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Systematic Review

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 comorbidities, 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. Risk of bias was assessed using ROBINS-I tool.[9] One author independently extracted data from the accepted articles which was critically reviewed by the other author. No assumptions were made regarding missing information; missing information was cited as not available (NA). Median values and interquartile range (IQR) for all studies were calculated for each data point using Microsoft Excel.

Results

Study selection and quality of the data

A PRISMA diagram of study selection appears in Figure 1.[10] We identified a total of 121 publications from the PubMed search. After initial review of abstracts for relevance, 47 manuscripts were selected for careful review. Of these, a total of 30 articles were accepted for reporting. Publications were rejected based on manuscript type: opinion (1), correspondence (1); irrelevance to primary endpoints (11), poor retention rate (1), genetic syndromes predisposing to more aggressive disease (1), and primary treatment other than AS (2). Likelihood of bias is high due to the retrospective nature of many of the accepted studies and are displayed 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 cm^3 (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

Table 1. Patient demographics, type of study, and risk of bias assessment of all relevant included studies.

Study	Risk of bias	Study design	Country performed	Number of subjects	Median age (IQR)	Median PSA, ng/mL (IQR)	Median prostate volume (cm^3)	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.*;[15] Siddiqui *et al.*[16]	Serious	Retrospective	United States of America (USA)	85	Mean (range): 60.2 ± 7.4 (40–79)	Mean (range): 4.8 ± 2.2 (0.2–10.9)	51.5 ± 18.9 (24–161)	Mean (range): 0.09 ± 0.03 (0.01–0.15)	2.1 ± 1.0	NA	Mean: 17.6 ± 2.7	NA
Hu *et al.*[17]	Low	Prospective single institution, single blind	USA	113	63 (58–68)	4.2 (2.6–6.3)	46.8 (36.1–64.5)	0.08 (0.05–0.14)	2 (1–2)	10.5 (4–32)	16 (14–18)	NA
Da Rosa *et al.*[18]	Low	Prospective, single institution, single blind	Canada	81	Mean (range): 64.8 (41–79)	Mean (range): 5.0 (1.1–17.6)	NA	NA	Mean (range): 1.9 (1–4)	NA	NA	NA
Abdi *et al.*[19]	Serious	Retrospective	Canada	111	62.9 (58.2–67.6)	6.1 (4.4–8.1)	NA	0.12 (0.08–0.19)	NA	NA	NA	NA
Diaz *et al.*[20]	Moderate	Retrospective	USA	152	Mean (range): 61.4 ± 7.1 (40–79)	Mean (range): 5.2 ± 3.2 (0.2–23.3)	Mean (range): 58 ± 28 (23–161)	Mean (range): 0.09 ± 0.03 (0.01–0.15)	Mean (range): 2.3 ± 1.2 (1–9)	NA	NA	NA
Kamrava *et al.*[21]	Low	Prospective, single institution	USA	245	Mean: 64 ± 7.4	4.8 ± 3.65 (2.9–6.7)	Mean: 50 ± 23	NA	1.5 ± 0.6	NA	Mean: 15 ± 3.1	NA
Ma *et al.*[22]	Moderate	Retrospective	USA	103	70 (66–74)	5.4 (3.2–7.4)	55 (40–80)	0.08 (0.06–0.13)	1.5	8 (7–13)	TB: 3 (3–6) SB: 12 (12–12)	NA
Tran *et al.*[23]	Moderate	Prospective, single institution	USA	207	66.7 (61.4–70.4)	5.9 (4.3–8.8)	42 (31–57)	0.15 (0.09–0.21)	NA	NA	TB: 2 (2–4) SB: 14	TB: 40% (20–64%) SB: 31% (14–50)
Frye *et al.*[24]	Serious	Retrospective	USA	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	Low-risk mean: 2.6 ± 1.3 intermediate risk mean: 2.7 ± 1.4	NA	NA	NA
Lai *et al.*[25]	Serious	Retrospective single institution	USA	76	Mean: 62.5 ± 7.0	Mean: 5.1 ± 2.0	NA	NA	Mean: 2.3 ± 0.95	Mean: 16.8 ± 5	NA	NA
Pepe *et al.*[11]	Serious	Prospective, single institution, single blind	Italy	100	66.0 (63.0–68.0)	7.5 (7.3–8.45)	NA	0.16 (0.15–0.18)	NA	NA	NA	NA
Borkowetz *et al.*[26]	Serious	Retrospective, single institution	Germany	83	67 (63–72)	6.9 (5.5–9.3)	44 (32–63)	0.12 (0.05–0.25)	1	NA	FB: 18 SB: 12	NA
Bloom *et al.*[27]	Moderate	Prospectively maintained database, retrospective study	USA	542	Mean + FB: 62.6 ± 7.1 Mean – FB: 60.9 ± 6.6	Mean + FB: 5.6 ± 3.1 Mean -FB: 5.4 ± 3.9	Mean + FB: 5.6 ± 3.1 Mean –FB: 5.4 ± 3.9	Mean + FB: 0.12 ± 0.07 Mean – FB: 0.11 ± 0.09	Mean + FB: 2.3 ± 1.4 Mean – FB: 2.0 ± 1.0	Mean + FB: 12 ± 6 Mean – FB: 12 ± 5	NA	NA

(continued)

Table 1. (Continued)

Study	Risk of bias	Study design	Country performed	Number of subjects	Median age (IQR)	Median PSA, ng/mL (IQR)	Median prostate volume (cm^3)	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.*[28]	Serious	Retrospective, single institution	Germany, United Kingdom (UK), Canada	273	Initial SB: 69 (64–75) Initial FB: 69 (64–74)	Initial SB: 6.2 (4.7–7.7) Initial TB: 5.8 (4.5–7.0)	Initial SB: 41.0 (31.0–4.0) Initial TB: 43.0 (31.0–57.0)	Initial SB: 0.15 (0.09–0.22) Initial FB: 0.15 (0.10–0.20)	NA	NA	Initial SB: 12 (10–12) Initial FB: 26 (24–28)	NA
Bloom *et al.*[29]	Moderate	Retrospective study of prospective database	USA, Germany	AA: 84 Non-AA: 431	Mean AA: 58.9 Non-AA: 63.0	Mean AA: 6.3 ± 4.2 Non-AA: 6.0 ± 3.8	Mean AA: 56.6 ± 28.9 Non-AA: 63.3 ± 24.4	NA	AA: 1 ±3.1 Non-AA:8 ± 3.1	Mean AA: 1.1 ± 0.5 Non-AA: 1.2 ± 0.05	NA	NA
Hsiang *et al.*[30]	Serious	Retrospective study	USA	122	63 (57–68)	5.6 (4.1–7.6)	49.9 (40.0–65.2)	0.11 (0.07–0.15)	NA	NA	NA	NA
Pepe *et al.*[13]	Moderate	Prospective	Italy	125	66.0 (63.0–68.0)	NA	NA	NA	NA	NA	NA	NA
Tosoian *et al.*[13]	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	NA
Liss *et al.*[31]	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	NA	8.3% (7.1–17.4)
Roscigno *et al.*[32]	Moderate	Retrospective, multi-institutional	Italy	389	Mean: 66.7	Mean: 6.50	Mean: 53.9	NA	NA	NA	18	NA
Ullrich *et al.*[33]	Serious	Retrospective	Germany, USA	55	66 ± 7	7.3 (4.9–9.7)	41 (30–54)	0.15 (0.11–0.27)	NA	NA	NA	NA
Röthlin *et al.*[34]	Moderate	Prospective	Switzerland	47	64 (60–68)	5.67 (3.9–7.73)	50 (33–58)	0.13 (0.10–0.14)	NA	NA	SB:13 (12–14) FB: 4 (4–6)	SB: 5% (2–15%) FB: 26% (4–40%)
Schiavina *et al.*[14]	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) Control: 12 (12–14)	NA
Caglic *et al.*[35]	Low	Prospective, single institution	UK, Russia	295	66 (61–69)	5.6 (4–7.9)	50 (34.9–71.0)	0.10 (0.1–0.2)	NA	9 (7–12)	NA	NA
Roscigno *et al.*[36]	Moderate	Prospective, multi-institutional	Italy	389	NA	NA	NA	NA	NA	NA	NA	NA
O'Connor *et al.*[37]	Moderate	Prospective study	USA	391	63 (58–68)	5.38 (3.95–7.87)	51 (38–72)	0.10 (0.07–0.14)	2 (IQR 1–3)	10 (7–14)	NA	NA

(continued)

Table 1. (Continued)

Study	Risk of bias	Study design	Country performed	Number of subjects	Median age (IQR)	Median PSA, ng/mL (IQR)	Median prostate volume (cm^3)	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.*[38]	Moderate	Prospectively maintained database	USA	579	62 (58–67)	4.81 (3.695–7.115)	48.25 (38.7–66.2)	0.096 (0.068–0.142)	NA	10.0 (8.0–13.0)	NA	NA
Okoro *et al.*[39]	Moderate	Prospective, single institution	USA	50	Mean: 61.4 ± 7.7	Mean: 5.34 ± 2.6	NA	Mean: 0.12 ± 0.07	2.6 ± 1.4	(if positive) Mean: 11 ± 5	Mean: 14.6 ± 1.4	NA
Eure *et al.*[40]	Serious	Prospective	USA, Canada	0	66 (62–68)	5.9 (4.99–6.42)	37 (33–44)	NA	NA	NA	17 (16–18)	NA
Median of all studies (IQR)	NA	NA	NA	NA	64.4 (62.8–66)	5.6 (5.2–6.0)	49.9 (43.9–51.3)	2.0 (1.7–2.3)	10.0 (9–11)	16.9 (15.0–17.7)	16 (14.7–17.5)	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.

the initial FB group were more likely to continue on AS (81% for initial FB *vs* 41% for initial SB, $p < 0.001$).[28] These data suggest that initial FB has significantly less upgrading than initial diagnosis on SB, thus FB improves appropriate selection of AS.

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, $p < 0.01$).[27]

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.[31]

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.[17] Similar findings were reported by Tran *et al.* in which 9% of men on AS that had a negative FB

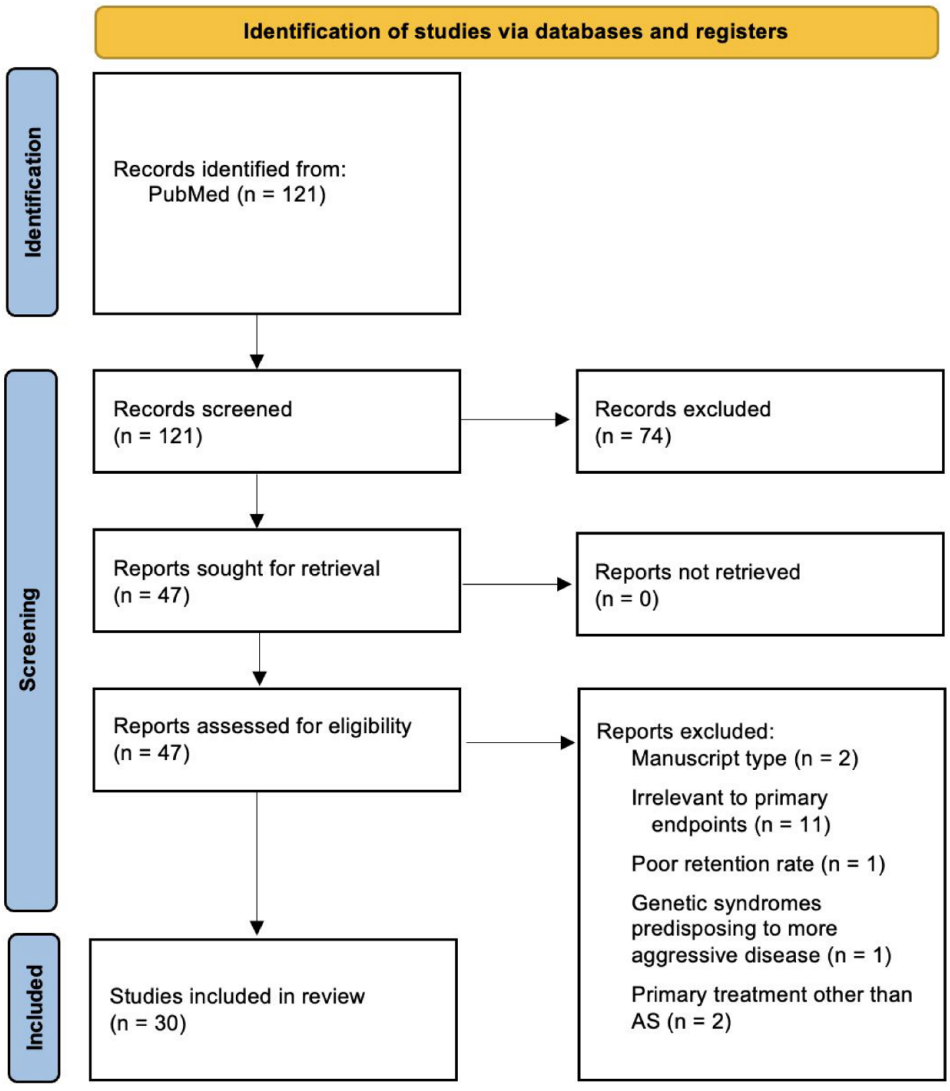

Figure 1. PRISMA diagram of study selection.

had major upgrading to Gleason score ⩾4 + 3 on simultaneous SB. In the same study, 24% of patients experienced upgrading on SB, and 14% experienced upgrading on FB.[23]

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, $p = 0.001$).[11] 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

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.*;[15] Siddiqui *et al.*[16]			25/85 (29)	# lesions on MRI, lesion density % of total volume, and MRI suspicion score
Hu *et al.*[17]	3/90 (3)	10/90 (11)	41 (36.3)	NA
Da Rosa *et al.*[18]	7 (37)	2 (11)	10 (53)	mpMRI suspicion level, PSA
Abdi *et al.*[19]	10 (16.1)	4 (6.4)	19 (30.6)	NA
Diaz *et al.*[20]	12/34 (35.3)	10/34 (29)	34 (22.4)	More lesions on mpMRI
Kamrava *et al.*[21]	31	52	63 (26)	Prostate volume, ROI category 5, PSA
Ma *et al.*[22]	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.*[23]	34	39/77 (51%) negative FB; ⩾4 + 3: 7/77 (9%)	NA	Older age (OR 1.10)
Frye *et al.*[24]	22/49 (44.9)	15/49 (30), $p = 0.03$	(24.5)	mpMRI progression
Lai *et al.*[25]	20/76 (26.3)	NA	NA	MRI suspicion score, PSAD, total lesion density on MRI, duration between biopsies
Pepe *et al.*[11]	11/16 (69)	12/16 (75)	16	NA
Borkowetz *et al.*[26]	32/83 (39)	31/83 (37)	40/83 (48)	NA
Bloom *et al.*[27]	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.*[28]	NA	NA	SB: 59%; FB: 19%	PRECISE score 4–5
Bloom *et al.*[29]	AA: 13/32 (40.6) non-AA: 87/258 (33.7)	NA	NA	NA
Hsiang *et al.*[30]	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.*[41]	NA	saturation biopsy: 9/45 (20)	NA	NA
Tosoian *et al.*[13]	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.*[31]	284	111	NA	NA
Roscigno *et al.*[32]	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 ⩾ 0.20: (9)	NA

(continued)

Table 2. (Continued)

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
Röthlin *et al.*[34]	Upgraded in 2/47 (4) missed 5/10 csPCa	Missed 1/10 csPCa	NA	No factors predicted missed PCa at FB
Schiavina *et al.*[14]	11 (17) at 3 month 2 (3.2%) at 12 month	14 (22.6) at 12 mo. $p < 0.001$	NA	NA
Caglic *et al.*[35]	NA	NA	NA	Higher PSA-D, index lesion size, Likert-type score, lower gland volume
Roscigno *et al.*[36]	NA	NA	mpMRI negative: (17); PIRADS 3: (35); PIRADS 4: (38); PIRADS 5: (52), $p < 0.001$	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% more patients with bilateral disease than SB alone	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.

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 GG3 was 0.94 (95% CI 0.91–0.97), and PSA-D was a risk factor for histologic progression with patients who had PRECISE score <4. They found that if they had biopsied only the patients with a positive change in MRI, they could have avoided 109 biopsies missing 3.7% of progression to GG3 disease.[37] Caglic *et al.* performed a prospective study of 295 men to assess the PRECISE scoring system. Overall, 5-year PFS was 82.2%.

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 $\geq$4) at detecting histologic progression was 75.6%, and specificity was 86.8%.[35] The use of the PRECISE scoring system may reduce need for repeat biopsy in patients with scores of 1–3, and scores $\geq$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 correlative 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.[16] 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 $\geq$ 0.20 ng/mL^2 had OR = 2.45 (p = 0.007) for predicting risk of reclassification, including patients with both negative and positive mpMRI.[32] 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

recurrence.[41] SelectMDx may have an adjunctive role with follow-up mpMRI's in patients who wish to forgo surveillance biopsy, but more studies are needed to validate its use.

Ability of mpMRI to detect progression and follow-up schedule. Several AS protocols have been described. The Johns Hopkins AS program recommended men to undergo confirmatory biopsy within 12 months of diagnosis, semi-annual PSA and DRE, and annual prostate biopsy. Definitive treatment is offered to grade reclassification ⩾ GG2 or volume reclassification (>2 positive cores or >50% tumor involvement of core).[13] The Prostate cancer Research International: Active Surveillance (PRIAS) protocol entails confirmatory SB within 12 months from AS enrollment, followed by follow-up biopsies at 4 years and 7 years.[32] In men who enrolled in an AS study at the National Cancer Institute, FB plus SB was performed at study enrollment followed by confirmatory FB after 12–24 months, semi-annual PSA, and annual mpMRI.[24] The AUA guidelines suggest obtaining serial mpMRI's at an interval of 2 years.[3]

Radiologic progression has been defined as increased suspicion score, lesion diameter, intensity of diffusion restriction of the lesion or number of lesions on mpMRI.[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 *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.[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 ($p < 0.02$).[20] Using the PRECISE scoring system, however, improves the ability to avoid repeat biopsies in patients with PRECISE score ⩽3; eliminating repeat biopsy in the 109 patients who had stable mpMRI's, only 3.7% would have missed pathological progression to ⩾GG3 disease at 2 years follow-up.[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.

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 30% of men can expect to be upgraded with the use of FB after diagnosis with SB.[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 *et al.*[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.[45] Furthermore, in patients eligible for AS undergoing RP, apical involvement of the tumor increased the risk of upstaging on final pathology.[46] mpMRI mitigates this risk by identifying apical lesions that otherwise would have been missed on SB.[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 *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.[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.*[20]	16.1 (12–56)	17/58	17/58	80% (CI: 0.65–0.91); 53% (CI: 0.28–0.77)	NA
Frye *et al.*[24]	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.*[25]	NA	NA	NA	Sensitivity 80%; specificity 81.25%; NPV 92.86%; PPV 57.1%	NA
Bloom *et al.*[27]	NA	NA	Negative FB median: 74.3 months; positive FB median: 44.6 months; $p < 0.01$	NA	NA
Dieffenbacher *et al.*[28]	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.*[25]	NA	NA	NA	NA	AA: 59.7 months; Non-AA: 60.5 months ($p = 0.26$)
Hsiang *et al.*[30]	NA	54 (44.3)	NA	NA	NA
Pepe *et al.*[41]	NA	PIRADS $\geqslant$ 3 in 4/9 cases (44.4)	NA	66.6% sensitivity; 87.7% specificity; 92.3% NPV, 54.5% PPV	NA
Tosoian *et al.*[13]	VLR: 68 (31–109); LR: 37 (14–74)	NA	NA	NA	NA
Liss *et al.*[31]	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.*[33]	NA	NA	NA	100% sensitivity; 42% specificity; 100% NPV; 66% PPV	NA
Caglic *et al.*[35]	Overall progression: 41 (13.9)			PRECISE SCORE $\geqslant$ 4: 75.6% sensitivity; 88.6% specificity	82.2% at 5 years
O'Connor *et al.*[37]	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 0.94 (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, Postive 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 *et al.*[49] 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 *et al.*[50] 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.[51]

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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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