

Title:

Cribriform Status at Follow-up Biopsy Is Critical for Predicting Active Surveillance Failure in the Magnetic Resonance Imaging Era

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Background:

MRI-driven active surveillance (AS) is standard management for low- and favorable intermediate-risk prostate cancer, designed to avoid or defer radical treatment while maintaining curative intent. Our previous study established the baseline imaging and histological predictors of AS failure, showing that while MRI-driven AS is highly safe for patients with grade group 1 (GG1) and MRI-invisible, cribriform-negative GG2 disease, baseline MRI visibility and cribriform morphology are strong independent predictors of AS failure. Nevertheless, baseline assessment is susceptible to misclassification and cannot capture the evolution of disease during surveillance. Our current study investigated whether follow-up MRI, repeat biopsy, and timing of cribriform detection predict AS failure in a multicenter cohort.

Methods:

This retrospective cohort study included 619 men on MRI-driven AS at two academic centers (UK/USA). The primary outcome, AS failure, was defined as a composite of PCa-specific mortality, radiological progression to metastatic disease, histological progression to GG 4 disease, or post-treatment biochemical recurrence. Key exposures include "final MRI status" and "final biopsy status", defined as the most advanced radiological and histological finding documented across all serial assessments during the AS follow-up period, as well as timing of cribriform $\geq$ GG2 detection.

Results:

Our cohort had a median follow-up of six years. Of the 39 patients (6%) that experienced AS failure, eight (1%) had metastatic events. Cribriform $\geq$ GG2 was identified in 82 patients (12%) at follow-up biopsy (three-fold increase from baseline 4%), and comparably across baseline GG1 (10%) and baseline non-cribriform (NC) GG2 (9%) subgroups. Three-year AS failure was 31% cribriform-positive vs 0-2% for stable or NC GG2-3 disease, and 64% of failures had cribriform GG $\geq$ 2. MRI progression was a weaker predictor (9% vs 5% stable MRI), with 44% of failures having stable MRI. Among 595 patients without baseline cribriform, six-year AS failure rates after first repeat biopsy were 34% (cribriform-positive), 7% (cribriform-negative), and 0.4% (no rebiopsy). PI-RADS 4 or 5 at baseline were the only independent predictors of cribriform on repeat biopsy.

Conclusions:

This study provides evidence that follow-up biopsy outperforms serial MRI and baseline biopsy for predicting AS failure. Our findings further suggest that cribriform detection at any AS biopsy warrants curative treatment, and men with baseline PI-RADS 4-5 are most likely to benefit from repeat biopsies within two years.

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Conflicts of Interest Disclosure Statement:

None