	287	108	395

Table 3.

Regression models for biopsy reclassification (n = 395).

	Univariate		Base Model		Base + MRI Model	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age	1.05 (1.02, 1.09)	0.003	1.08 (1.04, 1.12)	<0.001	1.07 (1.03, 1.12)	<0.001
BMI	1.01 (0.96, 1.07)	0.708	1.06 (1.00, 1.13)	0.062	1.06 (0.99, 1.13)	0.075
% positive cores	1.03 (1.02, 1.05)	<0.001	1.02 (1.00, 1.04)	0.031	1.02 (1.00, 1.04)	0.062
Log(Prostate size)	0.34 (0.19, 0.58)	<0.001	0.19 (0.09, 0.36)	<0.001	0.20 (0.10, 0.39)	<0.001
Log(PSA)	1.64 (1.16, 2.34)	0.006	2.17 (1.47, 3.30)	<0.001	2.08 (1.38, 3.20)	<0.001
≥2 Prior Neg Bx	0.34 (0.05, 1.24)	0.159	0.35 (0.05, 1.41)	0.19	0.32 (0.05, 1.34)	0.167
PIRADS[1] (1–2 reference)						
3	1.09 (0.52, 2.27)	0.816			0.74 (0.33, 1.65)	0.47
4	2.32 (1.29, 4.33)	0.006			1.54 (0.81, 3.02)	0.20
5	4.84 (2.34, 10.24)	<0.001			2.71 (1.21, 6.17)	0.016

[1]Likelihood Ratio Test for PIRAD p=0.014

Table 4.

Results of targeted versus systematic biopsies (n = 194 fusion biopsies).

		Targeted biopsies				
		no cancer	**GG 1**	**GG 2**	**GG 3**	**GG 4–5**
Systematic biopsies	**no cancer**	29	7	3	1	0
	GG 1	47	46	11	1	0
	GG 2	7	7	16	2	3
	GG 3	3	1	4	2	0
	GG 4–5	1	0	1	1	1