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Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

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Abstract

Introduction: The Prostate Imaging Reporting and Data System (PI-RADS) standardizes reporting of prostate MRI for the detection of clinically significant prostate cancer. We provide the protocol of a planned living systematic review and meta-analysis for (i) diagnostic accuracy (sensitivity and specificity), (ii) cancer detection rates of assessment categories and (iii) inter-reader agreement.

Methods and analysis: Retrospective and prospective studies reporting on at least one of the outcomes of interest are included. Each step that requires literature evaluation and data extraction is performed by two independent reviewers. Since PI-RADS is intended as a living document itself, a 12-month update cycle of the systematic review and meta-analysis planned.

This protocol is in accordance with the PRISMA-P statement. The search strategy including databases, study eligibility criteria, index and reference test definitions, outcome definitions and data analysis processes are detailed. A full list of extracted data items is provided.

Summary estimates of sensitivity and specificity (for PI-RADS ≥ 3 and PI-RADS ≥ 4 considered positive) are derived with bivariate binomial models. Summary estimates of cancer detection rates are calculated with random intercept logistic regression models for single proportions. Summary estimates of inter-reader agreement are derived with random effects models.

Ethics and dissemination: No original patient data is collected, ethical review board approval therefore is not necessary. Results are published in peer reviewed, open-access scientific journals. We make the collected data accessible as supplemental material to guarantee transparency of results.

Strengths and limitations of this study

- We establish an evidence-base for the diagnostic performance (diagnostic accuracy, cancer detection rates, inter-reader agreement) of PI-RADS that is continuously updated.
- Since PI-RADS is itself intended as a living document, our data synthesis will adapt accordingly if a new version of PI-RADS is released.
- The growing body of evidence will allow subgroup analyses for PI-RADS subcategories.
- We expect the majority of included studies to be retrospective cohort studies. This will affect the certainty of evidence that is generated by our project.

Introduction

Prostate MRI (magnetic resonance imaging) has emerged as a fundamental tool in the diagnostic pathway for prostate cancer [1]. Recently, it has been strongly recommended by international guidelines for diagnosis in various clinical settings [2,3] – including biopsy naïve patients and patients with prior negative biopsy and persistent suspicion of prostate cancer. Because of these strong recommendations, the number of prostate MRI examinations performed will substantially increase throughout the next years.

The interpretation of prostate MRI is standardized with a formal lexicon: the PI-RADS (Prostate Imaging Reporting and Data System). PI-RADS was introduced in 2012 [4], has been updated to version 2.0 (v2.0) in 2015 [5] and moved to version 2.1 (v2.1) in 2019 [6]. Analysis of T2-weighted, diffusion-weighted (DWI) and contrast enhanced images lead to assessment categories 1 to 5, for single lesions and the entire prostate. The higher the assessment category, the higher the probability of clinically significant cancer. The interpretation lexicon has been updated in each iteration of PI-RADS, meaning changes in MRI descriptor definition and influence of the single imaging sequences on final assessment categories have taken place. The PI-RADS lexicon is explicitly designed as a living document [7], meaning that the interpretation lexicon is adapted as evidence about the diagnostic performance is generated.

Currently, there is still more evidence regarding the v2.0 lexicon as compared to v2.1 lexicon. Regarding diagnostic accuracy, in 2017 Woo et al. performed a meta-analysis of 21 studies (3857 patients) using PI-RADv2.0 and reported a pooled sensitivity of 89% and a pooled specificity of 73% [8]. For PI-RADSv2.1, Park et al. performed a similar analysis in 2021 and reported a pooled sensitivity of 87% and specificity of 74% [9]. This initial analysis includes data from 10 studies and 1240 patients. The cancer detection rates of PI-RADSv2.0 have been estimated with 8% for PI-RADS 2, 13% for PI-RADS 3, 40% for PI-RADS 4 and 69% for PI-RADS

5 [10]. For v2.1 an initial systematic review and meta-analysis reported cancer detection rates of 2% for PI-RADS 1, 4% for PI-RADS 2, 20% for PI-RADS 3, 52% for PI-RADS 4 and 89% for PI-RADS 5 (lesion level analysis) [11]. The PI-RADS lexicon does, in the current edition, not give numeric definitions of the expected cancer rates in the assessment categories. Furthermore, no management recommendations are linked to the assessment categories.

To account for the continuously generated evidence of the diagnostic performance of PI-RADS and expected future iterations of the lexicon (with changes in descriptor definitions and assessment category definitions, and therefore expected changes in diagnostic performance), we want to establish a living systematic review and meta-analysis. This living review will estimate the diagnostic accuracy of the current PI-RADS (sensitivity and specificity), the cancer detection rates (CDR) of the assessment categories and inter-reader agreement of category assignment. We plan to perform update searches and analyses in 12-month cycles.

Our objective is the implementation of a living systematic review and meta-analysis of the diagnostic performance of prostate MRI with PI-RADS assessment (intervention, v2.1 and upcoming versions considered) for the detection of prostate cancer (outcome) in patients with suspicion for prostate cancer (participants). Diagnostic performance of prostate MRI will not be compared to another diagnostic test (comparator), reference standard is histopathology.

Methods and analysis

Study design and registration

This is a systematic review protocol, it follows the PRISMA-P (preferred reporting items for systematic reviews and meta-analyses – protocols) guidelines and format [12]. The systematic review has been registered with PROSPERO (international prospective register of systematic reviews) [*for peer review: following the recommendations of PROSPERO, registration will be made after peer review of this protocol*]. The PRISMA-P checklist for our protocol is enclosed as a supplement.

Study eligibility criteria

We include prospective and retrospective studies reporting on the diagnostic accuracy, and/or cancer detection rates of PI-RADS and/or inter-reader agreement of PI-RADS rating, starting with PI-RADSv2.1. Studies that use older versions of the lexicon are not considered. Studies reporting on a subset of PI-RADS categories are eligible. We consider studies published as full text in English. Date restriction is applied, considered studies need to be conducted in 2019 or later, that is after the release of the current PI-RADSv2.1. Studies are still considered as eligible if included patients were examined prior to this date but have been re-interpreted by blinded readers according to the current PI-RADS.

Study population

Our target populations are men with suspicion for prostate cancer, either biopsy naïve or with a prior negative biopsy. Biopsy naïve patients have a higher pretest probability for clinically significant cancer [13]. Biopsy status will be considered as a covariate in our analysis. Patients with known malignancy at the date of prostate MRI or with prior treatment of the prostate are not considered eligible.

Index test

Prostate MRI read according to the current PI-RADS (version 2.1 at the time of writing this protocol) is the diagnostic test of interest. We record MRI parameters of single studies to account for deviations from the proposed imaging protocol [14]. Experience of the involved radiologist(s) is recorded. We document whether MRI reading is performed without knowledge of the histopathological result. We investigate diagnostic performance on lesion level (up to four lesions per patient are possible) and patient level (equals highest assigned lesion category compared to overall histopathological result).

Comparators

Diagnostic accuracy and cancer detection rates of PI-RADS will not be compared to another diagnostic test.

Reference Test

Histopathological verification of suspicious lesions and the prostate can be performed in several ways. The type of targeted lesion biopsy is recorded (cognitive fusion, transrectal ultrasound MRI fusion, transperineal MRI ultrasound fusion, in-bore). A systematic biopsy and additional MRI-directed perilesional biopsies may also be performed. We record the type and result of targeted biopsy, type of systematic biopsy (if any) and type of perilesional biopsies (if any). Histopathological upgrade of targeted biopsies given the information from systematic biopsy is recorded. Furthermore, analysis of prostatectomy specimen is eligible as reference standard.

Outcomes

Primary outcome is the detection (sensitivity and specificity, cancer detection rates) of clinically significant cancer. The most widely adapted procedure in the literature regarding PI-RADS is to consider any occurrence of a histopathological Gleason pattern ≥ 3+4 as clinically

significant [10,11]. The PI-RADS lexicon offers a more elaborate definition, which is more challenging to establish in clinical routine: “Gleason score ≥ 7, including 3+4 with prominent but not predominant Gleason 4 component, and/or volume > 0.5cc, and/or extraprostatic extension” [14]. Especially the last point is, given that histopathological verification is performed by targeted lesion biopsy ± systematic biopsy (this is the case in the majority of individual cases and studies), often not possible to establish prior to surgery. Type of definition of clinically significant cancer will be considered as a covariate. Analysis is performed on lesion level (each lesion observed in the MRI examination, up to four lesions per patient, targeted biopsy as reference standard) and patient level (highest PI-RADS category as index test, lesion and systematic biopsy and (if performed) perilesional biopsy or prostatectomy as reference standard).

Secondary outcomes are the detection (sensitivity and specificity, cancer detection rates) of insignificant cancer, any cancer, Gleason ≥ 4+3 (if reported) and ≥ 3+4 with cribriform growth pattern (if reported). Although the PI-RADS lexicon explicitly does not aim at the detection of clinically insignificant cancer [14], knowledge about occurrence of these cancers is still important from a public health perspective. Patients with a diagnosis of clinically insignificant cancer will be closely monitored with active surveillance, including serial PSA testing, MRI and biopsies [15]. For primary outcome and secondary outcomes, we investigate the scenarios PI-RADS ≥ 3 and ≥ 4 considered positive for the estimation of sensitivity and specificity.

Inter-reader agreement of lesion and patient classification with PI-RADS (Cohen’s kappa-values) is defined as a secondary outcome.

Information sources and search strategy

We search the following databases for published studies: MEDLINE, Embase, Cochrane Library, ISRCTN (https://www.isrctn.com/). Furthermore, we search ClinicalTrials.gov, ICTRP (https://www.who.int/clinical-trials-registry-platform) and Deutsches Register Klinischer Studien for ongoing studies or completed studies not (yet) published. Time restriction will be applied. We consider all studies conducted from 03/2019 onwards – PI-RADSv2.1 has been published at 03/2019. Bibliographies of included articles will be manually checked for further eligible studies. The search strategy will be re-used for the planned update cycles in the living systematic review framework.

Our MEDLINE search is structured as follows: *((PIRADS) OR ("PI RADS") OR ("prostate imaging reporting and data system")) AND ("2019/03/01" [Date - Publication]: "3000/12/12" [Date - Publication])*. Searches of the other databases will be adapted accordingly, it will be doublechecked whether the inclusion of "*PI-RADS*" and "*prostate imaging: reporting and data system*" is relevant in the search strategies. This proposed search strategy is more inclusive than the strategy employed by Woo and colleagues for a comparable systematic review of the diagnostic accuracy of PI-RADSv2.0 [8].

Data management

Search results from the different databases are combined in a dedicated software environment (e.g. Rayyan, https://www.rayyan.ai/), duplicates will be removed. Backup copies are generated after the single database searches.

Selection process

Two independent reviewers evaluate eligibility of search results. First, selection is performed on title and abstract basis. Studies considered relevant (or potentially relevant) based on title and abstract screening are further considered based on their full text (full text screening). In

each step, discrepancies will be resolved by discussion and by consultation of a third reviewer, if needed. The reason for exclusion is recorded in each selection step.

Data collection process

Two independent reviewers extract data from the included studies in duplicate spreadsheets with predefined data items. We define a core set of data items (compare for table 1 and 2, which also list all extracted data items). If any items of this set are missing, authors of primary studies are contacted (at least twice) to obtain this missing data.

Table 1: Extracted data items – meta-data, MRI technique, reference test and patient characteristics

Data item(s)	levels	explanation
Meta-data of study†		journal / year / volume / authors
Study type†	prospective or retrospective observational or interventional	
MRI technique, index test		
vendor		manufacturer, magnet product type
field strength†	3 Tesla, 1.5 Tesla, other	
sequence parameters T2w		sequence type, slice thickness, gap, planes obtained
sequence parameters DWI		sequence type, slice thickness, gap, b-values used
sequence parameters DCE		sequence type, slice thickness, gap, temporal resolution
endorectal coil used	categorical	
spasmolytic agent used	categorical	
number of radiologists involved	numerical	
experience of radiologists involved	numerical (in years)	most experienced radiologist considered for diagnostic accuracy estimation
Reference test		
target lesion biopsy technique†	cognitive ultrasound fusion, MRI US fusion transrectal, MRI US fusion transperineal, in-bore	additionally: mean/median number of biopsy cores per lesion

systematic biopsy technique†	not performed, standard 8-12 cores, extended systematic biopsy (e.g. Ginsburg scheme), template biopsy, prostatectomy specimen used	additionally: mean/median number of systematic biopsy cores taken per patient
MRI-directed perilesional biopsies	categorical	if available, mean/median number of perilesional biopsies per lesion is recorded
Patient characteristics		
number of patients and/or number of lesions†	numerical	if information for lesion localization (peripheral zone and transition zone) is reported separately, this information is recorded
mean/median age†	numerical	
mean/median PSA†	numerical	
mean/median prostate volume	numerical	

PSA: prostate specific antigen, MRI: magnetic resonance imaging, US: ultrasound.
†: core data items - If missing, authors of the primary studies are contacted twice to obtain the missing data.

Table 2: Extracted data items - outcome data

Data item(s)	levels	explanation
Outcome data		
definition of csCA used	PI-RADS Lexicon definition, other definition	exact definition is recorded
number of lesions and patients with csCA†	numerical	
number of lesions and patients with ncsCA	numerical	
number of lesions and patients with Gleason score ≥ 4+3	numerical	
number of lesions and patients with Gleason score ≥ 3+4 and cribriform growth pattern	numerical	
sensitivity and specificity†	numerical	- reported in paper or reconstructed from presented data, 2x2

		contingency tables from paper or reconstructed are recorded - Scenarios PI-RADS ≥ 3 and PI-RADS ≥ 4 considered positive are examined - data is extracted on lesion level and patient level, for all extracted definitions of prostate cancer (csCA, ncsCA, Gleason score ≥ 4+3 and ≥ 3+4 with cribriform growth pattern)
cancer detection rates†	numerical	- number of malignant cases in each reported PI-RADS category divided by all cases in each PI-RADS category - data is extracted on lesion level and patient level, for all extracted definitions of prostate cancer (csCA, ncsCA, Gleason score ≥ 4+3 and ≥ 3+4 with cribriform growth pattern) - subcategories in PI-RADS 3 and 4 are recorded separately, if information is available - for low PI-RADS categories, the information will also be expressed as negative predictive value
reader agreement†	type of obtained inter-reader agreement metric, numerical value of metric	

csCA: clinically significant cancer, ncsCA: clinically non-significant/insignificant cancer

†: core data items (reporting of at least one defined outcome is required). If missing, authors of the primary studies are contacted twice to obtain the missing data.

Risk of bias assessment

For the evaluation of risk of bias and applicability of results (study level analysis each) the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) framework is used [16]. Two independent reviewers evaluate risk of bias and applicability of results in the domains patient selection, index test, reference standard and flow and timing (the latter not for applicability

evaluation). Discrepancies are resolved by discussion and by consultation of a third reviewer, if needed. From the results of the QUADAS-2 analysis, we will infer the overall risk of bias for obtained results. Studies are not excluded from data synthesis based on the QUADAS-2 evaluation alone.

Data synthesis and statistical analysis

Data describing patient populations of the included studies (e.g. mean age, mean PSA value, mean prostate volume, prior biopsy status) is presented in table format. Data synthesis of outcomes (diagnostic accuracy in terms of sensitivity and specificity, cancer detection rates, inter-reader agreement in terms of Cohen's kappa values) is performed given a set of homogeneous studies is identified. The required minimum set of homogeneous study characteristics is: (i) reading of prostate MRI is performed without knowledge of the histopathological results (ii) MRI is performed according to PI-RADS recommendations, (iii) for inter-reader agreement, comparable metrics are reported.

We derive pooled estimates of sensitivity and specificity with bivariate binomial models [17]. A summary ROC curve with a 95% confidence region is derived for graphical representation. We examine the scenarios with PI-RADS ≥ 3 and PI-RADS ≥ 4 considered as a positive test on lesion level and patient level (overall, four scenarios). Possible publication bias is visually assessed with funnel plots, Deek's test will be used to test for asymmetry [18]. Coupled forest plots of sensitivity and specificity and correlation between sensitivity and 1-specificity are analyzed for assessment of heterogeneity of results [19].

We expect cancer rates in the assessment categories to vary across studies; partly because of different local reading standards, partly because of local differences/thresholds for referral to prostate MRI and targeted biopsy, partly because of different pretest probabilities and thus differences in the patient cohorts examined. In other words, we assume a certain degree of

clinical and methodological heterogeneity between studies and do not expect results to vary because of random sampling error alone. For this reason we employ random intercept logistic regression models for meta-analysis of single proportions to derive summary estimates for cancer detection rates of the PI-RADS categories [20] and subcategories of PI-RADS 3 and 4. Heterogeneity of reported cancer detection rates is assessed with Higgins' I^2 statistic, with I^2>50% denoting substantial heterogeneity [19].

Meta-regression with the following covariates (if data is sufficient) is performed to examine possible causes of heterogeneity (diagnostic accuracy and cancer detection rates): type of study population (prior biopsy status), multiparametric vs biparametric MRI, definition of clinically significant cancer, type of lesion verification, lesion localization (peripheral zone vs transition zone), reader experience, pretest probability in the study population. Subgroup analyses of covariates are performed for univariate analyses.

The summary measure for inter-reader agreement (Cohen's kappa values) will be derived with a random effects model. This approach follows the method proposed by Sun [21]. We examine the role of reader experience as a covariate – two highly experienced readers can be expected to agree more often compared to two relatively unexperienced readers or two readers with different levels of experience.

If quantitative data synthesis is not considered appropriate for one or more defined outcomes, a synopsis of findings is given table format. Order of presentation is stratified by risk of bias and definition of clinically significant cancer used.

All statistical analyses are conducted using R (https://www.R-project.org/) [22].

GRADE assessment

Quality of evidence per outcome is analyzed according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) System [23], results from the QUADAS-2 analysis are used for risk of bias assessment in this context. Certainty of evidence is rated as high, moderate, low or very low. Results are made available in a summary of findings table.

Patient and public involvement

In the development phase of the project the Bundesverband Prostatakrebs Selbsthilfe e.V. (https://prostatakrebs-bps.de/) was involved in defining relevant research questions. The Bundesverband Prostatakrebs Selbsthilfe e.V. agreed to disseminate results in their network of support groups.

Living review framework

We plan to implement a 12-month cycle to update our literature search, study selection and data analysis. This is because an accumulation of evidence about the diagnostic performance of PI-RADS can be expected, especially for subcategories in categories 3 and 4. Furthermore, PI-RADS is itself intended as a living diagnostic algorithm [7] – that is, new iterations can be expected. Given that the diagnostic algorithm is further adapted, changes in diagnostic accuracy can be expected. If a new version of PI-RADS is released, our literature search strategy will remain unchanged. Data collection and reporting of results will pertain to the current version of PI-RADS.

We consider the living systematic review framework suitable for our project, because the scope and needs address the three demands as expressed in the initial discussion of living systematic reviews by Elliott et al. [24]:

(i) up-to-date information is important for decision making: For informed, shared decision making how to proceed with the result of a prostate MRI examination, accurate estimates of diagnostic accuracy of PI-RADS and cancer detection rates of the categories are crucial. Furthermore, management recommendations are planned to be linked to assessment categories in future versions of PI-RADS [14]. Before recommending biopsy, for example, there need to be an established expected cancer rate for a certain assessment category.

(ii) Certainty in the existing evidence is low: At the moment, we have limited evidence (meta-analyses do exist for diagnostic accuracy and cancer detection rates of PI-RADSv2.1, however they include relatively few patients [9,11]). Furthermore, we see a need to systematically review the performance of subcategories in PI-RADS categories 3 and 4.

(iii) There will be new research evidence: The publication field of prostate MRI and PI-RADS is highly dynamic, the number of relevant papers is increasing at a fast rate. We expect new accumulating evidence especially for subcategories (different lesion entities in categories 3 and 4). Furthermore, new evidence will be generated given a new iteration of PI-RADS is published. A timely evidence synthesis is warranted in this case.

Our search strategy and data used for analyses will be published as supplement to the systematic review and meta-analysis.

Ethics and dissemination

No original data is collected in this systematic review and meta-analysis, ethical review board approval therefore is not required. Results are published in peer reviewed, open-access

scientific journals. We make the collected data accessible as supplemental material to guarantee transparency of results.

Discussion

With the recently put forward strong recommendations for prostate MRI prior to biopsy in various national (e.g. [15,25]) and international guidelines [2,3], a rapidly increasing volume of prostate MRI examinations can be expected in the next years. The increasing number of examinations performed requires a standardized, evidence-based diagnostic workflow to streamline patient management.

PI-RADS, having been established in 2012, offers this standardization. PI-RADS provides a universally understood reporting language on the descriptor level and works well as a risk stratification tool for clinically significant prostate cancer [8]. For version 2.0, a systematic review and meta-analysis of inter-reader agreement reported an overall moderate to substantial agreement for PI-RADS category assignment [26]. The diagnostic accuracy of PI-RADS has been subject of a multitude of studies – initial estimates for sensitivity, specificity and the cancer detection rates are available for version 2.1 [9,11]. Park et al. report a pooled sensitivity/specificity of 81%/82% when PI-RADS ≥ 4 is used as a diagnostic threshold, compared to a sensitivity/specificity of 94%/56% when PI-RADS ≥ 3 is used [9]. Reported 95% confidence intervals in this analysis are relatively large, especially for specificity: for the 56% estimate, it ranges from 35 to 97% [9].

As evidence about the diagnostic performance of PI-RADS accrues, these estimates will become more precise. Or, given considerable heterogeneity of estimates between studies, the identification of covariates that affect diagnostic accuracy and cancer detection rates becomes possible. This knowledge could ultimately be included into PI-RADS itself or future guidelines.

At the moment, assessment categories 3 and 4 are assigned to a heterogeneous group of lesions each. For example, in the transition zone assessment category 3 comprises lesions with different appearance in T2 weighted images (atypical nodules and heterogenous lesions with obscured margins). Costa et al. report a cancer rate of 6% and 11% for these two lesion types, although this difference is not statistically significant in their study [27]. If there are systematic differences of cancer rate between lesion subtypes in the same PI-RADS assessment category, this might influence the planned linking of management recommendations to assessment categories [14].

Our living systematic review framework establishes an evidence base for precise estimates of diagnostic accuracy of the current PI-RADS (with different thresholds considered positive), the cancer detection rates of assessment categories and subcategories, and inter-reader agreement. The results can be employed by urologists, radiologists and patients for decision making after prostate MRI and help in the development of PI-RADS itself and future guidelines.

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Competing interests statement

Ivo Schoots is a full panel member of the PI-RADS steering committee (ASR/ESR). Fabian Bamberg has received unrestricted research grants and speaker bureau fees from Bayer Healthcare and Siemens Healthineers. Christian Gratzke has received grants/research support from Astellas Pharma, Bayer, GSK, MSD and Recordati and honoraria/consultation fees from Amgen, Astellas Pharma, Bayer, GSK, Ipsen, Janssen, Lilly Pharma, Recordati, Pfizer, Rottapharm, STEBA Biotech. Otherwise, we do not have a competing interest to declare.

Supplementary Material

PRISMA-P checklist

Authors' contributions

concept and design: Oerther, Schmucker, Schwarzer, Schoots, Benndorf

drafting and revising the manuscript: Oerther, Schmucker, Schwarzer, Schoots, Sigle, Gratzke, Bamberg, Benndorf

statistical planning: Schwarzer, Benndorf

guarantor of the review: Benndorf

Data statement

No data was collected for this protocol.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol* for "Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol"

Section and topic	Item No	Checklist item	Realized, line number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Will be registered after peer review of the protocol
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	5-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	368-372
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	355-357
Sponsor	5b	Provide name for the review funder and/or sponsor	355-357
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	355-357
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	91-99
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	103-107
METHODS			

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	103-107, 117-125
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	181-188
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	189-195
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	197-207
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	201, 207, 222
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	207-210
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	211-214
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	216-219
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	221-228
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	231-239
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	238-244, 261-265
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	253-258
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	266-268
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	241-244
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	271-275

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

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Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

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Abstract

Introduction: The Prostate Imaging Reporting and Data System (PI-RADS) standardizes reporting of prostate MRI for the detection of clinically significant prostate cancer. We provide the protocol of a planned living systematic review and meta-analysis for (i) diagnostic accuracy (sensitivity and specificity), (ii) cancer detection rates of assessment categories and (iii) inter-reader agreement.

Methods and analysis: Retrospective and prospective studies reporting on at least one of the outcomes of interest are included. Each step that requires literature evaluation and data extraction is performed by two independent reviewers. Since PI-RADS is intended as a living document itself, a 12-month update cycle of the systematic review and meta-analysis planned.

This protocol is in accordance with the PRISMA-P statement. The search strategy including databases, study eligibility criteria, index and reference test definitions, outcome definitions and data analysis processes are detailed. A full list of extracted data items is provided.

Summary estimates of sensitivity and specificity (for PI-RADS ≥ 3 and PI-RADS ≥ 4 considered positive) are derived with bivariate binomial models. Summary estimates of cancer detection rates are calculated with random intercept logistic regression models for single proportions. Summary estimates of inter-reader agreement are derived with random effects models.

Ethics and dissemination: No original patient data is collected, ethical review board approval therefore is not necessary. Results are published in peer reviewed, open-access scientific journals. We make the collected data accessible as supplemental material to guarantee transparency of results.

Strengths and limitations of this study

- We establish an evidence-base for the diagnostic performance (diagnostic accuracy, cancer detection rates, inter-reader agreement) of PI-RADS that is continuously updated.
- Since PI-RADS is itself intended as a living document, our data synthesis will adapt accordingly if a new version of PI-RADS is released.
- The growing body of evidence will allow subgroup analyses for PI-RADS subcategories.
- We expect the majority of included studies to be retrospective cohort studies. This will affect the certainty of evidence that is generated by our project.

Introduction

Prostate MRI (magnetic resonance imaging) has emerged as a fundamental tool in the diagnostic pathway for prostate cancer [1]. Recently, it has been strongly recommended by international guidelines for diagnosis in various clinical settings [2,3] – including biopsy naïve patients and patients with prior negative biopsy and persistent suspicion of prostate cancer. Because of these strong recommendations, the number of prostate MRI examinations performed will substantially increase throughout the next years.

The interpretation of prostate MRI is standardized with a formal lexicon: the PI-RADS (Prostate Imaging Reporting and Data System). PI-RADS was introduced in 2012 [4], has been updated to version 2.0 (v2.0) in 2015 [5] and moved to version 2.1 (v2.1) in 2019 [6]. Analysis of T2-weighted, diffusion-weighted (DWI) and contrast enhanced images lead to assessment categories 1 to 5, for single lesions and the entire prostate. The higher the assessment category, the higher the probability of clinically significant cancer. The interpretation lexicon has been updated in each iteration of PI-RADS, meaning changes in MRI descriptor definition and influence of the single imaging sequences on final assessment categories have taken place. The PI-RADS lexicon is explicitly designed as a living document [7], meaning that the interpretation lexicon is adapted as evidence about the diagnostic performance is generated.

Currently, there is still more evidence regarding the v2.0 lexicon as compared to v2.1 lexicon. Regarding diagnostic accuracy, in 2017 Woo et al. performed a meta-analysis of 21 studies (3857 patients) using PI-RADv2.0 and reported a pooled sensitivity of 89% and a pooled specificity of 73% [8]. For PI-RADSv2.1, Park et al. performed a similar analysis in 2021 and reported a pooled sensitivity of 87% and specificity of 74% [9]. This initial analysis includes data from 10 studies and 1240 patients. The cancer detection rates of PI-RADSv2.0 have

been estimated with 8% for PI-RADS 2, 13% for PI-RADS 3, 40% for PI-RADS 4 and 69% for PI-RADS 5 [10]. For v2.1 an initial systematic review and meta-analysis reported cancer detection rates of 2% for PI-RADS 1, 4% for PI-RADS 2, 20% for PI-RADS 3, 52% for PI-RADS 4 and 89% for PI-RADS 5 (lesion level analysis) [11]. The PI-RADS lexicon does, in the current edition, not give numeric definitions of the expected cancer rates in the assessment categories. Furthermore, no management recommendations are linked to the assessment categories.

To account for the continuously generated evidence of the diagnostic performance of PI-RADS and expected future iterations of the lexicon (with changes in descriptor definitions and assessment category definitions, and therefore expected changes in diagnostic performance), we want to establish a living systematic review and meta-analysis. This living review will estimate the diagnostic accuracy of the current PI-RADS (sensitivity and specificity), the cancer detection rates (CDR) of the assessment categories and inter-reader agreement of category assignment. We plan to perform update searches and analyses in 12-month cycles.

Our objective is the implementation of a living systematic review and meta-analysis of the diagnostic performance of prostate MRI with PI-RADS assessment (intervention, v2.1 and upcoming versions considered) for the detection of prostate cancer (outcome) in patients with suspicion for prostate cancer (participants). Diagnostic performance of prostate MRI will not be compared to another diagnostic test (comparator), reference standard is histopathology.

Methods and analysis

Study design and registration

This is a systematic review protocol, it follows the PRISMA-P (preferred reporting items for systematic reviews and meta-analyses – protocols) guidelines and format [12]. The systematic review has been registered in PROSPERO (CRD42022343931). The PRISMA-P checklist for our protocol is enclosed as a supplement.

Study eligibility criteria

We include prospective and retrospective studies reporting on the diagnostic accuracy, and/or cancer detection rates of PI-RADS and/or inter-reader agreement of PI-RADS rating, starting with PI-RADSv2.1. Studies that use older versions of the lexicon are not considered. Studies reporting on a subset of PI-RADS categories are eligible. We consider studies published as full text in English. Date restriction is applied, considered studies need to be conducted in 2019 or later, that is after the release of the current PI-RADSv2.1. Studies are still considered as eligible if included patients were examined prior to this date but have been re-interpreted by blinded readers according to the current PI-RADS.

Study population

Our target populations are men with suspicion for prostate cancer, either biopsy naïve or with a prior negative biopsy. Biopsy naïve patients have a higher pretest probability for clinically significant cancer [13]. Biopsy status will be considered as a covariate in our analysis. Patients with known malignancy at the date of prostate MRI or with prior treatment of the prostate are not considered eligible.

Index test

Prostate MRI read according to the current PI-RADS (version 2.1 at the time of writing this protocol) is the diagnostic test of interest. We record MRI parameters of single studies to account for deviations from the proposed imaging protocol [14]. Experience of the involved radiologist(s) is recorded. We document whether MRI reading is performed without knowledge of the histopathological result. We investigate diagnostic performance on lesion level (up to four lesions per patient are possible) and patient level (equals highest assigned lesion category compared to overall histopathological result).

Comparators

Diagnostic accuracy and cancer detection rates of PI-RADS will not be compared to another diagnostic test.

Reference Test

Histopathological verification of suspicious lesions and the prostate can be performed in several ways. The type of targeted lesion biopsy is recorded (cognitive fusion, transrectal ultrasound MRI fusion, transperineal MRI ultrasound fusion, in-bore). A systematic biopsy and additional MRI-directed perilesional biopsies may also be performed. We record the type and result of targeted biopsy, type of systematic biopsy (if any) and type of perilesional biopsies (if any). Histopathological upgrade of targeted biopsies given the information from systematic biopsy is recorded. Furthermore, analysis of prostatectomy specimen is eligible as reference standard.

Outcomes

Primary outcome is the detection (sensitivity and specificity, cancer detection rates) of clinically significant cancer. The most widely adapted procedure in the literature regarding PI-RADS is to consider any occurrence of a histopathological Gleason pattern ≥ 3+4 as clinically significant [10,11]. The PI-RADS lexicon offers a more elaborate definition, which is

more challenging to establish in clinical routine: “Gleason score ≥ 7, including 3+4 with prominent but not predominant Gleason 4 component, and/or volume > 0.5cc, and/or extraprostatic extension” [14]. Especially the last point is, given that histopathological verification is performed by targeted lesion biopsy ± systematic biopsy (this is the case in the majority of individual cases and studies), often not possible to establish prior to surgery. Type of definition of clinically significant cancer will be considered as a covariate. Analysis is performed on lesion level (each lesion observed in the MRI examination, up to four lesions per patient, targeted biopsy as reference standard; studies reporting only the results of targeted biopsies without additional systematic biopsy are eligible for the lesion level analysis only) and patient level (highest PI-RADS category as index test, lesion and systematic biopsy and (if performed) perilesional biopsy or prostatectomy as reference standard).

Secondary outcomes are the detection (sensitivity and specificity, cancer detection rates) of insignificant cancer, any cancer, Gleason ≥ 4+3 (if reported) and ≥ 3+4 with cribriform growth pattern (if reported). Although the PI-RADS lexicon explicitly does not aim at the detection of clinically insignificant cancer [14], knowledge about occurrence of these cancers is still important from a public health perspective. Patients with a diagnosis of clinically insignificant cancer will be closely monitored with active surveillance, including serial PSA testing, MRI and biopsies [15]. For primary outcome and secondary outcomes, we investigate the scenarios PI-RADS ≥ 3 and ≥ 4 considered positive for the estimation of sensitivity and specificity.

Inter-reader agreement of lesion and patient classification with PI-RADS (Cohen’s kappa-values) is defined as a secondary outcome.

Information sources and search strategy

We search the following databases for published studies, ongoing studies or completed studies not (yet) published: MEDLINE, Embase, Cochrane Library, ISRCTN, ClinicalTrials.gov, ICTRP and Deutsches Register Klinischer Studien (DRKS). Time restriction will be applied. We consider all studies conducted from 03/2019 onwards – PI-RADSv2.1 has been published at 03/2019. Bibliographies of included articles will be manually checked for further eligible studies. The search strategy will be re-used for the planned update cycles in the living systematic review framework.

Our MEDLINE search is structured as follows: *((PIRADS) OR ("PI-RADS") OR ("prostate imaging reporting and data system")) AND ("2019/03/01" [Date - Publication]: "3000/12/12" [Date - Publication])*. Searches of the other databases are adapted accordingly. Full search strategies of all databases are provided as a supplement to this protocol.

Data management

Search results from the different databases are combined in a dedicated software environment (e.g. Rayyan, https://www.rayyan.ai/), duplicates will be removed. Backup copies are generated after the single database searches.

Selection process

Two independent reviewers evaluate eligibility of search results. First, selection is performed on title and abstract basis. Studies considered relevant (or potentially relevant) based on title and abstract screening are further considered based on their full text (full text screening). In each step, discrepancies will be resolved by discussion and by consultation of a third reviewer, if needed. The reason for exclusion is recorded in each selection step.

Data collection process

Two independent reviewers extract data from the included studies in duplicate spreadsheets with predefined data items. We define a core set of data items (compare for table 1 and 2). If any items of this set are missing, authors of primary studies are contacted (at least twice) to obtain this missing data.

Risk of bias assessment

For the evaluation of risk of bias and applicability of results (study level analysis each) the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) framework is used [16]. Two independent reviewers evaluate risk of bias and applicability of results in the domains patient selection, index test, reference standard and flow and timing (the latter not for applicability evaluation). Discrepancies are resolved by discussion and by consultation of a third reviewer, if needed. From the results of the QUADAS-2 analysis, we will infer the overall risk of bias for obtained results. Studies are not excluded from data synthesis based on the QUADAS-2 evaluation alone.

Data synthesis and statistical analysis

Data describing patient populations of the included studies (e.g. mean age, mean PSA value, mean prostate volume, prior biopsy status) is presented in table format. Data synthesis of outcomes (diagnostic accuracy in terms of sensitivity and specificity, cancer detection rates, inter-reader agreement in terms of Cohen's kappa values) is performed given a set of homogeneous studies is identified. The required minimum set of homogeneous study characteristics is: (i) reading of prostate MRI is performed without knowledge of the histopathological results (ii) MRI is performed according to PI-RADS recommendations, (iii) for inter-reader agreement, comparable metrics are reported.

We derive pooled estimates of sensitivity and specificity with bivariate binomial models [17]. A summary ROC curve with a 95% confidence region is derived for graphical representation.

We examine the scenarios with PI-RADS ≥ 3 and PI-RADS ≥ 4 considered as a positive test on lesion level and patient level (overall, four scenarios). Possible publication bias is visually assessed with funnel plots, Deek's test will be used to test for asymmetry [18]. Coupled forest plots of sensitivity and specificity and correlation between sensitivity and 1-specificity are analyzed for assessment of heterogeneity of results [19].

We expect cancer rates in the assessment categories to vary across studies; partly because of different local reading standards, partly because of local differences/thresholds for referral to prostate MRI and targeted biopsy, partly because of different pretest probabilities and thus differences in the patient cohorts examined. In other words, we assume a certain degree of clinical and methodological heterogeneity between studies and do not expect results to vary because of random sampling error alone. For this reason we employ random intercept logistic regression models for meta-analysis of single proportions to derive summary estimates for cancer detection rates of the PI-RADS categories [20] and subcategories of PI-RADS 3 and 4. Heterogeneity of reported cancer detection rates is assessed with Higgins' I^2 statistic, with I^2>50% denoting substantial heterogeneity [19].

Meta-regression with the following covariates (if data is sufficient) is performed to examine possible causes of heterogeneity (diagnostic accuracy and cancer detection rates): type of study population (prior biopsy status), magnetic field strength, multiparametric vs biparametric MRI, definition of clinically significant cancer, type of lesion verification, lesion localization (peripheral zone vs transition zone), reader experience, pretest probability and mean/median PSA in the study population. Subgroup analyses of covariates are performed for univariate analyses.

The summary measure for inter-reader agreement (Cohen's kappa values) will be derived with a random effects model. This approach follows the method proposed by Sun [21]. We

examine the role of reader experience as a covariate – two highly experienced readers can be expected to agree more often compared to two relatively unexperienced readers or two readers with different levels of experience.

If quantitative data synthesis is not considered appropriate for one or more defined outcomes, a synopsis of findings is given table format. Order of presentation is stratified by risk of bias and definition of clinically significant cancer used.

All statistical analyses are conducted using R (https://www.R-project.org/) [22].

GRADE assessment

Quality of evidence per outcome is analyzed according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) System [23], results from the QUADAS-2 analysis are used for risk of bias assessment in this context. Certainty of evidence is rated as high, moderate, low or very low. Results are made available in a summary of findings table.

Patient and public involvement

In the development phase of the project the Bundesverband Prostatakrebs Selbsthilfe e.V. (https://prostatakrebs-bps.de/) was involved in defining relevant research questions. The Bundesverband Prostatakrebs Selbsthilfe e.V. agreed to disseminate results in their network of support groups.

Living review framework

We plan to implement a 12-month cycle to update our literature search, study selection and data analysis. This is because an accumulation of evidence about the diagnostic performance of PI-RADS can be expected, especially for subcategories in categories 3 and 4. Furthermore,

PI-RADS is itself intended as a living diagnostic algorithm [7] – that is, new iterations can be expected. Given that the diagnostic algorithm is further adapted, changes in diagnostic accuracy can be expected. If a new version of PI-RADS is released, our literature search strategy will remain unchanged. Data collection and reporting of results will pertain to the current version of PI-RADS.

We consider the living systematic review framework suitable for our project, because the scope and needs address the three demands as expressed in the initial discussion of living systematic reviews by Elliott et al. [24]:

(i) up-to-date information is important for decision making: For informed, shared decision making how to proceed with the result of a prostate MRI examination, accurate estimates of diagnostic accuracy of PI-RADS and cancer detection rates of the categories are crucial. Furthermore, management recommendations are planned to be linked to assessment categories in future versions of PI-RADS [14]. Before recommending biopsy, for example, there need to be an established expected cancer rate for a certain assessment category.

(ii) Certainty in the existing evidence is low: At the moment, we have limited evidence (meta-analyses do exist for diagnostic accuracy and cancer detection rates of PI-RADSv2.1, however they include relatively few patients [9,11]). Furthermore, we see a need to systematically review the performance of subcategories in PI-RADS categories 3 and 4.

(iii) There will be new research evidence: The publication field of prostate MRI and PI-RADS is highly dynamic, the number of relevant papers is increasing at a fast rate. We expect new accumulating evidence especially for subcategories (different lesion entities in categories 3 and 4). Furthermore, new evidence will be

generated given a new iteration of PI-RADS is published. A timely evidence synthesis is warranted in this case.

Our search strategy and data used for analyses will be published as supplement to the systematic review and meta-analysis.

Ethics and dissemination

No original data is collected in this systematic review and meta-analysis, ethical review board approval therefore is not required. Results are published in peer reviewed, open-access scientific journals. We make the collected data accessible as supplemental material to guarantee transparency of results.

Discussion

With the recently put forward strong recommendations for prostate MRI prior to biopsy in various national (e.g. [15,25]) and international guidelines [2,3], a rapidly increasing volume of prostate MRI examinations can be expected in the next years. The increasing number of examinations performed requires a standardized, evidence-based diagnostic workflow to streamline patient management.

PI-RADS, having been established in 2012, offers this standardization. PI-RADS provides a universally understood reporting language on the descriptor level and works well as a risk stratification tool for clinically significant prostate cancer [8]. For version 2.0, a systematic review and meta-analysis of inter-reader agreement reported an overall moderate to substantial agreement for PI-RADS category assignment [26]. The diagnostic accuracy of PI-RADS has been subject of a multitude of studies – initial estimates for sensitivity, specificity and the cancer detection rates are available for version 2.1 [9,11]. Park et al. report a pooled sensitivity/specificity of 81%/82% when PI-RADS ≥ 4 is used as a diagnostic threshold, compared to a sensitivity/specificity of 94%/56% when PI-RADS ≥ 3 is used [9]. Reported

95% confidence intervals in this analysis are relatively large, especially for specificity: for the 56% estimate, it ranges from 35 to 97% [9].

As evidence about the diagnostic performance of PI-RADS accrues, these estimates will become more precise. Or, given considerable heterogeneity of estimates between studies, the identification of covariates that affect diagnostic accuracy and cancer detection rates becomes possible. This knowledge could ultimately be included into PI-RADS itself or future guidelines.

At the moment, assessment categories 3 and 4 are assigned to a heterogeneous group of lesions each. For example, in the transition zone assessment category 3 comprises lesions with different appearance in T2 weighted images (atypical nodules and heterogenous lesions with obscured margins). Costa et al. report a cancer rate of 6% and 11% for these two lesion types, although this difference is not statistically significant in their study [27]. If there are systematic differences of cancer rate between lesion subtypes in the same PI-RADS assessment category, this might influence the planned linking of management recommendations to assessment categories [14].

Our living systematic review framework establishes an evidence base for precise estimates of diagnostic accuracy of the current PI-RADS (with different thresholds considered positive), the cancer detection rates of assessment categories and subcategories, and inter-reader agreement. The results can be employed by urologists, radiologists and patients for decision making after prostate MRI and help in the development of PI-RADS itself and future guidelines.

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Competing interests statement

Ivo Schoots is a full panel member of the PI-RADS steering committee (ASR/ESR). Fabian Bamberg has received unrestricted research grants and speaker bureau fees from Bayer Healthcare and Siemens Healthineers. Christian Gratzke has received grants/research support from Astellas Pharma, Bayer, GSK, MSD and Recordati and honoraria/consultation fees from Amgen, Astellas Pharma, Bayer, GSK, Ipsen, Janssen, Lilly Pharma, Recordati, Pfizer, Rottapharm, STEBA Biotech. Otherwise, we do not have a competing interest to declare.

Supplementary Material

PRISMA-P checklist

Search strategies

Authors' contributions

concept and design: Oerther, Schmucker, Schwarzer, Schoots, Benndorf

drafting and revising the manuscript: Oerther, Schmucker, Schwarzer, Schoots, Sigle, Gratzke, Bamberg, Benndorf

statistical planning: Schwarzer, Benndorf

guarantor of the review: Benndorf

Data statement

No data was collected for this protocol.

Full references

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Tables

Table 1: Extracted data items – meta-data, MRI technique, reference test and patient characteristics

Data item(s)	levels	explanation
Meta-data of study†		journal / year / volume / authors
Study type†	prospective or retrospective observational or interventional	
MRI technique, index test		
vendor		manufacturer, magnet product type
field strength†	3 Tesla, 1.5 Tesla, other	
sequence parameters T2w		sequence type, slice thickness, gap, planes obtained
sequence parameters DWI		sequence type, slice thickness, gap, b-values used
sequence parameters DCE		sequence type, slice thickness, gap, temporal resolution
endorectal coil used	categorical	
spasmolytic agent used	categorical	
number of radiologists involved	numerical	
experience of radiologists involved	numerical (in years)	most experienced radiologist considered for diagnostic accuracy estimation
Reference test		
target lesion biopsy technique†	cognitive ultrasound fusion, MRI US fusion transrectal, MRI US fusion transperineal, in-bore	additionally: mean/median number of biopsy cores per lesion
systematic biopsy technique†	not performed, standard 8-12 cores, extended systematic biopsy (e.g. Ginsburg scheme), template biopsy, prostatectomy specimen used	additionally: mean/median number of systematic biopsy cores taken per patient
MRI-directed perilesional biopsies	categorical	if available, mean/median number of perilesional biopsies per lesion is recorded

Patient characteristics		
number of patients and/or number of lesions†	numerical	if information for lesion localization (peripheral zone and transition zone) is reported separately, this information is recorded
mean/median age†	numerical	
mean/median PSA†	numerical	
mean/median prostate volume	numerical	

PSA: prostate specific antigen, MRI: magnetic resonance imaging, US: ultrasound.

†: core data items - If missing, authors of the primary studies are contacted twice to obtain the missing data.

455 Table 2: Extracted data items - outcome data

Data item(s)	levels	explanation
Outcome data		
definition of csCA used	PI-RADS Lexicon definition, other definition	exact definition is recorded
number of lesions and patients with csCA†	numerical	
number of lesions and patients with ncsCA	numerical	
number of lesions and patients with Gleason score ≥ 4+3	numerical	
number of lesions and patients with Gleason score ≥ 3+4 and cribriform growth pattern	numerical	
sensitivity and specificity†	numerical	- reported in paper or reconstructed from presented data, 2x2 contingency tables from paper or reconstructed are recorded - Scenarios PI-RADS ≥ 3 and PI-RADS ≥ 4 considered positive are examined - data is extracted on lesion level and patient level, for all extracted definitions of prostate cancer (csCA, ncsCA, Gleason score ≥ 4+3 and ≥ 3+4 with cribriform growth pattern)
cancer detection rates†	numerical	- number of malignant cases in each reported PI-RADS category divided by all cases in each PI-RADS category - data is extracted on lesion level and patient level, for all extracted definitions of prostate cancer (csCA, ncsCA, Gleason score ≥ 4+3 and ≥ 3+4 with cribriform growth pattern) - subcategories in PI-RADS 3 and 4

		are recorded separately, if information is available - for low PI-RADS categories, the information will also be expressed as negative predictive value
reader agreement†	type of obtained inter-reader agreement metric, numerical value of metric	

csCA: clinically significant cancer, ncsCA: clinically non-significant/insignificant cancer

†: core data items (reporting of at least one defined outcome is required). If missing, authors of the primary studies are contacted twice to obtain the missing data.

Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

Search strategies

database	*url*	*search*
MEDLINE	https://pubmed.ncbi.nlm.nih.gov/	*((PIRADS) OR ("PI-RADS") OR ("prostate imaging reporting and data system")) AND ("2019/03/01" [Date - Publication]: "3000/12/12" [Date - Publication])*
Embase	https://www.embase.com/landing?status=grey	*(PIRADS OR "PI-RADS" OR "prostate imaging reporting and data system") AND [2019-2022]/py* All article types considered but conference abstracts.
Cochrane Library	https://www.cochranelibrary.com/advanced-search	*PIRADS OR "PI-RADS" OR "prostate imaging reporting and data system"* date limit: with Cochrane Library publication date from Mar 2019 to date of search (search limit)
ISRCTN	https://www.isrctn.com/editAdvancedSearch	*PIRADS OR "PI-RADS" OR "prostate imaging reporting and data system";* search in "text search" field. date limit: filter from 03/2019 to date of search
ClinicalTrials.gov	https://clinicaltrials.gov/ct2/search/advanced	*PIRADS OR "PI-RADS" (synonym "prostate imaging reporting and data system is automatically included", doublecheck is performed);* search in "other terms" field. date limit: study start from 03/2019 to date of search
ICTRP	https://trialsearch.who.int/Default.aspx	*PIRADS OR "PI-RADS" OR "prostate imaging reporting and data system"* ; search in "standard search". date limit: date of registration from 03/2019 to date of search
Deutsches Register Klinischer Studien	https://www.drks.de/drks_web/	*PIRADS OR "PI-RADS" OR "prostate imaging reporting and data system"* date limit: date of registration from 03/2019 to date of search

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol* for "Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol"

Section and topic	Item No	Checklist item	Realized, line number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	118
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	5-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	364-368
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	349-351
Sponsor	5b	Provide name for the review funder and/or sponsor	349-351
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	349-351
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	86-98
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	107-112
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	107-112, 121-128

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	185-191
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	192-195
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	197-217
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	201, 207
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	207-210
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	447-452
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	455-458
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	212-219
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	222-228
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	229-257
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	246-252
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	258-260
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	232-235
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	263-267

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.