Serial prostate magnetic resonance imaging fails to predict pathological progression in patients on active surveillance

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Abstract

Introduction: Limited data guide urological practice when employing prostate magnetic resonance imaging (MRI) in active surveillance (AS) protocols. To determine the ability of prostate MRI to predict pathological progression in AS patients, we correlated findings of serial MRI with results of surveillance biopsies.

Methods: Patients on AS with ≥2 prostate MRI and ≥2 prostate biopsies were included. Prostate Imaging-Reporting and Data System (PI-RADS) score upgrade, as assigned by experienced radiologists, was used to assess the ability of imaging to predict pathological biopsy progression. Imaging test statistics and the odds ratio of pathological progression according to MRI upgrade were calculated.

Results: Of 121 patients meeting criteria, 36 (30%) demonstrated MRI upgrade. Biopsy progression was noted in 55 patients (46%). Of these, 20 patients (37%) had biopsy progression predicted by MRI upgrade, while the remaining (n=35) had no lesion upgrade on prostate MRI. Conversely, among those with no biopsy progression (n=66), 16 patients (24%) had a false-positive upgrade on serial MRI. We report a sensitivity and specificity of MRI change for pathological progression of 36% and 76%, respectively. Although MRI change was associated with a positive predictive value of 56% for pathological progression, patients with a high-suspicion lesion (PI-RADS >3) at any time were more likely to experience disease progression, (odds ratio 3.3, 95% confidence interval 1.6–8.0, p<0.01).

Conclusions: Given its modest sensitivity/specificity, serial prostate MRI should be used judiciously as a surveillance tool. However, when prostate MRI demonstrates a PI-RADS >3 lesion, a high index of suspicion should be maintained, as these patients are more likely to progress on AS.

Introduction

Prostate specific antigen (PSA)-based screening has improved the early detection of prostate cancer (PCa), resulting in more men being diagnosed and treated.[1] However, the majority of screen-detected PCa is low-risk and prospective cohort studies have shown that active surveillance (AS) is a safe option for initial management given the low likelihood of progression to metastatic disease and low cancer-related mortality.[2,3]

There is currently no consensus regarding the optimal protocol for AS. While most protocols include a combination of PSA testing, prostate biopsy, and digital rectal examination, others have incorporated prostate genetic biomarkers, testing for different PSA isoforms, as well as imaging using multiparametric prostate magnetic resonance imaging MRI (mpMRI).[4] Indeed, current National Comprehensive Cancer Network (NCCN) guidelines for AS suggest consideration of mpMRI, along with prostate biopsy, no more often than every 12 months.[5] Although these guidelines suggest a minimum time interval between imaging, they do not provide guidance on optimal use of MRI and how imaging results should influence treatment decisions, including surveillance biopsy and discontinuation of AS. Given this ambiguity, some have incorporated mpMRI in a serial fashion to allow for increased intervals between biopsies and to mitigate patient anxiety.[6] While foregoing prostate biopsy would likely result in greater compliance and reduced complications, the American Urological Association Multiparametric Prostate MRI Consensus Panel deems current data to be insufficient regarding repeat mpMRI without a prostate biopsy for monitoring men on AS.[7,8]

Here, we assess the utility of repeat mpMRI in the management of PCa patients on AS based on the ability of mpMRI to predict pathological progression. We hypothesize that serial MRI results do not provide additional information to impact decision-making in AS.

Methods

A retrospective chart review was conducted to identify PCa patients on AS having undergone ≥2 mpMRIs at University Hospitals Cleveland Medical Center from 2012–2020. Patient characteristics were compared using descriptive statistics. As per NCCN guidelines, low-risk PCa was defined as T1-T2a disease, Gleason grade group (GGG) 1 and PSA <10 ng/mL, while favorable-intermediate risk was defined as GGG1 or GGG2, PSA at diagnosis from 10–20 ng/mL, and <50% biopsy cores positive. Records were further screened to select patients with ≥2 prostate biopsies during their time on AS. Acceptable prostate biopsies were heterogeneous, including standard 12-core biopsies and MRI-fusion biopsies (UroNav and In-Gantry). All MRIs were read and scored by experienced, board-certified radiologists using the Prostate Imaging- Reporting and Data System (PI-RADS) version 2, where applicable.[9] Prostate mpMRIs obtained prior to 2016 (release of PI-RADS v2 recommendations) were re-reviewed and scored accordingly by radiologists. Patients whose MRI could not be assigned a PI-RADS score were excluded. In case of multiple PI-RADS lesions, the lesion with the highest score was used. MRI lesion upgrade was defined as an increase in PI-RADS score of the previously existing index lesion or the appearance of a new, high-suspicion lesion, defined as PI-RADS >3. Pathological progression was defined as increase in GGG score on subsequent prostate biopsy, as assigned by board-certified genitourinary pathologists.

Test statistics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated based on change between the first and second MRI in relation to pathological progression on prostate biopsy. The association between mpMRI and biopsy progression was examined using Fisher's exact test of contingency data, analyzed in Prism 9 (GraphPad Software Inc., San Diego, CA, U.S.) and STATA16 (StataCorp LLC, College Station, TX, U.S.). In addition to measuring the risk of pathological progression based on mpMRI upgrade, we also calculated the odds ratio (OR) of biopsy progression with a high-suspicion lesion (PI-RADS >3) present at any time on AS (i.e., regardless of upgrade). To determine whether results of mpMRI influenced treatment change, we compared the average time on AS among patients with and without mpMRI upgrade using a two-tailed unpaired t-test. Lastly, a multivariable logistic regression model was fit to determine if change in PI-RADS score on MRI could predict biopsy progression. An alpha level of 0.05 was chosen for statistical significance.

Results

A total of 121 patients meeting study criteria were identified. Patient demographics are demonstrated in Supplemental Table 1 (available in the Appendix at *cuaj.ca*), with no statistically significant differences in patient characteristics among patients with and without MRI upgrade. Data in Supplemental Table 2 (available in the Appendix at *cuaj.ca*) demonstrate patient demographics according to the presence of pathological progression. Patients who experienced pathological progression differed from patients without progression by median PSA at diagnosis only (median 5.8 vs. 4.7 ng/ml, respectively, p<0.05).

Figure 1A demonstrates the percentage of mpMRI change. While 30% of repeat mpMRI demonstrated PI-RADS upgrade, most studies either remained the same or demonstrated regression/resolution of the index lesion. Among 36 patients who experienced upgrade on mpMRI, 20 patients (56%) also demonstrated pathological progression on biopsy (Figure 1B). These patients were noted to progress to Gleason 3+4=7 (n=15) and Gleason 4+3=7 (n=4) disease, with one patient deemed to progress to Gleason 3+3=6 with higher volume of disease on biopsy.

The sensitivity and specificity of MRI upgrade for detecting pathological progression were 36.4% (95% confidence interval [CI] 23.6–49.0%) and 75.8% (65.4–86.0%), respectively (Figure 2A). The PPV and NPV of mpMRI upgrade for pathological progression were 55.6% (39.3–71.7%) and 58.8% (48.3–69.2%) respectively. Figure 2B demonstrates the relationship between MRI upgrade and biopsy progression. The likelihood of biopsy progression was not statisti-

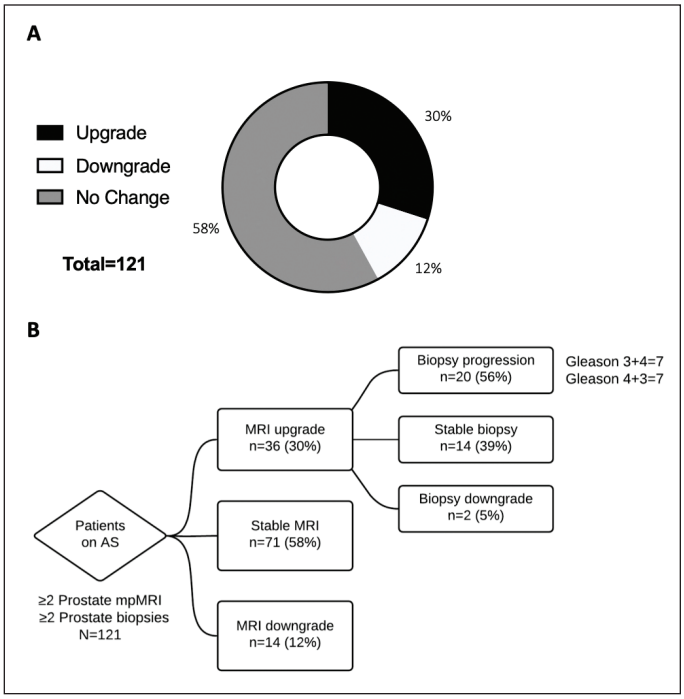

Figure 1. (A) Overall repeat magnetic resonance imaging (MRI) change from initial study, as a percentage of a total. **(B)** Study schema and relationship of MRI upgrade to pathological outcomes. AS: active surveillance; mp: multiparametric.

A

	Value	95% Confidence Interval
Sensitivity	0.364	0.236 – 0.490
Specificity	0.758	0.654 – 0.860
Positive Predictive Value	0.556	0.393 – 0.717
Negative Predictive Value	0.588	0.483 – 0.692

B

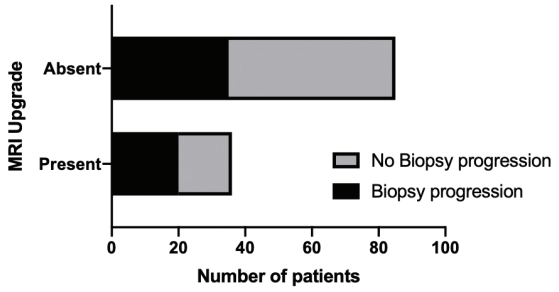

Figure 2. (A) Serial magnetic resonance imaging (MRI) upgrade test statistics. **(B)** Histogram of MRI upgrade and proportion of associated biopsy progression.

cally more likely in cases where MRI upgrade was present, owing to an OR of 1.786 (95% CI 0.8–3.8, p=0.16).

Patients with a high-suspicion lesion on mpMRI at any time during AS were more likely to experience biopsy progression (OR 3.3, 95% CI 1.6–8.0, p<0.01). The sensitivity and specificity of a single, high-suspicion lesion for predicting biopsy progression on AS were 78.1% (66.0–87.1%) and 50.0% (38.2–61.7%), respectively. Using the presence of a high-suspicion lesion at any time as the screening tool, the number needed to screen to detect biopsy progression on subsequent surveillance prostate biopsy was 3.3 men (95% CI 2.2–9.6).

Supplemental Figure 1 (available in the Appendix at *cuaj.ca*) demonstrates no statistically significant differences in time on AS between men with and without MRI upgrade (p=0.19).

On univariate regression, MRI upgrade did not predict biopsy upgrade (OR 1.8, 95% CI 0.8–3.9, p=0.15). On multivariate analysis including other factors such as age, PSA at diagnosis, followup time, grade group at diagnosis, risk category at diagnosis, prostate volume, number of MRIs, time between MRIs, and number of prostate biopsies, MRI upgrade did not predict biopsy progression (OR 2.5, 95% CI 0.6–9.6, p=0.19). ORs for pathological progression are detailed in Supplemental Table 3 (available in the Appendix at *cuaj.ca*).

Discussion

AS involves monitoring patients closely in order to offer treatment within a window of curability. Traditional clinical risk factors (PSA, digital rectal exam, and prostate biopsy) have been relatively successful in assessing patient risk in AS. However, limited data guide urological practice when employing mpMRI in AS protocols. Thus, our study specifically aimed to evaluate the utility of repeat/serial mpMRI in PCa patients on AS. We add several key findings to the paucity of literature in this regard.

First, our data demonstrate limited utility in repeating an mpMRI in AS patients, as most lesions do not change (81 of 121 patients [70%] without upgrade). In a study of 49 patients with low-risk PCa and mpMRI at least six months apart, Felker et al observed 39 of 49 patients (80%) had no progression of mpMRI. Furthermore, most lesions (67%) did not change in size.[10] This yielded a sensitivity and specificity of mpMRI of 37% and 90%, respectively. Similarly, in a study of 144 patients on a unique AS protocol of initial and yearly followup mpMRI in lieu of biopsy, Habibian et al demonstrated that only 14 of 144 patients (10%) had upgrade on mpMRIs, with a median followup of 48 months.[11] In their study, only seven of the 14 patients with MRI upgrade went on to obtain biopsy; thus, the rate of missed progression is unknown.

When compared to other studies in the literature, the current study includes a larger patient cohort and incorporates biopsy findings in all patients. We demonstrate 63% of incident progression is missed with MRI alone, as shown in Supplemental Tables 4, 5 (available in the Appendix at *cuaj.ca*). Indeed, several cases of pathological progression would have been missed by MRI alone, including progression to high-risk disease (Gleason 4+4=8 and 4+5=9).

The question remains whether there is a high likelihood of pathological progression if mpMRI upgrade is seen. In a cohort of 76 patients on AS for low-risk PCa, Eineluoto et al demonstrated that 33 of 76 patients (43%) had mpMRI upgrade, leading to 27 patients (82%) undergoing treatment change.[12] In our study, mpMRI PI-RADS upgrade demonstrated a PPV of only 55.6%. Interestingly, a drop in PPV of mpMRI was seen in the current study when including patients after 2017, suggesting that either increasing sample size or increasing experience with mpMRI interpretation may have led to a closer approximation of the true PPV of imaging or fewer discrepancies in initial PI-RADS scoring. Regardless, we highlight the need for judicious interpretation of repeat mpMRI results in PCa patients on AS.

A second important observation of our study is that the presence of high-suspicion lesions at any time is associated with increased pathological progression (OR 3.6, 95% CI 1.6–8.0). In their AS cohort, Kornberg et al looked at the risk of biopsy progression in 169 patients low-risk patients with a single mpMRI. Their results showed PI-RADS scores of 5 vs. 1–2 (hazard ratio [HR] 4.38, 95% CI 2.36–8.16, p<0.01) and 4 vs. 1–2 (HR 2.62, 95% CI 1.45–4.76, p<0.01) were significantly associated with an increased risk of a biopsy progression.[13] These results bolster the significance of previ-

ously described high sensitivity and PPV value of PI-RADS 4/5 lesions for detecting clinically significant PCa.[14-16] In this respect, mpMRI is a useful tool in patient counselling and determining candidacy for AS.

Indeed, some have argued that the most important role of mpMRI is that of risk-stratification to determine patient eligibility for AS at the onset of surveillance.[17] Our data supports this, as use of the presence of a high-suspicion lesion at any time, rather than MRI change, improved the sensitivity of mpMRI for detecting biopsy progression. Indeed, the U.K. National Institutes of Health and Care Excellence already recommends mpMRI as part of their AS initiation protocol.[18] Notably, men in our series were maintained on AS for the same median followup time regardless of mpMRI upgrade, suggesting that its use as a longitudinal benchmark was not predictive of treatment change.

Finally, given the inherent risk of infection, as well as patient discomfort and anxiety, the question of whether mpMRI can replace prostate biopsy has been debated.[19] Our data demonstrate currently available mpMRI technology cannot replace surveillance biopsy, as this would miss 35 of 55 patients (64%) with biopsy progression that had no upgrade on mpMRI (NPV=58%). In a recently published, large meta-analysis of 7321 patients, Sathianathen et al reported a NPV of mpMRI for detecting clinically significant PCa to be 86.8%.[20] Despite the higher NPV, the authors recommended proceeding with caution, as a negative mpMRI still missed clinically significant cancer in 7–10% of men not proceeding to biopsy. This sentiment largely agrees with prior studies that deem mpMRI not accurate enough to replace prostate biopsy.[21] In this regard, it is important to keep in mind that higher estimates of mpMRI NPV previously reported refer to the use of this technology in a diagnostic capacity, among allcomers, rather than as a tool for surveillance, as described in the current study. In other words, the question of whether mpMRI can replace initial prostate biopsy may be entirely different from whether it can replace surveillance biopsies. Thus, while the thought of replacing prostate biopsy with mpMRI in AS is attractive for patient and physicians alike, our study and others demonstrate that mpMRI should not replace prostate biopsy in either setting.

Limitations

We acknowledge this study is not without several limitations. Firstly, our study was retrospective. Future prospective, randomized studies are required to further assess the utility of MRI in AS. Secondly, our study had a limited sample size, and data were derived from a single institution. Using previously published rates of biopsy progression among men on AS,[22] we performed post-hoc power analysis, which demonstrated 100% power for detection of disease progression at an alpha level of 0.05 given the current sample size (data not shown). Additionally, to our knowledge, the current series is one of the largest incorporating both serial MRI and prostate biopsy pathological data for all patients in an AS setting. Thus, we feel confident that the results shown here reflect the true performance of mpMRI in AS.

Another important limitation of the current study relates to radiological interpretation. Given the retrospective nature and use of clinical data, radiologists were not blinded to patients' previous imaging. We are unable to determine the inter-radiologist variability when scoring mpMRIs, as these radiology reports were read in a clinical setting. As such, we only have access to final reports (often read by one radiologist at a time), not the details of peer review. Additionally, we were unable to capture changes in the size of lesions and their ADC values. These variables have been associated with disease progression in prior studies and were unable to be incorporated into the current study, as these were not commonly reported in clinical radiology reports. Indeed, whereas other studies have used imaging performed under a research protocol not available to treating clinicians,[23] the current study used clinical imaging reports accessible to any urologist. Given challenges and discrepancies in reporting, the concept of standardized reporting of mpMRI has been proposed and would pay special attention to include specific assessment of changes over time.[24] Despite these limitations, dedicated genitournary radiologists at our institution have experience reading prostate mpMRI daily in practice and have published on this topic. Thus, we have no reason to expect that experience or inter-observer variability play any greater role in determining the results of the current study when compared to others in the literature.

We also recognize that mpMRI continues to be expensive in some hospital systems and some clinicians may not have access to mpMRI and/or an experienced radiologist to interpret them. Our hope is to provide information for urologists in these settings to determine best practices for obtaining surveillance MRI.

Conclusions

With modest sensitivity and specificity, results from serial prostate mpMRI in PCa patients on AS should be interpreted judiciously. Specifically, change on mpMRI is infrequent and patients experience pathological progression that is missed by serial imaging. Certainly, a repeat mpMRI should not replace biopsy in men on AS, as a high proportion of clinically significant disease will be missed.

Importantly, if mpMRI demonstrates a PI-RADS >3 lesion at any point, a high index of suspicion should be maintained, as these patients are more likely to have pathological progression. In this regard, information gleaned from mpMRI can be used to risk-stratify patients and confirm candidacy

for AS. However, once a high-suspicion lesion has been identified, the benefit of further imaging is questionable.

Although data clearly support a role for MRI in aiding diagnosis of clinically significant PCa, the benefit of serial imaging in a surveillance capacity requires further research.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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