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Guidelines

What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel

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Abstract

Context: It remains unclear whether patients with a suspicion of prostate cancer (PCa) and negative multiparametric magnetic resonance imaging (mpMRI) can safely obviate prostate biopsy.
Objective: To systematically review the literature assessing the negative predictive value (NPV) of mpMRI in patients with a suspicion of PCa.
Evidence acquisition: The Embase, Medline, and Cochrane databases were searched up to February 2016. Studies reporting prebiopsy mpMRI results using transrectal or transperineal biopsy as a reference standard were included. We further selected for meta-analysis studies with at least 10-core biopsies as the reference standard, mpMRI comprising at least T2-weighted and diffusion-weighted imaging, positive mpMRI defined as a Prostate Imaging Reporting Data System/Likert score of ≥3/5 or ≥4/5,

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Prostate biopsy
Risk stratification

and results reported at patient level for the detection of overall PCa or clinically significant PCa (csPCa) defined as Gleason ≥7 cancer.
Evidence synthesis: A total of 48 studies (9613 patients) were eligible for inclusion. At patient level, the median prevalence was 50.4% (interquartile range [IQR], 36.4–57.7%) for overall cancer and 32.9% (IQR, 28.1–37.2%) for csPCa. The median mpMRI NPV was 82.4% (IQR, 69.0–92.4%) for overall cancer and 88.1% (IQR, 85.7–92.3) for csPCa. NPV significantly decreased when cancer prevalence increased, for overall cancer ($r = -0.64$, $p < 0.0001$) and csPCa ($r = -0.75$, $p = 0.032$). Eight studies fulfilled the inclusion criteria for meta-analysis. Seven reported results for overall PCa. When the overall PCa prevalence increased from 30% to 60%, the combined NPV estimates decreased from 88% (95% confidence interval [95% CI], 77–99%) to 67% (95% CI, 56–79%) for a cut-off score of 3/5. Only one study selected for meta-analysis reported results for Gleason ≥7 cancers, with a positive biopsy rate of 29.3%. The corresponding NPV for a cut-off score of ≥3/5 was 87.9%.
Conclusions: The NPV of mpMRI varied greatly depending on study design, cancer prevalence, and definitions of positive mpMRI and csPCa. As cancer prevalence was highly variable among series, risk stratification of patients should be the initial step before considering prebiopsy mpMRI and defining those in whom biopsy may be omitted when the mpMRI is negative.
Patient summary: This systematic review examined if multiparametric magnetic resonance imaging (MRI) scan can be used to reliably predict the absence of prostate cancer in patients suspected of having prostate cancer, thereby avoiding a prostate biopsy. The results suggest that whilst it is a promising tool, it is not accurate enough to replace prostate biopsy in such patients, mainly because its accuracy is variable and influenced by the prostate cancer risk. However, its performance can be enhanced if there were more accurate ways of determining the risk of having prostate cancer. When such tools are available, it should be possible to use an MRI scan to avoid biopsy in patients at a low risk of prostate cancer.

1. Introduction

A correlation with radical prostatectomy specimens has demonstrated that multiparametric magnetic resonance imaging (mpMRI) has excellent sensitivity in detecting prostate cancer (PCa) with a Gleason score of ≥7 [1–3]. As a result, prostate mpMRI is increasingly used in patients with a suspicion of PCa to localise abnormal areas before biopsy. A large body of literature has shown that targeted biopsies of suspicious lesions seen on mpMRI (TBx) improved the detection of clinically significant PCa (csPCa), at least in the repeat biopsy setting [4–6]. As a result, it is now recommended that an mpMRI is performed before repeat biopsy to allow TBx of suspicious lesions in addition to standard biopsies [7].

Some authors have recently suggested that, besides improving csPCa detection, mpMRI could also be used as a triage test so that patients with negative mpMRI findings could obviate biopsy. Such a strategy remains highly controversial [8] and depends upon the negative predictive value (NPV) of mpMRI. Therefore, the European Association of Urology Prostate Cancer Guidelines Panel undertook this systematic review and meta-analysis to assess the NPV of mpMRI in patients with a suspicion of PCa and, thus, its potential role in eliminating unnecessary prostate biopsy.

2. Evidence acquisition

2.1. Objective

Our primary aim was to systematically evaluate the performance of negative prebiopsy prostate mpMRI in predicting a negative biopsy result for overall PCa and csPCa in biopsy-naïve men and in men with previously negative biopsies. A further objective was to explore and define factors that may contribute to relevant thresholds in order to provide guidance for future studies.

2.2. Data acquisition and search strategy

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [9]. The review protocol was published in PROSPERO database (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42015021929). Databases searched included the Embase and OVID Medline databases, the Cochrane database of systematic reviews, and the Cochrane Central Register for Clinical Trials, covering from January 1, 2000 to February 13, 2016. Systematic or standard prostate biopsies were used as reference standards, with positive or negative cases of PCa being determined by histopathological examination. The detailed search strategy is presented in Supplement 1.

2.3. Inclusion and exclusion criteria

Included studies focused on men who were assessed for suspected PCa by mpMRI before undergoing prostate biopsy. Studies enrolling both biopsy-naïve men and men who had undergone previous negative biopsies were included. Prebiopsy prostate mpMRI was considered the index test and comprised T2-weighted imaging (T2WI) and at least one functional imaging technique (diffusion-weighted imaging [DWI], dynamic contrast-enhanced imaging [DCEI], or magnetic resonance spectroscopic imaging [MRSI]). For inclusion, studies had to report on

false negatives and true negatives, in order to calculate NPV (ie, results of systematic/standard prostate biopsies when the mpMRI was negative). When available, false positive and true positive findings were also noted to calculate the positive predictive value (PPV) and the cancer prevalence. There was restriction neither on the biopsy technique (transrectal or transperineal) nor on the number of biopsy cores. Studies using radical prostatectomy specimens as reference standards were excluded, as were studies evaluating men with histologically proven PCa. Studies with less than 50 participants were excluded. No language restrictions were applied.

2.4. Data collection and data extraction

Two reviewers (P.C.M. and T.V.D.B.) independently screened all abstracts and full-text articles for eligibility. Disagreement was resolved by consensus or reference to an independent third party (L.M.). All screening was performed using a predefined eligibility form.

Using a data extraction form developed a priori, the same two reviewers independently extracted data concerning study methodology, patient characteristics, technical characteristics of the MR scanners, mpMRI protocol, mpMRI scoring system, definition of positive mpMRI, biopsy protocol, and definition of csPCa. Any discrepancies concerning data extraction were resolved by consensus or reference to an independent arbiter (O.R. or T.B.L.).

2.5. Assessment of risk of bias

To assess the risk of bias (RoB), all included reports were reviewed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies [10].

2.6. Data synthesis and analysis

Outcome data regarding false negative and true negative values of mpMRI before prostate biopsy were recorded as reported by authors. When not available, data were indirectly derived from specificity, sensitivity, and prevalence values reported by authors using an online Bayesian statistics calculator (http://www.medcalc.com/bayes.html). Descriptive statistics were used to summarise baseline characteristics and outcomes, including median and interquartile range (IQR) for estimates of NPV across studies. A correlation between mpMRI NPV and a positive biopsy rate was established using the Pearson's correlation coefficient.

A meta-analysis was undertaken to calculate pooled NPV and PPV. To ensure appropriate clinical homogeneity of the studies included in the meta-analysis, we selected only the studies enrolling biopsy-naïve patients and/or patients with a history of negative biopsy, and fulfilling the following criteria that were defined a priori: (1) reference standard consisting of prostate biopsy with at least 10 samples on all patients; (2) mpMRI protocol comprising at least T2WI and DWI; (3) mpMRI results presented as a five-level score, using a subjective Likert scale or the Prostate Imaging Reporting Data System (PI-RADS) score [11]; (4) definition of positive mpMRI as a score $\geq$3/5 or $\geq$4/5; and (5) results reported on a per patient basis. In addition, only studies defining csPCa as Gleason $\geq$7 cancers were selected for the meta-analysis assessing the mpMRI NPV for csPCa. A bivariate random-effects approach was employed using the Midas package in Stata 12 (StataCorp LP, College Station, TX, USA). Since the NPV decreases and the PPV increases as the prevalence increases, post-test probability estimates of NPV and PPV were reported for the given values of the prevalence based on Bayes' theorem.

For other studies not included in the meta-analysis based on the criteria described above, a narrative synthesis of the data was performed. To explore and define clinical heterogeneity, subgroups were analysed at patient level based on the following variables: biopsy-naïve versus previous negative biopsy; patients with positive versus negative digital rectal examination (DRE); mpMRI performed with an endorectal versus without an endorectal coil; transrectal ultrasound (TRUS) versus template transperineal (TTP) biopsy approach; and $\leq$16 cores versus $>$16 cores as the reference standard. Studies reporting mpMRI NPV for patients with a prostate-specific antigen (PSA) level of $\leq$10 ng/ml were also reported separately.

3. Evidence synthesis

3.1. Quantity of evidence identified

The study selection process is depicted in the PRISMA flow diagram (Fig. 1). A total of 2980 abstracts were retrieved. After abstract screening and removal of duplicates, 240 articles were eligible for full text screening, of which 48 studies were eligible for inclusion [12–59].

3.2. Quality of studies

Out of the 48 included studies, 42 were single-centre and six were multicentre studies. Thirty-four studies were prospective and six were retrospective, whilst the design of the rest was unclear. RoB assessment using QUADAS-2 was performed for each of the individual studies (Fig. 2A and B). Overall, the RoB was highly heterogeneous across studies for all criteria, except for the reference standard domain, in which RoB was low in most studies.

3.3. Characteristics of studies

The 48 studies comprised a total of 9613 men who underwent prostate mpMRI followed by biopsy. The study and patient baseline characteristics are presented in Table 1. The patient population consisted of biopsy-naive men in nine studies, men with at least one previous negative biopsy in 16 studies, and both biopsy-naïve men and men with a history of previous negative biopsy in nine studies. In 14 studies, the biopsy history of the patients was unclear.

The magnetic field strength was 1, 1.5, and 3 T in one, 28, and 15 studies, respectively. Four studies used both 1.5 and 3 T MR systems. DWI and DCEI were used in 36 and

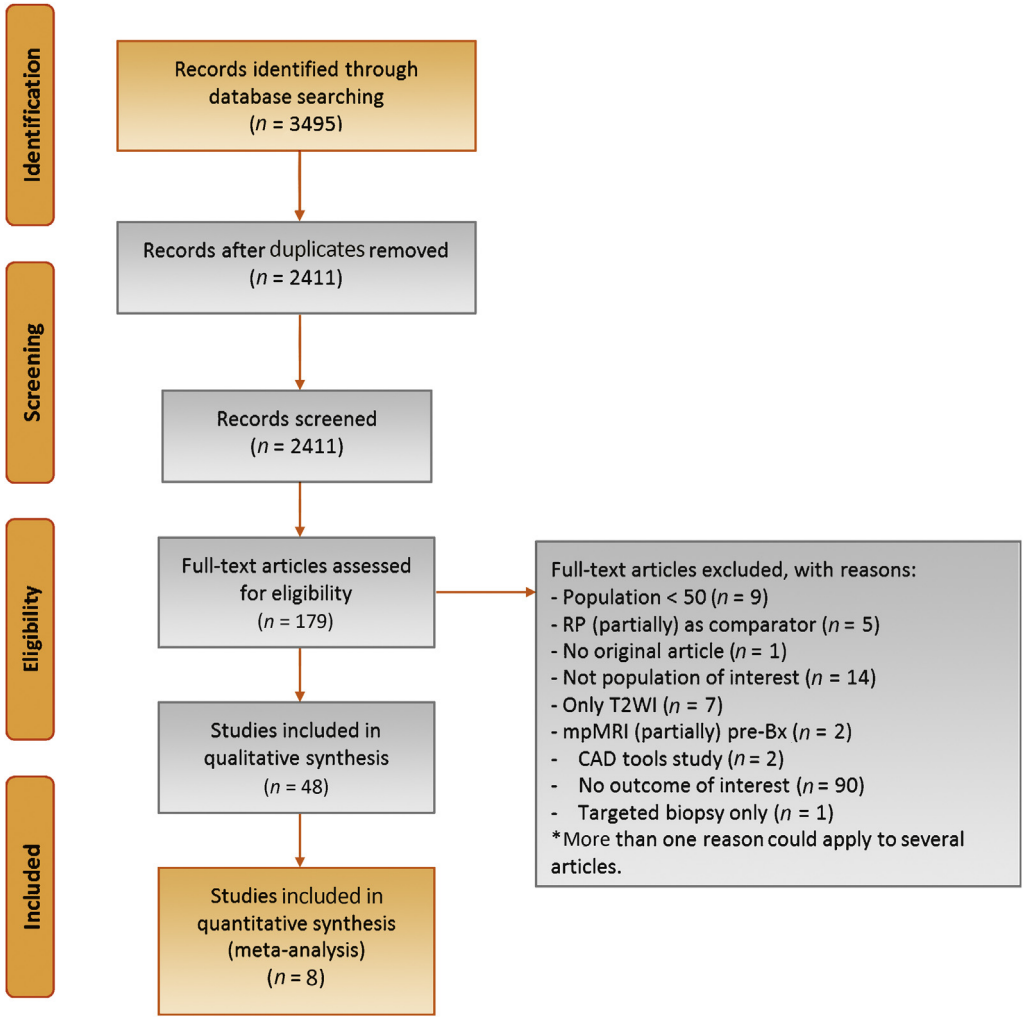

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart. Bx = biopsy; CAD = computer-aided diagnosis; mpMRI = multiparametric magnetic resonance imaging; RP = radical prostatectomy; T2WI = T2-weighted imaging.

35 studies, respectively. Nineteen studies also added MRSI. An endorectal coil was used in 18 studies. The definition of positive mpMRI varied across studies. The PI-RADS v1 score was used in 12 studies, a five-level subjective (Likert) score was used in eight studies, and one study reported data based on the two scoring systems. In-house criteria were used in 13 studies for defining positive mpMRI, and five studies used a dichotomous definition. Nine studies did not report on the criteria for positive mpMRI. No study used the PI-RADS v2 score.

Regarding the reference standard, TRUS-guided biopsies were used in 39 studies, TTP biopsies in six studies, and mixed TRUS-guided and TTP biopsies in two studies. In one study, the biopsy approach was unclear. The number of cores per biopsy procedure was ≤16 in 30 studies, >16 in nine studies, and variable among patients in three studies. For six studies, the number of biopsy cores taken was unclear.

3.4. *NPV of prebiopsy mpMRI*

At patient level, the median biopsy positivity rate (ie, cancer prevalence) was 50.4% (IQR, 36.4–57.7%) for overall cancer and 32.9% (IQR, 28.1–37.2%) for csPCa (Table 2). The median mpMRI NPV was 82.4% (IQR, 69.0–92.4%) for overall cancer and 88.1% (IQR, 85.7–92.3) for csPCa. NPV significantly decreased when cancer prevalence increased, both for overall cancer ($r = -0.64$, $p < 0.0001$) and csPCa ($r = -0.75$, $p = 0.032$; Fig. 3). In addition, NPV was highly dependent on the definition used for csPCa, with differences of up to 21% when several definitions were used in the same dataset [12,13,38,47,48].

Cancer prevalence tended to be higher and mpMRI NPV lower in the biopsy-naïve group as compared with the repeat biopsy group, in men with positive DRE as compared with men with negative DRE and when an endorectal coil was not used (Table 3). There were no clear differences in the prevalence and NPV of the other analysed subgroups (TRUS-guided vs TTP biopsy, biopsy procedures with ≤16 cores vs >16 cores; Table 3). However, comparisons must be interpreted with care, due to the small number of studies in some subgroups. In patients with a PSA level of ≤10 ng/ml, the median NPV for overall PCa was 86.3% (IQR, 73.3–93.6%) for a median cancer prevalence of 35.4% (IQR, 27.6–42.5%).

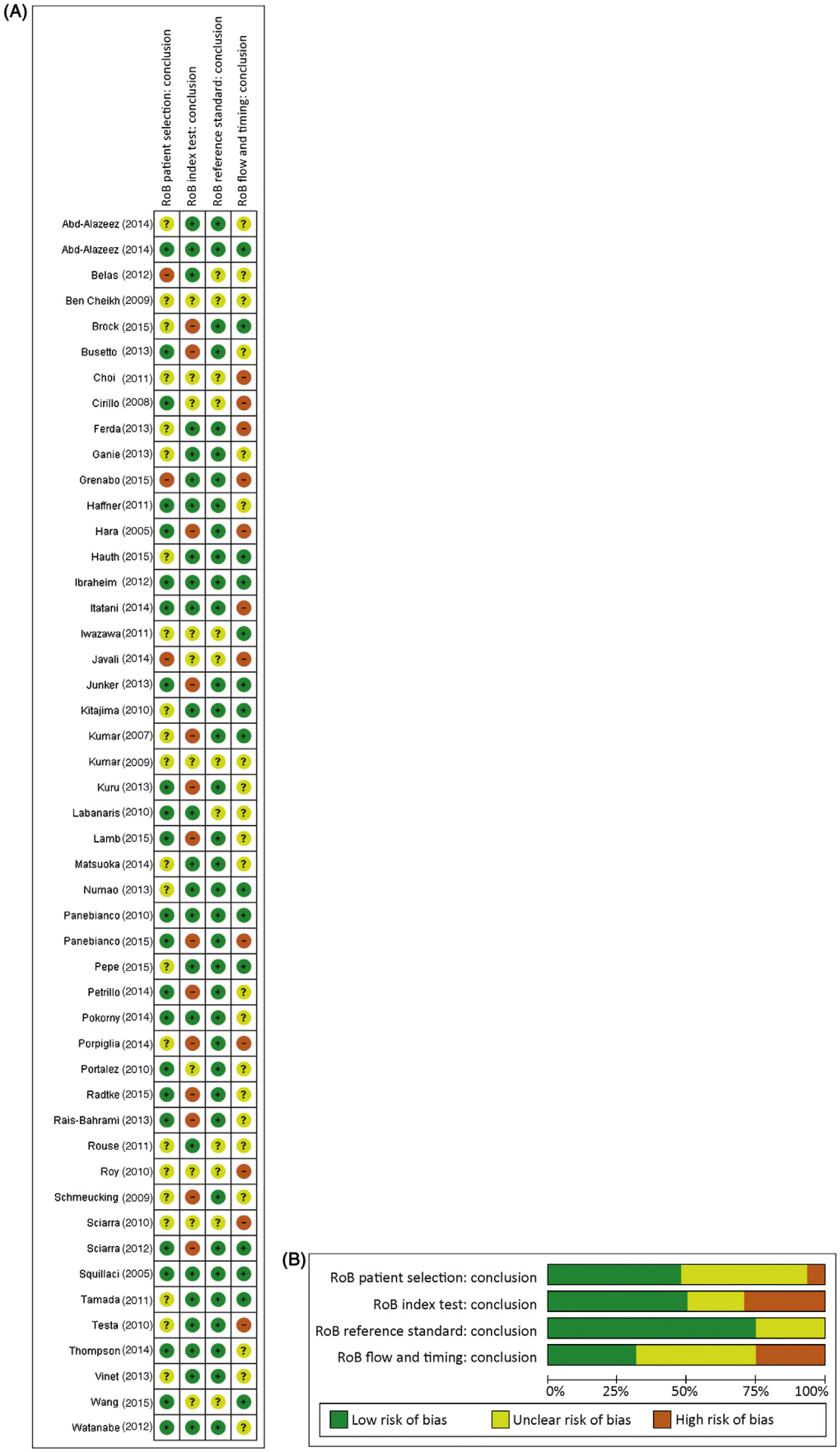

Fig. 2 – (A) Assessment of the risk of bias for included studies. (B) Risk of bias summary graph. RoB = risk of bias.

Table 1 – Baseline characteristics of included studies

Study	Study design	Period	Population	Pt Nb	Mean/ median* age (yr)	Mean/median* PSA (ng/ml)	Mean/ median* prostate volume (cm^3)	Magnetic field strength	MR pulse sequences	Endorectal coil	MR score	Definition of positive MRI	Reference standard
Hauth (2015) [25]	Prospective	2011–2013	FB	94	64 (43–83)	9 (3–31)	51 (17–140)	1.5 T	T2WI/DWI/ DCEI/MRSI	No	PI-RADS v1	≥3	11–13-core TRUS SBx + TBx
Lamb (2015) [36]	Retrospective	2013–2013	FB & PNB	173	NR	NR	NR	1.5 T	T2WI/DWI	NR	NR	NR	12-core TRUS SBx
Brock (2015) [15]	Prospective	2013–2014	PNB	168	64* (IQR 59–70)	9.2* (IQR 6.7–13.4)	55.4* (IQR 42–80)	3 T	T2WI/DWI/DCEI	No	PI-RADS v1	NR	12/24-core TRUS SBx + TBx
Grenabo Bergdahl (2016) [22]	Prospective	2013–2014	FB & PNB	83	69.3* (IQR 69–69.6)	1.6* (IQR 0.9–2.7)	NR	3 T	T2WI/DWI/ DCEI/MRSI	No	PI-RADS v1	≥3	10-core TRUS SBx + TBx
Wang (2015) [58]	Prospective	2002–2009	FB & PNB	586	70 (26–91)	11.11* (0.02–9794)	NR	1.5 T	T2WI/DWI/ DCEI/MRSI	Yes	PI-RADS v1	≥3	TRUS SBx
Pepe (2015) [41]	Prospective	2011–2014	PNB	100	64*	8.6* (4.2–10)	NR	3 T	T2WI/DWI/ DCEI/MRSI	No	PI-RADS v1	≥4	TPBx + TBx
Panebianco (2015) [39]	Prospective	2011–2014	FB (61.62%) & PNB (38.34%)	925 (1140 total cohort)	NR	NR	NR	3 T	T2WI/DWI/DCEI	Yes	PI-RADS v1	NR	14-core TRUS SBx; 45-core sat TPBx + TBx
Radtke (2015) [46]	Prospective	2013–2013	FB (63.3%) & PNB (36.7%)	294	64* (60–71)	7.3 (6.0)	47 (37.5)	3 T	T2WI/DWI/DCEI	No	PI-RADS v1	PI-RADS ≥2; PI-RADS ≥3; PI-RADS ≥4; PI-RADS = 5;	24-core TPBx + TBx
Itatani (2014) [27]	Retrospective	2004–2007	NR	193	68.9 (8.4); 70* (47–89)	11.8 (15.9); 7.9* (1.22–159)	NR	1.5 T	T2WI/DWI/DCEI	No	1–5 scale (Likert)	≥3	12–14-core TRUS SBx
Porpiglia (2014) [44]	Prospective	2011–2013	PNB	170	65* (60–70)	6.9* (5.2–9.8)	42* (36–48)	1.5 T	T2WI/DWI/DCEI	Yes	Dichotomous	Positive: at least 2/3 MR seq. with suspicious findings	18–24-core TRUS SBx (volume dependent)
Thompson (2014) [56]	Prospective	2012–2013	FB (88%) & PNB (12%)	150	62.4* (IQR 55.0–66.4)	5.6* (IQR 4.5–7.5)	40* (IQR 30–57)	1.5 T (47%) & 3 T (53%)	T2WI/DWI/DCEI	No	PI-RADS v1	≥3	Median of 30 TPBx (volume dependent)
Pokorny (2014) [43]	Prospective	2012–2013	FB	223	63* (IQR 57–68)	5.3* (IQR 4.1–6.6)	41* (IQR 30–59)	3 T	T2WI/DWI/DCEI	No	PI-RADS v1	≥3 (primary); ≥4	12-core TRUS SBx + TBx
Petrillo (2014) [42]	Prospective	2009–2010	NR	136	NR	NR	NR	1.5 T	T2WI/DWI/MRSI	Yes	1–5 scale (Likert)	≥3	12–16-core TRUS SBx (volume + PSA dependent)
Javali (2014) [29]	Retrospective	2002–2011	NR	140	Control: 62.4 (10.5); Study: 62.9 (12.1)	Control: 6.8 (2.3); Study: 6.87 (2.6)	Control: 44 (14.2); Study: 43 (18.4)	1.5 T	T2WI/MRSI	Yes	Dichotomous	Cit/[Cho + Cr] < 1.2	6-core TRUS SBx (n = 69), 12-core TRUS SBx (n = 119)
Abd-Alazeez (2014) [13]	Prospective	2007–2011	FB	129	62* (41–82)	5.8* (1.2–20)	40* (16–137)	1.5 & 3 T	T2WI/DWI/DCEI	No	PI-RADS v1	≥3 (primary); ≥4	20-core TPBx
Abd-Alazeez (2014) [12]	Retrospective	NR	PNB	54	64* (39–75)	10* (2–23)	53* (19–136)	1.5 & 3 T	T2WI/DWI/DCEI	No	PI-RADS v1	≥3 (primary); ≥4	≥20-core TPBx + TBx (n = 15)
Matsuoka (2014) [37]	Prospective	2007–2012	NR	135	67* (50–80)	7.0* (2.9–19.8)	25.4* (12.7–90.2)	1.5 T	T2WI/DWI	No	1–5 scale (Likert)	≥3	14-core TRUS SBX
Junker (2013) [30]	Retrospective	2011–2013	PNB	73	62 (7.4)	7.0* (5.1–12.9)	45* (34–61)	3 T	T2WI/DWI/DCEI	No	PI-RADS	PI-RADS ≥10 and ≥11 for all PCa PI-RADS ≥13 for significant PCa	10-core TRUS SBx + TBx
Busetto (2013) [16]	Prospective	2010–2012	PNB	163	66.4 (5.3)	6.8 (1.6)	NR	3 T	T2WI/DWI/ DCEI/MRSI	Yes	NR	NR	10-core TRUS SBx + TBx
Rais-Bahrami (2013) [47]	Prospective	2007–2012	NR	583	61.3 (8.4)	9.9 (13.1)	NR	3 T	T2WI/DWI/ DCEI/MRSI	Yes	1–4 scale (Likert)	≥2 ≥3	12-core TRUS SBx + TBx
Kuru (2013) [34]	Prospective	2010–2011	FB (51%) & PNB (49%)	347	65.3 (42–82)	9.85 (0.5–104)	48.7 (9–180)	3 T	T2WI/DWI/DCEI	No	1–3 scale (Likert)	≥2	12–36-core TRUS SBx (volume dependent) + TBx
Ferda (2013) [20]	Prospective	NR	NR	164	(49–74)	(4.2–123)	NR	3 T	T2WI/DWI/ DCEI/MRSI	No	NR	In house	TRUS SBx
Ganie (2013) [21]	NR	2007–2009	PNB	87	NR	NR	NR	1.5 T	T2WI/MRSI	Yes	MRSI Cho/ Cit ratio	In house	6 core TRUS SBx + MRI TBx

Table 1 (*Continued*)

Study	Study design	Period	Population	Pt Nb	Mean/ median* age (yr)	Mean/median* PSA (ng/ml)	Mean/ median* prostate volume (cm^3)	Magnetic field strength	MR pulse sequences	Endorectal coil	MR score	Definition of positive MRI	Reference standard
Vinet (2013) [57]	Prospective	2009–2011	FB	69	NR	5.2* (3.2–28)	NR	1.5 T (35 pts) & 3 T (34 pts)	T2WI/DWI/DCEI	No	1–5 scale (Likert)	≥3	12-core TRUS SBx + TBx
Numao (2013) [38]	Prospective	2006–2010	FB	351	65* (59–70)	6.3* (4.9–9.1)	32* (24–42)	1.5 T	T2WI/DWI/DCEI (no DCEI in 42 pts)	No	1–5 scale (Likert)	≥3	3D 26-core (12 TRUS SBx + 14 TPBx – 203 pts); 3D 14-core (6 TRUS SBx + 8 TPBx – 102 pts); TPBx 14 core (46 pts)
Belas (2012) [14]	Prospective	2010–2011	FB	71	66* (47–76)	7* (4–10)	45* (15–150)	1.5 T	T2WI/DWI/DCEI	No	TZ: 0–4 scale PZ: 0–10 scale	TZ: >2 PZ: >6	12-core TRUS SBx + TBx
Ibrahiem (2012) [26]	Prospective	2008–2009	FB	100	65.03 (7.13)	26.3 (24.2)	60.09 (28.7)	1.5 T	T2WI/DWI	No	NR	In house	12-core TRUS SBX
Sciarra (2012) [51]	Prospective	2008–2011	PNB	84	64.09 (46–76)	7.07 (4.2–15.5)	NR	3 T	T2WI/DWI/ DCEI/MRSI	Yes	NR	NR	10-core TRUS Bx + TBx
Portalez (2012) [45]	Prospective	2011	PNB	129	64.7 (47–79)	9.6 (2.7–40)	51.1 (12–192)	1.5 T	T2WI/DWI/DCEI	Mixed	1–5 scale (Likert) PI-RADS	Likert ≥3 PI-RADS ≥9	10–12-core TRUS SBx + TBx
Watanabe (2012) [59]	Prospective	2004–2008	NR	1448	72 (7.5)	NR	NR	1.5 T	T2WI/DWI	No	NR	ADC value $\leq 1.35 \times 10^{-3}$ mm^2/s	8-core TRUS SBx + TBx
Tamada (2011) [54]	Retrospective	2006–2009	NR	50	70 (40–84)	6.84* (4.06–9.94)	NR	1.5 T	T2WI/DWI/DCEI	No	NR	In house	12-core TRUS SBx
Choi (2011) [18]	NR	2009–2010	NR	51	67.16 (56–90)	14.16 (1.02–38.9)	42.98 (13.8–77.3)	3 T	T2WI/DWI	NR	NR	NR	10–12-core TRUS SBx + TBx
Iwazawa (2011) [28]	Retrospective	2008–2009	NR	178	68.8 (41–86)	20.51 (4.04–568.5)	NR	1.5 T	T2WI/DWI/DCEI	NR	1–4 scale (Likert)	NR	10–12-core TRUS SBx (TBx included in SBx chart)
Rouse (2011) [48]	Prospective	2005–2007	PNB	114	63.6 (41–83)	13.4 (0–228)	NR	1.5 T	T2WI/DWI/DCEI	NR	1–5 scale (Likert)	≥3	TRUS SBx
Haffner (2011) [23]	Prospective	2005–2009	FB	555	64* (47–83)	6.75* (0.18–100)	46* (15–200)	1.5 T	T2WI/DCEI	No	1–5 scale (Likert)	≥3	10-core TRUS SBx + TBx
Panebianco (2010) [40]	Prospective	2007–2009	PNB	150	61.2 (46–78)	9.42 (3.91)	41.17 (7.47)	1.5 T	T2WI/DCEI/MRSI	Yes	NR	In house	10-core TRUS SBx (TBx included in SBx chart)
Roy (2010) [49]	Not specified	2011–2009	FB (53%) & PNB (47%)	103	63 (52–78)	7*	NR	3 T	T2WI/DWI/DCEI	Yes	NR	NR	8-core TRUS SBx + TBx
Testa (2010) [55]	Not specified	2007	PNB	54	63.9 (52–76)	11.4 (3–42)	59.3 (30–150)	1.5 T	T2WI/MRSI	Yes	1–3 scale (Likert)	≥2	12-core TRUS SBx + TBx
Sciarra (2010) [52]	Prospective	2007–2009	PNB	110	63.5 (49–74)	NR	NR	1.5 T	T2WI/DCEI/MRSI	Yes	NR	In house	10-core TRUS SBx + TBx
Kitajima (2010) [31]	Prospective	2008–2009	NR	53	69* (56–84)	11.1* (4.2–112.1)	NR	3 T	T2WI/DWI/DCEI	No	1–5 scale (Likert)	≥3	20-core TPBx
Labanaris (2010) [35]	Prospective	2004–2008	PNB	260	NR	NR	NR	1 T	T2WI/DWI/DCEI	Yes	Dichotomous	In house	18-core TRUS SBx
Kumar (2009) [32]	NR	NR	NR	61	65.3 (9.3)	16.5 (0.21–155)	NR	1.5 T	T2WI/MRSI	Yes	NR	(Cit/(Cho + Cr) ≤ 1.2	TRUS Bx
Schmuecking (2009) [50]	NR	NR	FB & PNB	67	68	11.5	NR	1.5 T	T2WI/DCEI	No	NR	NR	20-core Bx
Cheikh (2009) [17]	Retrospective	2005–2008	PNB	93	63.2 (52–74)	9.63 (1.6–40)	NR	1.5 T	T2WI/DCEI	No	Dichotomous	In house	12-core TRUS SBx + TBx
Cirillo (2008) [19]	Prospective	2004–2006	PNB	54	65.5 (5.2)	10.8 (7.5)	NR	1.5 T	T2WI/MRSI	Yes	Dichotomous	In house	10-core TRUS SBx + TBx
Kumar (2007) [33]	Prospective	2003–2005	NR	83	NR	NR	NR	1.5 T	T2WI/MRSI	Yes	NR	NR	12-core TRUS SBx + TBx
Squillaci (2005) [53]	Prospective	2004–2005	NR	65	NR	NR	NR	1.5 T	T2WI/DCEI/MRSI	No	1–3 scale (Likert)	≥2	10-core TRUS SBx + TBx
Hara (2005) [24]	Prospective	2003–2004	FB	90	67.2 (NR)	NR	NR	1.5 T	T2WI/DCEI	No	1–3 scale (Likert)	≥2 = 3	14-core TRUS SBx

FB = first biopsy; IQR = interquartile range; PNB = previous negative biopsy; Pt = patient; Nb = number; MR = magnetic resonance; MRI magnetic resonance imaging; T2WI = T2-weighted imaging; DWI = diffusion-weighted imaging; DCEI = dynamic contrast-enhanced imaging; MRSI = magnetic resonance spectroscopic imaging; NR = not reported; Bx = biopsy; TRUS SBx = transrectal ultrasound-guided standard biopsy; TPBx = transperineal template biopsy; TBx = targeted biopsy; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting Data System; PSA = prostate-specific antigen; PZ = peripheral zone; TZ = transition zone.
Figures between parenthesis correspond to standard deviations; intervals between brackets correspond to full ranges or interquartile ranges when specified (IQR). The asterisk sign indicates median value (as opposed to mean value).

Table 2 – Diagnostic performance of prebiopsy multiparametric MRI using biopsy findings as reference standard

Study	Overall PCa prevalence (%)	Reporting level	Multiparametric MRI performance for PCa detection						Definition of csPCa	csPCa prevalence	Multiparametric MRI performance for csPCa detection					
			TN	FN	TP	FP	NPV	PPV			TN	FN	TP	FP	NPV	PPV
Hauth (2015) [25]	45.7	Patient	6	1	42	45	85.7%	48.3%	Low grade: GS ≤ 6 High grade: GS ≥ 7	NR	NR	NR	NR	NR	NR	NR
		Lesion	59	13	55	73	81.9%	43%								
Lamb (2015) [36]	65.9	Patient	23	22	92	36	51.1%	71.9%	GS ≥ 7	50.9%	31	14	71	57	68.9%	55.5%
Brock (2015) [15]	42.3	Patient	17	7	56	88	70.8%	SBx: 38.8% TBx: 22.2% Duo: 44.4%	Epstein: GS > 6 and/ or max CCL ≥50%	24.4%	SBx: 21	SBx: 3	SBx: 38 TBx: 27 duo: 47	SBx: 106 TBx: 117 duo: 97	87.5%	SBx: 26.4% TBx: 18.8% duo: 32.6%
Grenabo Bergdahl (2016) [22]	33.7	Patient	36	7	19	21	83.7%	47.5%	Clinically insignificant PCa: T1c, PSAd < 0.15, GS < 7, ≤2 positive cores, and unilateral cancer	NR	NR	NR	NR	NR	NR	NR
Wang (2015) [58]	58	Patient	165	8	332	81	95.4%	80.4%	NR	NR	NR	NR	NR	NR	NR	NR
Pepe (2015) [41]	37	Patient	23	8	29	40	74.2%	42%	GS ≥ 7 or GS 6 with CCL ≥ 50%	NR	NR	NR	NR	NR	100%	55.8%
Panebianco (2015) [39]	74.7	Patient	Group A (satBx): 104	Group A (satBx): 43	Group A: 186	Group A: 22	Group A (satBx): 70.7%	Group A: 89.4%	NR	60%	Group A: 147	Group A: 0	Group A: 183	Group A: 25	Group A: 100%	Group A: 88%
			Group B (TRUSGB NR TRUS G satBx): 93	Group B (TRUSGB NR TRUS G satBx): 37	Group B: 417 before and 425 after satBx	Group B: 23/440 and 15/440 after satBx.	Group B (TRUSGB–TRUS G satBx): 71.5%	Group B: 94.8% before and 96.6% after satBx		71.9%	Group B: 130	Group B: 0	Group B: 410	Group B: 30	Group B: 100%	Group B: 93.2%
Radtke (2015) [46]	51	Patient	≥2/5: 80 ≥3: 103 ≥4: 138 =5: 142	≥2/5: 18 ≥3/5: 38 ≥4/5: 78 =5/5: 126	≥2/5: 132 ≥3/5: 112 ≥4/5: 72 =5/5: 24	≥2/5: 64 ≥3/5: 41 ≥4/5: 6 =5/5: 2	≥2/5: 81.6% ≥ 3/5: 73.1% ≥ 4/5: 63.9% =5/5: 53%	≥2/5: 67.4% ≥ 3/5: 73.2% ≥ 4/5: 92.3% =5/5: 92.3%	GS ≥ 7	29.3%	≥2/5: 91 ≥3/5: 124 ≥4/5: 183 =5/5: 203	≥2/5: 7 ≥3/5: 17 ≥4/5: 33 =5/5: 65	≥2/5: 79 ≥3/5: 69 ≥4/5: 53 =5/5: 21	≥2/5: 117 ≥3/5: 84 ≥4/5: 25 =5/5: 5	≥2/5: 92.2% ≥3/5: 87.9% ≥4/5: 84.7% =5/5: 75.8%	≥2/5: 40.3% ≥3/5: 45.1% ≥4/5: 68% =5/5: 80.7%
Itatani (2014) [27]	13	Patient	168	25	NR	NR	87%	NR	(1) PSAd ≥ 0.1 or GP 4/5 or ≥ 3/6 pos cores; max CCL < 50% (2) PSAd ≥ 0.15 or GP 4/5 or max core length invasion < 3 mm (min 6 cores)	NR	NR	NR	NR	NR	NR	NR
Porpiglia (2014) [44]	30.6	Patient	107	5	47	11	95.5%	81%	NR	NR	NR	NR	NR	NR	NR	NR
Thompson (2014) [56]	61.3	Patient	35	16	76	23	68.6%	76.7%	Moderate or high risk Moderate risk: GS 7 (GP4 >5%) and <50% of positive cores or GS 6–7 (GP4 ≤ 5%) and either ≥30% of positive cores or max core length invasion ≥8 mm High risk: GS ≥ 7 (GP4 > 5%); ≥50% + cores or GS ≥ 8	34%	49	2	49	50	96%	49.5%
Pokorny (2014) [43]	63.7	Patient	≥3/5: 56 ≥4/5: 74	≥3/5: 25 ≥4/5: 40	≥3/5: 101 ≥4/5: 86	≥3/5: 41 ≥4/5: 23	≥3/5: 69.1% ≥4/5: 64.9%	≥3/5: 71.1% ≥4/5: 78.9%	NR	NR	NR	NR	NR	NR	NR	NR
Petrillo (2014) [42]	18.4	Patient	56	4	21	55	93%	28%	NR	NR	NR	NR	NR	NR	NR	NR
Javali (2014) [29]	16.4	Patient	49	1	22	68	98%	24.4%	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 (*Continued*)

Study	Overall PCa prevalence (%)	Reporting level	Multiparametric MRI performance for PCa detection						Definition of csPCa	csPCa prevalence	Multiparametric MRI performance for csPCa detection					
			TN	FN	TP	FP	NPV	PPV			TN	FN	TP	FP	NPV	PPV
Abd-Alazeez (2014) [13]	54.7	Lobe	≥3/5: 33	≥3/5: 14	≥3/5: 127	≥3/5: 84	≥3/5: 70%	≥3/5: 60%	Def 1: GS ≥ 4 + 3 and/ or max CCL ≥ 6 mm Def 2: GS ≥ 3 + 4 and/or max CCL ≥ 4 mm Def 3: GS ≥ 4 + 3 Def 4: GS ≥ 3 + 4 Def 5: max CCL ≥ 6 mm Def 6: max CCL ≥ 4 mm	Def 1: NR Def 2: 44.2% Def 3: 23.2% Def 4: 36% Def 5: 32.9% Def 6: 39.5%	Def 1: 46 Def 2: 42 Def 3: 47 Def 4: 43 Def 5: 46 Def 6: 43	Def 1: 1 Def 2: 5 Def 3: 0 Def 4: 4 Def 5: 1 Def 6: 4	Def 1: 45 Def 2: 72 Def 3: 13 Def 4: 50 Def 5: 39 Def 6: 59	Def 1: 166 Def2: 139 Def 3: 198 Def 4: 161 Def 5: 172 Def 6: 152	Def 1: 98 Def 2: 89 Def 3: 100 Def 4: 92 Def 5: 98 Def 6: 91	Def 1: 21 Def 2: 34 Deg 3: 6 Def 4: 24 Def 5: 19 Def 6: 28
			≥4/5: 87	≥3/5: 62	≥3/5: 79	≥3/5: 30	≥3/5: 58%	≥3/5: 73%			Def 1: 140 Def 2: 124 Def 3: 148 Def 4: 133 Def 5: 141 Def 6: 131	Def 1: 9 Def 2: 25 Def 3: 1 Def 4: 16 Def 5: 8 Def 6: 18	Def 1: 37 Def 2: 52 Def 3: 12 Def 4: 38 Def 5: 32 Def 6: 45	Def 1: 72 Def 2: 57 Def 3: 97 Def 4: 71 Def 5: 77 Def 6: 64	Def 1: 94 Def 2: 83 Def 3: 99 Def 4: 89 Def 5: 95 Def 6: 88	Def 1: 34 Def 2: 48 Def 3: 11 Def 4: 35 Def 5: 30 Def 6: 42
Abd-Alazeez (2014) [12]	47.2	Lobe	≥3/5: 26	≥3/5: 13	≥3/5: 38	≥3/5: 31	≥3/5: 66%	≥3/5: 55%	Def 1: GS ≥ 4 + 3 and/or max CCL ≥ 6 mm Def 2: GS ≥ 3 + 4 and/or max CCL ≥ 4 mm Def 3: GS ≥ 4 + 3 Def 4: GS ≥ 3 + 4 Def 5: max CCL ≥ 6 mm Def 6: max CCL ≥ 4 mm	Def 1: 18.5% Def 2: 31.5% Def 3: 4.6% Def 4: 21.3% Def 5: 16.7% Def 6: 25%	Def 1: 37 Def 2: 31 Def 3: 39 Def 4: 36 Def 5: 37 Def 6: 32	Def 1: 2 Def 2: 8 Def 3: 0 Def 4: 3 Def 5: 2 Def 6: 7	Def 1: 18 Def 2: 26 Def 3: 5 Def 4: 20 Def 5: 16 Def 6: 20	Def 1: 51 Def 2: 43 Def 3: 64 Def 4: 49 Def 5: 53 Def 6: 49	Def 1: 95 Def 2: 79 Def 3: 100 Def 4: 92 Def 5: 95 Def 6: 82	Def 1: 26 Def 2: 38 Def 3: 7 Def 4: 29 Def 5: 23 Def 6: 29
			≥4/5: 49	≥4/5: 25	≥4/5: 26	≥4/5: 8	≥4/5: 66%	≥4/5: 76%			Def 1: 70 Def 2: 63 Def 3: 73 Def 4: 68 Def 5: 70 Def 6: 64	Def 1: 4 Def 2: 11 Def 3: 1 Def 4: 6 Def 5: 4 Def 6: 10	Def 1: 16 Def 2: 23 Def 3: 4 Def 4: 17 Def 5: 14 Def 6: 17	Def 1: 18; Def 2: 11 Def 3: 30 Def 4: 17 Def 5: 20 Def 6: 17	Def 1: 94 Def 2: 85 Def 3: 99 Def 4: 92 Def 5: 94 Def 6: 86	Def 1: 47 Def 2: 67 Def 3: 12 Def 4: 50 Def 5: 41 Def 6: 49
Matsuoka (2014) [37]	64.8	Lobe	46	49	149	26	48.4%	85.1%	NR	NR	NR	NR	NR	NR	NR	NR
Junker (2013) [30]	53.4	Patient	≥10/15: 21 ≥11/15: 28	≥10/15: 4 ≥11/15: 12	≥10/15: 35 ≥11/15: 27	≥10/15: 13 ≥11/15: 6	≥10/15: 84% ≥11/15: 70%	≥10/15: 72.9% ≥11/15: 81.8%	GS ≥ 4 + 3	13.7%	≥13: 54	≥13: 2	≥13: 8	≥13: 9	≥13: 96.4%	≥13: 47%
Busetto (2013) [16]	41.7	Patient	59	7	61	36	89%	63%	NR	NR	NR	NR	NR	NR	NR	NR
Rais-Bahrami (2013) [47]	54.2	Patient	≥2/4: 80	≥2/4: 275	≥2/4: 187	≥2/4: 275	≥2/4: 66%	≥2/4: 59%	GS ≥ 7: GS ≥ 8	31.7%	NR	NR	NR	NR	GS ≥ 7: 91% GS ≥ 8: 91%	GS ≥ 7: 38% GS ≥ 8: 18%
			≥3/4: 251	≥3/4: 76	≥3/4: 16	≥3/4: 76	≥3/4: 51%	≥3/4: 82%			NR	NR	NR	NR	GS ≥ 7: 75% GS ≥ 8: 91%	GS ≥ 7: 67% GS ≥ 8: 41%
Kuru (2013) [34]	57.6	Patient	80	14	67	186	85.1%	73.5%	NR	NR	NR	NR	NR	NR	NR	NR
Ferda (2013) [20]	51.2	Patient	52	2	82	28	96.3%	74.5%	NR	NR	NR	NR	NR	NR	NR	NR
Ganie (2013) [21]	74.7	Patient	13	3	62	9	59.1%	95.4%	NR	NR	NR	NR	NR	NR	NR	NR
Vinet (2013) [57]	49.3	Patient	≥3/5: 11	≥3/5: 6	≥3/5: 28	≥3/5: 24	≥3/5: 64.7%	≥3/5: 53.8%	NR	NR	NR	NR	NR	NR	NR	NR
			≥4/5: 22	≥4/5: 11	≥4/5: 23	≥4/5: 13	≥4/5: 66.7%	≥4/5: 63.8%	NR	NR	NR	NR	NR	NR	NR	NR
Numao (2013) [38]	45	Patient	137	57	101	56	70.6%	64.3%	Def 1: GS ≥4 + 3 and/ or ≥20% positive cores and/or max CCL ≥5 mm Def 2: GS ≥ 3 + 4 and/ or ≥20% + cores and/or max CCL ≥5 mm Def 3: GS ≥ 3 + 4 and/ or ≥20% + cores	Def 1: 33.3% Def 2:37.8% Def 3: 35.8%	Def 1: 74 Def 2: 65 Def 3: 69	Def 1: 83 Def 2: 92 Def 3: 88	Def 1: 160 Def 2: 153 Def 3: 156	Def 1: 34 Def 2: 41 Def 3: 38	Def 1: 82.4% Def 2: 78.8% Def 3: 80.4%	Def 1: 58.8% Def 2: 58.5% Def 3: 56%

Belas (2012) [14]	53.5	Patient	22	12	23	13	64.7%	63.8%	NR	NR	NR	NR	NR	NR	NR	NR
Ibrahiem (2012) [26]	73.9	Patient	14	11	57	10	56%	85.1%	NR	NR	NR	NR	NR	NR	NR	NR
Sciarra (2012) [51]	34.5	Patient	41	4	25	14	91.1%	64.1%	NR	NR	NR	NR	NR	NR	NR	NR
Portalez (2012) [45]	48.1	Lesion	Likert: 357	Likert: 50	Likert: 81	Likert: 50	Likert: 95%	Likert: 38%	Max CCL >3 mm and/or GG 4/5	NR	NR	NR	NR	NR	NR	NR
			PI-RADS: 404	PI-RADS: 47	PI-RADS: 34	PI-RADS: 47	PI-RADS: 95%	PI-RADS: 58%								
Watanabe (2012) [59]	48.1	Patient	485	73	624	266	86.9%	70.1%	NR	NR	NR	NR	NR	NR	NR	NR
Tamada (2011) [54]	70	Patient	12	6	29	3	67%	91%	NR	NR	NR	NR	NR	NR	NR	NR
		Region	277	48	55	20	85%	73%								
Choi (2011) [18]	70.6	Patient	9	5	31	6	64.2%	75.7%	NR	NR	NR	NR	NR	NR	NR	NR
Iwazawa (2011) [28]	40.5	Region	887	86	232	219	91.1%	51.4%	NR	NR	NR	NR	NR	NR	NR	NR
Rouse (2011) [48]	33.7	Sextant	145	11	74	22	92.9%	77.1%	GS ≥ 7: Def 1: ≥3 mm Def 2: ≥5 mm	Def 1: 26.6% Def 2: 26.2%	Def 1: 153 Def 2: 153	Def 1: 3 Def 2: 3	Def 1: 64 Def 1: 63	Def 1: 32 Def 2: 33	Def 1: 98.1% Def 2: 98.1%	Def 1: 68.1% Def 2: 67%
	59.6	Patient	24	14	54	22	63.2%	71.1%		Def 1: 41.2% Def 2: 36.8%	Def 1: 30 Def 2: 31	Def 1: 4 Def 2: 3	Def 1: 43 Def 2: 39	Def 1: 4 Def 2: 3	Def 1: 88.2% Def 2: 91.2%	Def 1: 53.8% Def 2: 48.8%
Haffner (2011) [23]	54.4	Patient	154	50	240	111	75.4%	68.3%	NR	NR	NR	NR	NR	NR	NR	NR
Panebianco (2010) [40]	42.7	Patient	NR	NR	NR	NR	95.1%	88.2%	NR	NR	NR	NR	NR	NR	NR	NR
Roy (2010) [49]	55.9	Patient	NR	NR	NR	NR	71%	75%	NR	NR	NR	NR	NR	NR	NR	NR
Testa (2010) [55]	40.7	Patient	NR	NR	NR	NR	79.3%	64%	NR	NR	NR	NR	NR	NR	NR	NR
Sciarra (2010) [52]	50	Patient	61	4	66	9	93.8%	88%	NR	NR	NR	NR	NR	NR	NR	NR
Kitajima (2010) [31]	56.6	Patient	311	19	80	14	92.2%	85.1%	NR	NR	NR	NR	NR	NR	NR	NR
Labanaris (2010) [35]	73.9	Patient	17	73	96	74	81.11%	56.47%	NR	NR	NR	NR	NR	NR	NR	NR
Kumar (2009) [32]	21.7	Patient	39	3	10	8	92.8%	55%	NR	NR	NR	NR	NR	NR	NR	NR
Schmuecking (2009) [50]	NR	Lobe	NR	NR	NR	NR	96%	61%	NR	NR	NR	NR	NR	NR	NR	NR
Cheikh (2009) [17]	24.7	Patient	36	12	11	34	80%	22.9%	NR	NR	NR	NR	NR	NR	NR	NR
Cirillo (2008) [19]	31.5	Patient	19	0	17	18	100%	48.6%	NR	NR	NR	NR	NR	NR	NR	NR
Kumar (2007) [33]	13.3	Patient	39	0	11	33	100%	25%	NR	NR	NR	NR	NR	NR	NR	NR
Squillaci (2005) [53]	50.8	Patient	29%	8%	25%	3%	89%	80%	NR	NR	NR	NR	NR	NR	NR	NR
Hara (2005) [24]	41.5	Patient	≥2/3: 40 = 3/3: 47	≥2/3: 4 = 3/3: 8	≥2/3 30 = 3/3: 26	≥2/3: 8 = 3/3: 1	≥2/3: 90% = 3/3: 85%	≥2/3: 78.9% = 3/3: 96.3%	NR	NR	NR	NR	NR	NR	NR	NR

PCa = prostate cancer; MRI = magnetic resonance imaging; TN = true negative; FN = false negative; FP = false positive; TP = true positive; PPV = positive predictive value; NPV = negative predictive value; csPCa = clinically significant prostate cancer; max = maximum; CCL = cancer core length; PSAd = PSA density; GG = Gleason grade; GS = Gleason score; SBx = systematic biopsy; TBx = targeted biopsy; NR = not reported; PI-RADS = Prostate Imaging Reporting Data System; PSA = prostate-specific antigen.

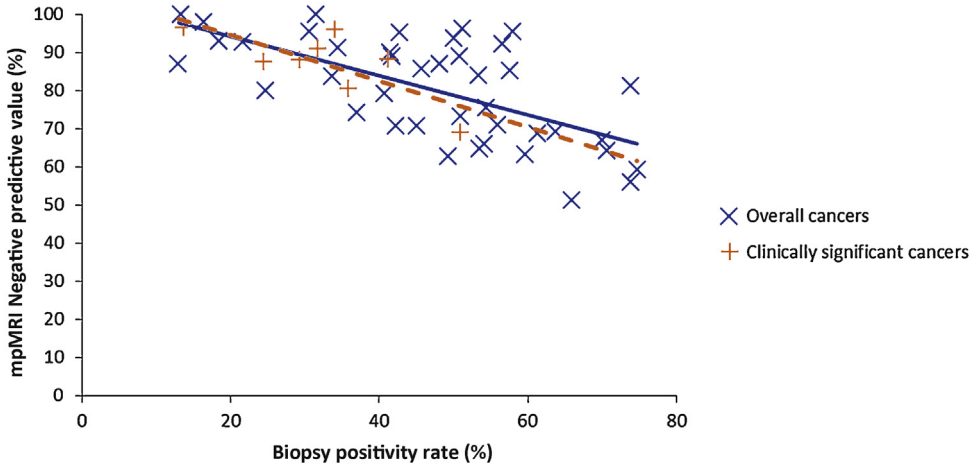

Fig. 3 – Negative predictive value of prebiopsy multiparametric MRI as a function of cancer prevalence (blue crosses: overall prostate cancer; red crosses: clinically significant prostate cancer). The blue line is the correlation line for overall prostate cancer; the red dotted line is the correlation line for clinically significant prostate cancer. mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging.

Table 3 – Reported ranges of negative predictive values for prebiopsy multiparametric MRI

	Nb of studies	Median PCa prevalence	Median mpMRI NPV	Nb of studies	Median csPCa prevalence	Median mpMRI NPV
Biopsy-naïve patients	8	51.4% (45.5–56.7)	69.9% (64.2–78)	1	35.8% (NA)	80.4% (NA)
Repeat biopsy	14	42% (35.1–52.6)	82.6% (75.5–93.1)	3	24.4% (19.1–32.8)	88.2% (87.9–92.3)
TRUS-guided biopsy	36	49.7% (34.3–57.7)	84.6% (68.6–92.8)	4	28.1% (21.7–36.5)	89.3% (82.9–92.4)
TTP biopsy	4	53.8% (47.5–57.8)	73.6% (72–78.7)	2	31.6% (30.5–32.8)	92% (89.9–94)
Biopsy with ≤16 cores	28	48.7% (39.2–54.8)	81.9% (66.8–89.3)	5	28.1% (21.8–36.5)	89.3% (82.9–92.4)
Biopsy with >16 cores	5	56.6% (51–61.3)	81.1% (73.1–92.2)	2	31.7% (30.5–32.8)	92% (89.9–93.9)
Positive DRE	1	73.9% (NA)	56% (NA)	0	–	–
Negative DRE	6	36% (34.6–46.8)	82.7% (74.2–93.1)	0	–	–
Endorectal coil	17	41.7% (30.6–55.9)	92.8% (79.3–95.4)	1	31.7% (NA)	91% (NA)
No endorectal coil	22	50.9% (41.7–56.1)	77.7% (69.5–86.6)	7	34% (26.9–46.1%)	87.9% (78.2–92.1)

PCa = prostate cancer; csPCa = clinically significant prostate cancer; NPV = negative predictive value; TRUS = transrectal ultrasound; TTP = template transperineal; DRE = digital rectal examination; PSA = prostate-specific antigen; NA = not applicable; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; Nb = number.
Intervals in parenthesis are interquartile ranges.

3.5. *Meta-analysis*

3.5.1. *NPV and PPV for overall PCa*

Eight studies reported NPV at patient level for overall PCa and fulfilled the inclusion criteria for meta-analysis (Table 4) [22,25,38,41,43,46,56,57].

Seven studies used a score of ≥3/5 for defining positive mpMRI (Fig. 4A and B) [22,25,38,43,46,56,57]. Fig. 4C shows the conditional probability plot of 1 – NPV and PPV as a function of overall PCa prevalence. Table 5 shows NPV and PPV estimates for the given values of PCa prevalence.

Only three studies used a score of ≥4/5 for defining positive mpMRI (Table 4) [41,46,57], and a formal meta-analysis could not be performed.

3.5.2. *NPV and PPV for Gleason ≥7 cancers*

Only one study reporting NPV at patient level for Gleason ≥7 cancers met the selection criteria for inclusion in the meta-analysis. It reported NPV and PPV of 87.9% and 45.1%, respectively, for a prevalence of 29.3% (Table 4) [46].

3.6. *Discussion*

3.6.1. *Principal findings*

We observed a large variability in reported NPV. Many factors, such as differences in mpMRI protocols, definition of negative mpMRI, or biopsy protocols, can explain this variability. However, two major causes of variability must be pointed out. First, the cancer prevalence was highly variable, ranging at patient level from 13% to 74.7% for overall PCa, and from 13.7% to 50.9% for csPCa. This variability was observed in both the biopsy-naïve and the repeat biopsy setting. As NPV depends on prevalence, this had a major impact on reported NPV (Fig. 3). Second, the definition of csPCa was highly variable from one series to another, and differences of up to 21% could be observed in NPV when different definitions of csPCa were used in the same dataset [12,13,38,47,48].

To account for clinical heterogeneity and to further explore the clinical relevance of the results, we carefully selected studies for inclusion in the meta-analysis based on

Table 4 – Prebiopsy multiparametric MRI results in the series selected for the meta-analysis

		Study	Prevalence [a] (%)	Neg MRI (%)	NPV (%)	PPV (%)	Spe (%)	Se (%)
All PCa	Score ≥ 3/5	Grenabo Bergdahl (2016) [22]	31.3	66.9	83.7	47.5	63.2	73.1
		Numao (2013) [38]	45	29.4	70.6	64.3	71.0	63.9
		Hauth (2015) [25]	45.7	14.3	85.7	48.3	11.8	97.7
		Vinet (2013) [57]	49.3	24.6	64.7	53.8	31.4	82.4
		Radtke (2015) [46]	51	27	73	73.2	71.5	74.7
		Thompson (2014) [56]	61.3	31.4	68.6	76.8	60.3	82.6
		Pokorny (2014) [43]	63.7	30.9	69.1	82.4	69.1	82.4
	Score ≥ 4/5	Pepe (2015) [41]	37	31	74.2	42	36.5	78.4%
		Vinet (2013) [57]	49.3	47.8	66.7	63.9	62.9	67.6%
		Radtke (2015) [46]	51	73.5	63.9	92.3	95.8	48%
Gleason ≥7 PCa	Score ≥ 3/5	Radtke (2015) [46]	29.3	27	87.9	45.1	59.6	80.2%

PCa = prostate cancer; MRI = magnetic resonance imaging; Neg MRI = proportion of negative magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Spe = specificity.
[a] Prevalence of overall prostate cancers (10 first lines) or Gleason ≥7 cancers (last line).

stringent criteria. Particularly, we included only studies that: (1) had biopsy protocols with at least 10 cores, since it is no longer recommended to obtain less than 10 cores per biopsy; (2) used DWI, which is the most informative technique, at least for cancers in the peripheral zone [60]; and (3) reported mpMRI findings using a five-level score, so that negative findings could be better defined. We accepted studies using a subjective (Likert) scale because experienced readers obtained equivalent [45,61,62] or better [63] results with the Likert score than with the PI-RADS v1 score.

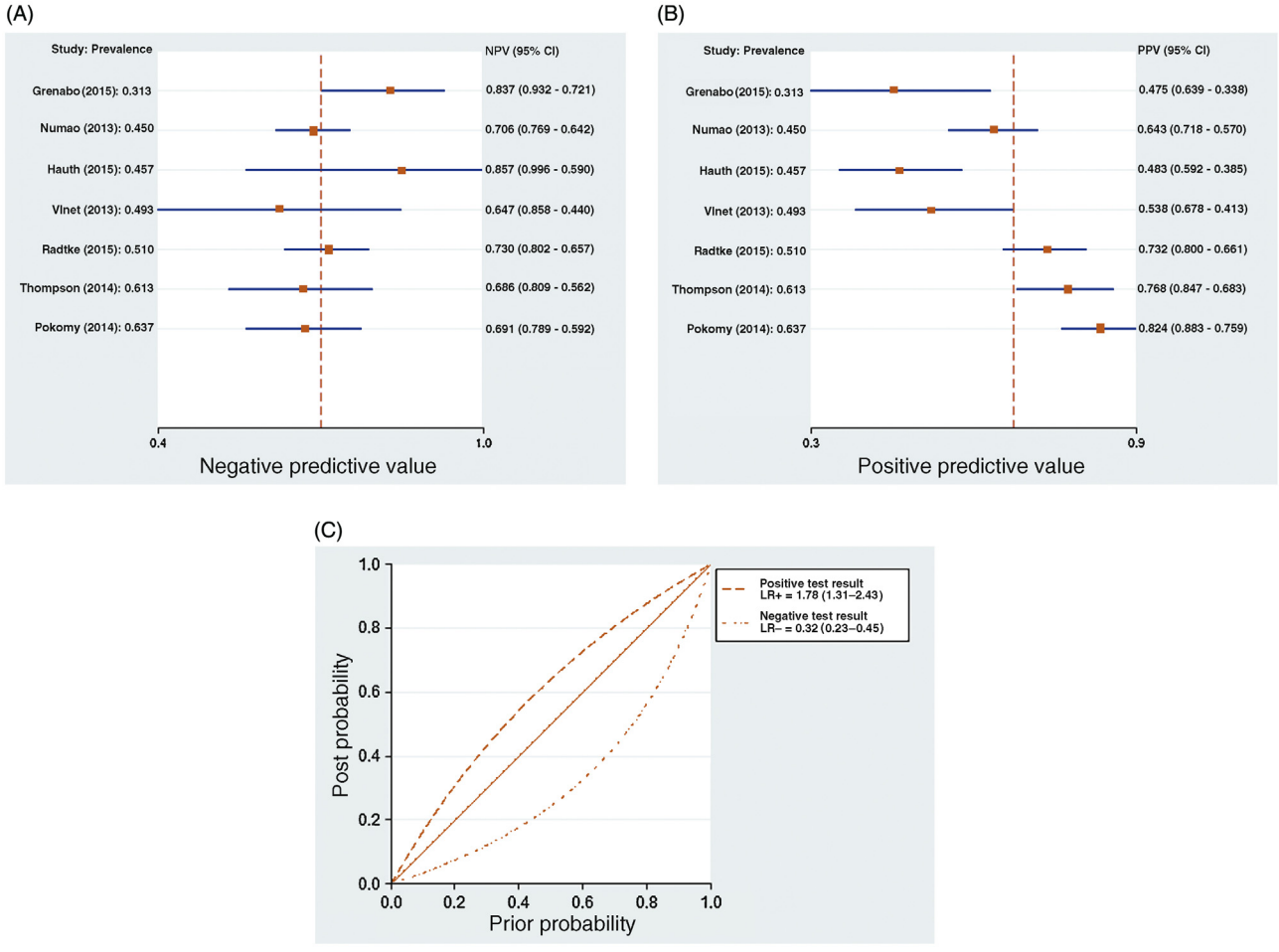

Fig. 4 – Forest plot showing the (A) NPV and (B) PPV of prebiopsy multiparametric MRI for overall prostate cancer in the seven studies selected for meta-analysis that used a cut-off score of ≥3/5 for defining positive MRI. Studies have been ranked according to cancer prevalence (left column). Intervals in the right column are 95% CIs of the (A) NPV or (B) PPV. As NPV and PPV vary with cancer prevalence, combined estimates of NPV and PPV have not been provided. (C) Conditional probability plot showing the estimation of the combined NPV and PPV in the seven studies, as a function of the prevalence of overall prostate cancer. The *x* axis (prior probability) indicates the overall prostate cancer prevalence. The *y* axis (posterior probability) indicates either PPV (dashed line, upper quadrant) or 1 – NPV (dotted line, lower quadrant). CI = confidence interval; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value.

Table 5 – Positive and negative predictive estimates for prebiopsy multiparametric MRI as a function of prostate cancer prevalence (meta-analysis)

PCaPrev	PPV	NPV
0.30	0.43 (0.34–0.53)	0.88 (0.77–0.99)
0.40	0.54 (0.45–0.64)	0.82 (0.70–0.94)
0.50	0.64 (0.55–0.73)	0.76 (0.64–0.88)
0.60	0.73 (0.65–0.80)	0.67 (0.56–0.79)
0.70	0.81 (0.75–0.87)	0.57 (0.47–0.67)
0.75	0.84 (0.79–0.89)	0.51 (0.42–0.59)

PCaPrev = prevalence of prostate cancer; PPV = positive predictive value; MRI = magnetic resonance imaging; NPV = negative predictive value. Intervals in parenthesis are 95% confidence intervals. A score of ≥3/5 was used to define positive MRI.

Owing to the large variations of NPV induced by differences in definitions of csPCa, we did not include different definitions in the meta-analysis since this would have introduced unacceptable clinical heterogeneity in the results, possibly resulting in erroneous and biased estimates. We, therefore, a priori restricted the definition of csPCa to cancers with a Gleason score of ≥7, given the low lethal potential of Gleason 6 cancers [64] and the lack of consensus among pathologists on the best method to measure biopsy core invasion length [65,66].

In this more homogeneous group of studies, the prevalence range was still large (31.3–63.7%). As a result, we modelled the evolution of NPV (and PPV) as a function of overall PCa prevalence. Unfortunately, we could not duplicate this for csPCa since only one study reporting NPV for Gleason ≥7 cancers met the inclusion criteria for meta-analysis.

3.6.2. *Reference standard*

We included only studies that reported the results of systematic/standard biopsy in patients with negative mpMRI and used the systematic/standard biopsy as a reference standard. It is well known that TRUS-guided biopsy harbours both random and systematic errors, as evidenced by the high rates of positivity of immediate repeat biopsy after a first series of negative biopsies [67,68], and as confirmed recently by the PROMIS trial [69]. Therefore, using TRUS-guided biopsy as a reference standard may have overestimated the NPV of mpMRI. However, studies using radical prostatectomy specimens as a reference standard have already reported mpMRI detection rates in relation to PCa Gleason score and volume [1]. In this review, we intended to address the more pragmatic question as to whether a negative mpMRI could predict a negative subsequent biopsy. This is an important question because if the NPV of mpMRI was sufficiently high in comparison with the reference standard of systematic/standard biopsies, then in practice a negative mpMRI result could indeed avoid the need for prostate biopsy. Therefore, studies reporting only biopsy results when the mpMRI was positive (eg, obtained through MRI-targeted, guided, or fusion biopsies with added systematic biopsies) were not included in this review.

3.6.3. *Impact on clinical practice and research*

It is now well established that mpMRI is a sensitive tool for detecting aggressive PCa [1–3,69]. However several reasons preclude its broad use as a triage test before biopsy.

Firstly, the population referred to prostate biopsy is not standardised. The large range of reported prevalence for overall PCa and csPCa suggests substantial heterogeneity in the way patients are selected for biopsy. Owing to this heterogeneity, we did not provide a pooled estimate for mpMRI NPV. The role of mpMRI as a triage test before prostate biopsy should be evaluated in the broader context of the selection of patients with a suspicion of (aggressive) PCa. In a recent retrospective study of 514 patients, mpMRI NPV for Gleason ≥7 cancers was 91% when the PSA density was ≤0.2 ng/ml/ml, and only 71% when the PSA density was >0.2 ng/ml/ml ($p = 0.003$) [70]. In another series of 288 biopsy-naïve patients, no csPCa (Gleason score ≥7 or maximum cancer core length ≥4 mm) was found in 44 patients with a PSA density of <0.15 ng/ml/ml and a PI-RADS v2 score of <3/5 [71]. We believe that such prestratification of the risk of csPCa is an interesting way for rationalising the use of mpMRI before biopsy. Patients found at very low risk would be spared both mpMRI and biopsy. Patients at a low risk—for whom mpMRI would have an NPV high enough to be used as a triage test—could avoid biopsy in case of negative mpMRI. Patients at a higher risk would need biopsy even in case of negative mpMRI. Many tools can be used to risk stratify the population of patients referred to biopsy, ranging from simple parameters such as PSA density to more complicated risk calculators [72,73]. The impact of these tools on the NPV of prebiopsy mpMRI needs to be carefully evaluated, both in the biopsy-naïve and in the repeat biopsy setting. For the moment, it is impossible to make any recommendations on the best way to risk stratify patients before referring them for mpMRI.

Secondly, the large variability in the definition of csPCa precludes any definitive conclusion on the ability of mpMRI to rule out aggressive cancer. The issue of the most appropriate definition of csPCa on biopsy is complex, since biopsy results may accurately reflect neither tumour burden nor aggressiveness. Nonetheless, there is an urgent need to standardise the histological definition(s) of csPCa, to allow meaningful comparisons between studies.

Thirdly, the specificity of mpMRI remains moderate, and there is a substantial proportion of false positives in the lesions scored 3/5 or 4/5 [1,74,75], even with the new PI-RADS v2 score [76]. In a series of 62 patients with 116 lesions biopsied under magnetic resonance/ultrasound fusion, the overall cancer detection rates for PI-RADS v2 scores of 3/5 and 4/5 were only 15.8% and 29.8%, respectively [77]. In theory, a triage test used to rule out a disease needs to be highly sensitive for this disease. However, if its specificity is too low, it will be clinically useless since most patients will be positive, whether they have the disease or not. Therefore, if mpMRI is to be used as a triage test in the future, there is a need to improve its specificity. This could be achieved by a continuous refinement of scores [78]. Promising results in characterising csPCa have also been reported with a quantitative analysis [79].

Finally, all published studies were conducted in specialised centres. The broad use of mpMRI as a triage test assumes good interobserver reproducibility. Unfortunately, interobserver reproducibility of existing scoring systems remains moderate [62,63,80] even with the use of the PI-RADS v2 score [80,81]. Studies evaluating on a large scale the reproducibility of mpMRI findings between expert and nonexpert centres are currently lacking.

3.6.4. How this review compares with other reviews

Three systematic reviews (including two meta-analyses) regarding the role of mpMRI in localised PCa have been published recently [4–6]. Crucially, all three reviews focused exclusively on the sensitivity of mpMRI-targeted, guided, or fusion biopsies in diagnosing overall PCa and csPCa, using TRUS-guided prostate biopsies as reference standards. The impact of systematic biopsies on the outcome was not addressed in any of the reviews, within either the index test or the reference standard. Our review had a totally different research question and objective, focusing on NPV of mpMRI to see if a negative mpMRI can avoid the need for a prostate biopsy. As MRI-targeted/guided/fusion biopsies are not relevant if the mpMRI was negative for cancer, it can be argued that the three reviews assessed a different index test altogether. As such, we believe that the findings of this review are novel and unique, and pave the way for further focused clinical studies.

3.6.5. Strengths and limitations

The current study represents the first systematic review addressing the role of mpMRI as a triage test before biopsy. The review elements were developed in conjunction with a multidisciplinary panel of experts (EAU Prostate Cancer Guidelines Panel), which included a patient representative, and the review was performed robustly in accordance with recognised standards. However, it is limited by the major heterogeneity of the existing literature in patient population, study design, and definitions of positive mpMRI and csPCa. It highlighted further areas of research that could help in defining the best use of mpMRI in the early detection of aggressive PCa in the future.

4. Conclusions

Although mpMRI can detect aggressive PCa with excellent sensitivity, a definitive conclusion on its role as a triage test before prostate biopsy will be possible only when three main issues are addressed. Firstly, because NPV depends on prevalence, and because overall PCa and csPCa prevalence was highly variable in the published series, it becomes mandatory to define the optimal way to pre-evaluate the risk of csPCa in patients with a suspicion of PCa. Depending on the risk category, mpMRI could then be used to obviate biopsies or not. Secondly, there is a need for consensus definitions of csPCa on biopsy findings to allow interstudy comparisons. Thirdly, although efforts have been made to standardise mpMRI technical protocols and interpretation in the past few years [11,60,76], there is still a crucial need to improve mpMRI specificity and inter-reader reproducibility.

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- The European Association of Urology Guidelines Office Board
- The European Association of Urology Prostate Cancer Guideline Panel

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Acquisition of data: Rouvière, Moldovan, Van den Broeck, Yuan.
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Drafting of the manuscript: Rouvière, Moldovan, Van den Broeck, Lam.
Critical revision of the manuscript for important intellectual content: Bellmunt, van den Bergh, Bolla, Briers, Van den Broeck, Cornford, Cumberbatch, De Santis, Fossati, Gross, Henry, Joniau, Lam, Matveev, Moldovan, van der Poel, van der Kwast, Rouvière, Schoots, Wiegel, Mottet.
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Appendix A. Supplementary data

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