Role of multi-parametric magnetic resonance imaging fusion biopsy in active surveillance of prostate cancer: a systematic review

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Abstract
Background: Our goal is to review current literature regarding the role of multi-parametric magnetic resonance imaging (mpMRI) in the active surveillance (AS) of prostate cancer (PCa) and identify trends in rate of reclassification of risk category, performance of fusion biopsy (FB) versus systematic biopsy (SB), and progression-free survival.

Methods: We performed a comprehensive literature search in PubMed and identified 121 articles. A narrative summary was performed.

Results: Thirty-two articles were chosen to be featured in this review. SB and FB are complementary in detecting higher-grade disease in follow-up. While FB was more likely than SB to detect clinically significant disease, FB missed 6.4–11% of clinically significant disease. Imaging factors that predicted upgrading include number of lesions on magnetic resonance imaging (MRI), lesion density, and MRI suspicion level.

Conclusion: Incorporating mpMRI FB in conjunction with SB should be part of contemporary AS protocols. mpMRI should additionally be used routinely for follow-up; however, mpMRI is not currently sensitive enough in detecting disease progression to replace biopsy in the surveillance protocol.

Keywords: active surveillance, fusion biopsy, MRI, prostate cancer

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Introduction
Active surveillance (AS) has become the recommended management strategy for very-low-risk and low-risk prostate cancer (PCa) to minimize overtreatment and subsequent morbidity from radical prostatectomy (RP) or radiation therapy. The utilization of AS has increased overtime, but there continues to be wide practice variation in implementation.1,2 The American Urological Association (AUA) and European Association of Urology (EAU) guidelines have both endorsed AS as the preferred management option for low-risk PCa.3,4 Accuracy of the initial prostate biopsy is essential in appropriately selecting patients for AS. The widely adopted 12-core systematic biopsy (SB), may miss clinically significant cancers, especially in the anterior zone, while extended or saturation biopsies improve detection; however, this must be balanced with the risks associated with over-diagnosis of clinically insignificant cancers.5,6 With the use of multi-parametric magnetic resonance imaging (mpMRI) fusion biopsies (FBs), detection of clinically significant PCa has been improved, although its role in AS protocols is currently a topic of debate.3,7 We seek to evaluate the literature to define the role of mpMRI and FB in AS, and identify trends in rate of reclassification of risk category, performance of FB versus SB, and progression-free survival.

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Methods

Search strategy and selection
A comprehensive literature search was performed on 2 December 2021 using the database PubMed. Articles were queried from the search criteria ([multiparametric MRI] AND [fusion biopsy] AND [active surveillance] AND [prostate cancer]).

Articles were reviewed independently by the authors and selected for inclusion based on Cochrane standard methodological procedures.8 Primary endpoints were number of lesions in MRI, total number of biopsy cores, rate of upgrading to clinically significant prostate cancer (csPCa), predictive factors of upstaging and progression-free survival. Inclusion criteria based on participants included all ages, all races, all co-morbidities, all life expectancies, with very-low-risk to low-risk PCa diagnosed with biopsy, with or without prior imaging. Exclusion criteria included higher risk disease, genetic syndromes predisposing to more aggressive disease, and patients undergoing other treatment modalities. All study designs – non-randomized, prospective, and retrospective studies – were included, given the paucity of prospective and randomized controlled trials on this topic. We excluded case reports, other review articles, non-English language manuscripts and manuscripts that were irrelevant to answering our primary endpoints. AS criteria included any participant enrolled in an AS protocol as defined by their institution; details for the average values for each study can be reviewed in Table 1.

Synthesis of results of individual studies

Clinical variables. Table 1 displays patient demographics for each study. For all combined studies, the median age was 64.4 (IQR 63–66), median prostate-specific antigen (PSA) 5.6 (IQR 5.2–6.0), median PSA density (PSA-D) 0.12 (IQR 0.10–0.13), median prostate volume 50 cm³ (IQR 44–51), median number of lesions on mpMRI 2.2 (IQR 1.7–2.3), median lesion size on mpMRI 10 mm (IQR 9–11), and median number of biopsy cores obtained 16.9 (IQR 15.0–17.7). Most studies utilized MRI/ultrasound (US) as their FB technique, with the exception that one study specified using the cognitive technique.11,12

Use at diagnosis. Appropriate patient selection and most accurately characterizing the cancer are paramount for enrolling patients on AS. In a prospective open-enrollment AS cohort at a tertiary institution, Tosoian et al. evaluated 1818 men with median follow-up of 5 years. While 40% of men underwent grade reclassification overall, the 537 men that had pre-enrollment mpMRI had a decreased risk of grade reclassification [hazard ratio (HR) 0.66, 95% confidence interval (CI), 0.46–0.95, \( p = 0.03 \)].13 The role of mpMRI in AS (ROMAS) trial randomized 62 patients to obtain mpMRI and FB if mpMRI was positive 3 months after AS enrollment and 62 patients to standard of care AS without mpMRI. Both groups underwent SB at 12 months. At confirmatory FB in the study group, 17.7% of patients had grade-group reclassifications; however, at the 12-month SB, the mpMRI group had a significantly lower rate of reclassification compared to the control group, with rates of 6.5% and 29% (\( p < 0.001 \)), respectively.14 A non-randomized prospective study of men electively enrolling in AS after initial FB versus initial SB underwent both FB and SB (median 26 cores) at 1, 2, and 4 years after initial diagnosis. The authors found men who had an initial FB had a lower disqualification rate from AS based on histopathologic upgrading (19% for initial FB vs 59% for initial SB, HR 2.56, 95% CI 1.70–3.85). Furthermore, at 4-year follow-up, men in...
| Study | Country | Study design | Number of subjects | Median age (IQR) | Median PSA, ng/mL (IQR) | Median prostate volume (cm³) | Median PSA density, ng/mL cm³, (IQR) | Median number of lesions on MRI | Median lesion size (mm) | Median total number of biopsy cores | Median core positive volume |
|-------|---------|--------------|--------------------|-----------------|-------------------------|-----------------------------|-----------------------------------|----------------------------------|-----------------------|---------------------------------|--------------------------|
| Stamatakis et al. | United States of America | Serious Retrospective | 15 | Mean (range): 60.2 ± 7.4 (40–79) | Mean (range): 4.8 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Siddiqui et al. | Canada | Low Prospective single institution, single blind | 81 | Mean: 63 (58–68) | 4.2 (2.6–3.8) | 50 (11–17.6) | Mean (range): 0.09 (0.03–0.15) | Mean: 2.1 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Hu et al. | USA | Low Prospective single institution, single blind | 113 | Mean (range): 60.2 ± 7.4 (40–79) | Mean (range): 4.8 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Abdi et al. | Canada | Serious Retrospective | 111 | Mean (range): 60.2 ± 7.4 (40–79) | Mean (range): 4.8 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Akiyama et al. | USA | Serious Retrospective | 245 | Mean: 64 (60–68) | 4.2 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Akiyama et al. | USA | Serious Retrospective | 103 | Mean (range): 64 (60–68) | 4.2 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Dias et al. | USA | Moderate Retrospective | 152 | Mean (range): 61.4 ± 7.1 (40–79) | Mean (range): 5.2 ± 3.2 (0.2–23.3) | 58 ± 28 (23–161) | Mean (range): 0.09 ± 0.03 (0.01–0.15) | Mean (range): 2.3 ± 1.2 (1–9) | Mean (range): 2.3 ± 1.2 (1–9) | Mean (range): 2.3 ± 1.2 (1–9) | Mean (range): 2.3 ± 1.2 (1–9) |
| Kamrava et al. | USA | Low Prospective, single institution | 245 | Mean: 64 ± 7.4 | 4.8 ± 3.65 | 6 (1–4) | Mean: 1.5 ± 0.15 | Mean: 1.5 ± 0.15 | Mean: 1.5 ± 0.15 | Mean: 1.5 ± 0.15 | Mean: 1.5 ± 0.15 |
| Ma et al. | USA | Moderate Retrospective | 103 | Mean (range): 64 (60–68) | 4.2 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Tran et al. | USA | Moderate Retrospective | 207 | Mean: 64 ± 7.4 | 4.2 (2.6–6.3) | 31–57 | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) |
| Frye et al. | USA | Low Prospective single institution | 166 | Low-risk mean: 61.7 ± 6.6; intermediate risk mean: 65.7 ± 6.7 | Low-risk mean: 5.69 ± 4.19; intermediate risk mean: 6.16 ± 3.54 | NA | Low-risk mean: 0.12 ± 0.09; intermediate risk mean: 0.13 ± 0.08 | NA | NA | NA | NA |
| Ma et al. | USA | Moderate Retrospective | 103 | Mean (range): 64 (60–68) | 4.2 (2.6–6.3) | 51.5 ± 18.9 (24–161) | Mean (range): 0.08 (0.05–0.10) | Mean (range): 2.1–2 | Mean: 10.5 ± 4.3 | Mean: 16 (4–32) | Mean: 16 (4–32) |
| Pepe et al. | Italy | Serious Prospective, single institution, single blind | 100 | Mean: 66.0 (63.0–68.0) | 7.5 (7.3–8.45) | 0.16 ± 0.15 (0.10–0.18) | NA | NA | NA | NA | NA |
| Borkowetz et al. | Germany | Serious Retrospective single institution, single blind | 83 | Mean: 64 (63–72) | 4.2 (2.6–6.3) | 31–57 | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) | Mean: 1.5 (0.9–2.1) |
| Blonska et al. | USA | Moderate Retrospective | 542 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 | Mean ± FB: 62 ± 7; Mean – FB: 60 ± 6 |

(continued)
| Study                      | Risk of bias | Study design                          | Country performed          | Number of subjects | Median age (IQR) | Median PSA, ng/mL (IQR) | Median prostate volume (cm³) | Median PSA density, ng/mL cm³, (IQR) | Median number of lesions on MRI | Median lesion size (mm) | Median total number of biopsy cores | Median core positive volume |
|---------------------------|--------------|---------------------------------------|-----------------------------|--------------------|------------------|------------------------|-----------------------------|-------------------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------------------|
| Dieffenbacher et al.      | Serious      | Retrospective, single institution     | Germany, United Kingdom     | 273                | 66 (64–75)       | 6.2 (4.7–7.7)         | 5.8 (4.5–7.0)              | 0.15 (0.09–0.22)                   | NA                             | NA                            | Initial SB: 12 (10–12) Initial FB: 26 (24–28) NA |
| Bloom et al.              | Moderate     | Retrospective study of prospective database | USA, Germany              | AA: 84 Non-AA: 431 | 58.9 (63.0)      | 6.3 (6.0 ± 6.8)        | 5.8 (4.5–7.8)              | 0.15 (0.11–0.16)                   | NA                             | AA: 0.1 ± 0.1 Non-AA: 0.12 ± 0.1 | NA                             |
| Hsiang et al.             | Serious      | Retrospective study                   | USA                         | 122                | 63 (57–68)       | 5.6 (4.1–7.6)         | 4.9 (4.0–6.5)              | 0.11 (0.07–0.15)                  | NA                             | NA                            | NA                             |
| Pepe et al.               | Moderate     | Prospective                            | Italy                       | 125                | 66.0 (63.0–68.0) | NA                    | NA                          | NA                                 | NA                             | NA                            | NA                             |
| Tosoian et al.            | Moderate     | Prospective                            | USA                         | 1818               | VLR: 66 (61–69); LR: 67 (62–71) | VLR: 4.6 (3.5–5.8); LR: 5.9 (4.5–7.8) | NA                          | VLR: 0.09 (0.07–0.12); LR: 0.17 (0.12–0.21) | NA                             | NA                            | NA                             |
| Liss et al.               | Moderate     | Prospective, multi-institutional      | USA, Canada                | 361                | 65 (59–69)       | 5.6 (3.9–8.2)         | 43.8 (32.1–60.3)           | 0.12 (0.08–0.16)                  | NA                             | NA                            | 8.3% (7.1–17.4) |
| Roscigno et al.           | Moderate     | Retrospective, multi-institutional    | Italy                      | 389                | Mean: 66.7       | Mean: 6.50             | Mean: 53.9                  | NA                                 | NA                             | NA                            | 18                             |
| Ulrich et al.             | Serious      | Retrospective                          | Germany, USA               | 55                 | 66 ± 7           | 7.3 (6.9–9.7)         | 41 (30–54)                 | 0.15 (0.11–0.27)                  | NA                             | NA                            | NA                             |
| Röthlin et al.            | Moderate     | Prospective                            | Switzerland                | 47                 | 64 (60–68)       | 5.67 (3.9–7.7)        | 50 (33–58)                 | 0.13 (0.10–0.16)                 | NA                             | NA                            | NA                             |
| Schiavina et al.          | Low          | Multi-institutional, randomized controlled trial | Italy                     | 62 in each group  | Study: 65 (59–69); Control: 65 (62–71) | Study: 5.86 (4.65–7.16); Control: 6.3 (4.66–7.33) | NA                          | Study: 0.12 (0.11–0.16); Control: 0.11 (0.08–0.12) | NA                             | NA                            | Study: 12 (12–14) SB: 13 (12–14) FB: 4 (4–6) SB: 5% (2–19%) FB: 26% (4–40%) |
| Caglic et al.             | Low          | Prospective, single institution       | UK, Russia                 | 295                | 66 (61–69)       | 5.4 (4.7–7.9)         | 50 (34.9–71.0)             | 0.10 (0.1–0.2)                    | NA                             | 9 (7–12)                       | NA                             |
| Roscigno et al.           | Moderate     | Prospective, multi-institutional      | Italy                      | 389                | NA               | NA                    | NA                         | NA                                 | NA                             | NA                            | NA                             |
| O’Connor et al.           | Moderate     | Prospective study                     | USA                        | 391                | 63 (58–68)       | 5.38 (3.95–7.87)      | 51 (38–72)                 | 0.10 (0.07–0.16)                 | 2 (IQR 1–3)                    | 10 (7–14)                      | NA                             |

(continued)
Table 1. (Continued)

| Study                        | Risk of bias | Study design                      | Country, performed | Median age (IQR) | Median PSA, ng/mL (IQR) | Median prostate volume (cm³) (IQR) | Median PSA density, ng/mL cm³, (IQR) | Median number of lesions on MRI | Median lesion size (mm) | Median total number of biopsy cores | Median core positive volume |
|------------------------------|--------------|-----------------------------------|--------------------|------------------|-------------------------|------------------------------------|-----------------------------------|-------------------------|--------------------------|-------------------------------|--------------------------|
| Williams et al.              | Serious      | Prospective, single institution   | USA, Canada        | 66 (62–68)       | 5.6 (5.0–6.0)           | 64.4 (62.8–66)                    | 11.7 (10.2–13.2)                  | NA                      | NA                       | NA                            | NA                       |
| Oberoi et al.26              | Moderate     | Prospective single institution    | USA                | 61.4 ± 2.7       | 5.34 ± 2.6              | 66 (62–68)                        | 11.7 (10.2–13.2)                  | NA                      | NA                       | NA                            | NA                       |
| Eure et al.30                | Serious      | Prospective                       | USA                | 66 (62–68)       | 5.9 (4.9–6.4)           | 64.4 (62.8–66)                    | 11.7 (10.2–13.2)                  | NA                      | NA                       | NA                            | NA                       |
| Median of all studies [IRR]  | NA           | NA                                | NA                 | NA               | NA                      | NA                                 | NA                                | NA                      | NA                       | NA                            | NA                       |

AA, African American; FB, fusion biopsy; IQR, interquartile range; MRI, magnetic resonance imaging; NA, not available; PSA, prostate-specific antigen; SB, systematic biopsy; TB, Targeted Biopsy.

Having a negative FB while on AS is a predictor of favorable AS outcomes. In a prospective study of 182 men who continued AS after initial FB, 122 had a positive FB, and 60 had a negative FB. Progression-free survival (PFS) was longer in the negative FB group compared to the positive FB group (74.3 vs. 44.6 months, respectively, \( p < 0.01 \)).

Rate of upgrading histology. FB and SB are complementary in detecting clinically significant disease. While the use of FB after enrollment in AS based on SB results does identify higher risk disease in an average 15–47% of patients, FB alone, without SB misses in an average of 5–11% of clinically significant disease. The Canary Prostate Cancer Active Surveillance Study (PASS), a prospective multi-institutional study of 361 patients undergoing AS, found, at median follow-up of 4.1 years (IQR 2.9–7.6), 27% of patients were upgraded from grade-group 1 (GG1) to grade-group 2 (GG2) or higher. Of patients who had a negative mpMRI, 17% were upgraded to GG2, and the negative predictive value (NPV) of mpMRI was 83% (95% CI 76–90). Further supporting the need for continued SB, 11% of FB’s found csPCa, while 13% of csPCa were found by SB alone. Although higher Prostate Image Reporting and Data System (PI-RADS) scores were associated with higher risk of csPCa, a negative mpMRI did not ensure the absence of csPCa. Thus, the authors determined FB should be performed adjunctively with SB.

Table 2 depicts the rate of upgrading to csPCa by FB and SB further demonstrating that forgoing either FB or SB would under-detect csPCa. Several studies further supporting the continued use of SB are worth mentioning. Hu et al. identified 113 men enrolled in AS who underwent confirmatory mpMRI FB and a simultaneous 12-core SB. They found a higher MRI suspicion score of 4–5 significantly increased the likelihood of grade reclassification [odds ratio (OR) 3.2, 95% CI 1.4–7.1, \( p = 0.006 \)]; however, in men with a negative FB, 11% had csPCa on SB. Similar findings were reported by Tran et al. in which 9% of men on AS that had a negative FB...
had major upgrading to Gleason score \( \geq 4 + 3 \) on simultaneous SB. In the same study, 24% of patients experienced upgrading on SB, and 14% experienced upgrading on FB.\(^2\)\(^3\)

One confounding factor in these studies is the number of biopsy cores obtained. In several of the studies comparing FB and SB detection, saturation biopsies were performed with an average number of cores obtained of 17 (range 12–30); thus, the higher sampling volume skews the results enabling the non-targeted biopsy to perform better than a standard 12-core biopsy presumably would. In a prospective study comparing results of 100 men who underwent simultaneous mpMRI FB, a 20-core extended biopsy and 30-core transperineal biopsy 6 months into AS, the extended systematic biopsies detected more csPCa compared to the FB cores (75% vs 68.8% respectively, \( p = 0.001 \)).\(^1\)\(^1\) Clinicians must balance the benefit of extended sampling templates improving PCa detection rates with the risk of over-diagnosis and the risk of biopsy complications.

Factors significant for grade-group progression. Table 3 demonstrates predictive factors for upgrading while on AS. The factors demonstrating consistent, statistically significant predictive utility across multiple studies in order of significance include higher PI-RADS score (or more

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**Figure 1.** PRISMA diagram of study selection.
Table 2. Rate of upgrading, predictive factors, follow-up, and progression for all relevant included studies.

| Study               | $n$ upgraded by FB (%) | $n$ upgraded by SB (%) | $n$ upgraded by SB and FB (%) | Predictive factors |
|---------------------|-------------------------|-------------------------|-------------------------------|--------------------|
| Stamatakis et al.   | 25/85 (29)              |                         |                               | # lesions on MRI, lesion density % of total volume, and MRI suspicion score |
| Hu et al.           | 3/90 (3)                | 10/90 (11)              | 41 (36.3)                     | NA                 |
| Siddiqui et al.     | 7 (37)                  | 2 (11)                  | 10 (53)                       | mpMRI suspicion level, PSA |
| Abdi et al.         | 10 (16.1)               | 4 (6.4)                 | 19 (30.6)                     | NA                 |
| Diaz et al.         | 12/34 (35.3)            | 10/34 (29)              | 34 (22.4)                     | More lesions on mpMRI |
| Kamrava et al.      | 31                      | 52                      | 63 (26)                       | Prostate volume, ROI category 5, PSA |
| Ma et al.           | NA                      | NA                      | 25/103 (24.3)                 | higher PI-RADS score (4 vs 3 OR 2.00, $p$=0.04; 5 vs 3 OR 4.74, $p$=0.02), right sided lesion |
| Tran et al.         | 34                      | 39/77 (51%) negative FB; >=4 + 3: 7/77 (9%) | NA | Older age (OR 1.10) |
| Frye et al.         | 22/49 (44.9)            | 15/49 (30), $p$=0.03    | 24.5                          | mpMRI progression |
| Lai et al.          | 20/76 (26.3)            | NA                      | NA                           | MRI suspicion score, PSAD, total lesion density on MRI, duration between biopsies |
| Pepe et al.         | 11/16 (69)              | 12/16 (75)              | 16                            | NA                 |
| Borkowetz et al.    | 32/83 (39)              | 31/83 (37)              | 40/83 (48)                    | NA                 |
| Bloom et al.        | NA                      | 224/542 (41.3)          | NA                            | All groups: Age, PSA density were positively correlated, negative fusion biopsy is negatively correlated, positive FB group: age, PSA density and largest lesion diameter |
| Dieffenbacher et al.| NA                      | NA                      | SB: 59%; FB: 19%              | PRECISE score 4–5  |
| Bloom et al.        | AA: 13/32 (40.6)        | NA                      | NA                            | NA                 |
|                     | non-AA: 87/258 (33.7)   |                         |                               |                    |
| Hsiang et al.       | 11 (38)                 | 11 (38)                 | 7 (24)                        | Older age, higher PI-RADS score on initial mpMRI, higher number of positive systematic cores on initial biopsy, higher maximum percent of targeted core tumor involvement on initial biopsy |
| Pepe et al.         | NA                      | saturation biopsy: 9/45 [20] | NA | NA |
| Tosoian et al.      | NA                      | NA                      | NA                            | pre-enrollment mpMRI had reduced risk of grade reclassification (HR 0.66) 95% CI 0.46–0.95, $p$=0.03; higher risk of reclassification in: older age, AA race, higher PSAD, number of positive cores, maximum core involvement, having a + mpMRI |
| Liss et al.         | 284                     | 111                     | NA                            | NA                 |
| Roscigno et al.     | 97/308 (30.8)           | NA                      | Total reclassified to GG3 [8]. mpMRI negative: [1.6]; PI-RADS 3: [4], PI-RADS 4: [11], PI-RADS 5: [22]; negative mpMRI or PI-RADS 3 + PSAD $\geq 0.20$: [9] | NA |

(continued)
suspicious lesions in studies prior to the adoption of PI-RADS scoring), PSA-D, older age, and the size of lesion on imaging or the volume of disease on biopsy. The presence of bilateral disease has also been shown to increase the risk of progression on AS (HR = 3.06; 95% CI = 1.31–7.13), and combined FB and SB improve detection of bilateral disease than either method alone.38

Models and nomograms. Several nomograms have been developed to identify patients at risk of pathologic progression while on AS and eliminate the need for routine follow-up biopsies in patients at lower risk of progression. The Prostate Cancer Radiologic Estimation of Change in Sequential Evaluation (PRECISE) score (Table 4) is a Likert-type-based grading system developed to rate follow-up mpMRI’s. PRECISE scores of 1–3 are considered stable, and scores of 4–5 are considered progression on mpMRI. In a prospective study of 391, AS men who underwent interval mpMRI after a median of 22 months, the NPV of a PRECISE score of 1–3 for upgrading from GG1 to GG2; PSAD was the only risk factor for progression from GG1 to GG3.

| Study                | n upgraded by FB (%) | n upgraded by SB (%) | n upgraded by SB and FB (%) | Predictive factors                                                                 |
|----------------------|----------------------|----------------------|------------------------------|----------------------------------------------------------------------------------|
| Ullrich et al.33     | NA                   | NA                   | 44 (80); 29 had progression  | NA                                                                               |
| Rothlin et al.34      | upgraded in 2/47 (4) | missed 5/10 csPCA    | NA                           | No factors predicted missed PCA at FB                                             |
| Schiavina et al.16   | 11 (17) at 3 month   | 2 (3.2%) at 12 month | NA                           | NA                                                                               |
| Caglic et al.35       | NA                   | NA                   | NA                           | Higher PSA-D, index lesion size, Likert-type score, lower gland volume            |
| Roscigno et al.34     | NA                   | NA                   | mpMRI negative: (17);       | Older age, PSAD, number of positive cores at baseline, PIRADS 3, 4, and 5       |
| O’Connor et al.37     | 170/621 [27.3] of imaging intervals | NA | 163/391 [41.7] | Stable MRI: change in PSA, PSAD, and the size of index lesion risk for progression from GG1 to GG2; PSAD was the only risk factor for progression from GG1 to GG3 |
| Williams et al.38     | 49/103 [47]          | NA                   | FB + SB detected 16%         | NA                                                                               |
| Okoro et al.39        | NA                   | NA                   | NA                           | Highest percentage core involvement on FB                                        |
| Eure et al.40         | NA                   | NA                   | NA                           | NA                                                                               |
| Median of all studies (IQR): | 26.6% [15.0–47.6] | 41.5% [36.3–46.8] | 30.6% [24.3–41.7] | NA                                                                               |

CI, confidence interval; FB, fusion biopsy; GG, grade group; HR, hazard ratio; IQR, interquartile range; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; NA, not available; OR, odds ratio; PI-RADS, Prostate Image Reporting and Data System; PRECISE, Prostate Cancer Radiologic Estimation of Change in Sequential Evaluation; PSA, prostate-specific antigen; PSA-D, PSA density; SB, systematic biopsy, ROI, Region of Interest.
Table 3. List of factors found to be significant predictors of upgrading on single variable or multivariate analysis, and number of studies confirming these findings.

| Predictive factors for upgrading | Number of studies confirming |
|---------------------------------|-------------------------------|
| PI-RADS score or suspicious lesion on mpMRI | 9 |
| PSA-D | 6 |
| Older age | 5 |
| Lesion size or density on mpMRI | 4 |
| % of total volume on initial biopsy, or number of positive cores | 4 |
| Gland volume | 3 |
| PSA | 3 |
| Number of lesions on mpMRI | 2 |
| Right-sided lesion | 1 |
| mpMRI progression | 1 |
| AA race | 1 |
| Having a positive mpMRI | 1 |

mpMRI, multi-parametric magnetic resonance imaging; PI-RADS, Prostate Image Reporting and Data System; PSA, prostate-specific antigen; PSA-D, PSA density.

Table 4. Definition of PRECISE criteria, O’Connor et al.35

| PRECISE criteria | Definition |
|------------------|------------|
| 1                | Resolution of features (no visible lesions) |
| 2                | Reduction in size/conspicuity of lesions |
| 3                | Stable MRI appearance; no new lesions |
| 4                | Increase in size/conspicuity of lesions |
| 5                | Definitive radiologic stage progression |

MRI, magnetic resonance imaging; PRECISE, Prostate Cancer Radiologic Estimation of Change in Sequential Evaluation.

Of the 41 patients that progressed, 19.5% had a PRECISE score of 3, 56.1% had PRECISE score of 4, and 19.5% had PRECISE score of 5. The sensitivity for progression on mpMRI (PRECISE score ≥4) at detecting histologic progression was 75.6%, and specificity was 86.8%. The use of the PRECISE scoring system may reduce need for repeat biopsy in patients with scores of 1–3, and scores ≥4 may trigger closer monitoring.

Two other nomograms that decrease the risk of needing an initial FB after SB have been published. The first, factors mpMRI features of number of lesions, highest PCA suspicion scores, and total lesion volume divided by the total prostate volume (lesion density). Of note, this study was performed prior to the adoption of PI-RADS; however, the mpMRI suspicion scores are correlated with PI-RADS scoring. This nomogram was evaluated in a retrospective review of an AS clinical trial. The initial mpMRI of 85 patients was scored and correlated to repeat biopsy outcomes, 25 of which had grade group progression on repeat biopsy. The use of this nomogram could spare 27–68% of AS patients a routine surveillance biopsy with a 71–97% sensitivity and 81–91% NPV. Another research team evaluated a similar nomogram to decrease the need for initial FB, which factored MRI suspicion scores, PSA-D, total lesion density, and number of days between biopsies. This test was compared to and outperformed the predictive power of PSA alone.25

Adjunctive studies. It is evident that patients with negative mpMRI’s and negative FB’s remain at risk of grade reclassification. Two adjunctive data points that have been associated with increased probability of upgrading include higher PSA-D and the urine biomarker SelectMDx. A retrospective study of 389 patients who underwent AS and had at least one follow-up biopsy evaluated the ability of PI-RADS score and PSA-D to predict grade reclassification. The authors reported PSAD ≥ 0.20 ng/mL2 had OR = 2.45 (p=0.007) for predicting risk of reclassification, including patients with both negative and positive mpMRI. A prospective study of 125 men undergoing AS underwent mpMRI FB, transperineal saturation biopsy (30 cores), and post-digital rectal exam (DRE) urine collection for SelectMDx analysis. Abnormal SelectMDx improved the ability of mpMRI alone to predict grade reclassification; however, together, they did not perform as well as FB + saturation biopsy in identifying
Radiologic progression has been defined as increased suspicion score, lesion diameter, intensity of diffusion restriction of the lesion or number of lesions on mpMRI.\textsuperscript{20,24,37} Table 5 depicts median follow-up and PFS for all relevant studies. The studies in this review suggest radiologic progression is not predictive of grade-group progression. Hsiang \textit{et al.} performed a retrospective analysis on 122 patients undergoing AS to evaluate the ability of serial mpMRI’s to predict pathological upgrading. Patients had at least two consecutive mpMRI’s obtained annually (median time between biopsies 13.5 months) followed by FB plus SB. About 44.3\% of men demonstrated radiologic progression including doubling of volume of the index lesion, increase in PI-RADS score, and/or increase in number of lesions. Only 12 of 54 with radiological progression had pathological progression, of which 17\% were found on SB only. The reported sensitivity and specificity for the ability of mpMRI to predict pathological progression were 41.3\% and 54.8\%, respectively.\textsuperscript{30} Another retrospective study of 58 men undergoing AS who had initial SB and FB and underwent subsequent mpMRI with SB and FB (median follow-up 16.1 months), 29.3\% had radiological progression and 9 of 17 had pathological progression, resulting in a similar sensitivity and specificity to the prior mentioned study of 53\% (95\% CI: 0.28–0.77) and 80\% (95\% CI: 0.65–0.91), respectively. Of the 41 stable mpMRI’s, 33 had a stable grade group on SB plus FB, with 20\% of men with stable mpMRI’s having pathological progression. The number needed to biopsy to detect 1 Gleason progression if only patients who had radiological progression underwent biopsy was 2.9 for FB and 8.74 for SB (\(p < 0.02\)).\textsuperscript{20} Using the PRECISE scoring system, however, improves the ability to avoid repeat biopsies in patients with PRECISE score \(\leq 3\); eliminating repeat biopsy in the 109 patients who had stable mpMRI’s, only 3.7\% would have missed pathological progression to \(\geq GG3\) disease at 2 years follow-up.\textsuperscript{37} Of note, there were no reported differences in the power of the magnet used, presence of endorectal coil, and experience of the centralized genitourinary radiologists between the latter two studies.

\textbf{Discussion}

This review demonstrates mpMRI with FB at time of AS enrollment significantly reduces the rate of upgrading and subsequently the rate of disqualification from AS. mpMRI also improves PFS on AS. Approximately 50\% of men can expect to be upgraded with the use of FB after diagnosis with SB.\textsuperscript{42,43} Multiple studies strongly suggest an imperative role of mpMRI plus FB at time of AS enrollment and should be performed in all men who are AS candidates. This is further confirmed by examining the AS failure rate at a 2-year follow-up period of the ASIST trial, a prospective multicenter trial randomizing men eligible for AS to confirmatory biopsy with SB versus mpMRI plus FB. Klotz \textit{et al.}\textsuperscript{44} reports that compared to the SB group, the mpMRI plus FB group had a 50\% reduction in the rate of AS failure. The majority of csPCa missed on prior SB are located in anterior or apical regions.\textsuperscript{45} Furthermore, in patients eligible for AS undergoing RP, apical involvement of the tumor increased the risk of upstaging on final pathology.\textsuperscript{46} mpMRI mitigates this risk by identifying apical lesions that otherwise would have been missed on SB.\textsuperscript{47} In addition, the number of biopsy cores obtained at confirmatory and repeated evaluations has been shown to improve selection of men with very-low-risk PCa. Pepe \textit{et al.} performed a prospective AS trial performing both saturation biopsy (range 24–32 cores) and FB (if indicated) during confirmatory and repeat biopsies and cite a reclassification rate of only 5.4\% 3 years from diagnosis.\textsuperscript{48} Clearly increasing the area of sampling increases the likelihood of finding clinically significant disease.
Table 5. Radiologic and pathologic progression cited for all relevant studies.

| Study            | Median length of follow-up (months) (IQR) | n progression on MRI (%) | n histologic progression (%) | Sensitivity/specificity/NPV/PPV for progression on MRI in f/u | Progression-free survival |
|------------------|-------------------------------------------|---------------------------|-----------------------------|------------------------------------------------------------|----------------------------|
| Diaz et al.      | 16.1 (12–56)                              | 17/58                     | 17/58                       | 80% [CI: 0.65–0.91]; 53% [CI: 0.28–0.77]                    | NA                         |
| Frye et al.      | Mean: 25.5 [3.2–96.4]                      | (64.5)                    | Histologic progression with stable mpMRI: (20.8)              | 77.6% sensitivity; 40.5% specificity; 81% NPV; 35% PPV       | Intermediate risk: 1.5 year (IQR 1.2–2.1); low risk: 2.1 year (IQR 1.2–4.0) |
| Lai et al.       | NA                                        | NA                        | NA                          | Sensitivity 80%; specificity 81.25%; NPV 92.86%; PPV 57.1%  | NA                         |
| Bloom et al.     | NA                                        | NA                        | NA                          | NA                                                         | NA                         |
| Dieffenbacher et al. | 48                                        | NA                        | SB: minor upgrading in 60; major upgrading in 17; FB: minor upgrading in 15; major upgrading in 0 | NA                         | NA                         |
| Bloom et al.     | NA                                        | NA                        | NA                          | AA: 59.7 months; Non-AA: 60.5 months (p = 0.26)              | NA                         |
| Hsiang et al.    | NA                                        | 54 [44.3]                 | NA                          | NA                                                         | NA                         |
| Pepe et al.      | NA                                        | PIRADS ≥ 3 in 4/9 cases [44.4] | NA                          | 66.6% sensitivity; 87.7% specificity; 92.3% NPV, 54.5% PPV  | NA                         |
| Tosoian et al.   | VLR: 68 [31–109]; LR: 37 [14–74]          | NA                        | NA                          | NA                                                         | NA                         |
| Liss et al.      | 4.1 years [2.0–7.6]                       | NA                        | NA                          | Negative mpMRI NPV: 83% [95% CI 76–90]; positive mpMRI PPV: 31% [95% CI 26–37] | NA                         |
| Ullrich et al.   | NA                                        | NA                        | NA                          | 100% sensitivity; 42% specificity; 100% NPV; 66% PPV        | NA                         |
| Caglic et al.    | Overall progression: 41 (13.9)            | NA                        | NA                          | PRECISE SCORE ≥ 4: 75.6% sensitivity; 88.6% specificity     | 82.2% at 5 years            |
| O’Connor et al.  | 35.6 [19.7–60.6]                          | NA                        | NA                          | GG1 to GG2: sensitivity 0.53 (0.44–0.61); NPV 0.76 (0.71–0.81); GG1 to GG3: sensitivity 0.65 (0.50–0.80); NPV 0.9 (0.91 to 0.96); GG2 to GG3: sensitivity 0.67 (0.53–0.80); NPV 0.86 (0.78–0.92) | NA                         |

CI, confidence interval; FB, fusion biopsy; GG, grade group; IQR, interquartile range; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; NA, not available; NPV, negative predictive value; PI-RADS, Prostate Image Reporting and Data System; PPV, Positive Predictive Value; PRECISE, Prostate Cancer Radiologic Estimation of Change in Sequential Evaluation; SB, systematic biopsy; VLR, Very Low Risk.

Given the current studies, the use of mpMRI to eliminate the need for follow-up biopsies is not supported. While mpMRI progression is associated with increased risk of pathological progression, and stable mpMRI is associated with a stable grade group, failing to biopsy patients with...
stable mpMRI’s will miss progression in approximately 20% of men. Other reports suggest approximately 10% of negative mpMRI’s harbor csPCa.\(^7\) Factors found to be predictive of upstaging in this study include higher PI-RADS score, PSA-D, older age, the size of lesion on imaging, and the volume of disease on biopsy. The median number of lesions identified on mpMRI was 2 (IQR 1.7–2.3) and the median number of biopsy cores obtained was 16 (IQR 14.7–17.5). Adjunctive nomograms such as the PRECISE score may be beneficial in grading radiological progression. Other nomograms such as PSA-D and SelectMDx have promising results to prevent need for further biopsy; however, they are currently utilized for the initial diagnostic stage, where mpMRI FB has already demonstrated itself to be imperative in the appropriate selection for AS. Further studies and longer follow-up are needed to test nomograms that may prevent the need for repeat surveillance biopsies and decrease the likelihood of missing pathological progression.

Further hindering use of serial mpMRI’s is cost. In a cost-analysis, mpMRI-based surveillance every 5 years improved survival by 4.47 quality-adjusted months and was cost-effective. At more frequent intervals, Sathianathen \textit{et al.}\(^4\) reported incremental cost-effectiveness ratios >800,000 USD per quality-adjusted life year. To optimize cost, longer AS protocol follow-up with increased intervals between serial mpMRI’s should be further evaluated.

There is little controversy surrounding the ability of mpMRI FB to increase the detection of csPCa compared to SB alone, and our findings are similar to Schoots \textit{et al.}\(^5\) Data support that mpMRI FB has an imperative role in selecting patients for AS and should be performed at the beginning of enrollment in all patients eligible for AS. More studies are needed in how to best incorporate mpMRI fusion data such as number of cores positive, percent core involvement, and lesion volume into selection criteria. With improved detection of clinically significant cancer, expanding criteria to include low volume GG2 disease would increase the number of men potentially eligible for AS. How to best follow these men and what triggers to use to proceed with definitive treatment remain active topics of study and debate. New imaging technology such as Prostate-Specific Membrane Antigen-targeted positron emission tomography-computed tomography (PSMA PET/CT) scans will undoubtedly be studied to try and enhance detection and progression in men on AS. In fact, one study suggests that PSMA PET/CT standardized uptake values (SUVs) were able to predict adverse pathology at the time of RP, and thus may be useful in determining AS candidacy and detection of disease progression.\(^5\)

Several limitations to this review include the small sample size, retrospective nature of some, and shorter follow-up for many of the studies. Furthermore, many studies were performed prior to the adoption of PI-RADS v2, and while the authors report their scoring systems correlate with the PI-RADS v2 system, the results may not be valid to today’s practice. In addition, the studies may not be generalizable because many report outcomes from tertiary centers, and all radiographic and pathologic analysis were performed by specialized genitourinary radiologists and pathologists, respectively, at centralized locations. Limitations of the review process include only one author extracting data and performing a bias assessment.

**Conclusion**

mpMRI FB in conjunction with SB more accurately selects patients for AS. mpMRI should additionally be used routinely for follow-up; however, mpMRI is not currently sensitive enough in detecting disease progression to replace biopsy in the surveillance protocol.

**Declarations**

\textit{Ethics approval and consent to participate}  
Not applicable.

\textit{Consent for publication}  
Not applicable.

\textit{Author contributions}  
Elizabeth E. Ellis: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.  
Thomas P. Frye: Conceptualization; Data curation; Formal analysis; Project administration; Supervision; Validation; Visualization; Writing – review & editing.  

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