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Predicting Active Surveillance Failure for Patients with Prostate Cancer in the Magnetic Resonance Imaging Era: A Multicentre Transatlantic Cohort Study

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Abstract

Background and objective: Magnetic resonance imaging (MRI)-driven active surveillance (AS) is increasingly used for management of prostate cancer (PC). The aim of our study was to determine the oncological safety of contemporary MRI-driven AS and identify patients at higher risk of AS failure.

Methods: This retrospective cohort study included AS patients with MRI-localised PC from three US and UK centres. The primary outcome was AS failure, which was defined as a composite of PC-specific mortality, metastasis, progression to grade group (GG) ≥ 4 , or post-treatment biochemical recurrence. The secondary outcome was disease progression, defined as histological progression to GG 3 or progression to locally advanced disease. Hazard ratios (HRs) were estimated using multivariable Cox models, and multiplicity-adjusted log-rank tests were applied to compare event-free survival across subgroups.

Key findings and limitations: The study cohort comprised 719 patients with median follow-up of 5.2 yr. Of these patients, 629 (87%) had stable disease; 36 (5%) experienced AS failure, including eight (1%) cases of metastasis and no PC-related deaths; and 54 (8%) had disease progression. Cribriform GG 2 histology was the strongest predictor of AS failure (HR 12.7, 95% confidence interval [CI] 4.8–33.6; $p < 0.001$), followed by tumour MRI visibility (HR 5.0, 95% CI 1.5–16.5; $p = 0.009$) and noncribriform GG 2 histology (HR 3.4, 95% CI 1.6–7.0; $p = 0.001$). Event-free survival was comparable for MRI-invisible

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noncribriform GG 2 and all GG 1 tumours (adjusted $p > 0.05$ for both outcomes). The study is limited by its retrospective design.

Conclusions and clinical implications: Contemporary MRI-based AS for PC is safe for suitable patients, including men with noncribriform GG 2 tumours, particularly those that are MRI-invisible. Conversely, patients with cribriform GG 2 disease are at higher risk of AS failure, so consideration of upfront treatment is warranted for this subgroup.

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ADVANCING PRACTICE

What does this study add?

With the introduction of magnetic resonance imaging (MRI)-based diagnosis of prostate cancer, the risk profile of patients now offered active surveillance (AS) has changed dramatically. Most patients enrolled in AS protocols now harbour MRI-visible, radiologically localised disease. Our multicentre study shows that AS is safe for most of these men, particularly those with grade group (GG) 1 or GG 2 noncribriform disease. Conversely, this is the first study to direct reporting unfavourable AS outcomes for men with GG 2 cribriform disease, with results supporting exclusion of these patients from AS in the current MRI era.

Clinical Relevance

This study underscores the safety and efficacy of MRI-driven active surveillance for most men with low- and intermediate-risk prostate cancer, particularly those with GG1 or non-cribriform GG2 disease. It highlights the critical need for upfront curative treatment in patients with cribriform GG2 disease due to their higher risk of surveillance failure. These findings are pivotal for refining patient selection criteria in active surveillance programs, thereby optimizing clinical outcomes and minimizing overtreatment. Associate Editor: Guillaume Ploussard.

Patient Summary

Our study assessed 719 men with localised prostate cancer managed with active surveillance based on MRI (magnetic resonance imaging). After 5 years, there were no prostate cancer deaths and only 5% of patients had adverse outcomes, most of whom had a tumour cell type called cribriform pattern. Our results suggest that MRI-based active surveillance of prostate cancer is generally safe, but men with cribriform tumours may need early treatment.

1. Introduction

Prostate cancer (PC) is among the most common malignancies with the highest mortality in Europe and the USA [1]. As minimisation of overtreatment is critical in early detection programmes, active surveillance (AS) is increasingly adopted to avoid or defer treatment-related side-effects while maintaining the window of opportunity for treatment with curative intent [2].

While some guidelines limit AS to patients with low-risk PC [3], some extend eligibility to patients favourable intermediate-risk grade group (GG) 2 disease, for whom AS is also considered safe [4]. Hence, a higher proportion of patients now commence AS with magnetic resonance imaging (MRI)-visible, radiologically localised GG 2 disease [5], which represents a significant demographic shift from the earlier low-risk AS cohorts with excellent outcomes [6].

To evaluate whether AS outcomes remain favourable in this evolving population and whether there are patient subgroups requiring closer monitoring or upfront treatment,

we conducted a retrospective cohort study across three academic centres in the UK and USA.

2. Patients and methods

2.1. Study design and cohort characteristics

This retrospective cohort study was approved by the institutional review boards of Cambridge University Hospitals (reference CUH/18/3592), University of California-San Diego (reference 191878), and University of Texas-San Antonio (reference HSC20150160H). We included men enrolled on AS between March 2012 and March 2024 meeting predefined inclusion criteria (Fig. 1A). Baseline multiparametric MRI was performed at AS entry. A standard 12-core systematic transrectal ultrasound-guided biopsy performed in patients with no MRI-visible disease. For patients with MRI-visible disease, a targeted MRI-ultrasound fusion biopsy (transrectal or transperineal) was performed, with two to four cores sampled per target in

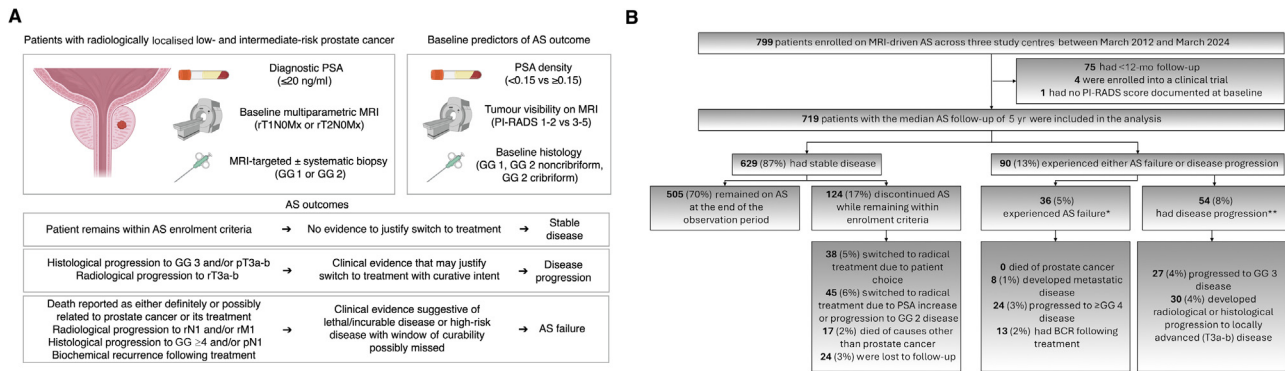


Fig. 1 – Study overview and Consolidated Standards of Reporting Trials (CONSORT) diagram. (A) Summary of the study inclusion criteria, exposures, and outcomes. (B) CONSORT diagram. AS = active surveillance; BCR = biochemical recurrence; GG = grade group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen. * Among patients who experienced AS failure, two developed metastatic disease only; 18 progressed to GG ≥ 4 only; eight had BCR following treatment only; and eight experienced several AS failure outcomes in differing sequences. ** Among patients who experienced disease progression, 24 progressed to GG 3 only; 27 developed radiological or histological progression to locally advanced (T3a–b) disease; and three experienced both AS progression outcomes in differing sequences.

addition to 12–24 background systematic cores (1–2 from each of the 12 anatomic sectors) [7]. In cases with discordance between the initial biopsy result and subsequent multiparametric MRI findings, a repeat targeted transperineal biopsy was performed within 3 mo; any patients upgraded on the basis of this confirmatory biopsy and no longer meeting the local AS enrolment criteria were considered to not have been enrolled on AS in the first place for the purpose of this study [8]. Exclusion criteria were: < 12 mo of follow-up, participation in a therapeutic clinical trial during AS, or any missing baseline data. Despite the inevitable variation in AS protocols across the three study centres representing different health care systems, AS follow-up for most patients included serial prostate-specific antigen (PSA) monitoring every 3 mo, annual MRI scans and clinic appointments, and repeat biopsies that were either protocol-mandated (36 mo) or triggered by three consecutive PSA increases and/or a significant increase in lesion size or suspected stage progression on MRI.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of results.

2.2. Outcomes and exposures

The primary outcome was AS failure, defined as a composite of oncological outcomes indicating that the intended AS benefit (deferring treatment while maintaining expectation of cure with initial definitive therapy) was lost. These oncological outcomes were: death from PC, radiological progression to metastatic disease, histological progression to GG ≥ 4 disease, or biochemical recurrence (BCR) following treatment (Phoenix definition [9]; Fig. 1A). As a secondary outcome, disease progression included histological progression to GG 3 disease or histological/definitive radiological progression to locally advanced disease. This progression endpoint reflects disease evolution that would justify commencement of radical treatment with curative intent in most cases (Fig. 1A). Importantly, disease progression and AS failure are not mutually inclusive endpoints.

AS failure can occur with or without prior evidence of disease progression, while patients who experience disease progression may not go on to meet AS failure criteria, particularly if they undergo timely curative treatment. This hierarchical relationship was incorporated into our endpoint definitions to distinguish between triggers for treatment escalation and ultimate oncological failure of AS.

Key exposures included common baseline biochemical (PSA density), radiological (MRI visibility: Prostate Imaging-Reporting and Data System [PI-RADS] scores of 3–5 vs 1–2), and histological (biopsy GG and cribriform status) predictors of AS outcomes in major clinical guidelines [3,10,11]. Age and absolute PSA were also evaluated. PI-RADS scores were assigned prospectively for the US cases. As Cambridge University Hospitals uses a Likert scale for its clinical workflow [8], all baseline MRI scans from this institution were retrospectively assigned PI-RADS scores by an experienced genitourinary radiologist who was blinded to clinical outcomes. Patients with documented GG 2 disease had their biopsies reviewed to assess cribriform status, defined as the presence of any amount of invasive cribriform carcinoma and/or intraductal carcinoma, according to the relevant International Society of Urological Pathology (ISUP) guidelines [12].

2.3. Statistical analysis

Multivariable Cox proportional-hazards models were generated to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for AS failure and disease progression. Right censoring was applied at the last AS follow-up date for patients with stable disease and for those who discontinued AS for reasons other than progression. For patients with metastasis or BCR occurring after definitive treatment, AS failure was recorded as occurring at the date of initial treatment, which may have altered the natural history of disease but failed to cure it. For patients to be considered recurrence-free, they had to undergo at least 36 mo of post-treatment follow-up. False discovery rate-adjusted (Hold-Sidak; $\alpha = 0.05$) log-rank tests were used to compare Kaplan-Meier survival curves across subgroups. Analyses

were conducted using MATLAB v2023b and GraphPad Prism v10.4.1. A two-sided p value of < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics and AS outcomes

By March 2024, 799 patients were enrolled on MRI-based AS across the three study centres (Fig. 1B). After excluding 80 patients, 719 remained for analysis. Of these 719 men, 36 (5%) experienced AS failure, including eight (1%) cases of metastasis. There were no PC-related deaths. A further 54/719 (8%) men had disease progression. The detailed cohort characteristics are shown in Table 1. Specifically, 551 patients (77%) had GG 1, 146 (20%) had noncribriform GG 2, and 22 (3%) had cribriform GG 2 disease at baseline biopsy. The proportion of men harbouring MRI-visible disease was 348/551 (64%) in the GG 1, 114/146 (78%) in the noncribriform GG 2, and 22/22 (100%) in the noncribriform GG 2 subgroup. Of the 168 men with GG 2 tumours, 136 (81%) had $\leq 10\%$ of Gleason pattern 4 (GP4) disease and 19 (11%) had between 15% and 45% GP4 disease; percentage GP4 was not recorded for 13 men (8%). Of 629/719 men (87%) with stable disease followed for a median of 5.2 yr (interquartile range 3.1–7.8), 124 discontinued AS despite meeting the enrolment criteria (Fig. 1B), bringing the final AS retention rate to 505/719 (70%).

3.2. Baseline predictors of AS failure

In comparison to GG 1 disease, the HR for AS failure was 12.7 (95% CI, 4.8–33.6; $p < 0.001$) for cribriform GG 2 disease and 3.4 (95% CI 1.6–7.0; $p = 0.001$) for noncribriform GG 2 disease (Fig. 2A). For MRI-visible tumours the HR for AS failure was 5.0 (95% CI 1.5–16.5; $p = 0.009$), whereas higher PSA density had no significant effect (HR 1.02, 95% CI 0.5–2.1; $p = 0.947$). Age and absolute PSA were not predictive of AS failure on multivariable analysis (Supplementary Table 1).

Subgroup analyses for survival revealed that cribriform GG 2 lesions—all of which were MRI-visible—were associated with the shortest AS failure-free survival in comparison to all other groups ($p < 0.05$ for all; Fig. 3A). The group with MRI-visible noncribriform GG 2 disease had the second highest risk, with significantly shorter AS failure-free survival in comparison to all GG 1 subgroups

(adjusted p value [p_{adj}] < 0.05 for all; Fig. 3A). Notably, AS failure-free survival was comparable for all GG 1 subgroups and the MRI-invisible noncribriform GG 2 group ($p_{\text{adj}} > 0.05$ for all; Fig. 3A).

3.3. Baseline predictors of disease progression

Similar overall trends were observed for disease progression, as well as a significant association between progression and increasing PSA density (HR 1.9, 95% CI 1.1–3.3; $p = 0.02$; Fig. 2B). Moreover, progression-free survival was significantly shorter for MRI-visible than for MRI-invisible GG 1 disease ($p_{\text{adj}} < 0.05$; Fig. 3B). Age and absolute PSA were not predictive of disease progression on multivariable analysis (Supplementary Table 2).

3.4. Risk groups for AS failure and disease progression

We identified three distinct risk subgroups for AS failure: (1) cribriform GG 2 disease; (2) MRI-visible noncribriform GG 2 cancer; and (3) all others, including MRI-invisible GG 2 and all GG 1 subgroups ($p_{\text{adj}} < 0.05$ for all; Fig. 3C). For disease progression, the three risk groups were: (1) cribriform GG 2 cancer; (2) MRI-visible noncribriform GG 1–2 disease; and (3) MRI-invisible noncribriform GG 1–2 cancer ($p_{\text{adj}} < 0.05$ for all; Fig. 3D).

4. Discussion

Overall, with an AS failure rate of 5% (including a metastasis rate of 1% and no PC-related deaths), our findings indicate excellent medium-term AS outcomes for patients with low- or favourable intermediate-risk disease who were all diagnosed, staged, and followed using MRI. As expected, patients with GG 1 disease at baseline were most likely to remain on AS. The group with MRI-invisible noncribriform GG 2 disease had outcomes indistinguishable from those for the GG 1 group. Conversely, patients with MRI-visible noncribriform GG 2 disease (who would now constitute the majority of AS cohorts in centres that omit biopsy for patients with negative MRI [5]) had a higher risk of AS failure that perhaps warrants closer surveillance. While beyond the scope of our study, dynamic risk-adjusted predictive models are currently being developed to determine the appropriate frequency and stringency of MRI-driven AS follow-up for these patients [13].

Table 1 – Baseline characteristics of the study cohort overall and by subgroup

Parameter	Overall cohort ($n = 719$)	Stable disease ($n = 629$)	AS failure ($n = 36$)	PC progression ($n = 54$)
Median age, yr (IQR)	65 (60–70)	65 (60–69)	69 (63–73)	67 (64–70)
Median AS follow-up, yr (IQR)	4.9 (2.9–7.5)	5.2 (3.1–7.8)	3.8 (2.5–5.6)	4.0 (2.6–4.7)
Median PSA, ng/ml (IQR)	5.8 (4.3–7.7)	5.7 (4.2–7.8)	6.2 (4.5–7.2)	6.1 (4.7–7.5)
Median PSAD, ng/ml/ml (IQR)	0.11 (0.08–0.17)	0.11 (0.08–0.17)	0.11 (0.08–0.18)	0.14 (0.10–0.20)
PI-RADS score, n (%)				
PI-RADS 1–2	225 (31)	216 (34)	3 (8)	6 (11)
PI-RADS 3–5	494 (69)	413 (66)	33 (92)	48 (89)
Grade group, n (%)				
Grade group 1	551 (77)	505 (80)	16 (44)	30 (56)
Grade group 2 noncribriform	146 (20)	114 (18)	14 (39)	18 (33)
Grade group 2 cribriform	22 (3)	10 (2)	6 (17)	6 (11)

AS = active surveillance; IQR = interquartile range; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density.

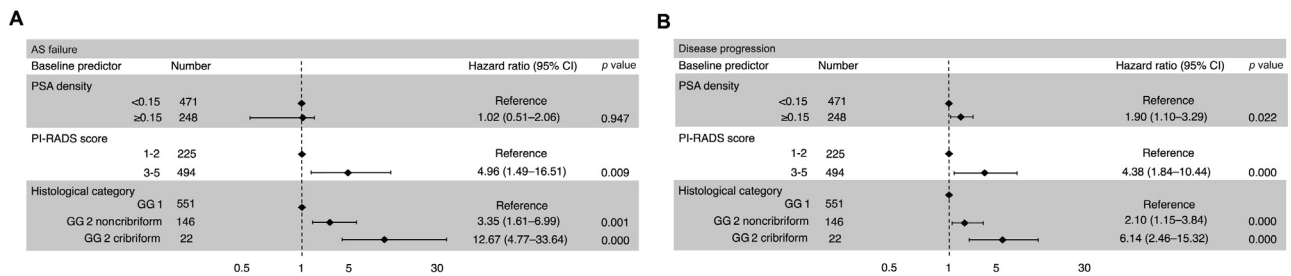


Fig. 2 – Outcome analysis. Multivariable Cox proportional-hazards regression results for (A) AS failure and (B) disease progression. Diamonds indicate hazard ratios, and horizontal lines indicate 95% CIs. AS = active surveillance; CI = confidence interval; GG = grade group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen.

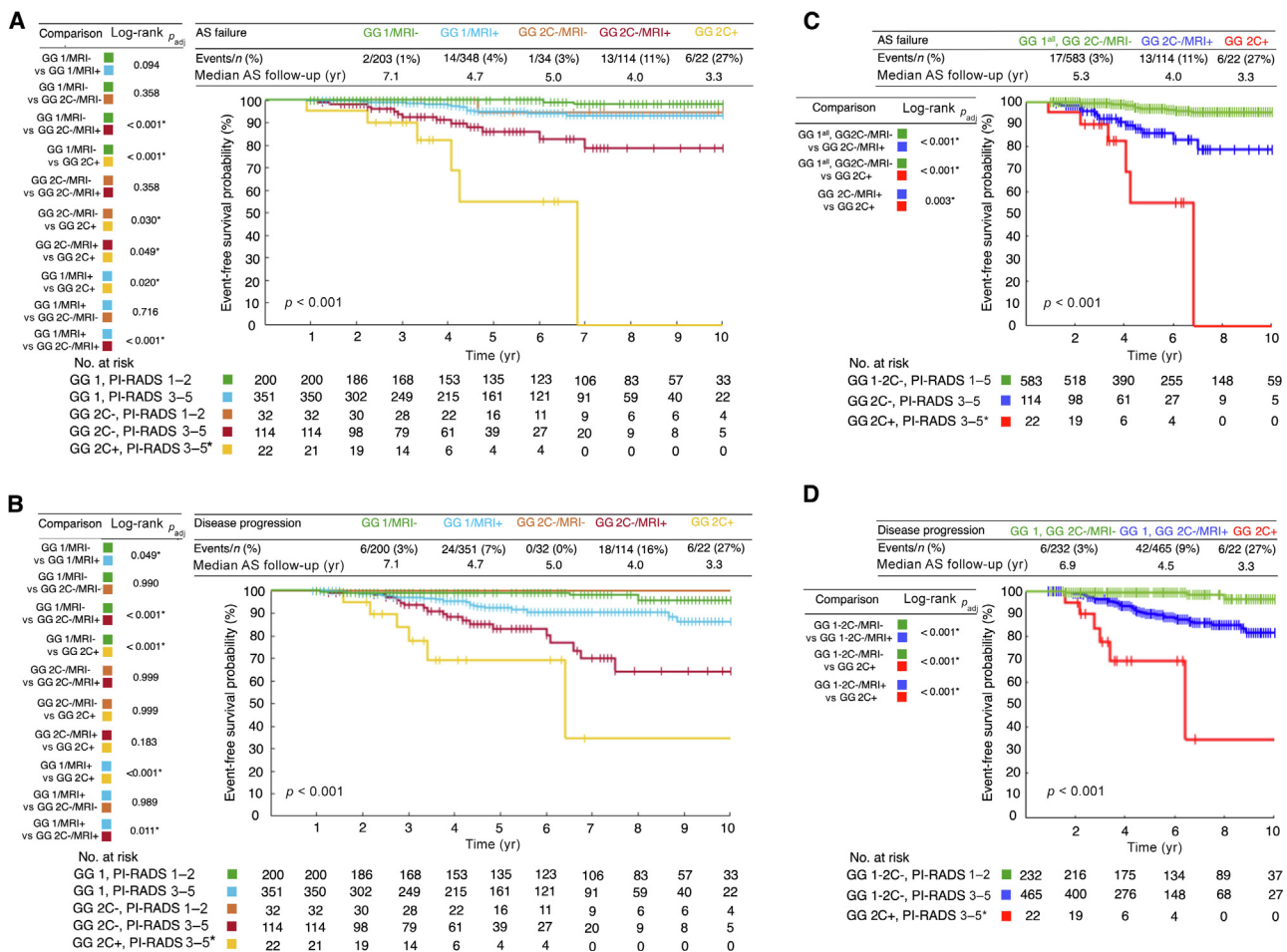


Fig. 3 – Subgroup Kaplan-Meier analyses of survival outcomes stratified by histological and radiological tumour characteristics, with adjustment for the false discovery rate. AS = active surveillance; C+ = cribriform-positive; C- = cribriform-negative; GG = grade group; MRI = magnetic resonance imaging; MRI+ = MRI-visible; MRI- = MRI-invisible; NC = noncribriform; PI-RADS = Prostate Imaging-Reporting and Data System; p_{adj} = adjusted p value; PSA = prostate-specific antigen; GG 1^{all}, GG 2C-/MRI- = all GG 1 cases and cases with MRI-invisible noncribriform GG 2 disease; GG 2C-/MRI+ = MRI-visible noncribriform GG 2 cases; GG 2C+ = GG 2 cribriform disease; GG 1, GG 2C-/MRI- = MRI-invisible GG 1 and noncribriform GG 2 cases; GG 1, GG 2C-/MRI+ = MRI-visible GG 1 and noncribriform GG 2 cases. * All cases of GG 2 cribriform disease had MRI-visible lesions (PI-RADS 3–5).

While MRI visibility and GG 2 disease have previously been identified as important predictors of AS progression [8,14–16], the definition of progression varied significantly across studies. Many studies of AS use GG upgrading as an endpoint, but this is questionable when upgrading from GG 1 to GG 2 does not exclude the patient from continued

AS eligibility, and may not even portend a worse prognosis at all, given the results presented here. While death from PC and progression to metastasis are undoubtedly the strongest and most meaningful endpoints, other outcomes have been increasingly used to encompass AS failure in recent studies. These include post-treatment disease recurrence

(representing a failure to deliver on the intention to cure the disease with initial therapy) and progression to high-risk (GG ≥ 4) disease, which would involve significant treatment escalation in comparison to intermediate-risk disease. On combining these four outcomes into one composite endpoint, we found that 11% of patients with MRI-visible noncribriform disease experienced some form of AS failure after median follow-up of 5.2 yr, which highlights the need for additional biomarkers that would allow early detection of progression to guide treatment for these men.

By contrast, we found that cribriform GG 2 morphology was the strongest predictor of adverse AS outcomes, with 27% of such patients experiencing AS failure. Although the current European guidelines already exclude patients with cribriform disease from AS, these recommendations are largely based on historic cohorts that received radical treatment [11] rather than contemporary cohorts managed with AS. In addition, the recommendations are not reflected in the North American or UK guidelines, which, when coupled with the substantial variation in AS practices, means that many patients with cribriform disease may be currently offered AS. To the best of our knowledge, our findings provide the first direct evidence of adverse AS outcomes in patients with cribriform disease and support recommendation of upfront treatment for these men.

Considering the significant variation of AS practices and common inclusion of patients with GG 2 cancer in AS programmes, our definition of disease progression was limited to histological progression to GG 3 or progression to locally advanced disease. Our aim was mainly to reduce bias associated with more subjective endpoints such as progression to treatment, for which the decision is often driven by patient or clinician preferences in the absence of hard clinical evidence of an evolving disease phenotype. Similar to AS failure, patients with cribriform GG 2 disease detected at baseline were at the highest risk of disease progression, with most of the progression events occurring within the first 4 yr of AS, indicating the lack of AS benefit for these men.

Notably, the proportion of patients experiencing disease progression (8%) was higher than the proportion meeting criteria for AS failure (5%), as expected given the broader and earlier nature of the progression definition. Patients with disease progression—such as those progressing to GG 3—often received timely curative treatment before meeting AS failure criteria. Conversely, patients could experience AS failure (eg, radiological metastasis or upgrading to GG ≥ 4) as a first event without prior evidence of intermediate progression. For example, some patients with cribriform GG 2 disease at baseline biopsy progressed directly to GG 4 on repeat biopsy or developed metastatic lesions on imaging without an earlier GG 3 finding. This supports the distinction between the two outcomes and reinforces the rationale for evaluating them separately.

Moreover, we acknowledge that some patients who experienced BCR after delayed treatment may have also had recurrence even if they had undergone immediate curative therapy at diagnosis. However, in the context of AS, BCR still signifies a failure of the strategy to preserve curative potential over time. Our definition of AS failure is therefore

intentionally outcome-based and focused on the clinical goal of AS: delaying treatment without sacrificing curability. While this does not imply causality, it reflects the pragmatic impact of surveillance on patient outcomes.

We also recognise that MRI image quality may influence lesion detectability and, by extension, the classification of tumours as “MRI-invisible.” While structured scoring systems for image quality such as PI-QUAL v1 and v2 [17,18] could provide insight into this issue, they are not reported as standard at all three study centres. Therefore, we relied on contemporaneous clinical MRI reports to reflect real-world practice across multiple centres. Although we did not retrospectively re-evaluate scan quality or lesion visibility, the exceptionally favourable outcomes in the MRI-invisible GG 2 subgroup (only 1 case of AS failure) suggest that significant lesions were unlikely to have been systematically missed at baseline. Future prospective studies incorporating formal assessments of image quality may help in better delineation of the contribution of technical factors to MRI invisibility and in supporting more nuanced risk stratification.

Our study is limited by its retrospective design and the inevitable lack of standardisation of AS protocols across the three centres representing different health care systems. Future prospective studies identifying appropriate AS schedules and novel predictors of AS failure for patients with MRI-visible noncribriform GG 2 disease will help in maximising the safety and efficiency of contemporary AS programmes. That said, considering the existing European guidelines and the growing recognition of the adverse nature of cribriform morphology strengthened by this study, further prospective studies investigating AS outcomes in patients with cribriform disease are unlikely to be supported. We also recognise that the study was conducted in academic centres, and reproducibility in community settings may be limited by inter-reader variability in radiology and pathology [19]. To enhance the generalisability of our findings, we used broad, clinically relevant categories, such as MRI-visible versus MRI-invisible disease, instead of exact PI-RADS scores. Likewise, we focused on grade group and binary cribriform status, both of which are mandated in pathology reporting under current ISUP and Genitourinary Pathology Society guidelines [20,21]. In addition, the feasibility of using percentage GP4 as an exposure was limited, as 81% of our cohort harboured $\leq 10\%$ GP4, and this metric has moderate reproducibility in low-volume disease, which is naturally over-represented in AS cohorts [22]. Finally, to minimise the impact of variable institutional practices and reader experience, radiological disease progression was limited to clear signs of gross locally advanced disease (rT3a–b) which would be reported explicitly and consistently regardless of the use of standardised reporting systems such as PRECISE [23]. While variability cannot be eliminated, our intent with these design choices was to reflect real-world practice and improve the applicability of our findings beyond specialist institutions. Meanwhile, we and others are developing and validating new technologies designed to facilitate objective and consistent interpretation of MRI and pathology in the future [24–28].

5. Conclusions

In conclusion, this study demonstrates the safety of MRI-driven AS at median follow-up of 5 yr and provides direct evidence supporting upfront treatment of patients with cribriform GG 2 disease. Our results also suggest that surveillance is likely to be adequate not only for GG 1 disease but also for noncribriform GG 2 cancer, particularly if the tumour is not visible on MRI.

Author contributions: Tyler M. Seibert 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.

Study concept and design: Sushentsev, Barrett, Seibert.

Acquisition of data: Sushentsev, Li, Xu, Warren, Hsu, Baxter, Panchal, Fernando.

Analysis and interpretation of data: Sushentsev, Pazukhina, Blyuss, Zaikin, Barrett, Seibert.

Drafting of the manuscript: Sushentsev, Barrett, Seibert.

Critical revision of the manuscript for important intellectual content: Sha-baik, Dale, Liss.

Statistical analysis: Pazukhina, Blyuss, Zaikin.

Obtaining funding: Sushentsev, Barrett, Seibert.

Administrative, technical, or material support: Kastner, Dale.

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Other: None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2025.06.012>.

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