Incorporating Magnetic Resonance Imaging and Biomarkers in Active Surveillance Protocols - Results From the Prospective Stockholm3 Active Surveillance Trial (STHLM3AS)

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Abstract

Background: Active surveillance (AS) for men with low-risk prostate cancer (PC) can lead to patient morbidity and healthcare overutilization. The aim of this study was to evaluate an AS protocol using the Stockholm3 test and magnetic resonance imaging (MRI) to reduce biopsy intensity.

Methods: We conducted a prospective multicenter study of 280 invited men from a contemporary screening study (STHLM3), with Gleason Score (GS) 3+3 PC on a current AS protocol. Patients underwent prostate-MRI and blood sampling for analysis of the Stockholm3 test including protein biomarkers, genetic variants, and clinical variables to predict risk of GS ≥3+4 PC followed by systematic biopsies and targeted biopsies (for Prostate Imaging Reporting and Data System version 2 ≥3 lesions) in all men. Primary outcomes were reclassification to GS ≥3+4 PC and clinically significant PC (csPCa), including unfavorable intermediate risk PC or higher based on National Comprehensive Cancer Network guidelines.

Results: Adding MRI-targeted biopsies to systematic biopsies increased sensitivity of GS ≥3+4 PC compared with systematic biopsies alone (relative sensitivity [RS] = 1.52, 95% confidence interval [CI] = 1.28 to 1.85). Performing biopsies in only MRI positive increased sensitivity of GS ≥3+4 PC (RS = 1.30, 95% CI = 1.04 to 1.67) and reduced number of biopsy procedures by 49.3% while missing 7.2% GS ≥3+4 PC and 1.4% csPCa. Excluding men with negative Stockholm3 test reduced the number of MRI investigations at follow-up by 22.5% and biopsies by 56.8% while missing 6.9% GS ≥3+4 PC and 1.3% csPCa.

Conclusion: Including MRI and targeted/systematic biopsies in the follow-up for men on AS increased sensitivity of PC reclassification. Incorporation of risk prediction models including biomarkers may reduce the need for MRI use in men with low-risk PC.

Active surveillance (AS) is the standard management strategy recommendation for most men with low-risk prostate cancer (PC) and more than a 10-year life expectancy (1-3). Supported by level 1 evidence, AS programs report near 99% cancer-specific survival and greater than 90% metastasis-free survival at 10-15 years of follow-up (4-7). AS generally consists of a strategy involving repeated prostate-specific antigen (PSA), digital rectal exam, and systematic prostate biopsies (SBx). Studies have, however, shown that serial systematic biopsies in these low-risk men lead to unintended morbidity and high healthcare costs (8,9).

Magnetic resonance imaging (MRI) targeted biopsies (TBx) have been shown to improve the detection of clinically significant PC (10,11). Multiple studies have shown that MRI can aid in AS selection, which has provided rationale for guidelines to recommend MRI prior to a confirmatory biopsy in an effort to reduce sampling error (1–3). Prospective studies have also evaluated the use of serial MRI for the monitoring of men on AS, with most results providing evidence of improved sensitivity with a combined biopsy strategy of systematic plus targeted biopsies (12-15). Despite these findings, the appropriate time interval or selection criteria for those...
benefiting from serial MRI is unknown. In fact, the only prospective, randomized control trial that used MRI indiscriminately in an AS setting found no difference in grade reclassification, suggesting the need for more refined and selective use of MRI in AS (16).

The use of biomarkers (eg, the 4K score, prostate health index [PHI] and PCA3) in AS has been demonstrated to improve prediction of grade reclassification in men on AS. However, the use of these tests in the evaluation of MRI selection is limited (17-19). Conversely, genomic classifiers that sequence tumor tissue have been shown to improve grade reclassification prediction and, when paired with MRI, demonstrate an independent and synergistic ability to predict PC upgrade (20,21). However, the combined use may be costly, and guidelines recommend against routine use of molecular tissue tests (22).

The Stockholm3 test is a risk model that includes protein markers, a polygenic risk score, and clinical variables associated with PC. Although the model has the ability to predict PC detection on systematic and targeted biopsies (23,24), the Stockholm3 model has not been evaluated in an AS setting for MRI selection or grade reclassification prediction. The aim of this paper is 2-fold: 1) to evaluate MRI-targeted biopsies with regard to cancer detection in comparison to conventional AS follow-up using systematic biopsies; 2) to evaluate the utility of the Stockholm3 test in an AS protocol to select men for MRI and subsequent biopsy to predict grade reclassification in men with Gleason Score (GS) 3 + 3 PC.

**Methods**

**Study Design**

STHLM3AS (NCT03956108) is a prospective, cross-sectional, multicenter study nested within the diagnostic screening-by-invitation STHLM3 study (23). The STHLM3 study invited 173 850 men and recruited 58 502 men for PC screening between 2012 and 2014. All participants provided written informed consent. A total of 1374 men, aged 50-69 years, were diagnosed with GS 3 + 3 in the study. Of these men, a total of 541 men currently on AS were invited to participate in the STHLM3AS study. Eligible individuals had to be alive without any severe comorbidity, contraindications for MRI (eg, pacemaker), or a history of initiating prostate cancer treatment. Between March 2018 and December 2019, 309 eligible patients were registered to the study and underwent MRI and blood sampling at study baseline. A total of 29 men were excluded because of declined biopsies (n = 21) and failed lab analysis (n = 8). The remaining 280 study participants underwent prostate biopsies and were included in the analysis (see Figure 1).

The primary endpoint was defined as detection of GS 3 + 4 PC using either systematic or targeted biopsies. As a secondary endpoint, clinically significant PC (csPCa) was evaluated including unfavorable intermediate risk PC or higher based on National Comprehensive Cancer Network (NCCN) guidelines (GS 3 + 4 and ≥50% cores positive, GS 3 + 4 and T2, or GS 3 + 4 and PSA ≥ 10 ng/mL). We evaluated the following biopsy strategies with respect to detected GS 3 + 4 cancer and csPCa: 1) SBx in all men, 2) MRI-TBx and SBx in all men, 3) MRI-TBx and SBx in MRI-positive men, and 4) MRI for Stockholm3-test positive men then MRI-TBx and SBx in MRI-positive men.

**Stockholm3 Test**

The Stockholm3 score predicts the probability of GS 3 + 4 cancer using a combination of 5 plasma biomarkers (total PSA, free PSA, hK2, Macrophage inhibitory cytokine-1 [MIC-1], microsemionprotein-beta [MSMB]), 101 germline genetic markers, and 5 clinical variables (age, first-degree family history of prostate cancer, a previous biopsy, digital rectal examination, and prostate volume assessed by transrectal ultrasound at PC diagnosis) (24). The Stockholm3 threshold was fixed to achieve the same sensitivity of GS 3 + 4 detection as PSA of 3 or more in the original STHLM3 study. All primary analyses were based on the standard Stockholm3 test threshold of 10%, used to screen for GS 3 + 4 cancer (26).

**Statistical Methods**

Relative sensitivity (RS) was computed as the sensitivity to detect GS 3 + 4 PC and clinically significant PC according to the NCCN guidelines using 1 diagnostic strategy relative to the sensitivity of the reference strategy (systematic biopsies in all men). Confidence intervals (CIs) are 2-sided 95% empirical bootstrap intervals based on 1000 bootstrap samples. We performed sensitivity analyses where we compared the proportion of cancer detection by each strategy stratified on patients with and without MRI prior to study inclusion. The P values were computed as 2-sample tests for equality of proportions at 5% statistical significance level (2-sided). The analyses were performed using R statistical software version 3.6.2.

**Magnetic Resonance Imaging**

All patients underwent a bi-parametric 3T MRI protocol including T2-weighted imaging covering the prostate in 3 orthogonal planes, T1-weighted axial, and diffusion-weighted imaging. MRI scans were assessed and reported in consensus by 2 experienced prostate cancer radiologists, according to the Prostate Imaging Reporting and Data System version 2 (PI-RADS), and up to 3 lesions with Prostate Imaging Reporting and Data System version 2 grade 3 or more were marked for TBx (25). Lesions were delineated in the MIM Symphony Dx software (MIM Software Inc, Cleveland, OH).

**Prostate Biopsies**

Men with negative MRI (ie, PI-RADS < 3) underwent 10-12 core SBx and men with positive MRI (ie, PI-RADS ≥ 3) underwent TBx and SBx. For TBx, MRI data was loaded into the MIM Symphony Dx software, and BK 3000 with BK Ultrasound tracking system was used. The first pathology review was performed centrally for all sites at Unilabs Stockholm by any of 2 experienced uropathologists. A second pathological reevaluation was performed by the same experienced uropathologist (LE), who performed the pathology assessment of all diagnostic biopsies in the STHLM3 study. The study participants who were originally upgraded from GS 3 + 3 cancer at diagnosis to GS 3 + 4 cancer in the study biopsy were all reevaluated in the second step together with a sample of benign and GS 3 + 3 biopsies. Of all study biopsies cores, 509 (13%) were reevaluated.
Results

Patient Characteristics

A total of 280 participants with GS 3+ prostate cancer underwent MRI and prostate biopsy (Table 1). Median age was 70 years (interquartile range [IQR] = 65-73 years), median PSA was 3.5 ng/mL (IQR = 2.6-4.9 ng/mL), and median time on active surveillance at the time of analysis was 4.6 years (IQR = 4.0-5.1 years) prior to study entry. Patients were followed according to clinical practice before study entry. Out of all patients, 63.2% (177 of 280) and 36.8% (103 of 280) had undergone 1 and 2 or more previous surveillance biopsies, respectively, and 35.7% (100 of 280) had undergone a previous MRI.

At study intervention, 279 men underwent systematic biopsies, and 50.7% (142 of 280) had PI-RADS of 3 or more lesions and underwent targeted biopsies. Diagnostic PSA density, PSA, Stockholm3 test, age at study intervention, and time on AS were statistically different between men without and men with a previous MRI prior to study inclusion at a 5% statistical significance level.

Cancer Detection Using Targeted Biopsy Strategies for AS

A total of 23.9% (67 of 280) of the men were upgraded to GS ≥3 + 4 PC and 10.0% (28 of 280) to csPCa on any biopsy modality. Overall upgrading in MRI-positive men was 40.1% (57 of 142), where 23.9% (34 of 142) was detected by systematic biopsies, and 24.6% (35 of 142) was detected by targeted biopsies. A total of 18.3% (26 of 142) of men with a positive MRI had a clinically significant cancer according to NCCN guidelines, whereas 10.6% (15 of 142) was detected by systematic biopsies, and 12.7% (18 of 142) was detected by targeted biopsies. The reference strategy, systematic biopsies in all men detected 65.7% (44 of 67) GS ≥3 + 4 PC and 60.7% (17 of 28) csPCa (Figure 2). Performing MRI-targeted biopsies and systematic biopsies in all men showed a 52% increased sensitivity to detect GS ≥3 + 4 cancer (RS = 1.52, 95% CI = 1.28 to 1.85) and a 65% increased sensitivity to detect csPCa (RS = 1.65, 95% CI = 1.27 to 2.45) compared with systematic biopsies. Omitting biopsies in MRI-negative men would reduce the number of biopsy procedures by 49.3% and still detect 30% more GS ≥3 + 4 cancer (RS = 1.30, 95% CI = 1.04 to 1.67) and 53% more csPCa (RS = 1.53, 95% CI = 1.13 to 2.36) compared with systematic biopsies, while missing 7.2% (10 of 138) of GS ≥3 + 4 PC and 1.4% (2 of 138) of csPCa in men with negative MRIs (Table 3). In the overall cohort, 5.0% (14 of 280) harbored GS ≥4 + 3 cancer, 1.4% (4 of 280) had a high or very high-risk cancer, as defined by NCCN, and all of these men had a positive MRI (PI-RADS ≥ 3) (Supplementary Table 1, available online). In a sensitivity analysis, we stratified patients based on if they had a previous MRI, and there were no statistically significant differences in proportions of

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**Figure 1.** Flow chart STHLM3AS study.
Table 1. Patient characteristics of 280 men with Gleason Score 3 + 3 on active surveillance included in the STHLM3AS studya

| Variable                                                                 | No (n = 180) | Yes (n = 100) | Overall (n = 280) | p<sup>b</sup> |
|-------------------------------------------------------------------------|--------------|---------------|-------------------|--------------|
| **Clinical staging at baseline**                                         |              |               |                   |              |
| Diagnostic T stage, No. (%)                                             |              |               |                   | .77          |
| T0-T1                                                                   | 171 (95.0)   | 92 (92.0)     | 263 (93.9)        |              |
| T2                                                                      | 9 (5.0)      | 7 (7.0)       | 16 (5.7)          |              |
| Missing                                                                 | 0            | 1 (1.0)       | 1 (0.4)           |              |
| **Diagnostic PSA, ng/mL**                                               |              |               |                   | .08          |
| Median (IQR)                                                            | 3.60 (3-4.5) | 3.80 (3-5)    | 3.60 (3-4.6)      |              |
| Missing                                                                 | 0            | 1             | 1                 |              |
| **Diagnostic PSA density, ng/mL<sup>2</sup>**                           |              |               |                   | .02          |
| Median (IQR)                                                            | 0.08 (0.1-0.1)| 0.09 (0.1-0.1)| 0.09 (0.1-0.1)    |              |
| Missing                                                                 | 0            | 1             | 1                 |              |
| **Diagnostic prostate volume**                                          |              |               |                   | .76          |
| Median (IQR)                                                            | 41 (31-50)   | 41 (31-50)    | 40 (29-56)        |              |
| Missing                                                                 | 0            | 0             | 0                 |              |
| **Diagnostic Stockholm3 test**                                          |              |               |                   | .22          |
| Median (IQR)                                                            | 0.11 (0.1-0.2)| 0.14 (0.1-0.2)| 0.12 (0.1-0.2)    |              |
| Missing                                                                 | 2            | 1             | 3                 |              |
| **Diagnostic ratio of positive cores**                                  |              |               |                   | .39          |
| Median (IQR)                                                            | 0.09 (0.1-0.2)| 0.10 (0.1-0.2)| 0.10 (0.1-0.2)    |              |
| Missing                                                                 | 1            | 1             | 2                 |              |
| **Clinical staging at study intervention**                               |              |               |                   | .08          |
| Clinical T stage, No. (%)                                               |              |               |                   |              |
| T0-T1                                                                   | 163 (90.6)   | 97 (97.0)     | 260 (92.9)        |              |
| T2                                                                      | 17 (9.4)     | 3 (3.0)       | 20 (7.1)          |              |
| **PSA, ng/mL**                                                          |              |               |                   | <.001        |
| Median (IQR)                                                            | 3.26 (2.5-4.6)| 4.23 (3-6)   | 3.52 (2.6-4.9)    |              |
| **PSA density, ng/mL<sup>2</sup>**                                      |              |               |                   | .06          |
| Median (IQR)                                                            | 0.07 (0.05-0.11)| 0.08 (0.06-0.11)| 0.07 (0.05-0.11) |              |
| **Stockholm3 test**                                                     |              |               |                   | .01          |
| Median (IQR)                                                            | 0.19 (0.1-0.3)| 0.24 (0.1-0.4)| 0.20 (0.1-0.3)    |              |
| **Ratio of positive cores**                                             |              |               |                   | .40          |
| Median (IQR)                                                            | 0.08 (0-0.3) | 0.20 (0-0.3)  | 0.11 (0-0.30)     |              |
| **Age, y**                                                              |              |               |                   | .01          |
| Median (IQR)                                                            | 70 (66-73)   | 68 (64-71)    | 70 (65-73)        |              |
| Missing                                                                 | 0            | 1             | 1                 |              |
| **Prostate volume**                                                     |              |               |                   | .05          |
| Median (IQR)                                                            | 45 (35-60)   | 53 (35.8-66.2)| 48 (35-62)        |              |
| **Previous biopsy**                                                     |              |               |                   | .42          |
| Median (IQR)                                                            | 1 (1-2)      | 1 (1-2)       | 1 (1-2)           |              |
| **PI-RADS, No. (%)**                                                    |              |               |                   | .22          |
| ≤2                                                                      | 89 (49.4)    | 49 (49.0)     | 138 (49.3)        |              |
| 3                                                                       | 63 (35.0)    | 42 (42.0)     | 105 (37.5)        |              |
| 4                                                                       | 23 (12.8)    | 7 (7.0)       | 30 (10.7)         |              |
| 5                                                                       | 5 (2.8)      | 2 (2.0)       | 7 (2.5)           |              |
| **Systematic biopsies, No. (%)**                                        |              |               |                   | .23          |
| Benign                                                                  | 82 (45.6)    | 33 (33.0)     | 115 (41.1)        |              |
| 3 + 3                                                                   | 72 (40.0)    | 48 (48.0)     | 120 (42.9)        |              |
| 3 + 4                                                                   | 21 (11.7)    | 15 (15.0)     | 36 (12.9)         |              |
| 4 + 3                                                                   | 3 (1.7)      | 3 (3.0)       | 6 (2.1)           |              |
| 4 + 4                                                                   | 2 (1.1)      | 0             | 2 (0.7)           |              |
| > 4 + 4                                                                 | 0            | 0             | 0                 |              |
| Missing                                                                 | 0            | 1 (1.0)       | 1 (0.4)           |              |
| **Gleason Score in systematic biopsies, No. (%)**                       |              |               |                   | .57          |
| Benign                                                                  | 42 (23.3)    | 27 (27.0)     | 69 (24.6)         |              |
| 3 + 3                                                                   | 26 (14.4)    | 13 (13.0)     | 39 (13.9)         |              |
| 3 + 4                                                                   | 18 (10.0)    | 8 (8.0)       | 26 (9.3)          |              |
| 4 + 3                                                                   | 3 (1.7)      | 3 (3.0)       | 6 (2.1)           |              |

(continued)
### Table 1. (continued)

| Variable | Previous MRI | | Overall |
|----------|--------------|----------------|----------|
|          | No (n = 180) | Yes (n = 100) | (n = 280) |
| 4 + 4    | 0            | 0             | 0        |
| >4 + 4   | 3 (1.7)      | 0             | 3 (1.1)  |
| Missing  | 88 (48.9)    | 49 (49.0)     | 137 (48.9) |
| Overall biopsy Gleason Score, No. (%) | | | 0.24 |
| Benign   | 71 (39.4)    | 31 (31.0)     | 102 (36.4) |
| 3 + 3    | 67 (37.2)    | 44 (44.0)     | 111 (39.6) |
| 3 + 4    | 34 (18.9)    | 19 (19.0)     | 53 (18.9) |
| 4 + 3    | 4 (2.2)      | 6 (6.0)       | 10 (3.6) |
| 4 + 4    | 1 (0.6)      | 0             | 1 (0.4)  |
| >4 + 4   | 3 (1.7)      | 0             | 3 (1.1)  |
| Gleason Score >3 + 4 detected by biopsy procedure, No. (%) | | | 0.57 |
| Systematic biopsies | 26 (14.4) | 18 (18.0) | 44 (15.7) |
| Targeted biopsies | 24 (13.3) | 11 (11.0) | 35 (12.5) |
| Overall | 42 (23.3) | 25 (25.0) | 67 (23.9) |
| NCCN: csPCa detected by biopsy procedure, No. (%) | | | 0.55 |
| Systematic biopsies | 9 (5.0) | 8 (8.0) | 17 (6.1) |
| Targeted biopsies | 12 (6.7) | 6 (6.0) | 18 (6.4) |
| Overall | 17 (9.4) | 11 (11.0) | 28 (10.0) |
| Time on AS, y | | | 0.01 |
| Median (IQR) | 4.70 (4.2-5.3) | 4.20 (3.8-4.7) | 4.56 (4.5-5.1) |
| Missing | 0 | 1 | 1 |

aData are presented as median (interquartile range) for continuous variables and as No. (%) for categorical variables. Percentages may not total 100 because of rounding.

bDifferences between medians and frequencies were evaluated using Kruskal-Wallis test and $\chi^2$ test respectively (2-sided).

### Table 2. Patient characteristics of men with negative diagnostic testsa

| Variable | Negative Stockholm3 (n = 63) | Negative MRI and negative Stockholm3 (n = 42) | Negative Stockholm3 or negative MRI (n = 159) |
|----------|-----------------------------|-----------------------------------------------|-----------------------------------------------|
| Previous MRI, No. (%) | 17 (27.0) | 60 (95.2) | 4 (6.9) |
| Clinical T stage, No. (%) | 49 (35.5) | 133 (96.4) | 10 (23.8) |
| 1     | 133 (96.4) | 60 (95.2) | 10 (23.8) |
| 2     | 3 (4.6) | 5 (3.6) | 2 (4.8) |
| Overall biopsy Gleason Score, No. (%) | 40 (95.2) | 4 (2.2) | 153 (96.2) |
| Benign | 70 (50.7) | 27 (64.3) | 79 (49.7) |
| 3 + 3 | 58 (42.0) | 11 (26.2) | 69 (43.4) |
| 3 + 4 | 10 (7.2) | 4 (9.5) | 11 (6.9) |
| >4 + 4 | 0 | 0 | 0 |
| NCCN: csPCa, No. (%) | 63 (100.0) | 136 (98.6) | 42 (100.0) |
| No | 49 (35.5) | 10 (23.8) | 157 (98.7) |
| Yes | 3 (4.6) | 2 (4.8) | 2 (1.3) |
| Median PSA, ng/mL, (IQR) | 3.3 (2.5-4.5) | 2.7 (1.7-3.4) | 3.1 (2.3-4.5) |
| Median PSA density, ng/mL² (IQR) | 0.1 (0.0-0.1) | 0.1 (0.0-0.1) | 0.1 (0.0-0.1) |
| Median cancer length in TBx, mm (IQR) | NA | NA | NA |
| Median cancer length in SBx, mm (IQR) | 0.0 (0.0-1.0) | 0.0 (0.0-0.5) | 0.0 (0.0-0.5) |
| Median Stockholm3 test (IQR) | 0.5 (0.0-2.9) | 0.00 (0.0-0.8) | 0.5 (0.0-2.8) |
| Median previous biopsy (IQR) | 1.0 (1.0-2.0) | 1.0 (1.0-2.0) | 2.6 (1.8-3.4) |
| Median ratio of positive biopsies (IQR) | 0.0 (0.0-0.1) | 0.0 (0.0-0.1) | 0.0 (0.0-0.1) |
| Median time on AS, y (IQR) | 4.4 (4.0-5.3) | 4.6 (4.0-5.0) | 4.5 (4.1-5.5) |

aAS = active surveillance; csPCa = clinically significant prostate cancer, unfavorable intermediate risk or higher according to NCCN guidelines; IQR = interquartile range; MRI = magnetic resonance imaging; negative MRI = Prostate Imaging Reporting and Data System version 2, 1-2; NCCN = National Comprehensive Cancer Network; negative Stockholm3 = <10% risk of Gleason Score ≥ 3 + 4; PSA = prostate-specific antigen; SBx = systematic prostate biopsies; Stockholm3 = Stockholm3-test percentage risk score of Gleason Score ≥ 3 + 4; TBx = targeted biopsies.
Risk Prediction Models Using the Biomarker Stockholm3

Adding the Stockholm3 test as a selection tool before MRI increased sensitivity by 27% to detect GS $\geq 3 + 4$ cancer (RS $= 1.27$, 95% CI $= 1.02$ to 1.65) and by 53% to detect csPCa (RS $= 1.53$, 95% CI $= 1.13$ to 2.36) compared with performing SBx on all men, while decreasing the number of MRI investigations by 22.5% and the number of biopsied men by 56.8% (Figure 2). Of the men with negative Stockholm3 test, 7.9% (5 of 63) harbored GS $\geq 3 + 4$ PC, and no participants with a negative Stockholm3 test had csPCa according to NCCN guidelines. In men with negative Stockholm3 test and a negative MRI, 9.5% (4 of 42) harbored GS $\geq 3 + 4$ PC and 0% csPCa. In men with a negative Stockholm3 test or a negative MRI, 6.9% (11 of 159) had GS $\geq 3 + 4$ PC and 1.3% (2 of 159) had csPCa.

Discussion

We conducted the prospective STHLM3AS trial to evaluate the value of MRI in the monitoring of men with low-risk PC on AS. Secondly, we evaluated the Stockholm3 test within the context of MRI and biopsy selection in the monitoring of men with low-risk PC on AS. Our results suggest that incorporating MRI findings during follow-up surveillance biopsies increases the sensitivity for detection of GS $\geq 3 + 4$ PC and csPCa compared with...
systematic biopsy alone. In this cohort, few men with a negative MRI harbored csPCas (1.4%). When using the Stockholm3 model to stratify men needing MRI evaluation, 22.5% of the men could avoid MRI and 56.8% could avoid biopsy while delaying the detection of few upgraded csPCAs (1.3%).

Outside the setting of AS, studies have shown that incorporating MRI-targeted biopsies with systematic biopsies is more sensitive for cancer detection (27). Retrospective data from AS cohorts have suggested similar findings (28,29). Prospectively, Liss et al. (30) showed the combined approach with targeted and systematic biopsies together would identify an additional 13% of men with GS ≥3 + 4 PC. In the Active Surveillance Magnetic Resonance Imaging Study (ASIST) trial, Klotz et al. (16) again showed that although targeted biopsies identified GS ≥3 + 4 PC well, cancers that otherwise would be seen on systematic biopsies may be missed. Our results show that adding MRI-targeted biopsies to systematic biopsies during follow-up increased sensitivity of GS ≥3 + 4 PC by 52% and csPCAs by 65%, independent of whether a previous MRI was performed. Although the presence of an MRI lesion may help predict reclassification, overwhelming evidence suggests that associated systematic biopsies in the setting of a positive MRI for AS will detect additional cancer.

There is an ongoing debate and conflicting evidence whether the absence of clinically significant MRI findings is an adequate selection tool to forgo biopsy during AS. Our study showed that adding MRI in the follow-up for men on AS could reduce the number of prostate biopsies by around 50% by excluding men with a negative MRI while missing 1.4% of men with csPCa and missing no GS ≥4 + 3 PC. Similar to our results, a prospective observational study by Gallagher et al. (13) showed low rates of upgrading on SBx to GS ≥3 + 4 cancer (1.8%) in men with negative MRI in their study of 211 men. In the recent report from the Canary Prostate Active Surveillance (PASS) multicenter prospective study, results showed that MRI was associated with a NPV of 83% for detecting GS ≥3 + 4 PC in a cohort of 361 men; however, only 4% (4 of 111) of the MRI-negative men had a GS ≥4 + 3 PC (30). Notably, in the PASS protocol, MRI was not mandated but was left to each clinician’s discretion possibly rendering a selection bias. Similarly, the prospective single-arm Magnetic Resonance Imaging in Active Surveillance (MRIAS) trial, including 172 men eligible for AS, reported that 11% and 4% of the MRI-negative men had GS ≥3 + 4 or ≥4 + 3 PC, respectively (12).

Results from a retrospective analysis of 207 men from Memorial Sloan Kettering Cancer Center showed that 15% of men with negative MRI had GS ≥3 + 4 PC on scheduled SBx at 3 years (29). However, the authors do not describe GS ≥4 + 3 cancers that are missed. By forgoing negative MRI, these studies describe rates of missing GS ≥3 + 4 PC from 2% to 15% and missing GS ≥4 + 3 from 0% to 4%, with lower rates observed in prospective trials. Based on these results, it may be warranted to de-escalate biopsy intensity in men without concerning features on MRI, in particular given the low adherence to AS protocols because of the intensive biopsy recommendations (31).

Although the literature points to increased detection of cancer with MRI-targeted biopsies and high NPVs, long-term data regarding AS safety is based on surveillance with systematic biopsies (4–7), and ubiquitous use of MRI may be unnecessary in patients at lower risk of reclassification. Our results show that by adding the Stockholm3 test as an initial triage tool would reduce the number of MRIs by 22.5% and lead to the reduction of 56.8% of biopsies while missing small numbers of csPCas. The Stockholm3, as well as other biomarkers such as the 4Kscore, PHI, and urinary PCA3, has shown predictive ability to select appropriate candidates for MRI in a cancer detection setting (24, 32–34). The use of biomarkers in AS with MRI, however, is limited. Schwen et al. (17) used retrospective data to evaluate PHI combined with MRI in AS reclassification; however, in our study, we describe a stratified use of prediction tools rather than combined use, which may be needed to reduce resource overutilization. Studies have shown an improved cost-benefit ratio with AS using surveillance biopsies compared with treatment and related morbidity for low-risk prostate cancer (35). Sathianathan et al. (36) demonstrated the cost utility of MRI with a Markov model during the natural history of men on AS for low-risk PC. The authors showed the use of MRI (at a cost of less than $640) at a frequency of no more than 5 years in an AS protocol was cost effective. However, if MRI was used more frequently or was a higher cost, the cost-effectiveness benefit was lost. Assuming that risk prediction models such as the Stockholm3 test are cheaper than MRI, our study suggests that the use of an additional triage tool for biopsy may be able to reduce the health economic burden within an AS protocol while maintaining outcomes.

This is the largest published prospective trial evaluating the use of a biomarker prior to MRI for disease monitoring in men on AS. The strengths of our study are the controlled selection of patients from a contemporary screening study, centralized radiology, and pathology, including the reevaluation of pathology specimens by the same highly experienced pathologist (LE). The interpretation of these results should be made within the context of this selected cohort. The STHLM3 screening study was initially used to select men for biopsy based on PSA and the Stockholm3 test, so it is plausible that the value of the Stockholm3 test may be greater in a man diagnosed with low-risk PC that is Stockholm3 naive. Given the cross-sectional enrollment of patients on AS, patients who were treated prior to trial enrollment period were excluded and may incorporate a survival bias. Apart from its nonrandomized design, a further limitation of our study is that the urologist performed both SBx and TBx in the same session, thus possibly affecting SBx outcomes, because MRI information was not blinded. Reflecting current clinical practice of AS during the study period, there was a proportion of patients who hadn’t undergone a previous MRI before inclusion in the study, which could introduce misclassification bias. However, sensitivity analysis including only men with a previous MRI did not alter our conclusions. Furthermore, some participating urologists were newly introduced to fusion biopsies (ie, in their learning curves), which could bias the results, likely toward regression to the mean.

Including MRI in AS protocols would increase the detection of csPCa and reduce the number of men who need to undergo biopsies considerably compared with current standard of care. Our results show that men with negative MRI could postpone biopsy, reduce the number of biopsies needed by half, and only miss 1.4% of csPCa. The uniform use of MRI in an AS protocol may, however, overutilize healthcare resources. We show that the incorporation of a risk prediction tool to select men for MRI can decrease the number of MRI investigations needed by 23%. Further validation of these findings is needed as well as investigation into resource allocation and risk prediction for low-risk PC reclassification of men on AS protocols.

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Data Availability
The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study.

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