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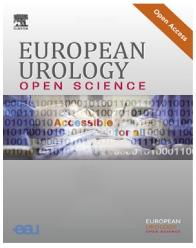

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Magnetic Resonance Imaging–guided Active Surveillance of Prostate Cancer: Time to Say Goodbye to Protocol-based Biopsies

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Abstract

Traditional protocols for active surveillance (AS) are commonly based on digital rectal examination, prostate-specific antigen (PSA), and standard transrectal biopsy, meaning that initial classification errors and inaccurate lesion monitoring can occur. Protocol-based biopsies are performed to assess changes in cancer grade and extent at prespecified intervals, but this approach represents a barrier to AS adherence and tolerability. There is evidence to support the use of magnetic resonance imaging (MRI) during AS, as this technique (associated with favourable PSA kinetics) offers an opportunity to follow patients on AS without the need for routine, protocol-based biopsies in the absence of signs of radiological progression provided that image quality, interpretation, and reporting of serial imaging are of the highest standards.

Patient summary: In this report we looked at the role of magnetic resonance imaging (MRI) scans in avoiding unnecessary prostate biopsies for patients being monitored for low- or intermediate-risk prostate cancer. We conclude that patients on active surveillance can be monitored with MRI scans over time and that biopsies could be used only when there are changes on MRI or a rising prostate-specific antigen (PSA) not explained by an increase in prostate size.

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Many groups worldwide perform protocol-based standard transrectal prostate biopsies to assess changes in cancer grade and extent at prespecified intervals, but this approach represents a barrier to the adherence to and tolerability of active surveillance (AS) [1]. Protocol-based biopsies are performed at different time points throughout AS and differ from confirmatory biopsies, which are usually performed within 12 mo from diagnosis and inclusion in AS programmes.

Although the compliance with prostate-specific antigen (PSA) testing is high, data from the PRIAS study [2] and the USA [3] show that the compliance with protocol-based biopsies is lower, as patients consider prostate biopsy the least pleasant aspect of AS because of the risks associated with the procedure.

The widespread adoption of magnetic resonance imaging (MRI) during AS may help to reduce the frequency of surveillance biopsies and improve the sensitivity for detecting significant cancer. Although the European Association of Urology guidelines fully recommend the use of MRI for inclusion and before confirmatory biopsies in AS, its use for surveillance biopsies is still a matter of debate [4]. By contrast, the UK National Institute of Health and Care Excellence guidelines support the use of MRI during AS in both scenarios [5].

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The multicentre randomised ASIST trial initially showed no difference in upgrading rate between standard rebiopsy and MRI with two cores targeted to a lesion during AS [6]. Conversely, at 2-yr follow-up, baseline MRI before confirmatory biopsy resulted in 50% fewer failures of AS and less progression to higher-grade disease, confirming the value of MRI in the AS setting [7]. However, it should also be acknowledged that the compliance for continued AS beyond the 2-yr time point in the PRIAS study was not better in the group of patients undergoing MRI-directed biopsy [8].

The MRIAS trial [9] was a single-arm study that enrolled men suitable for AS following baseline saturation + MRI-targeted biopsy who were followed for 3 yr with annual surveillance MRI, 6-mo PSA, and exit biopsy at 3 yr. Per-protocol biopsies were performed for predefined triggers, such as a new or persistent lesion or rising PSA kinetics. The majority of patients (71%) avoided biopsy before 3 yr, the progression rate was relatively low (21%), and the incidence of high-risk cancer missed by MRI was 1%.

One of the key aspects of prostate MRI during AS is the concept of tumour visibility [10–12]. Medium-term outcomes from our imaging-based AS cohort at University College London Hospital (which includes patients with up to Gleason 3 + 4 disease at entry biopsy and baseline plus serial MRI) [13] have shown a significant difference (in terms of treatment, transition to watchful waiting, Gleason $\geq$ 4 + 3 on follow-up biopsy or death) between MRI-visible and -nonvisible lesions for both low- and intermediate-risk disease (Fig. 1). We observed that most patients, particularly those with Gleason 3 + 3 cancer and nonvisible disease at baseline, remained on imaging-based surveillance at 5 yr and that the treatment rate was similar to that reported from standard AS cohorts with comparable follow-up but predefined follow-up biopsies [14].

In addition, we observed 8/672 (1.19%) metastatic events in our cohort, and metastasis was more common in the Gleason 3 + 4 MRI-visible group. This compares well to the Sunnybrook cohort [15], in which 18/980 (1.8%) patients who had follow-up biopsies developed bone metastases over median follow-up of 6.3 yr.

Given the growing adoption of serial prostate MRI during AS, it is also worth mentioning the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations that were published to facilitate robust data collection [16]. Use of the PRECISE scoring system when reporting MRI at baseline and follow-up during AS allows assessment of the natural history of prostate cancer on MRI, and promising results have been published by different groups [17]. The data from these studies show that patients with stable MRI findings (ie, PRECISE 1–3) and PSA kinetics should avoid routine rebiopsy. However, it should be acknowledged that a recent systematic review by Rajwa and colleagues [18] showed that serial prostate MRI (using either the PRECISE or other MRI criteria) alone for patients on AS is still not accurate enough to reliably exclude prostate cancer progression, and therefore other clinical factors and blood markers (eg, PSA density) along with serial MRI are required to safely tailor the intensity of follow-up biopsies.

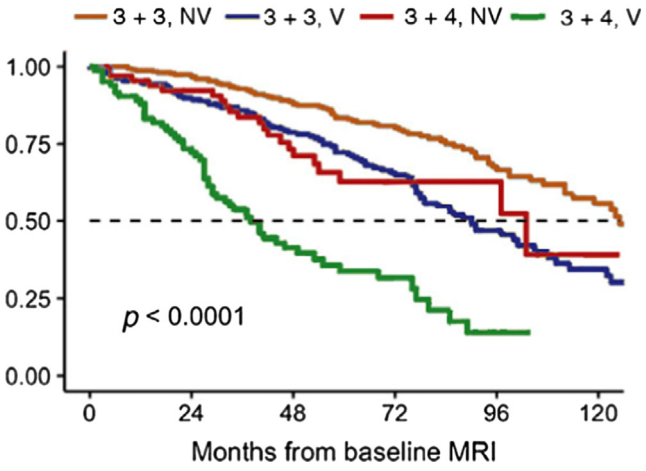

Fig. 1 – Kaplan-Meier event-free survival curves with time to treatment, transition to watchful waiting, and death as events, stratified by baseline Gleason grade and MRI visibility in our cohort at University College London Hospital. There was a significant difference in event-free survival between the groups (log-rank test, $p < 0.001$) and although men with Gleason 3 + 4 cancer had a different trajectory to those with Gleason 3 + 3, MRI-visible disease at baseline was associated with shorter event-free survival in both Gleason groups. MRI = magnetic resonance imaging; NV = nonvisible; V = visible. Reprinted from Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging-based active surveillance for prostate cancer: a large cohort study. Eur Urol 2020;78:443–51.

Furthermore, use of MRI with targeted biopsies for patients already on AS increases the cumulative probability of AS disqualification due to Gleason grade group reclassification (risk inflation), and appropriate risk thresholds have yet to be defined when MRI and MRI-targeted biopsies are used [10].

MRI, like any other tests, is not perfect and can occasionally miss high-grade disease, but as we are shifting towards an era of personalised medicine, it is reasonable to conclude that:

1. We should avoid routine rebiopsy in the presence of stable findings on serial MRI (especially when there is no visible lesion) associated with stable PSA kinetics (Fig. 2).
2. MRI will help us to define each patient's individualised risk and document the decision to avoid or proceed with biopsy.

In conclusion, our view is that MRI (associated with favourable PSA kinetics) is the key player for avoiding unnecessary follow-up biopsies and excluding disease progression during AS provided that image quality, interpretation, and reporting of serial imaging are of the highest standards.

Author contributions: Francesco Giganti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

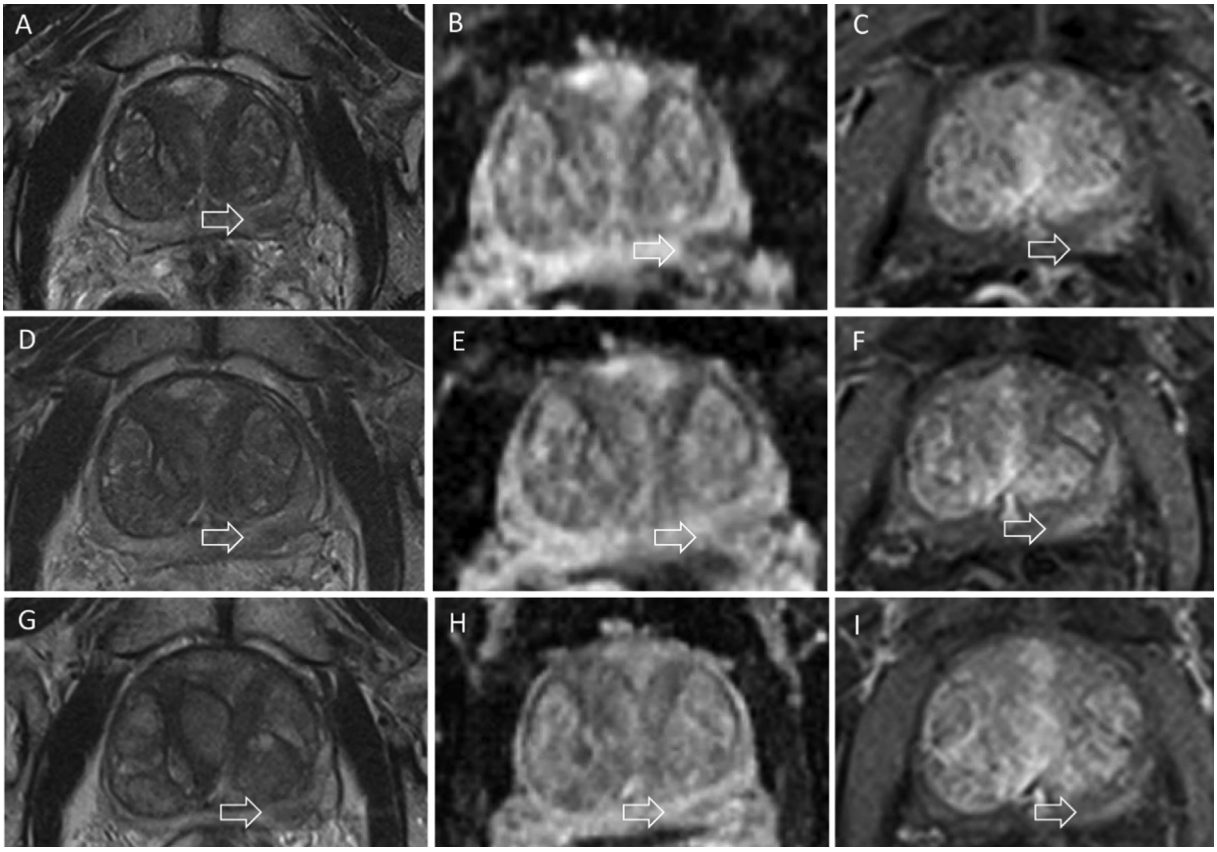

Fig. 2 – Magnetic resonance images of a 73-yr-old patient presenting with prostate-specific antigen (PSA) of 5.6 ng/ml. Baseline images show a Prostate Imaging-Reporting and Data System 4/5 lesion (arrows) in the left peripheral zone at midgland on (A) T2-weighted imaging, (B) on the apparent diffusion coefficient map from diffusion-weighted imaging and (C) on dynamic contrast-enhanced sequences. Targeted biopsy revealed Gleason 3 + 3 disease in two out of four cores involving 40% of the cores. The patient opted for active surveillance. Subsequent prostate magnetic resonance images at (D–F) 1 yr and (G–I) 5 yr show the stability of the lesion on all sequences along with relatively stable PSA findings (6.7 and 6.5 ng/ml, respectively). The patient is still on active surveillance and was biopsied only after baseline imaging.

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Analysis and interpretation of data: Giganti, Stavrinides.
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References

[1] Lam TBL, Maclennan S, Willemse PM, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE study). Eur Urol 2019;76:790–813.
[2] Bokhorst LP, Alberts AR, Rannikko A, et al. Compliance rates with the Prostate Cancer Research International Active Surveillance (PRIAS) protocol and disease reclassification in noncompliers. Eur Urol 2015;68:814–21.
[3] Loeb S, Walter D, Curnyn C, Gold HT, Lepor H, Makarov DV. How active is active surveillance? Intensity of followup during active surveillance for prostate cancer in the United States. J Urol 2016;196:721–6.
[4] Mottet N, Cornford P, van den Bergh RCN, et al. EAU guidelines: prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2021.
[5] National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management. London, UK: NICE; 2019. http://www.nice.org.uk/guidance/ng131.

[6] Klotz L, Loblaw A, Sugar L, et al. Active surveillance magnetic resonance imaging study (ASIST): results of a randomized multicenter prospective trial. Eur Urol 2019;75:300–9.
[7] Klotz L, Pond G, Loblaw A, et al. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. Eur Urol 2020;77:311–7.
[8] Luiting HB, Remmers S, Valdagni R, et al. What is the effect of MRI with targeted biopsies on the rate of patients discontinuing active surveillance? A reflection of the use of MRI in the PRIAS study. Prostate Cancer Prostat Dis. In press. https://doi.org/10.1038/s41391-021-00343-2.
[9] Amin A, Scheltema MJ, Shnier R, et al. The Magnetic Resonance Imaging in Active Surveillance (MRIAS) trial: use of baseline multiparametric magnetic resonance imaging and saturation biopsy to reduce the frequency of surveillance prostate biopsies. J Urol 2020;203:910–7.
[10] Schoots IG, Osses DF, Drost FJH, et al. Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PI-RADS and PSA-density, with different thresholds for significant disease. Transl Androl Urol 2018;7:132–44.
[11] Jayadevan R, Felker ER, Kwan L, et al. Magnetic resonance imaging-guided confirmatory biopsy for initiating active surveillance of prostate cancer. JAMA Netw Open 2019;2:e1911019.
[12] Chu CE, Cowan JE, Lonergan PE, et al. Diagnostic accuracy and prognostic value of serial prostate multiparametric magnetic resonance imaging in men on active surveillance for prostate cancer. Eur Urol Oncol. In press. https://doi.org/10.1016/j.euo.2020.11.007.
[13] Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging-based active surveillance for prostate cancer: a large cohort study. Eur Urol 2020;78:443–51.
[14] Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. Eur Urol 2013;64:981–7.
[15] Yamamoto T, Musunuru B, Vesprini D, et al. Metastatic prostate cancer in men initially treated with active surveillance. J Urol 2016;195:1409–14.
[16] Moore CM, Giganti F, Albersten P, et al. Reporting magnetic resonance imaging in men on active surveillance for prostate cancer: the PRECISE recommendations—a report of a European School of Oncology task force. Eur Urol 2017;71:648–55.
[17] Giganti F, Kasivisvanathan V, Allen C, Moore CM. The importance of being PRECISE in prostate magnetic resonance imaging and active surveillance. Eur Urol 2021;79:560–3.
[18] Rajwa P, Pradere B, Quhal F, et al. Reliability of serial prostate magnetic resonance imaging to detect prostate cancer progression during active surveillance: a systematic review and meta-analysis. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2021.05.001.

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