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Diagnostic Accuracy of ^{18}F-Prostate Specific Membrane Antigen (PSMA) PET/CT Radiotracers in Staging and Restaging of Patients With High-Risk Prostate Cancer or Biochemical Recurrence: An Overview of Reviews

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The aim of this overview was to consolidate existing evidence syntheses and provide a comprehensive overview of the evidence for ^{18}F-prostate specific membrane antigen (PSMA) PET/CT in the staging of high-risk prostate cancer and restaging after biochemical recurrence. An overview of reviews was performed and reported in line with the preferred reporting items for overview of reviews (PRIOR) statement and synthesis without meta-analysis (SWiM) reporting guidelines. A comprehensive database and grey literature search were conducted up to July 18, 2023. Systematic reviews were assessed using the risk of bias in systematic reviews (ROBIS) tool. The certainty of the evidence was assessed using grading of recommendations, assessment, development and evaluations (GRADE). 11 systematic reviews were identified; 10 were at high or unclear risk of bias. Evidence reported on a per-patient, per-lymph node, and per-lesion basis for sensitivity, specificity and overall accuracy was identified. There was a lack of data on dose, adverse events and evidence directly comparing ^{18}F-PSMA PET/CT to other imaging modalities. Evidence with moderate to very low certainty indicated high sensitivity, specificity and accuracy of ^{18}F-PSMA PET/CT in patients with high-risk prostate cancer and biochemical recurrence. There was considerably lower certainty evidence and greater variability in effect estimates for outcomes for the combined intermediate/high-risk cohort. While evidence gaps remain for some outcomes, and most systematic reviews were at high or unclear risk of bias, the current evidence base is broadly supportive of ^{18}F-PSMA PET/CT imaging in the staging and restaging of patients with high-risk prostate cancer and biochemical recurrence.

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Introduction

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide.[1] In Europe, incidence rates vary with the highest estimates observed in Northern and Western European countries such as Ireland (250.9 per 100,000 person-years) compared to more Southern and Eastern European countries such as Montenegro (62.5 per 100,000 person-years).[2] Evidence-based treatment strategies have been developed, and guidelines offer recommendations for specific sub-populations according to stage and risk.[3,4] Accurate diagnosis, staging, and risk stratification are therefore essential in ensuring that optimal treatment strategies are offered and that the best possible patient outcomes are achieved.

A number of different prostate specific membrane antigen (PSMA) targeted radiotracers are increasingly being applied in clinical practice in an attempt to improve diagnostic accuracy of staging. While some national and international guidelines have adopted and recommended the use of PSMA positron emission tomography in combination with computer tomography (PET/CT), others have not or have offered weak (as opposed to strong) recommendations.[3-6]

Radiolabelling PSMA-targeted agents with ^{18}F instead of ^{68}Ga may provide several advantages, including improved image resolution and a longer half-life, which may offer improved transportation logistics and access to the radiopharmaceutical.[7-10] Preliminary scoping of this topic identified a number of relevant systematic reviews and meta-analyses, however individually these each appeared to be limited in the scope of their assessment. While some focused on diagnosis, others focused on detection rate, per-patient or per-lesion diagnostic accuracy, and considered different comparators or populations (e.g., patients with high-risk prostate cancer versus those with biochemical recurrence, that is, those with a rising prostate specific antigen [PSA] after definitive treatment with surgery or radiotherapy).

We present an overview of reviews which aimed to systematically collate existing evidence syntheses on a range of diagnostic accuracy measures exploring the use of ^{18}F-PSMA PET/CT in the staging and restaging of prostate cancer, using a range of comparators, in patients with high-risk and intermediate/high-risk prostate cancer, and those with biochemical recurrence. The secondary objectives were to grade the certainty of the available evidence and highlight the existing evidence gaps. This work was conducted as part of an assessment carried out in Ireland by the Health Information and Quality Authority (HIQA) for the justification of the practice at the population level.[11]

Methods

This overview of reviews was registered on the Open Science Framework (OSF) and reported in line with the PRIOR statement (see Supplementary Materials).[12] A protocol was pre-published and developed in line with the preferred reporting items for systematic reviews and meta-analyses extension for systematic review protocols (PRISMA-P).[13,14] The inclusion and exclusion criteria were based on the population, intervention, comparator and outcome (PICO).

Data on detection rates (also sometimes called 'detection performance', 'diagnostic performance', or 'positivity rate') were excluded as they do not provide any insight into the diagnostic accuracy.[18,19]

Search Strategy

Electronic searches were conducted in Medline (EBSCO), Embase (Ovid), Google Scholar and the Cochrane Database for Systematic Reviews up to the July 18, 2023, and supplemented by a targeted search of the grey literature. No language or date restrictions were applied to the eligibility criteria or the search strategy. The full search strategy can be found here on Zenodo: https://doi.org/10.5281/zenodo.8159119.

Forward citation searching and searching of reference lists of included reviews was conducted to identify other possibly relevant reviews. DeepL Translate was used to obtain translations of non-English language documents.[20] The European Medicines Agency (EMA) website was checked for European Public Assessment Reports (EPARs) for marketed forms of ^{18}F-PSMA.

Screening and Data Extraction

Title & abstract and full-text screening were completed by two independent reviewers. A standardized, electronic data extraction tool (available from OSF repository) was developed and independently piloted on four systematic reviews by two reviewers.[12] Data was extracted by a single reviewer and checked by a second reviewer. A small number of minor disagreements were resolved by discussion. Where discrepant data were identified during cross-referencing of data between systematic reviews, the reference in the bibliography, the calculations provided in the reviews, the primary study abstract, and the primary study itself were checked to resolve the discrepancy in that order until the discrepancy was resolved.

Further details on the methods for screening and data extraction are available from the published protocol.[13] Authors were contacted where required for additional information or supplementary materials.

Risk of Bias

Two reviewers independently appraised each selected systematic review using the risk of bias in systematic reviews (ROBIS) tool.[21] As outlined in the PICO (Table 1) the Cochrane definition of a systematic review was used and all reviews were required to have some form of risk of bias or quality assessment of their primary studies.[15] The risk of bias assessment of the primary studies included within systematic reviews, as reported by the systematic review authors, was collected. Where systematic reviews contained the same primary study, but concluded differing levels of bias, both judgements were noted and these informed the GRADE approach.

Table 1 PICOS Table

PICOS	Description
Population	Adults aged 18 years and older with high-risk prostate cancer*,† undergoing primary staging or adults with biochemically recurrent/persistent prostate cancer* undergoing restaging.
Intervention:	^{18}F-PSMA PET/CT used to stage or restage prostate cancer.
Comparison:	➢ Reference standards ○ Histopathology ○ Clinical follow up - as defined by the study (including alternative imaging). ➢ Comparators ○ Conventional imaging using bone scan, CT or MRI ○ ^{68}Ga-PSMA PET/CT
Outcomes:	Any of the following as they relate to TNM staging for prostate cancer: ➢ sensitivity ➢ specificity ➢ accuracy‡ ➢ positive and negative predictive value ➢ positive and negative likelihood ratios ➢ radiation dose ➢ adverse events (e.g., hypersensitivity, headache, fatigue, dysgeusia, paresthesia).
Study Design:	➢ Only systematic reviews and meta-analyses were considered for inclusion within this overview of reviews. Cochrane defines a systematic review as one which attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question.[15] It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.[16,17] According to the Cochrane definition, the key characteristics of a systematic review are: ○ a clearly stated set of objectives with pre-defined eligibility criteria for studies ○ an explicit, reproducible methodology ○ a systematic search that attempts to identify all studies that would meet the eligibility criteria ○ an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias and ○ a systematic presentation, and synthesis, of the characteristics and findings of the included studies. ➢ Additionally, included reviews had all of the following characteristics: ○ a systematic search of at least two databases. ○ a suitable analysis or subgroup analysis of risk groups or risk factors that allows reviewers to determine the effects on patients with high-risk (or intermediate/high-risk) prostate cancer or those with biochemically recurrent prostate cancer. ○ a quality assessment was also accepted in lieu of an established risk of bias tool such as QUADAS-2.
Languages:	Only articles for which an adequate English translation could be obtained were included.

Abbreviation: ^{18}F, Fluorine-18; ^{68}Ga, Gallium-68; CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; PSMA, prostate specific membrane antigen; QUADAS, quality assessment of diagnostic accuracy studies; TNM, tumor, nodes, metastasis.

*any definition of high-risk or biochemical recurrence as defined by systematic review authors were accepted.

†cohorts of patients with intermediate/high-risk prostate cancer which could not be disaggregated were also included.

‡all measures of accuracy as defined by the review were accepted.

Synthesis

This overview assumed that improvements in diagnostic accuracy will result in better treatment allocation and improvements in patient related outcomes such as overall survival and health-related quality of life. The standardized metrics were sensitivity, specificity and accuracy as reported in the included review. If the requisite data on true and false positives or negatives were available at the systematic review level, but not calculated and reported within the review itself, sensitivity and specificity were calculated. Data on adverse events and radiation dose were also extracted. Where available, relative measures against the comparators specified in our PICO were also synthesized.

Results were synthesized narratively and reported in line with the Synthesis Without Meta-analysis (SWiM) reporting guidelines (see Supplementary Materials).[22] Findings were synthesized firstly by population, that is, patients with high-risk prostate cancer, intermediate or high-risk cancer and patients with biochemically recurrent prostate cancer. Within those populations, findings were reported on a per-patient basis and under the TNM staging system, that is, findings related to the staging of the tumor, lymph nodes and metastases. Thereafter, we outline sections which synthesize the available evidence on the studies comparing the diagnostic accuracy of different ^{18}F-PSMA radiopharmaceuticals, comparative studies with other imaging modalities, adverse

events, and radiation dose. Forest plots were generated using R Studio.

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

A modified version of the grading of recommendations, assessment, development, and evaluation (GRADE) was used to generate the summary of findings tables as there is currently no guidance on how to conduct GRADE within overviews of reviews. As none of the included reviews performed a GRADE assessment, the principles of GRADE were instead applied to estimate the certainty of the evidence for each outcome considered important to this review, in keeping with JBI guidance.[23]

Overlap

Overlap of primary studies in each of the included systematic reviews were identified and handled in line with the Cochrane guidance.[15] Each primary study's data from overlapping systematic reviews was extracted and presented only once in the summary of findings tables.[24,25] A citation matrix was used to visualize the amount of overlap and the level of overlap was determined by calculating the corrected covered area (CCA).[26] A CCA of 0-5 indicates slight overlap, 6-10 moderate overlap, 11-15 high overlap and >15 very high overlap. Additionally, a pair-wise assessment of overlap between individual systematic reviews and a graphic representation of Overlap for OVErviews (GROOVE) was presented to better visualize discrete areas of overlap as opposed to global overlap.[26] These assessments of overlap were limited to the primary studies included within the systematic reviews which contributed to the data collection, rather than all studies included within the systematic review.

Results

Search Results

After removal of duplicates, 433 title and abstracts were assessed for eligibility. Eighty three articles required full text review, after which 11 systematic reviews were included.[27-37] An overview of the article selection process is presented in the PRISMA flowchart (see Fig. 1). A full list of studies excluded during full text screening with the rationale for their exclusion is available from the OSF repository.[12]

Review Characteristics

Eleven systematic reviews were included in this overview of reviews.[27-37] The characteristics of the included systematic reviews are presented in Table 2. From the 11 included systematic reviews, 37 unique primary studies contributed relevant data.[38-74] Seven studies were reported as having data on patients with high-risk or very high-risk prostate cancer,[38,44,46,47,50,51,60] 10 on those with either intermediate or high-risk prostate cancer,[39,40,48,49,52,57,59,61,73,74] and 18 on patients with

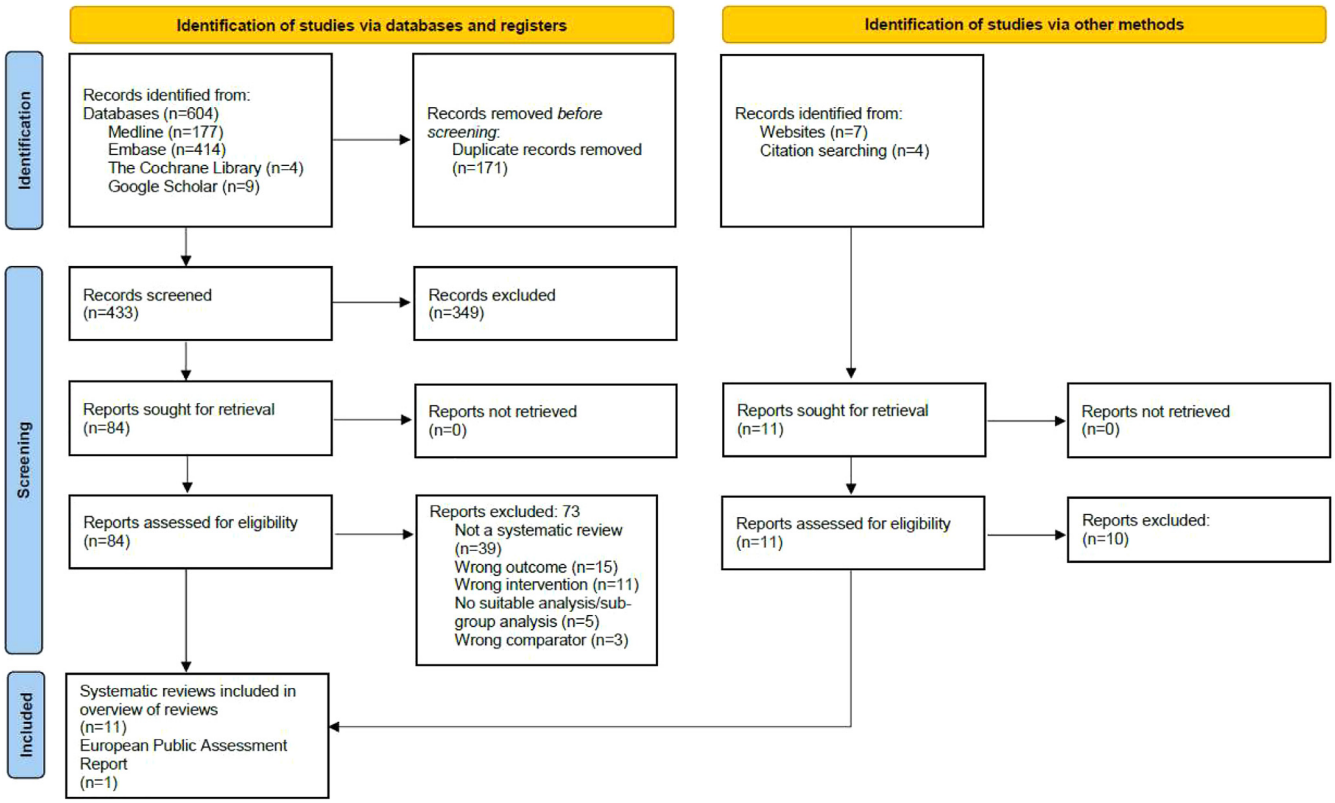

Figure 1 PRISMA flow diagram.

Table 2 Characteristics of Included Systematic Reviews

Author (Year)	Search Date	Indication	Outcomes of relevance to this overview	No. primary studies* (No. participants†)	^{18}F-PSMA PET tracer	COI and Funding	Risk of bias‡
Awenat [27] (2021)	**Dec 2020**	**Primary staging**	**Per-patient sensitivity, specificity and accuracy Per-lesion sensitivity, specificity and accuracy Injection activity Adverse events**	**6 (269)**	**1007**	**No COIs declared No external funding declared**	**High**
Evangelista[28] (2022)	NR	Primary staging + restaging following BCR	Per Patient Sensitivity Injection activity	1 (62)	DCFPyL 1007	Grant support and consulting fees from Novartis/AAA, AstraZeneca, Janssen, Merck/MSD, Mundipharma, Point Biopharma	High
Huang[29] (2022)	Sept 2021	Primary staging	Localized tumor sensitivity, specificity, PPV and NPV Per-lymph node sensitivity, specificity, PPV and NPV	6 (239)	1007	No COIs declared No funding declared. Primo Biotechnology Co. Ltd provided expert advice in idea creation and data management	Unclear
Jeet[30] (2023)	Mar 2022	Primary staging + restaging following BCR	Per-lesion sensitivity, specificity and accuracy Per-lymph node sensitivity, specificity and accuracy Injection activity	8 (676)	DCFPyL 1007 rhPSMA-7	No COIs declared No funding declared	Low
Liu[31] (2022)	Feb 2021	Primary staging + restaging following BCR	Per-patient sensitivity and specificity Per-lesion sensitivity and specificity Injection activity	11 (799)	1007	No COIs declared No funding declared	Unclear
Pang[33] (2023)	Aug 2022	Primary staging	Per-patient sensitivity and specificity Per-lesion sensitivity and specificity Injection activity	3 (151)	DCFPyL	No relevant COIs or funding	High
Pan[32] (2021)	NR	Primary staging + restaging following BCR	Per-patient sensitivity, specificity and accuracy	9 (426)	DCFPyL	No relevant COIs or funding	High
Sood[34] (2023)	Aug 2022	Primary staging + restaging following BCR	Extracapsular sensitivity, specificity, PPV and NPV Seminal vesicle sensitivity, specificity, PPV and NPV Per-lymph node sensitivity, specificity, PPV and NPV	3 (396)	DCFPyL	No COIs declared No funding declared	High
Wang[35] (2023)	May 2022	Primary staging	Per-segment sensitivity and specificity Extracapsular sensitivity and specificity Seminal vesicle sensitivity and specificity Per-lesion sensitivity and specificity Per-lesion sensitivity and specificity when combined with mpMRI Per lesion sensitivity ratio and specificity ratio Injection activity	5 (254)	DCFPyL 1007	No COIs declared No funding declared Primo Biotechnology Co. Ltd provided expert advice in idea creation and data management	Unclear
Yang[36] (2023)	Dec 2022	Restaging following BCR	Per-patient sensitivity and specificity Per-lesion sensitivity and specificity Per lesion sensitivity ratio and specificity ratio Injection activity	16 (1162)	DCFPyL 1007	No COIs declared No funding declared	Unclear
Zhao[37] (2022)	NR	Primary staging	Per-patient sensitivity and specificity Per-lesion sensitivity and specificity Injection activity	1 (10)	1007	Stock interests in Nuada Medical Ltd. Consultancy for Sonatherm Inc., Angiodynamics	Unclear

Abbreviations: ^{18}F,- Fluorine-18; BCR, biochemical recurrence; COI, conflict of interest; MA, meta analysis; NR, not reported; PET, positron emission tomography; PSMA, prostate specific membrane antigen; ROBIS, risk of bias in systematic reviews; SR, systematic review.

*Refers to the number of primary studies which contributed relevant data.

†Refers to the total number of participants in the study who underwent an ^{18}F-PSMA PET/CT. Numbers of participants may not be reflective of the number of events.

‡Risk of bias determined from ROBIS assessment.

biochemical recurrence.[41-43,45,53,54,56,58,62-65,67-72] One further study considered all patients for primary staging however data could be disaggregated into risk groups,[75] and a final study was described as including those with known metastatic disease.[66] Seventeen of the 37 studies were prospective, and 20 were retrospective. A table summarizing the key characteristics of these primary studies is included in the supplementary material.

All of the reviews were published between 2021 and 2023; the most recent specified search end date was December 2022.[36] Three of the reviews only included evidence in relation to ^{18}F-DCFPyL,[32-34] four reviews only included evidence in relation to ^{18}F-PSMA-1007,[27,29,31,37] three included evidence in relation to both ^{18}F-DCFPyL and ^{18}F-PSMA-1007,[28,35,36] while one review included evidence in relation to ^{18}F-DCFPyL, ^{18}F-PSMA-1007, and ^{18}F-rhPSMA-7.[30]

Six of the included reviews focused on primary staging,[27,29,32,33,35,37] one on restaging,[36] and four considered both primary staging and restaging[28,30,31,34] of patients with prostate cancer. Unless otherwise specified, it appeared that the systematic review authors calculated accuracy estimates from primary studies as the proportion of all participants within a study that were correctly classified.

The reference standard for primary studies was general histopathological diagnosis. However, in some settings (particularly studies on patients with biochemical recurrence) other imaging modalities with or without clinical follow up served as the reference standard. After cross-referencing systematic reviews, only two primary studies did not have their reference standard reported by the included reviews.[66,75] Alternative imaging comparators included multi-parametric MRI, ^{68}Ga-PSMA PET/CT or CT and bone scintigraphy.

Risk of Bias

Systematic Reviews

As assessed by the ROBIS tool, the majority of reviews had multiple methodological flaws, with five reviews deemed at 'high' risk of bias,[27,28,32-34] five at 'unclear' risk of bias[29,31,35-37] and one at 'low' risk of bias.[30] The main issues of concern identified during the risk of bias assessment included not referencing a protocol or stating explicit aims; unclear inclusion/exclusion criteria; search strategies which were considered not comprehensive; not providing justification for foreign language exclusions; not describing their quality process for screening, issues with data extraction and quality appraisal; not discussing the risk of bias or the effect of heterogeneity in the context of the results of the primary studies and inappropriate pooling of heterogeneous results. A table and figure summarizing the judgement for each ROBIS domain is included in the Supplementary Material.

In reviewing the data in relation to primary staging, studies were also identified that presented data related to the diagnostic accuracy of ^{18}F-PSMA PET/CT for cohorts that comprised both those with intermediate-risk and those with high-risk prostate cancer, but which did not present disaggregated data for the high-risk cohort. For completeness, this evidence is included, reported separately, and was considered relative to the evidence only on patients with high-risk prostate cancer.

Primary Studies

Across the 11 systematic reviews, 37 unique primary studies were identified that were of relevance to the research questions in this overview of reviews. Eight[29-31,33-37] of the 11 systematic reviews used the QUADAS-2 tool to assess risk of bias in the primary studies.[76] One review used the CASP checklist to assess quality;[28] however the two studies which contributed data to this overview were also assessed using QUADAS-2 in other included systematic reviews. Another review[77] used a quality assessment tool from the National Institute of Health (NIH), however details on the quality of the primary studies were not available. A third review[27] used the original QUADAS tool, which has been superseded by QUADAS-2.[78] A table and figure summarizing QUADAS-2 is included in the supplementary material. In total, three of the 37 primary studies had no QUADAS-2 assessment. The use of an outdated risk of bias tool and issues with the approach to risk of bias were captured within the ROBIS assessment.

In general, the systematic reviews found low risk of bias in the primary studies that were assessed. However, high risk of bias was reported in eight studies due to issues with their reference standards, in seven studies due to issues with the index test and in six studies because of flow and timing. Only three studies were at high risk of bias due to patient selection. In total, 15 primary studies were assessed as having high risk of bias in at least one QUADAS-2 domain.

Overlap Within Included Reviews

Graphical and quantitative investigations into the overlap between systematic reviews was conducted. The CCA was estimated at 8.38% (moderate overlap).[26] A citation matrix and a Graphical Representation of Overlap for OVErviews (GROOVE)[26] was generated to assess the CCA between every possible pair of reviews (nodes), and produce a graphical representation of this assessment (see Supplementary Material). The overlap between pairs of systematic reviews was very high, high, and moderate in eight, four and nine of the 55 nodes, respectively. A total of 34 of the 55 nodes had no overlap or slight overlap (<5%).

Primary Staging of High-Risk Prostate Cancer

Per-Patient Data

No pooled estimates of per-patient sensitivity were identified for high-risk prostate cancer. Data from three systematic reviews provided information on four primary studies with data in this area.[27,31,32] Two of these were retrospective studies[46,50] with only 10 patients each and which estimated a sensitivity of 1.00 (no confidence intervals reported by the systematic review). Two prospective studies, one with 25 patients[47] and another with 79 patients[38] estimated per-patient sensitivity to be 0.90 (95% CI 0.82-0.96) and 0.85 (95% CI 0.62-0.97), respectively. The certainty of the evidence was considered to be low (see Figure 2, Table 3).

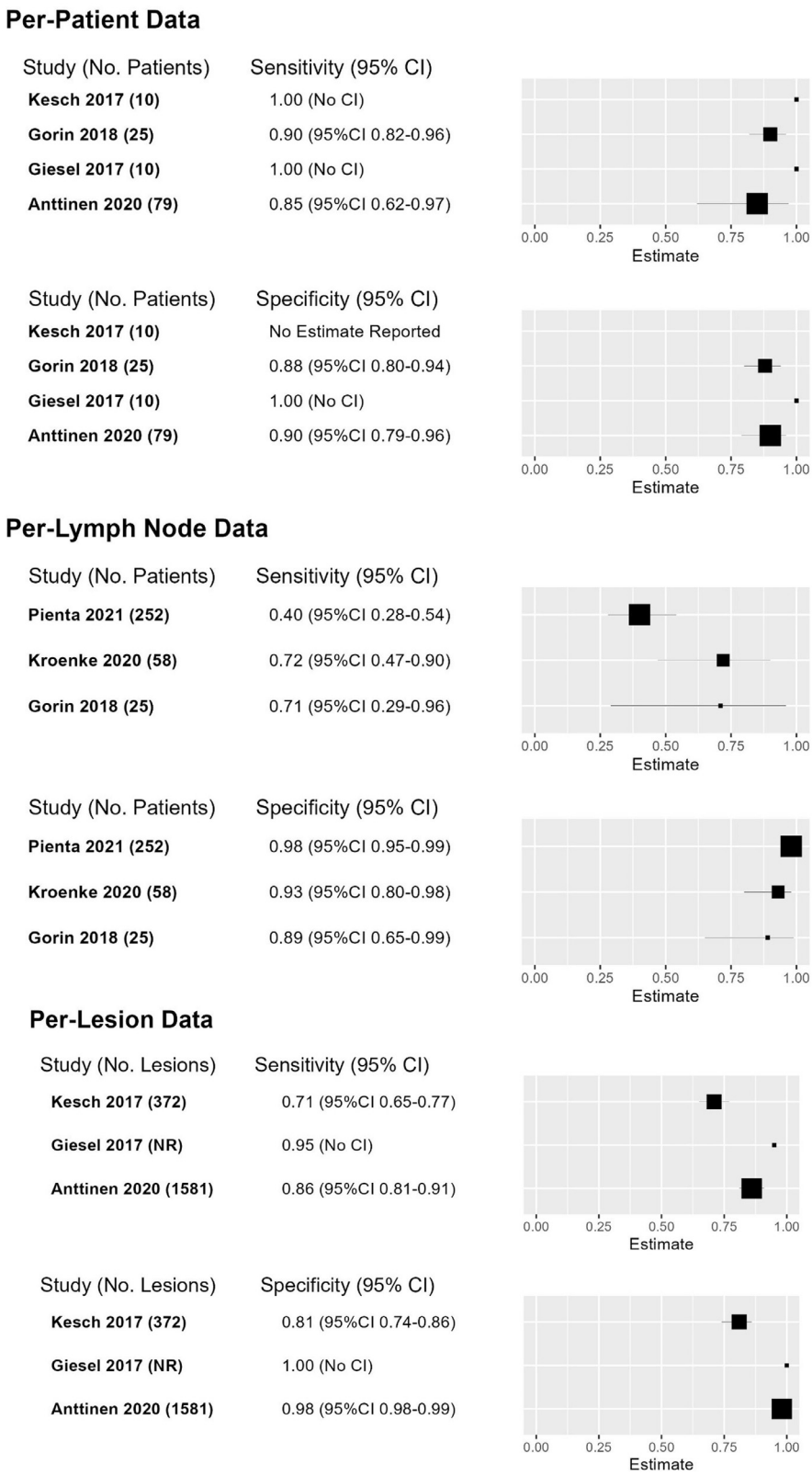

Figure 2 Forest plots of sensitivity and specificity on a per-patient, per-lymph node and per-lesion basis for patients with high-risk prostate cancer. **Key:** NR, Number of lesions not reported by the systematic review. **Note:** All estimates extracted as reported by the included systematic reviews.

Table 3 Summary of Findings Table for High-Risk Prostate Cancer

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants or lesions (studies)	Certainty of the evidence (GRADE)
Per-patient sensitivity	0.85 (0.62-0.97) 0.90 (0.82-0.96) 1.00 (No CI) 1.00 (No CI)	Not reported‡	124 patients (4 studies)	⊕⊕◯◯ LOW [a,b]
Per-patient specificity	0.90 (0.79-0.96) 0.88 (0.80-0.94) 1.00 (No CI)	Not reported‡	114 patients (3 studies)	⊕⊕⊕◯ MODERATE [a]
Per-patient accuracy	1.00 (No CI) 0.80-0.89 (No CI)	Not reported‡	89 patients (2 studies)	⊕⊕◯◯ LOW [a,b,c]
Per-lymph node sensitivity	0.40 (0.28-0.54) 0.72 (0.47-0.90) 0.71 (0.29-0.96)	Not reported‡	335 patients (3 studies)	⊕⊕◯◯ LOW [a,b,d]
Per-lymph node specificity	0.98 (0.95-0.99) 0.93 (0.80-0.98) 0.89 (0.65-0.99)	Not reported‡	335 patients (3 studies)	⊕⊕⊕◯ MODERATE [a]
Per-lymph node Accuracy	0.82 (No CI) 0.86 (No CI) 0.84 (No CI)	Not reported‡	335 patients (3 studies)	⊕⊕◯◯ LOW [a,b]
Per-lesion sensitivity	0.86 (0.81-0.91) 0.71 (0.65-0.77) 0.95 (No CI)	Not reported‡	461 lesions (3 studies)	⊕◯◯◯ VERY LOW [a,b,c,d]
Per-lesion specificity	0.98 (0.98-0.99) 0.81 (0.74-0.86) 1.00 (No CI)	Not reported‡	461 lesions (3 studies)	⊕⊕◯◯ LOW [a,b,c]
Per-lesion accuracy	1.00 (No CI) 0.93 (No CI)	Not reported‡	≥372† lesions (2 studies)	⊕⊕◯◯ LOW [a,b,c,e]
Dose	Not reported§	Not reported‡	-	-
Adverse events	Not reported§	Not reported‡	-	-

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

[a]Risk of bias in the reviews.

[b]Imprecision in the results, wide confidence intervals (or no confidence intervals) or too few events.

[c]Concerns regarding publication bias, the search strategy or inclusion and exclusion criteria.

[d]Inconsistency of estimates across studies.

[e]Risk of bias in the primary studies (as determined from QUADAS-2 assessments in the systematic reviews).

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

*Figures are presented for each of the primary studies reported in the reviews (unless otherwise specified) and are presented in descending order from the largest study to the smallest.

†372 lesions reported for one study of 10 patients, the number of lesions was not reported in the second study of 10 patients.

‡Not reported by the *systematic reviews*.

No pooled estimates of per-patient specificity were identified for high-risk prostate cancer. Three primary studies with data in this area were identified from three different systematic reviews.[27,31,32] One was a retrospective study based on only ten patients which estimated a specificity of 1.00 with no confidence intervals reported.[46] Two prospective studies, one with 25 patients[47] and another with 79,[38] estimated per-patient specificity to be 0.88 (95% CI 0.80-0.94) and 0.90 (95% CI 0.79-0.96), respectively. The certainty of the evidence was considered to be moderate.

Three systematic reviews reported limited data for per-patient accuracy.[27,29,31] One retrospective studies with 10 patients identified estimated the accuracy on a per-patient basis to be 0.80-0.89 (range was for four accuracy values from two readers that conducted a 'pessimistic' and 'optimistic' analysis, no confidence intervals reported).[46] A

prospective study with 79 patients estimated an accuracy of 1.00 (no confidence intervals reported).[38] The certainty of evidence for accuracy was considered to be low.

T-staging Data

No information on the use of ^{18}F-PSMA PET/CT T-staging for cohorts with high-risk prostate cancer alone was identified.

Per-Lymph Node Data

No pooled estimates of per-lymph node sensitivity were identified for high-risk prostate cancer. Data from the tables and supplementary materials of two systematic reviews[30,34] provided information on three primary studies[47,51,60] with data in this area. One retrospective study of 58 patients reported a sensitivity of 0.72 (95% CI 0.47-0.90).[51] Two prospective studies with 25[47] and 252[60] patients estimated sensitivity to be 0.71 (95% CI 0.29-0.96)[47] and 0.40 (95% CI 0.28-0.54), respectively. Sood et al. noted that in this later study (the OSPREY trial) the sensitivity increased to 0.60 (no confidence interval given) in patients where lymph nodes were greater than 5 mm.[60] The certainty of the evidence was considered to be low.

No pooled estimates of per-lymph node specificity were identified for high-risk prostate cancer. Data from the tables and supplementary materials of two systematic reviews provided information on three primary studies with data in this area.[30,34] One retrospective study of 58 patients reported a specificity of 0.93 (95% CI 0.80-0.98).[51] Two prospective studies with 25 and 252 patients estimated specificity to be 0.89 (95% CI 0.65-0.99)[47] and 0.98 (95% CI 0.95-0.99),[60] respectively. The certainty of the evidence was considered to be moderate.

Three studies identified from one review had estimates of accuracy in patients with high-risk prostate cancer.[30] Two prospective studies with 25[47] and 252[60] patients estimated accuracy to be 0.84 and 0.82 respectively (no confidence intervals reported). One further retrospective study of 58 patients constructed a receiver operator characteristic (ROC) curve and estimated accuracy, based on the area under the curve (AUC) to be 0.86.[51] The certainty of evidence was considered to be low.

Sood et al. identified two studies reporting per-lymph node positive predictive value (PPV) and negative predictive value (NPV) in high-risk prostate cancer.[34] These two prospective studies had 252[60] and 28[47] patients, respectively, and estimated the PPV to be 0.87 and 0.71 (no confidence intervals reported), respectively. The per-lymph node NPV was estimated to be 0.83 and 0.89, respectively (no confidence intervals reported).

Per-Lesion Data

No pooled estimates of per-lesion sensitivity or specificity were identified for high-risk prostate cancer. Data from the tables and supplementary materials of three systematic reviews provided information on three primary studies with sensitivity and specificity data in this area.[27,31,35] Data on the number of lesions were often not reported by reviews.

One retrospective study of ten patients (number of lesions not reported) estimated a sensitivity of 0.95 (no confidence interval provided).[46] A second retrospective study of ten patients (372 lesions) estimated the sensitivity to be 0.71 (95% CI 0.65-0.77).[50] One prospective study with 79 patients (1581 lesions) estimated per-lesion sensitivity to be 0.86 (95% CI 0.81-0.91).[38] The certainty of the evidence was considered to be very low.

One retrospective study of 10 patients (number of lesions not reported) reported a specificity of 1.00 (no confidence intervals were reported).[46] A second retrospective study of 10 patients (372 lesions) estimated the specificity to be 0.81 (95% CI 0.74-0.86).[50] One prospective study with 79 patients (1581 lesions) estimated per-lesion specificity to be 0.98 (95% CI 0.98-0.99).[38] The certainty of the evidence was considered to be low.

Two retrospective studies,[46,50] each with 10 patients, were identified from one systematic review and estimated the accuracy to be 0.93 and 1.00 (no confidence intervals reported).[27] There were 212 lesions in one of these studies, and the number of lesions was not reported in the other. The certainty of the evidence was considered to be low.

Primary Staging of Intermediate/High-Risk Prostate Cancer

Per-Patient Data

No pooled estimates of per-patient sensitivity were identified for intermediate/high-risk prostate cancer. Four studies[52,59,61,74] were identified from two systematic reviews[27,33] that provided evidence for sensitivity for a cohort of patients with intermediate/high-risk prostate cancer. Three retrospective studies identified from these systematic reviews had modest sample sizes of 53,[61] 65[59], and 56[74] patients and estimated the sensitivity for this population to be 0.98 (no confidence intervals reported in the review), 0.97 (95% CI 0.89-1.00) and 0.90 (95% CI 0.78-0.97), respectively. One small prospective study of 16 patients reported a sensitivity of 1.00, but no confidence intervals were reported by the review.[52] The certainty of the evidence for per-patient sensitivity was considered to be low (see Figure 3, Table 4).

No pooled estimates of per-patient specificity were identified for intermediate/high-risk prostate cancer. Two retrospective studies identified by one systematic review provided data on per-patient specificity in patients with intermediate/high-risk prostate cancer.[33] One study with a sample of 65 patients was reported as having a specificity of 0.00 (95% CI 0.00-0.60).[59] The second study with a sample of 56 patients was reported as having a specificity of 1.00 (95% CI 0.54-1.00).[74] The certainty of the evidence for per-patient specificity was considered to be very low.

One systematic review reported the per-patient accuracy based on one prospective study of 16 patients, and estimated the accuracy to be 1.00 (no confidence intervals reported).[27,52] The certainty of the evidence for per-patient accuracy was considered to be very low.

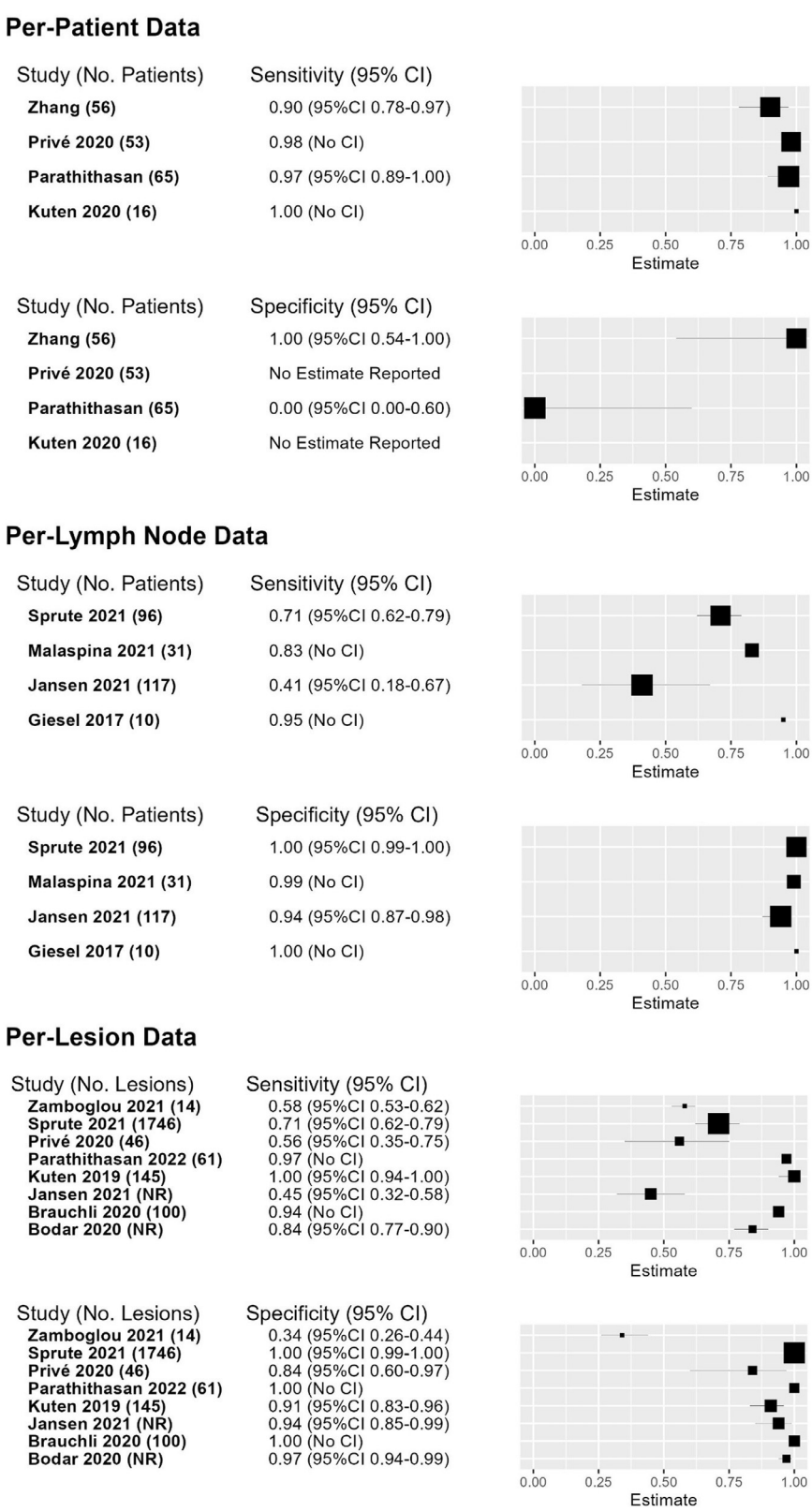

Figure 3 Forest plots of sensitivity and specificity on a per-patient, per lymph node and per-lesion basis for patients with intermediate/high-risk prostate cancer. **Key:** NR, Number of lesions not reported by the systematic review. **Note:** All estimates extracted as reported by the included systematic reviews.

Table 4 Summary of Findings Table for Intermediate/High-Risk Prostate Cancer

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants or lesions (studies)	Certainty of the evidence (GRADE)
Per-patient sensitivity	0.98 (No CI) 0.97 (0.89-1.00) 0.90 (0.78-0.97) 1.00 (No CI)	Not reported§	190 patients (4 studies)	⊕⊕◯◯ LOW [a,b,c,d]
Per-patient specificity	0.00 (0.00-0.60) 1.00 (0.54-1.00)	Not reported§	121 patients (2 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Per-patient accuracy	1.00 (No CI)	Not reported§	16 patients (1 study)	⊕◯◯◯ VERY LOW [a,b,c,d,f]
Per-segment sensitivity	0.61 (0.52-0.70)	Not reported§	30 patients (1 study)	⊕◯◯◯ VERY LOW [b,c,f]
Per-segment specificity	0.88 (0.84-0.94)	Not reported§	30 patients (1 study)	⊕◯◯◯ VERY LOW [b,c,f]
Per-segment accuracy	0.81 (No CI)	Not reported§	30 patients (1 study)	⊕◯◯◯ VERY LOW [b,c,f]
Extracapsular sensitivity	0.95 (0.88-0.99) 0.57 (No CI) 0.18 (No CI)	Not reported§	269 patients (3 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Extracapsular specificity	0.32 (0.15-0.54) 0.84 (No CI) 0.97 (No CI)	Not reported§	269 patients (3 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Extracapsular accuracy	Not reported§	Not reported§	-	-
Seminal vesicle sensitivity	0.80 (0.44-0.97) 0.53 (No CI)	Not reported§	169 patients (2 studies)	⊕◯◯◯ VERY LOW [b,c,d,e]
Seminal Vesicle specificity	0.85 (0.55-0.98) 0.90 (No CI)	Not reported§	169 patients (2 studies)	⊕⊕◯◯ LOW [b,c,d]
Seminal vesicle accuracy	Not reported§	Not reported§	-	-
Per-lymph node sensitivity	0.41 (0.18-0.67) 0.83 (No CI) 0.71 (0.62-0.79) 0.95 (No CI)	Not reported§	335 patients (4 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Per-lymph node specificity	0.94 (0.87-0.98) 0.99 (No CI) 1.00 (0.99-1.00) 1.00 (No CI)	Not reported§	335 patients (4 studies)	⊕⊕◯◯ LOW [a,b,c,d]
Per-lymph node Accuracy	0.87 (No CI) 0.98 (No CI)	Not reported§	212 (2 studies)	⊕⊕◯◯ LOW [a,b,c,d]
Per-lesion sensitivity	0.45 (0.32-0.58) 0.84 (0.77-0.90) 1.00 (0.94-1.00) 0.58 (0.53-0.62) 0.71 (0.62-0.79) 0.94 (No CI) 0.97 (No CI) 0.56 (0.35-0.75)	Not reported§	≥2,112 lesions† (8 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Per-lesion specificity	0.94 (0.85-0.99) 0.97 (0.94-0.99) 0.91 (0.83-0.96) 0.34 (0.26-0.44) 1.00 (0.99-1.00) 1.00 (No CI) 1.00 (No CI) 0.84 (0.60-0.97)	Not reported§	≥2,112 lesions† (8 studies)	⊕⊕⊕◯ MODERATE [a,b,d]
Per-lesion accuracy	0.68 (No CI) 0.95 (No CI)	Not reported§	>145 lesions‡ (2 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]

Table 4 (*Continued*)

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants or lesions (studies)	Certainty of the evidence (GRADE)
Dose	Not reported§	Not reported§	-	-
Adverse events	Not reported§	Not reported§	-	-

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

[a]Risk of bias in the primary studies (as determined from QUADAS-2 assessments in the systematic reviews).

[b]Risk of bias in the reviews.

[c]Imprecision in the results, wide confidence intervals (or no confidence intervals) or too few events.

[d]Concerns regarding publication biases, the search strategy or inclusion and exclusion criteria.

[e]Inconsistency of estimates across studies.

[f]Inconsistency was considered serious as there was just one study.

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

*Figures are presented for each of the primary studies reported in the reviews (unless otherwise specified) and are presented in descending order from the largest study to the smallest.

†The number of lesions was not report in two studies which had a total of 146 patients.

‡The number of lesions was not report in one study which had a total of 116 patients.

§Not reported by the *systematic reviews.*

T-staging data

No pooled estimates for T-staging outcomes were identified for intermediate/high-risk prostate cancer. Jeet et al. was the only review which contained relevant data on per-segment sensitivity and specificity, where each segment corresponds to an anatomic mapping model of the prostate.[30] A single prospective study based on a cohort of 30 patients with intermediate/high-risk prostate cancer (and 420 segments) reported a per-segment sensitivity of 0.61 (95% CI 0.52-0.70) and a per-segment specificity of 0.88 (95% CI 0.84-0.94).[39] The certainty of the evidence for per-segment sensitivity and specificity was considered to be very low. An accuracy estimates of 0.81 (no confidence intervals reported) was reported by this systematic review based on this prospective study of 30 patients.[30,39] The certainty of the evidence for per-segment accuracy was considered to be very low.

Three systematic reviews[29,34,35] that provided evidence from three primary studies for the sensitivity of extracapsular extension in intermediate/high-risk prostate cancer. Two retrospective studies identified by the reviews had a sample size of 100[40] and 53,[61] and estimated the sensitivity of extracapsular extension in this population to be 0.95 (95% CI 0.88-0.99) and 0.57 (no confidence interval reported) respectively. One prospective study with 116 patients estimated the sensitivity of extracapsular extension to be 0.18 (no confidence interval reported).[49] The certainty of the evidence for extracapsular extension sensitivity was considered to be very low.

The same three studies had data on extracapsular specificity which was identified by two reviews.[34,35] Two retrospective studies identified by the reviews had a sample size of 100[40] and 53,[61] and estimated the specificity of extracapsular extension in this population to be 0.32 (95% CI 0.15-0.54) and 0.84 (no confidence intervals reported), respectively. A prospective study of 116 patients estimated the specificity of extracapsular extension to be 0.97 (no confidence interval reported).[49] The certainty of the evidence for extracapsular extension specificity was considered to be very low.

The prospective study of 116 patients also provided an estimate for extracapsular extension PPV and NPV of 0.80 and 0.66 (no confidence intervals reported), respectively.[49] The PPV of seminal vesicle involvement was estimated to be 0.48 and the NPV to be 0.92 (no confidence intervals reported).

Two studies identified from two systematic reviews provided evidence on the sensitivity of seminal vesical involvement in patients with intermediate/high risk prostate cancer.[34,35] One retrospective study of 53 patients (26 of which had seminal vesicle involvement) estimated the sensitivity for seminal vesicle involvement to be 0.80 (95% CI 0.44-0.97).[61] One prospective study of 116 patients estimated a sensitivity of 0.53 (no confidence interval reported).[49] The certainty of the evidence for seminal vesicle sensitivity was considered to be very low.

Two studies identified from two systematic reviews provided evidence on the specificity of seminal vesical involvement in patients with intermediate/high risk prostate cancer.[34,35] One retrospective study of 53 patients (26 of which had seminal vesicle involvement) estimated the sensitivity for seminal vesicle involvement to be 0.85 (95% CI 0.55-0.98).[61] One prospective study of 116 patients

estimated a specificity of 0.90 (no confidence interval reported).[49] The certainty of the evidence for seminal vesicle specificity was considered to be low.

Per-Lymph Node Data

No pooled estimates for per-lymph node outcomes were identified for intermediate/high-risk prostate cancer. Four studies identified by three systematic reviews had data on per-lymph node sensitivity in a cohort with intermediate/high-risk prostate cancer.[29,30,34] Two retrospective studies with 96 patients[70] and 10 patients[46] estimated the sensitivity to be 0.71 (95% CI 0.62-0.79) and 0.95 (no confidence intervals given), respectively. Two prospective studies with 116 patients[49] and 31 patients[57] estimated the sensitivity to be 0.41 (95% CI 0.18-0.67) and 0.83 (no confidence intervals reported), respectively. The certainty of the evidence for per-lymph node sensitivity was considered to be very low.

Four studies identified by three systematic reviews had data on per-lymph node specificity in a cohort with intermediate/high-risk prostate cancer.[29,30,34] Two retrospective studies with 96 patients[70] and 10[46] patients estimated the specificity to be 1.00 (95% CI 0.99-1.00) and 1.00 (no confidence intervals reported), respectively. Two prospective studies with 116 patients[49] and 31 patients[57] estimated the specificity to be 0.94 (95% CI 0.87-0.98) and 0.99 (no confidence intervals reported), respectively. The certainty of the evidence for per-lymph node specificity was considered to be low.

One systematic review reported on two studies which had data on per-lymph node accuracy.[30] Two prospective studies with 116[49] and 96[70] patients estimated per-lymph node accuracy to be 0.87 and 0.98, respectively (no confidence intervals reported). The certainty of the evidence was estimated to be very low.

Two systematic reviews provided estimates obtained from four primary studies on per-lymph node PPV and NPV for patients with intermediate/high-risk prostate cancer.[29,34] Two retrospective studies with samples of 96[70] and 10[46] patients which estimated the PPV and NPV to be 0.91 (95% CI 0.84-0.96) and 1.00 (95% CI 0.82-1.00), and 0.98 and 1.00 (no confidence intervals were provided for either NPV estimates), respectively. Two prospective studies with 31[57] and 116[49] patients estimated the PPV to be 0.96 (95% CI 0.91-0.98) and 0.54 (no confidence intervals reported), and the NPV to be 0.97 and 0.90 (no confidence intervals reported), respectively.

Per-Lesion Data

No pooled estimates for per-lesion outcomes were identified for intermediate/high-risk prostate cancer. Eight studies identified from six systematic reviews[27,30,31,33,35,37] had per-lesion sensitivity data for intermediate/high-risk prostate cancer. Four prospective studies with 116 patients (number of lesions not reported),[49] 30 patients (number of lesions not reported),[39] 16 patients (145 lesions)[52] and 10 patients (14 lesions)[73] estimated per-lesion sensitivity to be 0.45 (95% CI 0.32-0.58), 0.84 (95% CI 0.77-0.90), 1.00 (95% CI 0.94-1.00) and 0.58 (95% CI 0.53-0.62), respectively. Four retrospective studies on intermediate/high-risk prostate cancer with 96 patients (1,746 lesions),[70] 100 patients (100 lesions),[40] 65 patients (61 lesions),[59] and 53 patients (46 lesions)[61] estimated per-lesion sensitivity to be 0.71 (95% CI 0.62-0.79), 0.94 (no confidence interval reported), 0.97 (no confidence interval reported), and 0.56 (95% CI 0.35-0.75), respectively. The certainty of the evidence for per-lesion sensitivity was considered to be very low.

Eight studies identified from six systematic reviews[27,30,31,33,35,37] had per-lesion specificity data for intermediate/high-risk prostate cancer. Four prospective studies with 116 patients (number of lesions not reported),[49] 30 patients (number of lesions not reported),[39] 16 patients (145 lesions)[52] and ten patients (14 lesions)[73] estimated per-lesion specificity to be 0.94 (95% CI 0.85-0.99), 0.97 (95% CI 0.94-0.99), 0.91 (95% CI 0.83-0.96) and 0.34 (95% CI 0.26-0.44), respectively. Four retrospective studies on intermediate/high-risk prostate cancer with 96 patients (1,746 lesions),[70] 100 patients (100 lesions),[40] 65 patients (61 lesions),[59] and 53 patients (46 lesions)[61] estimated per-lesion specificity to be 1.00 (95% CI 0.99-1.00), 1.00 (no confidence interval reported), 1.00 (no confidence interval reported), and 0.84 (95% CI 0.60-0.97), respectively. The certainty of the evidence for per-lesion sensitivity was considered to be moderate.

Two studies from two systematic reviews had per lesion accuracy data for intermediate/high-risk prostate cancer.[27,30] Two prospective studies with 116[49] and 16 patients[52] (145 lesions) reported the per-lesion accuracy to be 0.68 and 0.95 (no confidence intervals reported), respectively. The certainty of the evidence per per-lesion accuracy was considered to be very low.

Restaging After Biochemical Recurrence

Per-Patient Data

One systematic review by Yang et al.[36] included a meta-analysis that provided a pooled estimate for sensitivity based on five studies with a total of 367 patients. The estimated sensitivity was 0.92 (95% CI 0.86-0.96), with no evidence of heterogeneity (I^2=0.0%; P = 0.727).

Sensitivity data from five other primary studies were identified from the tables and supplementary materials of three other systematic reviews.[28,31,32] Two prospective studies with 130 patients[64] and 40 patients[71] estimated per-patient sensitivity to be 0.90 (95% CI 0.82-0.95) and 0.88 (95% CI 0.73-0.96), respectively. Three retrospective studies with 102,[63] 100,[62] and 25[67] patients estimated per-patient sensitivity to be 0.86 (95% CI 0.78-0.92), 0.95 (95% CI 0.89-0.98), and 0.60 (95% CI 0.39-0.79), respectively. The certainty of evidence for sensitivity was considered to be moderate (see Figure 4, Table 5).

Based on a meta-analysis of five studies, Yang et al. estimated the pooled per-patient specificity for patients with biochemical recurrence to be 0.83 (95% CI 0.41-0.97).[36] Specificity data from one other primary study was identified from the tables and supplementary materials of two other systematic reviews.[31,32] One prospective study with 130

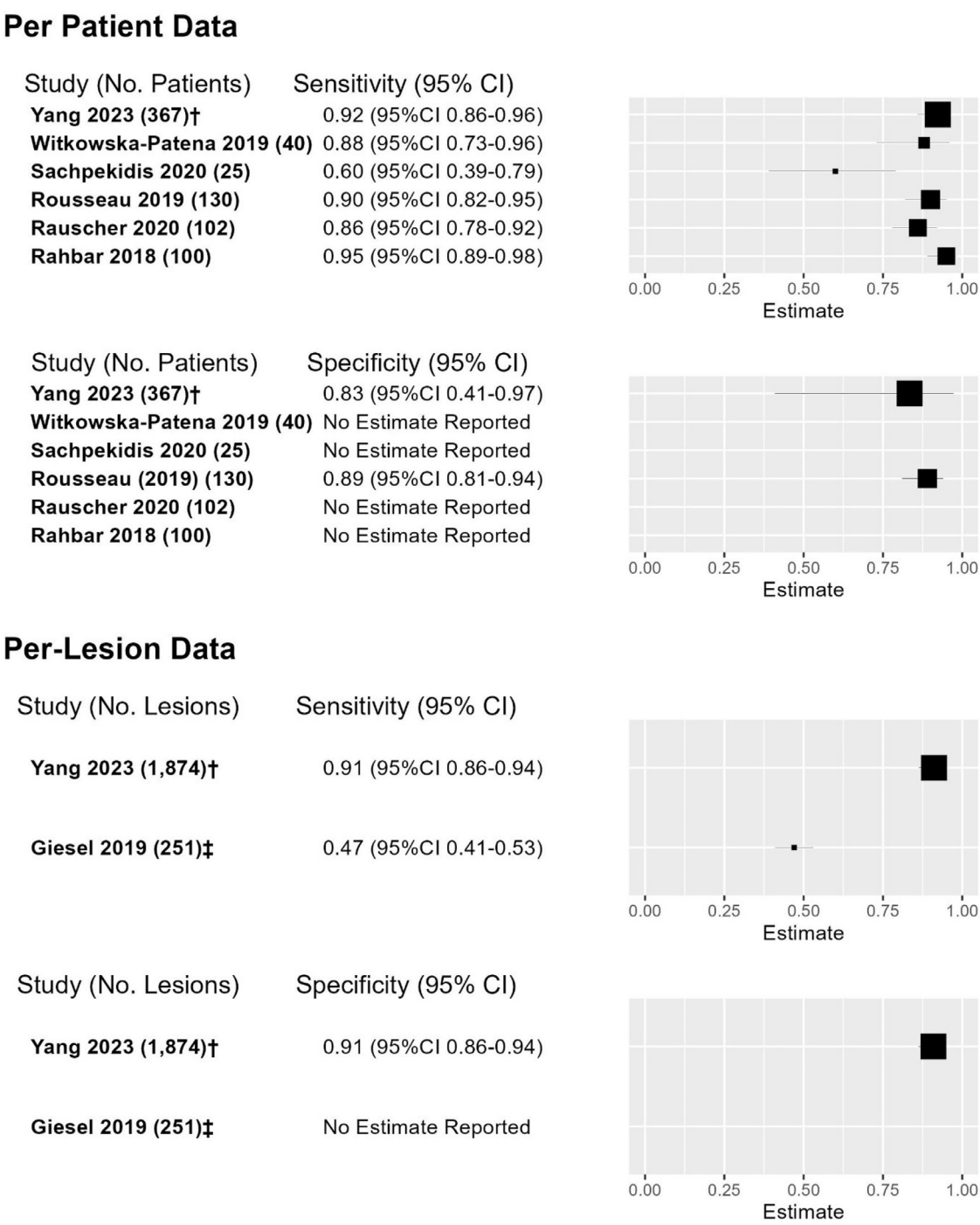

Figure 4 Forest plots of sensitivity and specificity on a per-patients and per-lesion basis for patients with biochemically recurrent prostate cancer. **Notes:** † results from meta-analysis. ‡Although Yang et al. included a per-patient estimate from this primary study, they did not capture a per-lesion estimate which was identified from other systematic reviews.

patients estimated the per-patient specificity to be 0.89 (95% CI 0.81-0.94).[64] The certainty of the evidence for per-patient specificity was considered to be low.

No per-patient accuracy estimates from the 11 systematic reviews was found for patients with biochemical recurrence.

Per-patient sensitivity was also analyzed by PSA level by some reviews and primary studies. While pooled results were often not specific to the research questions in the current overview, three studies identified by one review included subgroup analysis relating to PSA.[31] One retrospective study of 251 patients did not find a statistically significant difference in sensitivity when they compared those with a PSA>2 ng/mL (0.94 95% CI 0.87-0.98) and a PSA $\leq$ 2ng/mL (0.91 95% CI 0.80-0.97).[45] A second retrospective study of 100 patients which reported data at a per-patient level also did not find a statistically significant difference in sensitivity

Table 5 Summary of Findings Table for Biochemically Recurrent Prostate Cancer

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants or lesions (studies)	Certainty of the evidence (GRADE)
Per-patient sensitivity	0.92 (0.86-0.96)† 0.90 (0.82-0.95) 0.86 (0.78-0.92) 0.95 (0.89-0.98) 0.88 (0.73-0.96) 0.60 (0.39-0.79)	Not reported§	791 patients (10 studies)	⊕⊕⊕◯ MODERATE [a,b,c,g]
Per-patient specificity	0.83 (0.41-0.97)† 0.89 (0.81-0.94)	Not reported§	524 patients (7 studies)	⊕⊕◯◯ LOW [a,b,c,d,e]
Per-patient accuracy	Not reported§	Not reported§	-	-
Per-lymph node sensitivity	Not reported§	Not reported§	-	-
Per-lymph Node specificity	Not reported§	Not reported§	-	-
Per-lymph node accuracy	Not reported§	Not reported§	-	-
Per-lesion sensitivity	0.91 (0.86-0.94)‡ 0.47 (0.41-0.53)	Not reported§	1874 lesions (12 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Per-lesion Specificity	0.91 (0.86-0.94)‡	Not reported§	1874 lesions (11 studies)	⊕⊕◯◯ LOW [a,b,c,d]
Per-lesion Accuracy	0.81% (No CI)	Not reported§	36 lesions (1 Study)	⊕⊕◯◯ LOW [b,d,e,f]
Dose	Not reported§	Not reported§	-	-
Adverse Events	Not reported§	Not reported§	-	-

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Risk of bias in the reviews.

[b]Risk of bias in the primary studies (as determined from QUADAS-2 assessments in the systematic reviews).

[c]Concerns regarding publication bias, the search strategy or inclusion and exclusion criteria.

[d]Inconsistency of estimates across studies or a small single study.

[e]Imprecision in the results, wide confidence intervals (or no confidence intervals) or too few events.

[f]Inconsistency was considered serious as there was just one study.

[g]Large and consistent effect sizes taken into account.

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

*Figures are presented for each of the primary studies reported in the reviews (unless otherwise specified) and are presented in descending order from the largest study to the smallest.

†Figures are from the meta-analyzed results of 367 patients from 5 studies.

‡Figures are from the meta-analyzed results of 1874 lesions from 11 studies.

§Not reported by the *systematic reviews.*

when stratified by PSA values (PSA>2 ng/mL: 0.95 (95% CI 0.89-0.98) vs. PSA ≤2 ng/mL: 0.92 (95% CI 0.84-0.96)).[62] One further prospective study of 40 patients estimated per-patient sensitivity for patients with a PSA ≤2ng/mL to be 0.49 (95% CI 0.31-0.66).[71]

Data according to PSA levels was also available for specificity.[31] One retrospective study of 251 patients did not find a statistically significant difference in specificity when they compared those with a PSA>2 ng/mL and PSA ≤2 ng/mL: 0.28 (95% CI 0.21-0.36), vs. 0.24 (95% CI 0.18-0.31).[45] A second retrospective study of 100 patients could not estimate specificity for patients with a PSA of >2 ng/mL, however the specificity for patients with a PSA of ≤2 ng/mL was estimated to be 1.00 (95% CI 0.48-1.00).[62] One further prospective study of 40 patients estimated that per-patient specificity for patients with a PSA ≤2 ng/mL was 1.00 (95% CI 0.48-1.00).[71]

Per-Lymph Node Data

No data were identified on per-lymph node sensitivity, specificity, or accuracy in patients with biochemical recurrence in the five systematic reviews identified.

Per-Lesion Data

The systematic review by Yang et al. included a meta-analysis that provided a pooled estimate for sensitivity on a per-lesion basis based on a total of 1874 lesions. The pooled estimate, based on 11 studies, was 0.91 (95% CI 0.86-0.94); however, significant heterogeneity was observed I^2=70.06% ($P < 0.01$).[36] One other study, identified by Liu et al.[31], reported data from a large prospective study of 251 patients which estimated the per-lesion sensitivity to be 0.47 (95% CI 0.41-0.53).[45] While this study was included by Yang et al. in their systematic review, this estimate was not included in their per-lesion analysis. The certainty of the evidence was considered to be very low.

Yang et al. estimated the pooled per-lesion specificity based on 1874 lesions for patients with biochemical recurrence to be 0.91 (95% CI 0.86-0.94). No additional primary studies or data were identified by the other five systematic reviews for this outcome. The certainty of the evidence was considered to be low.

One systematic review[30] reported on a prospective study of 80 patients which estimated the per-lesion accuracy to be 0.81 (no confidence interval given).[54] The certainty of the evidence for this outcome was considered to be low.

Comparative Data

Differences Between ^{18}F-PSMA Radiopharmaceuticals

One meta-analysis of 16 studies on patients with biochemically recurrent prostate cancer was identified which compared ^{18}F-PSMA-DCFPyL with ^{18}F-PSMA-1007.[36] The review authors combined per-patient and per-lesion outcomes to generate the pooled estimates for these radiopharmaceuticals. Sensitivity and specificity were estimated to be 0.90 (95% CI 0.85−0.94) and 0.89 (95% CI 0.85−0.93) for ^{18}F-PSMA-DCFPyL, and 0.93 (95% CI 0.86−0.96) and 0.93 (95% CI 0.70−0.99) for ^{18}F-PSMA-1007, respectively. Of note, substantial heterogeneity was observed for ^{18}F-PSMA-DCFPyL (I^2 = 68.91%, P=0.002); lower heterogeneity was noted for ^{18}F-PSMA-1007 (I^2 = 40.99%, $P < 0.105$).

Differences Between ^{18}F-PSMA and ^{68}Ga-PSMA Radiopharmaceuticals

Evangelista et al.[28] reported on one study[42] which conducted an iterative match-paired analysis of 191 retrospectively enrolled patients with biochemical recurrence, observing that for low PSA concentration, the PSA stratified sensitivity curve was more robust and superior for ^{18}F-DCFPyL than for ^{68}Ga-PSMA-11. The average sensitivity was 0.80 for ^{18}F-DCFPyL and 0.68 for ^{68}Ga-PSMA-11 in patients with PSA levels ranging between 0.5 and 3.5 ng/mL (no confidence intervals reported).

Differences Between ^{18}F-PSMA and MRI

On a per-patient level, limited comparative evidence with multiparametric MRI (mpMRI) was identified from the reviews for high-risk or biochemically recurrent patients. Wang et al.[35] reported on one prospective study of 26 high-risk patients with a PSA >10/ng which found a non-statistically significant per-patient sensitivity ratio ml of 1.04 (95% CI 0.96-1.12) in favor of ^{18}F-PSMA PET/CT.[44]

Two systematic reviews[29,31] reported on a single primary retrospective study of 53 patients which reported comparative data for T-staging .[61] This study found that ^{18}F-PSMA PET/CT correctly staged seminal vesicle invasion (pT3b) more often than mpMRI (that is, the accuracy was 0.90 vs. 0.76), whereas mpMRI correctly staged extracapsular extension (pT3a) more often than ^{18}F-PSMA PET/CT (that is, the accuracy was 0.90 vs. 0.57). No confidence intervals were reported for these estimates.

On a per-lesion level, relatively more data were available. Zhao et al.[37] reported on one prospective study of 10 patients with intermediate/high-risk prostate cancer (14 lesions) with a per-lesion sensitivity and specificity for MRI compared to ^{18}F-PSMA PET/CT of 0.53 (95% CI 0.48-0.57) versus 0.58 (95% CI 0.53-0.62) and 0.91 (95% CI 0.84-0.96) versus 0.34 (95% CI 0.26-0.44), respectively.[73]

Liu et al.[31] identified three studies that compared MRI and ^{18}F-PSMA PET/CT, in patients with a PSA greater than 2ng/ml. A retrospective study comprising 10 patients with high-risk prostate cancer (372 lesions) estimated the per-lesion sensitivity for MRI and ^{18}F-PSMA PET/CT to be 0.86 (95% CI 0.79-0.92) and 0.71 (95% CI 0.65-0.77), respectively.[50] A second retrospective study comprising 53 patients with intermediate/high-risk prostate cancer (46 lesions) reported per-lesion sensitivity estimates of 0.74 (95% CI 0.54-0.89) and 0.56 (95% CI 0.35-0.75) for MRI and ^{18}F-PSMA PET/CT, respectively.[61] One prospective study including 79 patients with high-risk prostate cancer (1581 lesions) estimated the per-lesion sensitivity for MRI to be 0.37 (95% CI 0.30-0.44) compared with 0.86 (95% 0.81-0.91) for ^{18}F-PSMA PET/CT.[38] The same two studies estimated the per-lesion specificity of MRI compared to ^{18}F-PSMA PET/CT to be 0.64 (95% CI 0.57-0.70) versus 0.81 (95% CI 0.74-0.86) and 0.79 (95% CI 0.54-0.94) versus 0.84 (95% CI 0.60-0.97), respectively.[50,61] Partial information on these studies was obtained from several reviews.

Relative statistics comparing ^{18}F-PSMA PET/CT to MRI were also found in literature. Systematic reviews by Wang et al.[35] and Huang et al.[29] reported further on Kesch et al.'s[50] study of 10 patients (212 lesions) with high-risk prostate cancer, which estimated the per-lesion sensitivity ratio to be 0.83 (95% CI 0.74-0.92) for patients with a PSA of ≥10 ng/mL in favor of mpMRI. Conversely, the same study estimated the per-lesion specificity ratio to be 1.27 (95% CI 1.12-1.44) in favor of ^{18}F-PSMA PET/CT.[35] The total agreement sensitivity of ^{18}F-PSMA PET/CT was found to be lower than that of mpMRI for localizing the primary prostate tumor (0.71 vs. 0.86, no confidence intervals reported), but the total agreement PPV was higher (^{18}F-PSMA PET/CT vs mpMRI 0.83, 95% CI 0.77-0.88, vs. 0.60, no confidence interval reported) with fewer false positives.[50] This study found the per-lesion near total agreement (defined as allowing a discrepancy of up to 1 region in any direction) PPV for ^{18}F-PSMA PET/CT and mpMRI was similar (0.91 vs 0.91, no confidence interval reported) while the accuracy was greater for ^{18}F-PSMA PET/CT compared

with mpMRI (0.93 vs. 0.87, no confidence interval reported).

Data on per-lesion sensitivity ratio was also reported by Wang et al. for two studies which looked at patients with intermediate/high-risk prostate cancer. One study of 100 patients estimated the per-lesion sensitivity ratio to be 1.11 (95% CI 1.00-1.22) for patients with intermediate/high-risk prostate cancer with a PSA <10 ng/mL.[40] Another with 65 patients estimated a per-lesion sensitivity ratio for patients with a PSA >10 ng/ml of 1.04 (95% CI 0.95-1.12) in favor of ^{18}F-PSMA PET/CT.[59] One of these studies also estimated the per-lesion specificity ratio to be 1.00 (95% CI 0.80-1.25).[40]

When ^{18}F-PSMA PET/CT was combined with mpMRI the per-lesion sensitivity and specificity were estimated to be 0.81 (no confidence intervals provided) and 0.81 (no confidence intervals reported), respectively for patients with high-risk prostate cancer.[50] Another study with 100 patients with intermediate/high-risk prostate cancer estimated the combined per-lesion sensitivity of ^{18}F-PSMA PET/CT and mpMRI to be 0.82 (no confidence intervals) and the combined per-lesion specificity to be 0.67 (no confidence intervals provided).[40]

Differences Between ^{18}F-PSMA PET/CT and Conventional Imaging

No evidence was found in this overview comparing ^{18}F-PSMA PET/CT to the combined findings from bone scintigraphy and CT thorax abdomen pelvis (TAP), or to either of these modalities individually.

Adverse Events

Three systematic reviews stated that no adverse events due to ^{18}F-PSMA were reported in the included primary studies.[27,29,79] The other eight systematic reviews did not refer to any possible adverse events. None of the 11 systematic reviews were designed to explicitly seek outcome data on adverse events.

The European Public Assessment Report (EPAR) for one marketed form of ^{18}F-PSMA did detail adverse events from three trials. Among the 797 patients in the three studies, a total of 108 treatment-emergent adverse events (TEAEs) were reported in 69 (8.6 %) patients, with headache (1.4%), dysgeusia (loss of taste) (1.0%), and fatigue (0.5%) being the most frequent. Three serious TEAEs (hypersensitivity, headache, and paresthesia) were reported, all experienced by one patient who had a significant history of allergic reactions. For this patient only hypersensitivity was assessed as drug-related; all three serious TEAEs were resolved. In total, eight patients (1%) reported serious adverse events (SAEs); seven with recurrent or metastatic prostate cancer and one with high-risk prostate cancer.

Radiation Dose

A large range of activities was reported by systematic reviews. Seven of the 11 systematic reviews provided estimates of injection activity,[27,29,31,33,35-37] however none of the reviews provided any estimates of patient dose in milli-Gray (mGy) or milli-Sieverts (mSv).

Huang et al.[29] calculated the mean of means from 12 studies, and estimated an injection activity of 277.3MBq with a range of 111 MBq to 458 MBq. The injection activity was greater than 240MBq in nine of their 12 included studies. Estimates from additional individual studies included by the other six systematic reviews were included within this range.[27,29,31,33,35,37] Three individual studies identified from the tables of Awenat et al.[27] reported weight-based estimates of injection activity. Two of these three studies reported an estimate of 4 MBq/kg,[48,52] while 4.44MBq/kg was reported in the other study.[80] The EPAR for one marketed form of ^{18}F-PSMA PET/CT notes an effective dose of 4.2 mSv when the maximal recommended activity of 360MBq is administered in a 70 kg-weighted patient.[81]

Discussion

In this overview of reviews, we aimed to consolidate existing evidence syntheses and provide a comprehensive overview of the evidence on the diagnostic accuracy of ^{18}F-prostate specific membrane antigen (PSMA) PET/CT in the staging of high-risk prostate cancer and restaging after biochemical recurrence. We identified 11 systematic reviews, which in turn gathered data from 37 primary studies, and have highlighted remaining gaps in the current evidence.

In general, systematic reviews included in this overview of reviews were at high or unclear risk of bias. Overlap across reviews was moderate, reflecting both limitations in search strategies and differences in the included systematic reviews' research questions. While many diagnostic accuracy outcomes were found to have low or very low certainty of evidence, the evidence was broadly supportive of ^{18}F-PSMA PET/CT given the high sensitivity and specificity reported. The combination of patients with both intermediate and high risk prostate cancer reduced the certainty of the evidence with greater variability in estimates. This likely relates to the lower prevalence of metastatic disease in intermediate-risk prostate cancer patients, resulting in spectrum effects that greatly influence the sensitivity and specificity outcomes.[82] Specific evidence on tumor staging, lymph node staging and overall accuracy was absent or lacking. While sensitivity, specificity and accuracy expressed as proportions were the main diagnostic accuracy outcomes, other outcomes such as predictive values, were not generally considered despite their importance in interpreting test results for a given individual. Dose and adverse events were also not well captured by existing systematic reviews, likely in part due to poor reporting in the primary literature, however the large range of injection activities found is unlikely to be totally explained by variations in patient weight.

While limited comparative data was found in the systematic reviews, there was evidence that different ^{18}F-PSMA radiopharmaceuticals used in PET/CT were broadly similar in their diagnostic accuracy and had some superiority over

^{68}Ga-PSMA PET/CT. However, there are differences in their pharmacokinetic and pharmacodynamics properties.[46]Total equivalence between ^{68}Ga-PSMA PET/CT and ^{18}F-PSMA PET/CT should not be assumed and the individual justification of radiotracers available to patients within a given region should be considered where more than one radiotracer is available.

One primary study of particular relevance to this area was not included as its outcomes were not in keeping with that of the systematic reviews identified. The CONDOR study by Morris et al. assessed the correct localization rate (CLR) in patients with biochemical recurrence, defined as the percentage of patients with a one-to-one correspondence between at least one lesion identified on ^{18}F-PSMA PET/CT by the readers of the scan and the composite reference standard (consisting of histology where available, subsequent correlative imaging findings and post- radiation PSA response in descending priority).[83] As CLR was defined as "at least one lesion", this study does not provide insight as to whether additional lesions or all lesions are correctly identified. Patients in this study also required negative or equivocal (indeterminate) findings on standing imaging, but because of the unstandardized imaging work up of these patients (which may have included CT, MRI, bone scan, ^{18}F-fluciclovine or ^{11}C-Choline PET) the comparative findings were difficult to definitively interpret. They did, however, conclude a favorable CLR of 84.8% to 87.0%, and the lower bound of the 95% CI ranged from 77.8% to 80.4% which was superior to that of their unstandardized imaging work up. Although this study was excluded within the body of evidence synthesized, its findings are consistent with the findings of this overview of reviews.

Where histopathological confirmation is not possible, alternative reference standards likely introduce error and bias. A general consideration in this area of research is that the "truth" in men with negative ^{18}F-PSMA PET/CT results is often unknown because verification is usually not required in clinical practice. However, confirmation of true negatives in a number of studies could have been improved with follow-up. False negatives may be attributed to inexperienced readers of these scans, small-volume disease, the obscuration of lesions in or adjacent to organs with high ^{18}F-PSMA uptake (for example, the liver) or excretory organs (for example, bladder, urethra, ureters) where signal is high due to the concentration of metabolized ^{18}F-PSMA.

A particular challenge of this overview was the lack of definitions provided by systematic reviews, or at times the lack of consistent definitions across systematic reviews. For example, it is known that definitions of high-risk prostate cancer or biochemical recurrence can vary. This overview accepted the definitions of high-risk or biochemical recurrence as provided by the review authors. However, if definitions vary there is potential for bias when comparing between studies and this limits the potential to pool data. Most authors did not specify the exact nature of their 'per-patient' analysis. The approach taken was to assume that in the high-risk setting, 'per-patient' analysis referred to 'any findings of regional or distant nodal disease or metastatic disease' and in the biochemical recurrence setting it referred to 'any finding of prostate cancer'. Similarly, the definition of 'per-lesion' was often unclear and was at times incorrectly reported as per-patient. Therefore, where the denominator and calculations were available, attempts were made to confirm whether the figures were per-patient or per-lesion.

Similarly, there was some data on characteristics of primary studies which were misreported by systematic reviews. Discrepant data were resolved where possible through cross-referencing, however it is possible that residual misreporting and data extraction errors remain. Confidence intervals were often not reported for primary studies, however where a bivariate meta-analysis was planned a priori, these did not necessarily need to be extracted by the systematic review.

Reviews in this overview often combined per-patient and per-lesion data to provide pooled estimates for sensitivity, specificity, accuracy and other outcomes. While some aggregate outcomes consistent with our PICO were data extracted and are included in the OSF repository, they were not reported in the results section as it was thought that the pooling of this data may not be appropriate, and likely produces estimates that are not reflective of the diagnostic accuracy of the test on either a per-patient or per-lesion level.[12] This is supported by the observation that in Yang et al.'s meta-analysis heterogeneity significantly increased when per-patient data was pooled with per-lesion data.[36] One exception to this approach was made when we reported on subgroup analyses comparing ^{18}F-PSMA-DCFPyL to ^{18}F-PSMA-1007, where pooled per-patient and per-lesion data was reported as no other estimates were available. Caution is urged when attempting to interpret such pooled data. Some systematic review authors also pooled data from biochemically recurrent patients and data from primary staging of patients with low, intermediate, and high-risk prostate cancer in varying proportions. We attempted to overcome such limitations by referring to individual primary study results rather than the pooled results in the meta-analyses, aided by the use of a structured narrative synthesis which was reported in line with SWiM reporting guidelines.

Finally, it must be acknowledged that no patient relevant outcome data (for example, survival data) were identified as part of this overview, which instead focused on diagnostic test accuracy. There is an assumption that improvements in diagnostic test accuracy will result in improved staging and risk stratification thereby optimizing the potential to improve patient relevant outcomes (for example, survival). Future studies may investigate the underlying assumption that improvements in test accuracy leads to improvements in patient outcomes, such as overall survival, for these cohorts. Some initial findings have indicated ^{18}F-PSMA PET/CT may impact on treatment allocation.[30,34] Future research may further explore the hypothesis that the low prevalence of metastatic disease in patients with nonhigh-risk prostate cancer leads to spectrum effects and poorer diagnostic accuracy outcomes.

Statements and Declarations

Competing interests: No competing interests were disclosed. Data Availability Statement: The datasets generated during and/or analyzed during the current study are available in the OSF repository, https://doi.org/10.17605/OSF.IO/QMEZ5.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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CRediT authorship contribution statement

Andrew Dullea: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Lydia O'Sullivan:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. **Kirsty K. O'Brien:** Methodology, Formal analysis, Writing – review & editing. **Marie Carrigan:** Methodology, Writing – review & editing. **Susan Ahern:** Methodology, Writing – review & editing. **Maeve McGarry:** Methodology, Writing – review & editing. **Patricia Harrington:** Methodology, Writing – review & editing. **Kieran A. Walsh:** Methodology, Supervision, Writing – review & editing. **Susan M. Smith:** Methodology, Supervision, Writing – review & editing. **Máirín Ryan:** Funding acquisition, Methodology, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.semnuclmed.2024.05.003.

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