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Abstract

Context: Although magnetic resonance imaging (MRI) is broadly implemented into active surveillance (AS) protocols, data on the reliability of serial MRI in order to help guide follow-up biopsy are inconclusive.
Objective: To assess the diagnostic estimates of serial prostate MRI for prostate cancer (PCa) progression during AS.
Evidence acquisition: We systematically searched PubMed, Scopus, and Web of Science databases to select studies analyzing the association between changes on serial prostate MRI and PCa progression during AS. We included studies that provided data for MRI progression, which allowed us to calculate diagnostic estimates. We compared Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) accuracy with institution-specific definitions.
Evidence synthesis: We included 15 studies with 2240 patients. Six used PRECISE criteria and nine institution-specific definitions of MRI progression. The pooled PCa progression rate, which included histological progression to Gleason grade $\geq$2, was 27%. The pooled sensitivity and specificity were 0.59 (95% confidence interval [CI] 0.44–0.73) and 0.75 (95% CI 0.66–0.84) respectively. There was significant heterogeneity between included studies. Depending on PCa progression prevalence, the pooled negative predictive value for serial prostate MRI ranged from 0.81 (95% CI 0.73–0.88) to 0.88 (95% CI 0.83–0.93)

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and the pooled positive predictive value ranged from 0.37 (95% CI 0.24–0.54) to 0.50 (95% CI 0.36–0.66). There were no significant differences in the pooled sensitivity (p = 0.37) and specificity (p = 0.74) of PRECISE and institution-specific schemes.
Conclusions: Serial MRI still should not be considered a sole factor for excluding PCa progression during AS, and changes on MRI are not accurate enough to indicate PCa progression. There was a nonsignificant trend toward improved diagnostic estimates of PRECISE recommendations. These findings highlight the need to further define the optimal triggers and timing of biopsy during AS, as well as the need for optimizing the quality, interpretation, and reporting of serial prostate MRI.
Patient summary: Our study suggests that serial prostate magnetic resonance imaging (MRI) alone in patients on active surveillance is not accurate enough to reliably rule out or rule in prostate cancer progression. Other clinical factors and biomarkers along with serial MRI are required to safely tailor the intensity of follow-up biopsies.

1. Introduction

Active surveillance (AS) is a safe and increasingly utilized management strategy for low-risk and selected intermediate-risk prostate cancer (PCa) patients [1–3]. AS allows one to safely defer or avoid radical treatment without compromising cancer control provided that evidence of understaging or cancer progression can be identified in a timely manner [1–3]. To date, regular prostate biopsies remain the standard to assess changes in cancer grade and extent, but are a barrier to patient adherence and tolerability of AS [1,2]. A prostate biopsy is consistently identified by patients as the least pleasant aspect of AS and is also associated with healthcare expense as well as procedural risks such as bleeding, infection, discomfort, and urinary retention [4]. As a result, there is a sustained interest in developing increasingly noninvasive and cost-effective approaches that reliably identify disease progression [4–9].

Magnetic resonance imaging (MRI) of the prostate has been an extensively studied diagnostic tool for identifying significant PCa [10,11]. There has been a rapid implementation of prebiopsy MRI worldwide, which has followed efforts to standardize prostate MRI assessment reporting schemes and a large body of evidence indicating their accuracy [11]. For example, the most popular Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) classification, despite meaningful interobserver variability, achieves favorable diagnostic estimates, with negative predictive values (NPVs) reaching approximately 80% for clinically significant PCa (Gleason grade [GG] $\geq$2) [11]. Furthermore, the latest trials demonstrated a higher detection rate of significant PCa using MRI-targeted biopsy and when combining MRI-targeted with systematic transrectal ultrasound (TRUS) biopsies, than using standard TRUS biopsy alone [12–14]. Although the diagnostic accuracy of MRI is imperfect at identifying all clinically significant, the majority of tumors identified on systematic biopsy are of low grade [12,15]. Nonetheless, current guidelines suggest targeted and systematic biopsies when diagnostic MRI is suspicious [1,2]. This approach, although minimalizes the risk of missing MRI-invisible clinically significant PCa, continues to overdetect GG = 1 PCa, which increases the need for AS.

Many major centers and providers have increasingly adopted MRI as a surrogate for prostate biopsy in the AS setting to avoid unnecessary, uncomfortable, invasive, and possibly complication-associated biopsies [16,17]. With a growing reliance on prostate MRI as a surrogate for prostate biopsy during AS, there is an increasing need to define its diagnostic accuracy for detecting grade progression [18]. However, at present no clear statements on the diagnostic accuracy of MRI-guided AS can be drawn, as the data from real-life cohorts are heterogeneous and inconclusive [18–20]. In general, present evidence has shown reasonably high rates of discordance between serial MRI findings and prostate biopsy results [18,19]. There have been attempts to standardize serial prostate MRI reporting on AS, with recently developed and most recognized Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations [20,21]. To date, no comprehensive synthesis of the existing evidence has been conducted to clearly inform the accuracy of serial prostate MRI alone, assessed using PRECISE and institution-specific definitions, as a marker for PCa progression in patients on AS.

We aimed to perform a systematic review and meta-analysis of available studies analyzing the diagnostic utility of serial MRI in AS of PCa. Our goal was to summarize the present state of knowledge and provide pooled diagnostic estimates of MRI progression for PCa reclassification during AS, with special focus on PRECISE recommendations.

2. Evidence acquisition

2.1. Search strategy

We registered the study with the International Prospective Register of Systematic Reviews (registration number: CRD42021230724). This systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (PRISMA 2009 checklist, Supplementary Table 1). We queried the PubMed, Scopus, and Web of Science

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databases on January 11, 2021, to identify studies addressing the predictive role of serial (at least two scans) MRI for PCa progression during AS. The MRI scans had to been assessed at AS entry (either at diagnostic or at confirmatory biopsy). The search terms included the following: "prostate cancer", "MRI", "magnetic resonance imaging", and "active surveillance". Two investigators performed an independent initial screening based on the titles and abstracts, and noted the cause of exclusion of ineligible reports. Full texts were retrieved and evaluated for eligibility. In case of discrepancies, disagreements were solved by the authors' consensus.

2.2. Study selection

We included studies if these analyzed patients with PCa managed with AS (population) who underwent serial prostate MRI with MRI progression (intervention) comparing with patients without MRI progression (comparison). We analyzed diagnostic differences for PCa progression on AS (outcome) in prospective and retrospective studies (study design). PCa progression definition must have included GG progression (upgrading) to GG $\geq$2. Included reports provided true positives (TPs) defined as instances of both MRI progression and PCa progression, true negatives (TNs) regarded as stable or regressive MRI without PCa progression, false positives (FPs) regarded as MRI progression without PCa progression, and false negatives (FNs) regarded as stable or regressive MRI with PCa progression, which allowed us to construct 2 $\times$ 2 contingency tables. We considered studies eligible if patients underwent systematic and MRI-targeted biopsies. Reviews, meta-analyses, letters, editorials, meeting abstracts, authors' replies, case reports, and non-English articles were excluded. In case of duplicate publications, either the higher-quality or the most recent publication was selected. We scanned references of included manuscripts for additional studies of interest.

2.3. Data extraction

Two reviewers separately extracted data on baseline study and patients characteristics as well as the number of TPs, FPs, FNs, and TNs for the main outcome (PCa progression) and the secondary outcome (upgrading to GG $\geq$3). We further extracted data on the definition of MRI progression and categorized it into two categories: PRECISE and institution-specific (own) definitions. Disagreements were resolved at the authors' consensus meeting.

2.4. Quality assessment and risk of bias

The risk of bias of included studies was evaluated according to risk of bias with the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [22]. The index test was defined as MRI progression. PCa progression was used as a reference. We did not conduct a statistical assessment of bias, as this it is not recommended in diagnostic test accuracy meta-analysis [22].

2.5. Statistical analysis

All statistical analyses were performed using R version 4.0 (2020; R Foundation for Statistical Computing, Vienna, Austria) and Cochrane Collaboration Review Manager software (RevMan v.5.4; Cochrane Collaboration, Oxford, UK). Statistical significance was set at $p < 0.05$. Pooled sensitivity, specificity, positive predictive value (PPV), NPV, and diagnostics odds ratio (DOR) were calculated with "mada" and "meta" packages. Forest plots with 95% confidence interval (CI) were calculated and depicted. Cochrane Q test and the I^2 test were used to evaluate the heterogeneity. Significant heterogeneity was indicated by $p < 0.05$ in the Cochrane Q tests and $I^2 > 50\%$. We developed a hierarchical summary receiver operating curve (SROC) and calculated the area under the curve (AUC) to examine the diagnostic accuracy of MRI progression tested overall and defined using PRECISE criteria or institutional definitions. The bivariate random model that plotted sensitivity, specificity, PPV, NPV, and DOR was applied to compare PRECISE and other MRI progression definitions. A meta-ANOVA analysis was performed to assess the impact of moderating variables and examine potential sources of heterogeneity [23]. Various progression prevalence ranges (20–30%), previously described in the literature, were applied to calculate NPVs and PPVs to cover possible different clinical scenarios [1,7,24]. We further performed sensitivity analyses to increase homogeneity and confirm the reliability of our results. The first sensitivity analysis comprised studies that defined PCa progression as pathological progression (GG upgrading and/or increases in tumor volume), without any criterion of radiological or clinical progression. The second sensitivity analysis included studies that considered PCa progression only as GG upgrading. Furthermore, we performed a sensitivity analysis of studies, which included only patients diagnosed with GG1 at baseline. The sensitivity analysis was performed to avoid the impact of the variable proportions of GG2 patients in the included studies.

3. Evidence synthesis

3.1. Study selection and characteristics

The search string is depicted in Figure 1 (PRISMA flowchart). In total we included 15 studies with 2240 patients (Table 1) [17,20,25–37]. Three studies were prospective and 12 were retrospective. The inclusion criteria for AS differed between studies, but in general included low- and intermediate-risk PCa. PCa progression was defined as GG upgrading in all studies, with some studies also defined PCa progression as increases in tumor volume and/or core positivity (Table 2). Furthermore, in Dieffenbacher et al's [31] cohort, the definition of PCa progression also included increases in the prostate-specific antigen (PSA) level (11% of progression events), and in a study of Caglic et al [25] in 17% of patients PCa progression was determined due to MRI stage progression to T3. Seven studies included patients diag-

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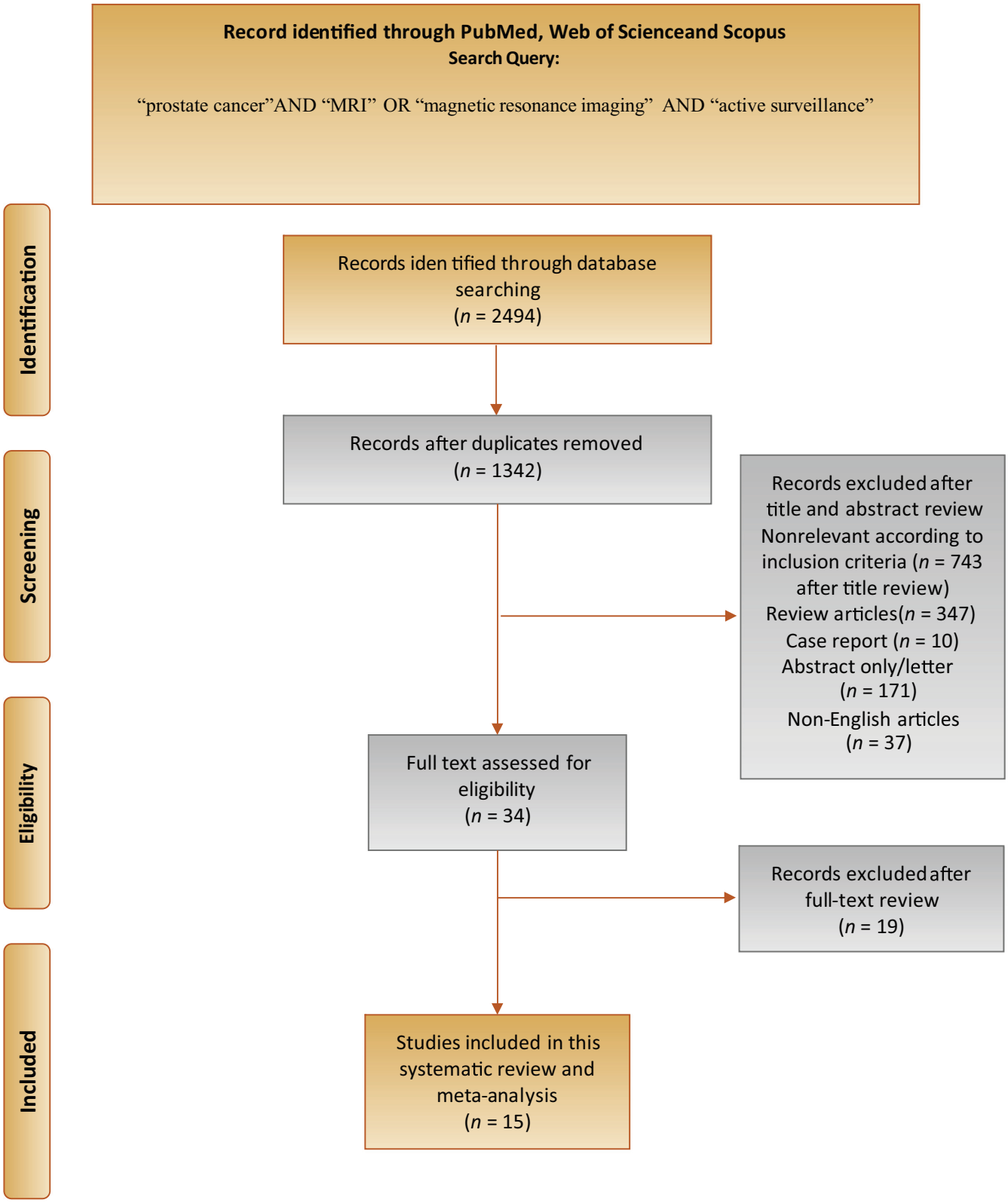

Fig. 1 – PRISMA flowchart. MRI = magnetic resonance imaging; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

nosed with both GG1 and GG2, while eight included patients with only GG1 PCa. MRI-targeted and systematic biopsies were considered as standard at entry and surveillance rebiopsy. Only one study included a significant proportion of patients who did not undergo MRI-targeted biopsy after baseline MRI [20]. The length of follow-up ranged from 12 to 74.5 mo. There was heterogeneity in terms of primary as well as serial MRI assessment reporting

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Table 1 – Characteristics of 15 included studies, which analyzed the association between serial MRI and PCa progression

Author [reference]	Year	Country	Design	Enrollment/ study period	*N*	AS eligibility criteria	GG1 (%)	GG2 (%)	Age (yr), median (IQR) [a]	PSA (ng/ml), median (IQR) [a]	PSAD (ng/ml/cc), median (IQR) [a]	FU (mo), median (IQR) [a]	Serial MRI assessment
Amin [17]	2020	USA	P	2012–2017	100	cT1–2, GG = 1, GG = 2 with <10% pattern 4, <2 cores involved with pattern 4	92	8	64.5 (57.25–69)	4.7 (3.4–6.6)	0.11 (0.08–0.15)	36 (25–39)	Institution specific
Caglic [25]	2021	UK	RP	2011–2018	295	Age 50–80, cT1–2, GG = 1, GG = 2 with <10% pattern 4, <50% of all cores, <50% core involvement and ≤2 cores involved with pattern 4, PSA ≤20 ng/ml	84	16	66 (61–69)	5.6 (4–7.9)	0.10 (0.07–0.16)	50 (33–67)	PRECISE
Chesnut [26]	2020	USA	RP	2013–2016	207	GG=1; NCCN low to very low risk	100	0	61 (57–66)	4.4 (3.6–5.5)	ND	49.2 (42–56.4)	Institution specific
Fujihara [27]	2020	USA	RP	ND	68	GG = 1, life expectancy >10 yr	100	0	62 (57–67)	4.8 (3.5–8.0)	0.10 (0.06–0.15)	33.6 (19.2–57.5)	Institution specific
Giganti [20]	2021	UK	RP	2005–2020	306	GG ≤2, PSA ≤20 ng/ml	80	20	62 (56–67)	6.3 (4.7–8.4)	0.12 (0.09–0.2)	74.5 (53–98)	PRECISE
O'Connor [28]	2020	USA	RP	2007–2020	391	GG = 1, GG = 2 without aggressive features on MRI	73.4	26.6	63 (58–68)	5.38 (3.95–7.87)	0.10 (0.07–0.14)	35.6 (19.7–60.6)	PRECISE
Osses [29]	2020	The Netherlands	RP	2013–2019	111	GG = 1	100	0	66 (60–70)	6.8 (5.1–9.1)	0.17 (0.11–0.25)	33 [b]	PRECISE
Ullrich [30]	2020	Germany	RP	2011–2017	55	GG ≤2	76.4	23.6	Mean 66 (SD 7)	7.3 (4.9–9.7)	0.17 (0.11–0.27)	19 (13–33)	PRECISE
Dieffenbacher [31]	2021	Germany	RP	2010–2018	158	cT1c-T2a, GG = 1 with ≤3 cores involved, PSA <10 ng/ml, PSAD ≤0.2 ng/ml/cc	100	0	Initial systematic biopsy: 69 (64–75); initial fusion biopsy: 69 (64–74)	Initial systematic biopsy: 6.2 (4.7–7.7); initial fusion biopsy: 5.8 (4.5–7.0)	Initial systematic biopsy: 0.15 (0.09–0.22); initial fusion biopsy: 0.15 (0.10–0.20)	Initial systematic biopsy: 12 (9–16); initial fusion biopsy: 22 (20–25)	PRECISE
Hsiang [32]	2021	USA	RP	2012–2018	122	Low-risk PCa	100	0	63 (57–68)	5.6 (4.1–7.6)	0.11 (0.07–0.15)	13.5 (12.3–17.7)	Institution specific
Elkjaer [33]	2018	Denmark	P	2014–2016	50	<cT2b, GG = 1, <4 cores involved, <50% core involvement, PSA <10 ng/ml	100	0	66 (62–69)	Mean 6.4 (95% CI 5.8–6.9)	ND	1-yr follow-up	Institution specific
Thurtle [34]	2018	UK	P	2011–2015	104	cT1-T2, GG ≤2, <50% core involvement, ECOG ≤1, PSA ≤20 ng/ml	85.5	14.5	64 (59–68)	6.8 (5.2–9.4)	0.13 (0.09–0.18)	39 (27–51)	Institution specific
Frye [35]	2017	USA	R	2007–2015	166	GG = 1, GG = 2 with <33% cores involved	77.1	22.9	Low risk: 61.7 (SD 6.6); intermediate risk: 65.7 (SD 6.7)	Low risk: 5.69 (SD 4.19); intermediate risk: 6.16 (SD 3.54)	Low risk: 0.12 (SD 0.09); intermediate risk: 0.13 (SD 0.08)	Mean 25.5 (range: 3.2–96.4)	Institution specific
Felker [36]	2016	USA	RP	2011–2015	49	GG = 1	100	0	Mean 65.4 (SD 8.0)	5.0 (4.0)	Mean 0.10 (SD 0.08)	Mean 28.3 (range: 11–43) mo	Institution specific
Walton Diaz [37]	2015	USA	R	2007–2014	58	cT1c, GG = 1, ≤2 cores involved, ≤50% core involvement, PSAD ≤0.15 ng/ml/cc	100	0	Mean 61.4 (SD 7.1)	Mean 5.2 (SD 3.2)	Mean 0.09 (SD 0.03)	16.1 (range: 12–56)	Institution specific

AS = active surveillance; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GG = Gleason grade; IQR = interquartile range; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; *N* = number; ND = no data; PCa = prostate cancer; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; PSA = prostate-specific antigen; PSAD = PSA density; P = prospective; R = retrospective; RP = retrospective assessment of prospective study; SD = standard deviation.

[a] Unless specified otherwise.

[b] Outcome measured at 1-yr surveillance.

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Table 2 – MRI assessment and PCa progression in included studies

Author [reference]	Year	MRI modality	Primary MRI assessment category	Experience	MRI timing	Baseline biopsy	MRI interval	Rebiopsy type	Serial MRI assessment	MRI progression definition	PCa progression (%)	PCa progression definition
Amin [17]	2020	3 T mpMRI	PI-RADS v1	2 radiologists; experience: >1000 mpMRI scans	Baseline	MRI targeted, systematic, template biopsies	Annual	MRI targeted, systematic, template biopsies	Institution specific	Increase in PI-RADS, persistent PI-RADS 4/5 lesion	21	GG ≥2, >10% pattern 4, >2 cores with pattern 4
Caglic [25]	2021	1.5 or 3 T mpMRI	Likert	2 radiologists; experience: 10 and 13 yr	Baseline	MRI targeted, systematic	Annual	MRI targeted, systematic	PRECISE	PRECISE ≥4 [a]	14	GG upgrade, not meeting initial AS criteria, T3 on MRI
Chesnut [26]	2020	3 T mpMRI	Likert, PI-RADS v2	6 radiologists: specializing in genitourinary radiology	Baseline or confirmatory biopsy	MRI targeted, systematic	18 mo	MRI targeted, systematic	Institution specific	Increase in MRI score, new EPE	32	GG ≥2
Fujihara [27]	2020	3 T mpMRI	PI-RADS v1, v2, v2.1	2 urologists; experience: >1000 MRI biopsies, >10 yr	Baseline [b]	MRI targeted, systematic	12–24 mo, and based on clinical factors	MRI targeted, systematic	Institution specific	Increase in suspicion score, increase in volume, ADC decrease	19	GG ≥2
Giganti [20]	2021	1.5 or 3 T mpMRI	PI-RADS v2	1 radiologist; experience: >7 yr	Baseline	MRI targeted [c], systematic	12–24 mo, and based on clinical factors	MRI targeted systematic	PRECISE	PRECISE ≥4	42	GG upgrade
O'Connor [28]	2020	3 T mpMRI	PI-RADS v2, NIH	2 radiologists; experience: >13 yr	Baseline [d]	MRI targeted, systematic	12–24 mo	MRI targeted, systematic	PRECISE	PRECISE ≥4	20	GG ≥2
Osses [29]	2020	3 T mpMRI	PI-RADS v1, v2	1 radiologist; experience: >7 yr	Baseline	MRI targeted, systematic	Annual	MRI targeted, systematic	PRECISE	PRECISE ≥4	32	GG ≥2
Ullrich [30]	2020	3 T mpMRI	PI-RADS v2.1	2 radiologists; experience: 5 and 10 yr	Baseline or confirmatory biopsy	MRI targeted, systematic	Median 19 (IQR 13–33) mo	MRI targeted, systematic	PRECISE	PRECISE ≥4	53	GG upgrade
Dieffenbacher [31]	2021	3 T mpMRI	PI-RADS v2	2 radiologists; experience: >12 yr	Baseline or confirmatory biopsy	MRI targeted, extended systematic	12–24 mo	MRI targeted, extended systematic	PRECISE	PRECISE ≥4	18	GG ≥2, >2 cancer cores, PSAD >0.2 ng/ml, PSA >10 ng/ml, cT2b
Hsiang [32]	2021	3 T mpMRI	Likert, PI-RADS v2	1 experienced radiologist	Baseline	MRI targeted, systematic	Median 13.5 (12.3–17.7) mo	MRI targeted, systematic	Institution specific	PI-RADS increase, increase in the number of ROIs, lesion volume doubling	24	GG ≥2
Elkjaer [33]	2018	3 T mpMRI	PI-RADS v2	1 radiologist; experience: >10 yr	Baseline	MRI targeted, systematic	Annual	MRI targeted, systematic	Institution specific	New PI-RADS 4-5 lesion	20	GG ≥2, >3 cancer cores, >50% core involvement

Table 2 (*Continued*)

Author [reference]	Year	MRI modality	Primary MRI assessment category	Experience	MRI timing	Baseline biopsy	MRI interval	Rebiopsy type	Serial MRI assessment	MRI progression definition	PCa progression (%)	PCa progression definition
Thurtle [34]	2018	1.5 or 3 T mpMRI	Likert, Pi-RADS v1, v2	Expert radiologist	Baseline	MRI targeted, systematic	Annual	MRI targeted, systematic	Institution specific	Increase in the number of lesion, lesion size, stage progression	19	GG upgrade
Frye [35]	2017	3 T mpMRI	Institution specific	2 radiologists; experience: 9 and 12 yr	Baseline	MRI targeted, systematic	Annual	MRI targeted, systematic	Institution specific	Increase in suspicion score, lesion diameter, appearance of new lesion	30	GG upgrade
Felker [36]	2016	3 T mpMRI	Institution specific	2 radiologists; experience: >1000 prostate MRI scans	Baseline	MRI targeted, systematic	Mean 28.3 (range 11–43) mo	MRI targeted, systematic	Institution specific	Increase in suspicion score, increase in volume, ADC decrease	39	GG ≥2
Walton Diaz [37]	2015	3 T mpMRI	Institution specific	2 radiologists; experience: 7 and 14 yr	Confirmatory biopsy	MRI targeted, systematic	Median 16.1 (range 12–56) mo	MRI targeted, systematic	Institution specific	Increase in suspicion score, lesion diameter, lesion number	29	GG ≥2

ADC = apparent diffusion coefficient; AS = active surveillance; EPE = extraprostatic extension; GG = Gleason grade; IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; PSA = prostate-specific antigen; PSAD = PSA density; ROI = region of interest.

[a] before PRECISE era: increase in the number of lesion, lesion size, and stage progression.

[b] In 19% from the primary cohort (others not specified).

[c] 20% at entry.

[d] In 36.3% (others not specified).

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schemes. Six studies (40%) assessed surveillance MRI in line with PRECISE recommendations, while nine (60%) used institution-specific definitions of MRI progression. The PCa progression rates ranged from 14% to 53%, and upgrading to GG ≥3 ranged from 3% to 14%. There were significant differences in terms of MRI intervals.

The summary of the risk of bias and applicability concerns is presented in Figure 2. Authors' judgments about each domain for each included study are represented in Supplementary Figure 1. Overall, in retrospective studies, which used their definition of MRI progression, the risk of bias of index test was high. There was an unclear risk of bias as to reference standard because included studies did not indicate whether pathologists were blinded to serial MRI results.

3.2. Meta-analysis

3.2.1. MRI progression in all studies

The diagnostic variables of the included studies are presented in Table 3. The pooled PCa progression rate was 27%. There was significant heterogeneity between included studies (Fig. 3 and 4). Forest plots revealed that the pooled sensitivity, specificity, PPV, and NPV were 0.587 (95% CI 0.442–0.733), 0.750 (95% CI 0.660–0.840), 0.496 (95% CI 0.384–0.608), and 0.848 (95% CI 0.802–0.893), respectively. The pooled DOR was 4.950 (95% CI 2.746–8.966). We constructed an SROC curve (Fig. 5), and MRI progression reached an AUC of 0.73 for the detection of PCa progression.

3.2.2. MRI progression by assessment definition

To further explore the diagnostic accuracy of MRI progression across varying definitions and standardized reporting scheme (PRECISE), we calculated pooled estimates and compared them in bivariate analyses (Fig. 3 and 4). For PRECISE, pooled sensitivity, specificity, PPV, NPV, and DOR were 0.658 (95% CI 0.440–0.875), 0.732 (95% CI 0.599–0.866), 0.505 (95% CI 0.314–0.695), 0.877 (95% CI 0.811–0.944), and 7.234 (95% CI 2.340–22.367), respectively. Simultaneously, we compared PRECISE with the pooled results of studies that used institutional definitions of MRI progression. For institution-specific analyses, the results were as follows: pooled sensitivity 0.534 (95% CI 0.391–0.678), pooled specificity 0.762 (95% CI 0.632–0.892), pooled PPV 0.491 (95% CI 0.339–0.643), pooled NPV 0.825 (95% CI 0.768–882), and pooled DOR 3.600 (95% CI 1.946–6.659). There were no significant differences between PRECISE and institutional definitions for pooled sensitivity ($p = 0.37$), specificity ($p = 0.74$), PPV ($p = 0.92$), NPV ($p = 0.24$), and DOR ($p = 0.37$). The SROC curve derived from the bivariate model is presented in Figure 6. The AUC values

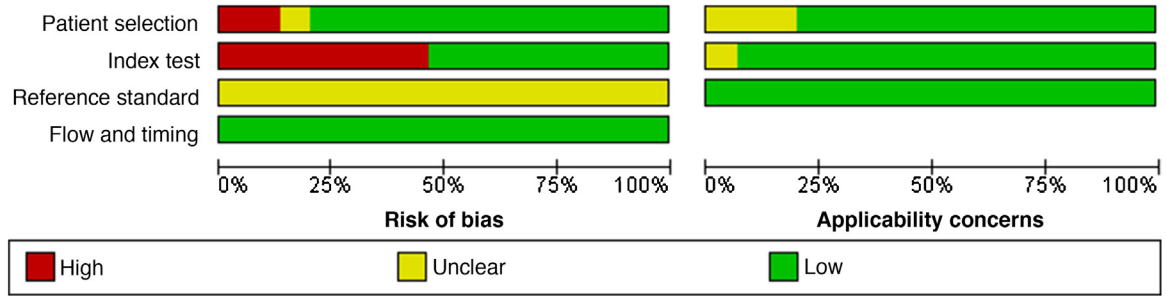

Fig. 2 – Graph of risk of bias and applicability concerns: review authors' judgments about each domain presented as percentages across included studies.

Table 3 – Diagnostic performance of MRI progression in included studies

Author [reference]	Serial MRI assessment	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV
Amin [17]	Institution specific	13	16	8	63	0.62	0.80	0.45	0.89
Caglic [25]	PRECISE	31	29	10	225	0.76	0.89	0.52	0.96
Chesnut [26]	Institution specific	20	28	46	113	0.30	0.80	0.42	0.71
Fujihara [27]	Institution specific	8	17	5	38	0.62	0.69	0.32	0.88
Giganti [20]	PRECISE	109	62	19	116	0.85	0.65	0.64	0.86
O'Connor [a] [28]	PRECISE	64	204	58	295	0.53	0.59	0.24	0.84
Osses [29]	PRECISE	7	10	28	66	0.20	0.87	0.41	0.70
Ullrich [30]	PRECISE	29	15	0	11	1.00	0.42	0.66	1.00
Dieffenbacher [31]	PRECISE	17	13	12	116	0.59	0.90	0.57	0.91
Hsiang [32]	Institution specific	12	42	17	51	0.41	0.55	0.22	0.75
Elkjaer [33]	Institution specific	7	0	3	40	0.70	1.00	1.00	0.93
Thurtle [34]	Institution specific	10	10	10	74	0.50	0.88	0.50	0.88
Frye [35]	Institution specific	39	68	10	49	0.80	0.42	0.36	0.83
Felker [36]	Institution specific	7	3	12	27	0.37	0.90	0.70	0.69
Walton Diaz [37]	Institution specific	9	8	8	33	0.53	0.80	0.53	0.80

FN = false negative; FP = false positive; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; TN = true negative; TP = true positive.
[a] Data provided for MRI intervals.

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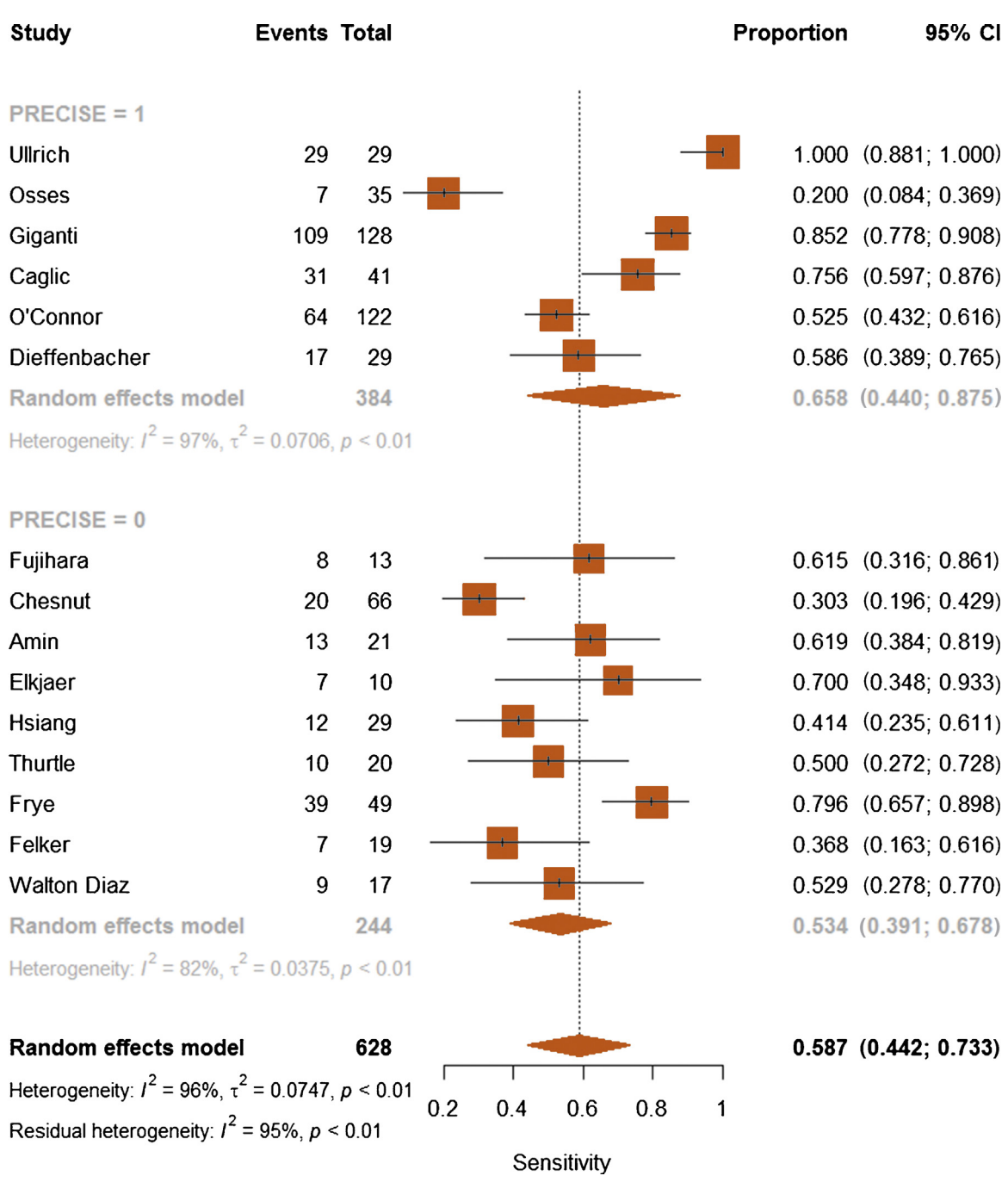

Fig. 3 – Forest plots for pooled sensitivity or all studies, stratified by serial MRI assessment reporting scheme type. PRECISE = 1 indicates studies using PRECISE recommendations for MRI progression, and PRECISE = 0 indicates studies using institution-specific definitions of MRI progression. CI = confidence interval; MRI = magnetic resonance imaging; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

were 0.79 for PRECISE and 0.67 for institution-specific definitions of MRI progression.

Considering NPV variability and its inverse association with disease prevalence, we adjusted and calculated pooled estimates for previously reported ranges of pathological progression (Supplementary Table 2) [1,2,24,38]. Setting prevalent PCa progression at 20%, the pooled NPVs of MRI progression using PRECISE recommendations and institutional-specific definitions were 0.896 (95% CI 0.810–0.965) and 0.868 (95% CI 0.806–0.918), respectively. When adjusted at a rate of 30%, the pooled NPVs of MRI progression were 0.833 (95% CI 0.714–0.942) for PRECISE and 0.791 (95% CI 0.710–0.870) for institutions-specific definitions. For all studies, PPV ranged from 0.369 (95% CI 0.244–0.535) to 0.501 (95% CI 0.358–0.662).

3.2.3. *MRI progression for upgrading to GG ≥3*

Four studies provided specific data on GG upgrading to GG ≥3 disease (Supplementary Table 3). The pooled incidence of progression to GG ≥3 was 8%. Two studies included only

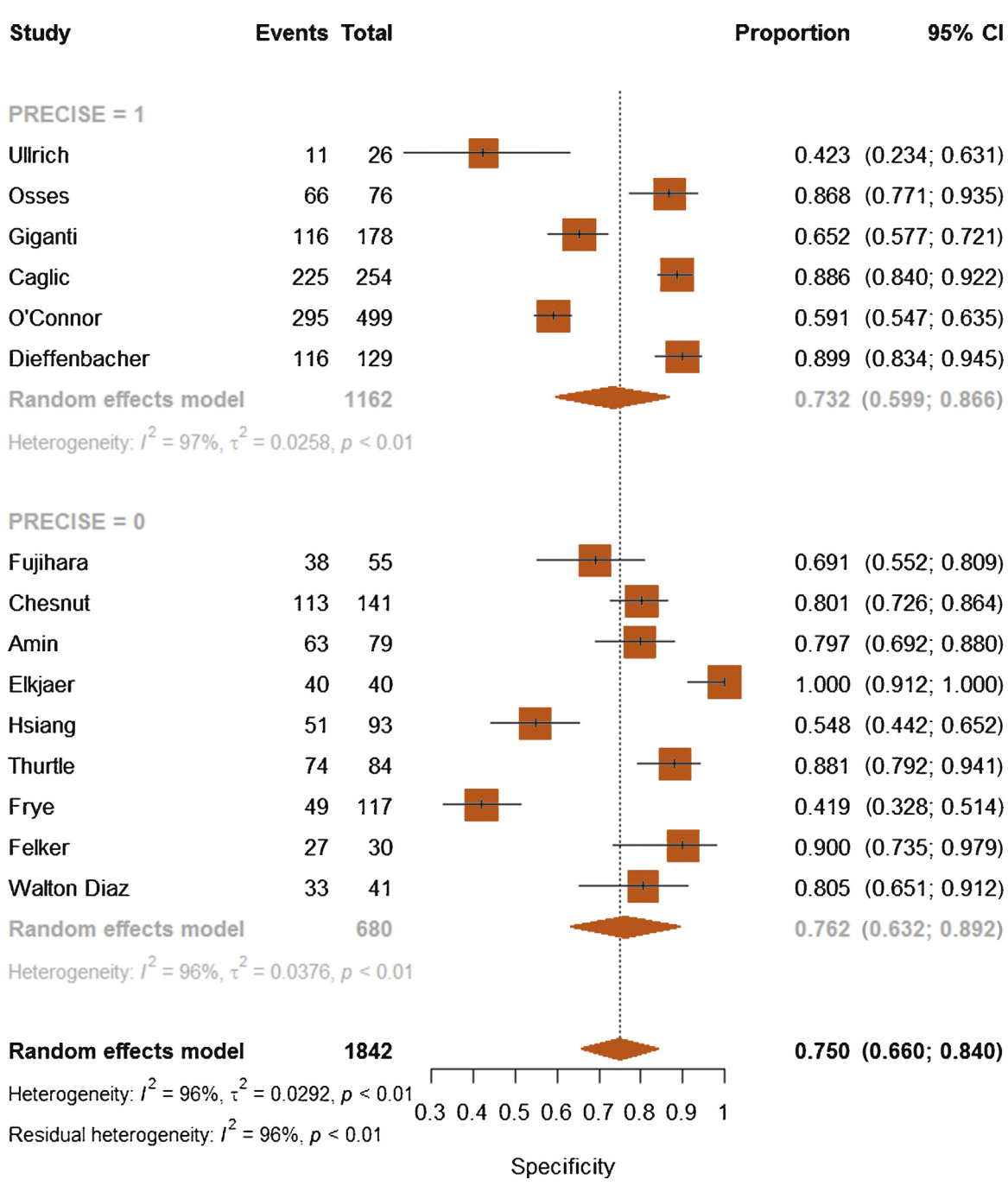

Fig. 4 – Forest plots for pooled specificity or all studies, stratified by serial MRI assessment reporting scheme type. PRECISE = 1 indicates studies using PRECISE recommendations for MRI progression, and PRECISE = 0 indicates studies using institution-specific definitions of MRI progression. CI = confidence interval; MRI = magnetic resonance imaging; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

GG1, and two both GG1 and GG2 patients. For MRI progression, pooled estimates were as follows: sensitivity 0.695 (95% CI 0.465–0.925), specificity 0.619 (95% CI 0.446–0.793), PPV 0.134 (95% CI 0.059–0.209), NPV 0.954 (95% CI 0.907–0.100), and DOR 2.801 (95% CI 1.391–5.644). The AUC calculated from the SROC curve was 0.65.

3.2.4. *Sensitivity analyses*

3.2.4.1. MRI progression for PCa progression defined only as pathological progression. To exclude the possible impact of nonpathological features on PCa progression, we excluded two studies using PRECISE criteria, in which PCa progression was defined using clinical, and not biopsy, features in 11% and 17% of patients [25,31]. This approach resulted in the inclusion of 13 studies, out of which four used PRECISE recommendations (Table 2). The pooled results from 13 studies followed a similar pattern for the pooled sensitivity, specificity, PPV, NPV, and DOR: 0.574 (95% CI 0.410–0.737), 0.726 (95% CI 0.615–0.836), 0.490 (95% CI 0.364–0.615), 0.832 (95% CI 0.789–0.875), and 3.801 (95% CI

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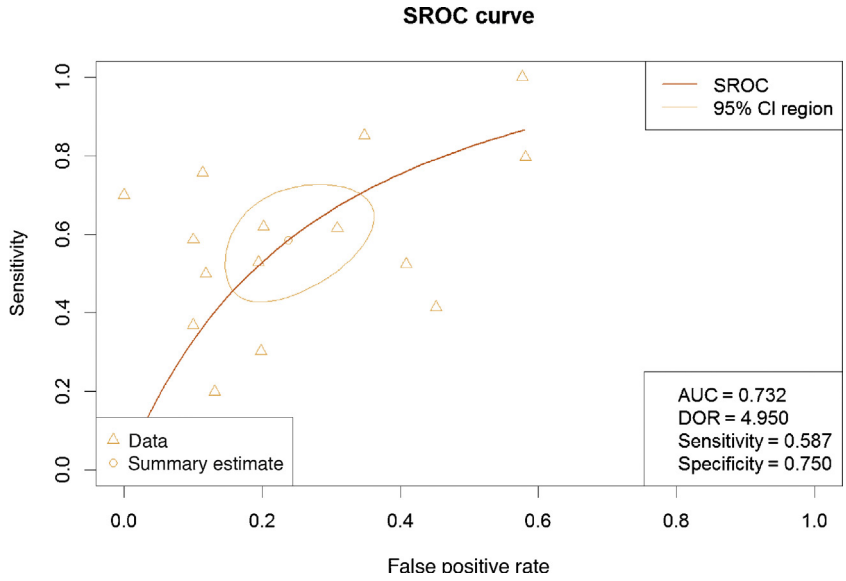

Fig. 5 – Summary receiver operating characteristic curve for all studies. PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

2.165–6.671), respectively. The AUC calculated from the SROC curve was 0.70. For four studies, which used PRECISE recommendations, the pooled results also did not significantly differ from institution-specific definitions and were as follows: sensitivity 0.650 (95% CI 0.367–0.933, $p = 0.49$), specificity 0.680 (95% CI 0.503–0.793, $p = 0.29$), PPV 0.487 (95% CI 0.226–0.748, $p = 0.97$), NPV 0.844 (95% CI 0.764–0.925, $p = 0.71$), and DOR 4.323 (95% CI 1.160–16.107, $p = 0.92$).

3.2.4.2. MRI progression for PCa progression defined only as GG upgrading. For further sensitivity analysis, we excluded two studies that used the criterion of PCa volume progression [17,33]. This approach resulted in the inclusion of 11 studies that used GG upgrading as the only definition of PCa progression (Table 2). The pooled diagnostic estimates remained similar and were as follows: sensitivity 0.559 (95% CI 0.379–0.740), specificity 0.694 (95% CI 0.598–0.790), PPV 0.445 (95% CI 0.325–0.565), NPV 0.817 (95% CI 0.769–0.864), and DOR 3.217 (95% CI 1.816–5.698). The AUC calculated from the SROC curve was 0.69. There were no significant differences between studies using PRECISE recommendations and institution-specific definitions for sensitivity ($p = 0.4$), specificity ($p = 0.48$), PPV ($p = 0.64$), NPV ($p = 0.37$), and DOR ($p = 0.63$).

3.2.4.3. MRI progression in AS patients with GG1 PCa. We conducted a sensitivity analysis of eight studies that included only patients with GG1 PCa at AS entry. In this subset, the pooled PCa progression rate was 27%. In this more homogeneous subgroup, MRI progression had pooled sensitivity of 0.439 (95% CI 0.319–0.559), specificity of 0.819 (95% CI 0.723–0.915), PPV of 0.516 (95% CI 0.326–0.706), NPV of 0.803 (95% CI 0.729–0.877), and DOR of 3.629 (95% CI 1.635–8.055). The AUC calculated from the SROC curve was 0.65.

3.3. *Discussion*

We present the first systematic review and meta-analysis that analyzed the diagnostic estimates of prostate MRI progression during AS, defined using PRECISE criteria as well as other definitions. Our study reports several key findings. First, serial MRI, despite favorable diagnostic performance, is not accurate enough to exclude PCa progression during AS, although it had a high NPV for excluding upgradation to GG $\geq$3 disease. Second, considering the marginal PPVs for identifying disease progression, MRI progression alone should not be the only trigger for biopsy but needs to be considered among other clinical factors in a decision-making process. Third, the pooled diagnostic estimates of PRECISE were similar to the definitions of MRI progression at individual expert centers. Overall, the consistency of these findings, including sensitivity analyses among selected subsets that more directly assessed pathological upgrade, implies reliability and robustness of these results.

Our pooled results, across all tested PCa progression prevalence, suggest that MRI-guided AS in 1000 men would result in avoidance of biopsy in 649–683 patients, while missing the detection of PCa progression in 83–124 men. Moreover, 175–200 biopsies out of 317–351 solely triggered by MRI progression would be considered negative for PCa progression. A recent diagnostic meta-analysis made a call for international standardization of serial MRI assessment in favor of PRECISE recommendations [19]. Considering our meta-analysis, there was a nonsignificant trend toward improved performance of PRECISE recommendations, with up to 654 biopsies avoided and risk of up to 103 PCa progressions missed. Of note, similar results were obtained in the sensitivity analyses. Despite no statistically significant differences in pooled individual diagnostic estimates

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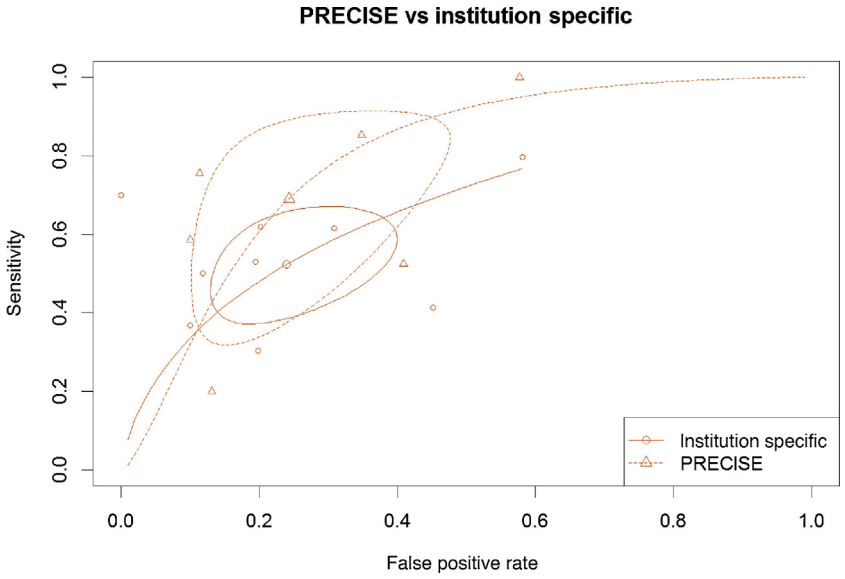

Fig. 6 – Summary receiver operating characteristic (SROC) curve (bivariate model). AUC = area under the curve; CI = confidence interval; DOR = diagnostics odds ratio; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

between PRECISE and institution-specific definitions, PRECISE is so far the most reliable tool to limit intrareader variability and standardize reporting of serial MRI during AS [20,21,39].

Present studies indicate the utility of MRI implementation in AS protocols as it allows improved patient selection and lowers the rates of AS disqualification while maintaining noninferior oncological outcomes [14,40]. Clinical utility of prostate MRI may be augmented by the integration of other tools including biomarkers [41,42]. Indeed, some of the established biomarkers that are readily available achieve similar and/or complementary diagnostic estimates. For example, in the study of Hsiang et al [32], PSA density (PSAD) ≥0.15 at follow-up had a higher NPV (0.807, 95% CI 0.746–0.856) than MRI progression for excluding PCa upgrading (0.750, 95% CI 0.677–0.810). Similarly, Felker et al [36] found that PSAD (AUC: 0.80, NPV: 0.81, 95% CI 0.64–0.92) outperformed MRI progression (AUC: 0.63, NPV: 0.70, 95% CI 0.34–0.93) for significant PCa prediction and exclusion, and combination of MRI with clinicopathological variables led to the improvement of diagnostic estimates (AUC: 0.91, NPV: 0.96, 95% CI 0.77–0.99). Of note, in a study of Giganti et al [20], the kinetics of PSAD was significantly associated with PRECISE ≥4. There is also a growing interest in dedicated MRI reading software programs and radiomics, which may further improve diagnostic estimates of serial MRI [43,44]. On the contrary, our results imply that presently serial MRI is a robust stand-alone tool for GG ≥3 cancer exclusion, which parallels higher primary detection of GG ≥3 cancers by MRI and lower rates of PCa progression to GG ≥3 [12]. Furthermore, in a recent study of Chu et al [45], published after our formal literature search, both consistently visible and increasingly suspicious lesions were associated with GG ≥2 detection and definitive treatment.

However, in some clinical settings, a risk of missing cancer progression up to 15–20%, which was determined by our results, may be acceptable. In a microsimulation model, de Carvalho et al [46] found that among low-risk PCa patients over 65 yr of age, even one biopsy round reduced quality-adjusted life years (QALYs). In addition, Loeb et al [6] found that patients over 65-yr of age did not significantly benefit from AS, comparing with watchful waiting in terms of QALYs. Therefore, in specific scenarios, serial MRI may replace prostate biopsies and allow for relaxed AS, bearing in mind the chance of a missed or delayed diagnosis of PCa progression. Stavrinides et al [16] analyzed a 5-yr outcome of MRI-based AS, in which serial MRI replaced repetitive biopsies in AS protocol, which were performed in cases of MRI, clinical, or PSA progression. During a median of 58 (interquartile range 37–82) mo, active treatment uptake and metastasis were similar to those of previously described cohorts, which included scheduled prostate biopsies [16]. These suggest that in a short-term period, MRI and clinically driven AS could be safe. Long-term outcomes of this approach should be evaluated further, acknowledging the fact that 10–20% of PCa lesions are invisible on MRI, and they may harbor aggressive genetic aberrations with metastatic potential [11,47].

There is an association between prostate MRI reading and radiologists' experience, which is minimalized by the implementation of standardized reporting schemes [11,21,48]. In general, in all included studies, MRI assessments were reported to be performed by experienced radiologists, and therefore these results can have limited applicability to the general community. Furthermore, recently Giganti et al [49] introduced the Prostate Imaging Quality (PI-QUAL) system, which scores MRI quality, and revealed that only 60% of all MRI scans in the PRECISION trial had at least good quality. These emphasize the role of

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MRI quality itself and underline the need for a better quality program assessment for MRI reading. Despite a trend toward improved diagnostic estimates of PRECISE recommendations, our findings indicate that at present, there are some technical boundaries of prostate MRI and its assessment, which do not allow achievement of sufficient diagnostic performance to determine PCa progression during AS [20,21]. Standardization of MRI reports in AS follow-up is a key element [21]. It is crucial to follow PRECISE recommendations and fulfill case reports to minimalize unstandardized comparisons. Furthermore, there is still no consensus on which measurements are most reliable to assess MRI progression (ellipsoid formula, volume by planimetry, biaxial measurements of maximum diameters on an axial slice, or single measurement of maximum diameter), and we believe that they should all be reported routinely and in future studies [21]. Therefore, before the broad implementation of MRI-guided AS, the credibility of serial MRI reading and quality, optimal MRI triggers, and intervals must be studied further.

3.3.1. *Limitations*

Our study has some limitations. First of all, most of the included studies were retrospective and associated with a meaningful risk of bias. Moreover, in studies using the standardized reporting scheme, some patients were enrolled between the formal publication of PRECISE recommendations, and MRI scoring was done retrospectively. Furthermore, MRI progression definitions, MRI protocols, and the AS protocols differed between studies. We found significant heterogeneity between included studies in terms of diagnostic performances of serial MRI. Finally, most studies analyzed well-established AS cohorts with MRI evaluated only by experienced radiologists specialized in prostate imaging; these results may thus not apply to the general community.

4. Conclusions

Serial prostate MRI, despite its central role in AS, cannot be a stand-alone factor for excluding PCa progression and triggering a rebiopsy in PCa patients on AS. Our results suggest that MRI-guided AS in 1000 men would result in the avoidance of follow-up biopsy in up to 683 patients, while missing up to 124 cases of PCa progression. PRECISE recommendations offer some improvements in serial MRI assessment; however, at present, other clinical factors along with serial MRI are required to tailor AS and follow-up biopsies safely. Prospective large-cohort studies are needed to further determine the reliability of serial MRI to detect PCa progression.

***Author contributions*:** Pawel Rajwa had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rajwa, Pradere, Shariat, Ploussard.
Acquisition of data: Rajwa, Pradere.
Analysis and interpretation of data: Rajwa, Pradere, Krzywon, Shim, Ploussard.
Drafting of the manuscript: Rajwa, Pradere, Quhal, Mori, Laukhtina, Huebner, Ploussard.
Critical revision of the manuscript for important intellectual content: Baltzer, Renard-Penna, Leapman, Shariat.
Statistical analysis: Rajwa, Krzywon, Shim, D'Andrea.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Shariat, Ploussard.
Other: None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2021.05.001.

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