

Diagnosis and staging of patients with prostate cancer

Disclaimer

This guideline (“the Guideline”) was developed by a multidisciplinary Guideline Development Group (“the Group”) and is based upon the best clinical evidence available together with the clinical expertise of the Group members. The Guideline supersedes all previous Health Service Executive (HSE), National Cancer Control Programme (NCCP) and National Clinical Effectiveness Committee (NCEC) guidelines for radiological diagnosis and staging of patients with prostate cancer. The NCCP is part of the HSE and any reference in this disclaimer to the NCCP is intended to include the HSE. Please note, the Guideline is for guidance purposes only. The appropriate application and correct use of the Guideline is the responsibility of each health professional. The Guideline Development Group’s expectation is that health professionals will use clinical knowledge and judgment in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgment in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary. The NCCP accepts no liability nor shall it be liable, whether arising directly or indirectly, to the user or any other third party for any claims, loss or damage resulting from any use of the Guideline.

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1.0 Terms used in this guideline

Prostate assessment

A prostate assessment consists of four parts 1) clinical history, 2) a clinical exam (DRE) 3) a Urine (UA / MSU) and 4) Blood (PSA) test.

Raised age related PSA

Raised age related PSA is defined as the following:

- Under 50 years of age $\geq 2\mu\text{g/L}$
- 50-59 $\geq 3\mu\text{g/L}$
- 60-69 $\geq 4\mu\text{g/L}$
- 70+ $\geq 5\mu\text{g/L}$

For more information, please see the NCCP National Prostate Cancer GP Referral Guideline - <https://www.hse.ie/eng/services/list/5/cancer/profinfo/resources/gpreferrals/gp-prostate-referral-form-and-guideline.html>

Biopsy

The biopsy that the Guideline Development Group recommend is a systematic biopsy plus a targeted biopsy of focal lesions.

Systematic prostate biopsy

A systematic prostate biopsy is based on systematic prostate sampling and a minimum number of 12 cores should be taken.

Clinically significant prostate cancer

The Guideline Development Group define clinically significant prostate cancer as any prostate cancer of Gleason score 7 and above.

Risk stratification of prostate cancer patients

Prostate cancer patients are risk stratified according to the National Comprehensive Cancer Network® (NCCN®) prostate cancer risk stratification (Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.3.2022. © National Comprehensive Cancer Network, 2022). The NCCN risk groups are defined using the following clinical/pathological features:

Very low risk group

Has all of the following: cT1c, Grade Group 1, PSA $< 10\mu\text{g/L}$, fewer than 3 prostate biopsy fragments/cores positive, $\leq 50\%$ cancer in each fragment/core, PSA density $< 0.15\text{ ng/mL/g}$.

Low risk group

Has all of the following but does not qualify for very low risk: cT1-cT2a, Grade Group 1, PSA $< 10\mu\text{g/L}$.

Intermediate risk group

Has all of the following: no high risk group features, no very high risk group features, has one or more intermediate risk factors (IRF) (cT2b-cT2c, Grade Group 2 or 3, PSA $10-20\mu\text{g/L}$).

Favourable intermediate risk group

Has all of the following: 1 IRF, Grade Group 1 or 2, $< 50\%$ biopsy cores positive (e.g. < 6 of 12 cores)*.

Unfavourable intermediate risk group

Has one or more of the following: 2 or 3 IRFs, Grade Group 3, $\geq 50\%$ biopsy cores positive (e.g. ≥ 6 of 12 cores)*.

High risk group

Has no very high risk features and has exactly one high risk feature: cT3a OR Grade Group 4 or Grade Group 5 OR PSA >20 $\mu\text{g/L}$.

Very high risk group

Has at least one of the following: cT3b-cT4, Primary Gleason pattern 5, 2 or 3 high risk features, >4 cores with Grade Group 4 or 5.

*An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) can be considered as a single positive core.

The multidisciplinary Guideline Development Group

A multidisciplinary Guideline Development Group was responsible for the development of this National Clinical Guideline. This included representatives from relevant professional groups (radiology, pathology, urology, radiation oncology, palliative care and nursing) with expertise in the diagnosis and staging of patients with prostate cancer, patients, a physicist, a medical ethicist, a methodologist, research officers and clinical librarians. (Details of Guideline Development Group members are provided in 2.0 Membership of the Guideline Development Group)

Quality of evidence

The extent to which one can be confident that an estimate of effect is correct. (GRADE, 2013)

Strength of a recommendation

The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. (GRADE, 2013)

Benefits and Harms

Benefits refer to improved quality of life and reductions in mortality and morbidity.

There are physical risks of harm such as sepsis, exposure to radiation and there are also emotional and psychological risks of harm such as anxiety and depression.

Preferences and values

The patient preferences and values statements were developed by the multidisciplinary Guideline Development Group including patient representatives. Patient members were given priority during guideline meetings to discuss preferences and values.

The Guideline Development Group tried to identify what an informed patient and their families would prefer. The value statements refer to what the Guideline Development Group believe are the values that are driving patient and family preferences.

Good practice points

Good practice points are based on the clinical expertise of the Guideline Development Group.

Practical considerations around patient care

These are statements developed with the patient Guideline Development Group members on issues that were important to them with regards to their own experience of the diagnosis and staging of their cancer.

Shared decision-making approach

A shared decision-making approach is between the healthcare professional and the patient. It provides patients with a measure of understanding and control over their treatment. Clinicians should disclose the potential benefits and harms of a treatment to the patient. Clinicians should also help elicit patients' values regarding treatment. Men should be allowed to have family members present during shared decision-making if they would like to. Written information on the items relevant to shared decision-making, including the benefits and harms of the treatment options, should be provided to all patients being investigated for prostate cancer.

Sensitivity

The proportion of people with disease who have a positive test. (CEBM website)

Specificity

The proportion of people free of a disease who have a negative test. (CEBM website)

Positive predictive value (PPV)

The proportion of people with a positive test who have disease. (CEBM website)

Negative predictive value (NPV)

The proportion of people with a negative test who are free of disease. (CEBM website)

2.0 Membership of the Guideline Development Group

Name	Title/Position	Role on guideline group*
Patient Representatives		
Mr Tom Hope	Patient Representative	Writing member
Mr Peter Moran	Patient Representative	Member (until Nov 2019)
Radiology		
Professor Conor Collins	Consultant Radiologist, SVUH	Writing member
Dr Ruth Dunne	Consultant Radiologist, BH	Writing member
Professor Peter Beddy	Consultant Radiologist, SJH	Writing member
Dr Amy O'Brien	Radiology Specialist Registrar,	Member
Dr Marion Hanley	Radiology Specialist Registrar, BH	Member (from Jan 2020)
Dr Bryan Buckley	Radiology Specialist Registrar, TUH	Member (from Jan 2020)
Pathology		
Dr Teresa McHale	Consultant Histopathologist, GUH	Member
Dr Tom Crotty	Consultant Histopathologist, SVUH	Member
Surgery		
Mr David Galvin	Consultant Urologist, MMUH, SVUH	Clinical chair and writing member
Mr Eamonn Rogers	Consultant Urologist, GUH	Writing member
Mr Richard Power	Consultant Urologist, BH	Member
Radiation Oncology		
Dr Brian O'Neill	Consultant Radiation Oncologist, SLRON	Member
Dr Pierre Thirion	Consultant Radiation Oncologist, SLRON	Member
Palliative Care		
Dr Valerie O'Reilly	Consultant in Palliative Medicine, Milford Care Centre	Member
Nursing		
Ms Elizabeth McEvoy	Urology Cancer Coordinator, TUH	Member (until Nov 2019)
Ms Lynn Casey	Advanced Nurse Practitioner Urology, TUH	Member
Medical Ethics		
Professor Leah McClimans	Associate Professor, Philosophy, UCC	Writing member
Library		
Mr Gethin White	HSE Librarian, HSE East	Information services
Ms Marie Carrigan	HSE Librarian, SLRON	Information services
NCCP		
Dr Eve O'Toole	Head of Evidence and Quality Hub, NCCP	Methodology chair and writing member
Dr Helena Gibbons	Senior Research Officer, NCCP	Project manager, senior researcher and writing member
Ms Eileen Nolan	National Programme Manager for Urological Cancers, NCCP	Member

* Writing members were active participants at a minimum of 66% of Guideline Development Group meetings where guideline recommendations were formulated. Members were participants at a number of guideline scoping or recommendation meetings.

2.1 Guideline contributors

Name	Title/Position	Role on guideline group*
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Dr Laura Greene	Radiology Specialist Registrar, UHW	Contributor
Dr Shane McAnearney	Radiology Specialist Registrar, Royal Victoria Hospital	Contributor
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Dr Gerard McVey	Consultant Radiation Oncologist, SLRON	Contributor
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*Contributors provided information in their area of expertise to the Guideline Development Group

3.0 Clinical questions

Summary of clinical questions and recommendations

Here follows a list of all the recommendations in this updated section of the guideline, along with the quality of evidence and strength of each recommendation.

Clinical question 3.1

For men with suspected prostate cancer referred from a urologist, is MRI recommended pre prostate biopsy?

Recommendation 3.1.1: In men with suspected prostate cancer referred from a urologist multiparametric MRI is recommended pre prostate biopsy.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.1.2: If the patient is not a suitable candidate for multiparametric MRI then a systematic prostate biopsy should be offered as a first line test.

Quality of Evidence:

Grade of recommendation:

Good practice point

The imaging must be performed in accordance with the latest version of the PI-RADS technical guidelines. MRIs must be read by in-house radiologists experienced in reading prostate MRIs who regularly attend the prostate multidisciplinary meeting.

All patients with suspected prostate cancer should be made aware of support services available to them.

Practical considerations around patient care

- All patients with suspected prostate cancer should have access to a Clinical Nurse Specialist or Advanced Nurse Practitioner.
- The Clinical Nurse Specialist, Advanced Nurse Practitioner or urologist should explain clinically significant prostate cancer and clinically insignificant prostate cancer to patients.

Clinical question 3.2

How is an abnormal MRI finding defined and what abnormality on an MRI requires a targeted biopsy?

Recommendation 3.2.1: The Guideline Development Group recommends the use of the most recent version of the PI-RADS scoring system for prostate MRI interpretation.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.2.2: In patients with focal lesions graded PI-RADS 4 and 5 a biopsy is recommended. This includes a systematic biopsy and targeted biopsy of focal lesions.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.2.3: In patients with focal lesions graded PI-RADS 3 a biopsy should be considered. This includes a systematic biopsy and targeted biopsy of focal lesions.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

Patients with PI-RADS ≤ 3 are at low risk of clinically significant prostate cancer however additional risk stratification may be used in determining the need for a biopsy (refer to Clinical question 3.5).

For patients at high risk of TRUS sepsis a transperineal approach is recommended (refer to [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#)).

For timing of IV antibiotic prophylaxis refer to the [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#).

Practical considerations around patient care

- The benefits and harms of a prostate biopsy following an MRI should be communicated to all patients using a shared decision-making approach.
- Written information on the items relevant to shared decision-making, including the benefits and harms of proceeding to biopsy, should be provided to all patients being investigated for prostate cancer.
- Men should be allowed to have family members present during shared decision-making if they would like to.

Clinical question 3.3

In men with abnormal MRI findings, which type of targeted biopsy should be performed?

Recommendation 3.3.1: A targeted biopsy of focal lesions should be performed using either MRI (guided) transrectal/transperineal US fusion or cognitive registration biopsy.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

Targeted biopsies are extremely operator dependant and should only be performed in a high volume centre by appropriately trained professionals.

A minimum number of 12 cores should be taken for a systematic biopsy.

Clinical question 3.4

For men being investigated for prostate cancer without an MRI targetable lesion should they have a prostate biopsy?

Recommendation 3.4.1: For patients with a negative MRI (i.e. PI-RADS 1 or 2) omitting a biopsy should be considered, following the shared decision-making model.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.4.2: For patients with a negative MRI (i.e. PI-RADS 1 or 2) and a high clinical suspicion of prostate cancer the Guideline Development Group recommends a systematic prostate biopsy.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.4.3: For patients with a negative MRI (i.e. PI-RADS 1 or 2) who do not proceed to biopsy PSA should be monitored regularly at 6 months and then annually.

Quality of Evidence: Low

Grade of recommendation: Strong

Good practice point

- Advanced Nurse Practitioners should be available for shared decision-making with patients being investigated for prostate cancer.

For patients at high risk of TRUS sepsis a transperineal approach is recommended (refer to [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#)).

For timing of IV antibiotic prophylaxis refer to the [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#).

Practical considerations around patient care

- Written information on the items relevant to shared decision-making, including the benefits and harms of proceeding to biopsy, should be provided to all patients being investigated for prostate cancer.
- Men should be allowed to have family members present during shared decision-making if they would like to.

Clinical question 3.5

In men with intermediate risk prostate cancer should staging investigations be performed?

Recommendation 3.5.1: In men with favourable intermediate risk* prostate cancer who have had a pre-biopsy MRI the use of further staging scans is not recommended.

*Favourable intermediate risk is defined as having all of the following: one intermediate risk factor (cT2b–cT2c, Grade Group 2 or 3, PSA 10–20 µg/L), Grade Group 1 or 2 and <50% biopsy cores positive (e.g. <6 of 12 cores).

Quality of Evidence: Low

Grade of recommendation: Strong

Recommendation 3.5.2: In men with unfavourable intermediate risk* prostate cancer who have had a pre-biopsy MRI the routine use of further staging scans is not recommended.

*Unfavourable intermediate risk is defined as having one or more of the following: two or three intermediate risk factors (cT2b–cT2c, Grade Group 2 or 3, PSA 10–20 µg/L), Grade Group 3, ≥ 50% biopsy cores positive (e.g. ≥6 of 12 cores).

Quality of Evidence: Low

Grade of recommendation: Weak

Recommendation 3.5.3: PSMA PET-CT is not recommended for primary staging of low risk prostate cancer patients.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

A clinician may decide to do further staging investigations if there are clinical features that may increase a patients individual risk following discussion at MDT.

Practical considerations around patient care

- The benefits and harms of further staging investigations should be communicated to all patients using a shared decision-making approach.
- Men should be allowed to have family members present during shared decision-making if they would like to.

Clinical question 3.6

In men with high risk prostate cancer what staging investigations should be performed?

Recommendation 3.6.1: PSMA PET-CT should be considered for primary staging in high risk* prostate cancer patients who are suitable for definitive treatment.

*High risk is defined as having no very high risk features and having exactly one high risk feature: cT3a OR Grade Group 4 or Grade Group 5 OR PSA >20 µg/L.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

If PSMA PET-CT is not available within 4 weeks then conventional imaging including an isotope bone scan, CT and MRI prostate (in those that have not had one to date) should be performed as an alternative with a view to proceeding to treatment.

Practical considerations around patient care

- All high risk prostate cancer patients should have access to a Clinical Nurse Specialist/Advanced Nurse Practitioner to explain their test and test results.

Clinical question 3.7

For men with biochemical recurrence of prostate cancer what is the role of PSMA PET-CT?

Recommendation 3.7.1: In men with a biochemical recurrence of prostate cancer following primary treatment (surgery or radiotherapy) PSMA PET-CT should be considered if it will influence patient management following discussion at a multidisciplinary team meeting.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

- The timeframe to PSMA PET-CT will vary with different clinical circumstances and should be determined by the multidisciplinary team.
-
- If PSMA PET-CT is not available within the timeframe recommended by the multidisciplinary team then conventional imaging including an isotope bone scan, CT and MRI should be performed as an alternative with a view to proceeding to treatment.

Practical considerations around patient care

- All men with biochemical recurrence of prostate cancer undergoing a PSMA PET-CT scan should have access to a Clinical Nurse Specialist/Advanced Nurse Practitioner to explain the PSMA PET-CT test and test results.
- All men with biochemical recurrence of prostate cancer undergoing any diagnostic test should have access to a Clinical Nurse Specialist/Advanced Nurse Practitioner to explain the test and test results.

Clinical question 3.1

For men with suspected prostate cancer referred from a urologist, is MRI recommended pre prostate biopsy?

Quality of Evidence

Three prospective studies PROMIS (Ahmed et al., 2017), MRI-FIRST (Rouvière et al., 2019), 4M (van der Leest et al., 2019), a randomised controlled trial PRECISION (Kasivisvanathan et al., 2018), and a Cochrane review (Drost et al., 2019) addressed this clinical question.

For detection of clinically significant cancer, multiparametric magnetic resonance imaging (mpMRI) was more sensitive (93%, 95% CI 88–96%) than TRUS-biopsy (48%, 95% CI 42–55%) and less specific (41%, 36–46% for mpMRI vs 96%, 94–98% for TRUS-biopsy) (Ahmed et al., 2017). These findings are in agreement with a recent Cochrane review (Drost et al., 2019).

Studies have shown that 21–49% of men could potentially avoid prostate biopsy if they had a mpMRI prior to biopsy (Ahmed et al., 2017, Kasivisvanathan et al., 2018, van der Leest et al., 2019, Rouvière et al., 2019). Ahmed et al., (2017) and Kasivisvanathan et al., (2018) conclude that mpMRI is better at ruling out disease as a first line test and TRUS is better at ruling in disease. These studies were performed on both 1.5T and 3T machines.

Benefit and Harm

Using mpMRIs as a first line test will help some patients avoid unnecessary harms. If a mpMRI indicates that a biopsy is not needed, then the patient will avoid the discomfort and possible embarrassment sometimes associated with a biopsy. These same patients will also avoid possible side-effects of a biopsy, such as sepsis and scar tissue. In addition, mpMRI-directed biopsy pathways tend to detect fewer instances of clinically insignificant cancer than biopsies do, so some patients will avoid the stress and anxiety of a diagnosis of clinically insignificant cancer.

Using mpMRI as a first line test is more efficient than biopsying all men. If mpMRI shows clinically significant cancer, the imaging helps to target the site for biopsy and provides information for local staging.

Like all tests, the mpMRI is not perfect. mpMRIs may result in false positive results (up to 50%) (Ahmed et al., 2017). Patients who receive a false positive result will undergo the discomfort and associated side-effects of a biopsy plus the stress and anxiety of waiting for the result. On the other hand, 3–11% of patients may get false negative results for clinically significant cancer (van der Leest et al., 2019, Rouvière et al., 2019, Ahmed et al., 2017). In these relatively rare cases, the use of mpMRI will delay treatment.

Additionally, some people may find mpMRIs claustrophobic or they may not be able to have a mpMRI scan (for example in cases of pacemakers, cochlear implants) or may have reasons (for example metal hip replacements) where the image quality is poor.

Preferences and values

The multidisciplinary Guideline Development Group including patient representatives recognise knowledge as an important patient value. The Guideline Development Group believes that informed patients will prefer a mpMRI as a first line test over a TRUS biopsy because a mpMRI preserves patient's comfort and dignity. The Guideline Development Group assumes that patients or their families are well-informed about the limitations of mpMRIs, as well as informed about the difference between "clinically significant" and "clinically insignificant" cancer. This means that the values of disclosure and understanding are embedded into patient/clinical communication. As such the

Guideline Development Group believes that informed patients will prefer a mpMRI as a first line test over a TRUS biopsy because a mpMRI is more efficient and may eliminate the need for an invasive, uncomfortable procedure.

(Driving value- dignity, communication and comfort)

Resources, capacity and other considerations

One cost-effectiveness study was used to address this clinical question.

Faria et al. (2018) developed a cost-effectiveness model of health outcomes and costs of men referred to secondary care with a suspicion of prostate cancer prior to any biopsy in the UK National Health Service. Information from the PROMIS diagnostic study was used (Ahmed et al., 2017). Unit costs were reported in pound sterling from a 2015 price base.

The study assessed the performance of mpMRI, TRUS biopsy and transperineal mapping biopsy. The model examined 383 diagnostic strategies, based on possible sequences of the three tests, two pathological definitions of clinically significant prostate cancer and different cutoffs of the Likert score. A number of sensitivity analyses were conducted on the aspects of the short- and long-term components of the model.

The study found that the use of mpMRI first followed by an MRI-targeted TRUS biopsy in men in whom the mpMRI suggests a suspicion for clinically significant cancer, and a follow-up systematic biopsy if no clinically significant cancer is found, under the most sensitive clinically significant cancer definitions and cutoffs detects more clinically significant cancers per pound spent than a strategy using TRUS biopsy first (sensitivity = 0.95 [95% CI 0.92–0.98] vs 0.91 [95% CI 0.86–0.94]) and is cost effective (ICER = £7,076 [£8350/QALY gained]) (Faria et al., 2018).

This would suggest the recommendations will be cost-effective in the identification of clinically significant cancer.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Access to pre biopsy MRI

Men with suspected prostate cancer, referred from a urologist will require access to pre biopsy MRI. The Guideline Development Group highlighted that this may require updating MRI scanners and increasing MRI capacity. Trained personnel to acquire and interpret a pre biopsy prostate MRI will also be required. Therefore both capital and revenue costs will be required to establish the pathway.

Recommendation 3.1.1:

In men with suspected prostate cancer referred from a urologist multiparametric MRI is recommended pre prostate biopsy.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.1.2:

If the patient is not a suitable candidate for multiparametric MRI then a systematic prostate biopsy should be offered as a first line test.

Quality of Evidence: High

Grade of recommendation: Strong

Good practice point

- The imaging must be performed in accordance with the latest version of the PI-RADS technical guidelines. MRIs must be read by in-house radiologists experienced in reading prostate MRIs who regularly attend the prostate multidisciplinary meeting.
- All patients with suspected prostate cancer should be made aware of support services available to them.

Practical considerations around patient care

- All patients with suspected prostate cancer should have access to a Clinical Nurse Specialist or Advanced Nurse Practitioner.
- The Clinical Nurse Specialist, Advanced Nurse Practitioner or urologist should explain clinically significant prostate cancer and clinically insignificant prostate cancer to patients.

Clinical question 3.2

How is an abnormal MRI finding defined and what abnormality on an MRI requires a targeted biopsy?

Quality of Evidence

Two meta-analyses (Zhang et al., 2017, Woo et al., 2017), a randomised controlled trial PRECISION (Kasivisvanathan et al., 2018) and three prospective studies PROMIS (Ahmed et al., 2017), MRI-FIRST (Rouvière et al., 2019) and 4M (van der Leest et al., 2019) addressed this clinical question.

The Guideline Development Group recommend that MRI findings are classified using the most recent version of Prostate Imaging Reporting and Data system (PI-RADS). Two meta-analyses have found that PI-RADS V2 demonstrates good diagnostic accuracy for any prostate cancer detection with high sensitivity and moderate specificity ranging from 0.85-0.89 and 0.71-0.73, respectively (Zhang et al., 2017, Woo et al., 2017). In a subgroup analysis by Woo et al. (2017) the overall pooled sensitivity for determining clinically significant prostate cancer was 0.89 (95% CI 0.84–0.92) and specificity was 0.64 (95% CI 0.46–0.78). At a cutoff of PI-RADS ≥ 4 for determining clinically significant prostate cancer, the sensitivity and specificity were 0.90 (95% CI 0.85–0.94) and 0.62 (95% CI 0.45–0.77) respectively. At a cutoff of PI-RADS ≥ 3 for determining clinically significant prostate cancer, sensitivity was 0.96 (95% CI 0.87–0.99) and specificity reduced to 0.29 (0.05–0.77) (Woo et al., 2017). In addition to the meta-analysis data, the mean pooled positive predictive value (PPV) for determining clinically significant prostate cancer at a cutoff of PI-RADS ≥ 3 in four prospective studies was 49.9% (van der Leest et al., 2019, Ahmed et al., 2017, Kasivisvanathan et al., 2018, Rouvière et al., 2019).

The PRECISION trial (Kasivisvanathan et al., 2018) also found the detection rate of clinically significant cancer in biopsy naive men with PI-RADS 3, 4, or 5 lesions was 12%, 60%, and 83%, respectively. The percentage of negative mpMRI (PI-RADS score ≤ 2) in PRECISION was 28% (Kasivisvanathan et al., 2018). The evidence supports the use of targeted biopsy for PI-RADS 4 and 5 lesions.

The prostate biopsy that the Guideline Development Group recommend is a systematic biopsy plus a targeted biopsy of focal lesions.

Benefit and Harm

The benefits of using PI-RADS is that it provides a standardised acquisition, interpretation and reporting of prostate MRIs.

PI-RADS consists of a scale from 1-5 with increasing risk of clinically significant cancer. Scores of PI-RADS 4 and 5 reflect strong suspicion of clinically significant prostate cancer. The benefit of taking biopsies from patients with these scores is to confirm cancer so treatment can begin as soon as possible with the ultimate aim of improving mortality, morbidity and quality of life. A PI-RADS score of 3 is inherently ambiguous in terms of clinically significant or clinically insignificant cancer. The benefit of taking biopsies from patients with this score is to clarify an unavoidable ambiguity. Doing so will provide patients and clinicians with certainty regarding need for treatment.

Although PI-RADS is standardised, expertise is required. The level of experience and expertise with PI-RADS varies, and with it the accuracy of the scores.

Preferences and values

The multidisciplinary Guideline Development Group values maximising benefits and minimising harms for each patient. They also recognise that in doing this the tools at our disposal are imperfect

and carry with them uncertainties. In this context patient trust is very important. The Guideline Development Group agrees that providing patients with PI-RADS scores of 3 with a biopsy is the best way to clarify ambiguity. Providing a biopsy for patients with a PI-RADS score of 4 or 5 is the best way to move forward with treatment if needed.

(Driving value- ambiguity and uncertainty)

Resources capacity and other considerations

There was no relevant cost-effectiveness literature found to address this clinical question.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Variability in MRI interpretation

There is intra and inter-rater variability associated with MRI interpretation therefore multidisciplinary meetings with radiologic-pathologic correlations are required. An audit of the volume of indeterminate lesions (PI-RADS 3) is recommended by the Guideline Development Group.

Recommendation 3.2.1:

The Guideline Development Group recommends the use of the most recent version of the PI-RADS scoring system for prostate MRI interpretation.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.2.2:

In patients with focal lesions graded PI-RADS 4 and 5 a biopsy is recommended. This includes a systematic biopsy and targeted biopsy of focal lesions.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.2.3:

In patients with focal lesions graded PI-RADS 3 a biopsy should be considered. This includes a systematic biopsy and targeted biopsy of focal lesions.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

- Patients with PI-RADS ≤ 3 are at low risk of clinically significant prostate cancer however additional risk stratification may be used in determining the need for a biopsy (refer to Clinical question 3.5).
- For patients at high risk of TRUS sepsis a transperineal approach is recommended (refer to [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#)).
- For timing of IV antibiotic prophylaxis refer to the [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#).

Practical considerations around patient care

- The benefits and harms of a prostate biopsy following an MRI should be communicated to all

patients using a shared decision-making approach.

- Written information on the items relevant to shared decision-making, including the benefits and harms of proceeding to biopsy, should be provided to all patients being investigated for prostate cancer.
- Men should be allowed to have family members present during shared decision-making if they would like to.

Clinical question 3.3

In men with abnormal MRI findings, which type of targeted biopsy should be performed?

Quality of Evidence

Indirect evidence from the multicenter randomised controlled trial FUTURE (Wegelin et al., 2019) and two meta-analyses (Xiang et al., 2019, Tu et al., 2019) addressed this clinical question.

The prostate biopsy that the Guideline Development Group recommend is a systematic biopsy plus a targeted biopsy of focal lesions. There are two methods of targeted biopsy using software fusion or cognitive techniques. This can be done using a transperineal or a transrectal approach.

The FUTURE trial compared detection rates of overall prostate cancer and clinically significant prostate cancer in patients with prior negative biopsies for three MRI-based targeted biopsy techniques. Patients with PI-RADS ≥ 3 lesions were randomised 1:1:1 for one targeted biopsy technique: MRI-transrectal ultrasound (TRUS) fusion targeted biopsy (FUS-TB), cognitive registration TRUS targeted biopsy (COG-TB), or in-bore MRI targeted biopsy (MRI-TB). There were no significant differences in the detection rates of overall prostate cancer or clinically significant prostate cancer among the groups. There were significant differences in the number of cores taken per technique: the median number of cores was four for FUS-TB (IQR 3–5), three for COG-TB (IQR 3–4), and two for MRI-TB (IQR 2–3; $p < 0.05$) (Wegelin et al., 2019).

In the setting of a systematic biopsy, transperineal and transrectal approaches have shown comparable accuracy in detecting prostate cancer (Xiang et al., 2019). The transperineal approach has also been shown to significantly protect patients from rectal bleeding and fever but can significantly increase patient pain compared to the transrectal approach (Xiang et al., 2019). In a pooled analysis of four studies using MRI targeted biopsy, more clinically significant prostate cancer was detected in patients with positive mpMRI using the transperineal approach, with an accuracy rate of 62.2% (204/328) compared to 41.3% (130/315) for the transrectal approach (odds ratio = 2.37; 95% CI, 1.71-3.26) (Tu et al., 2019). No data was presented on patient safety and complications.

Benefit and Harm

Both transperineal and transrectal biopsies can be performed under local anaesthetic, conscious sedation or other anaesthetic approaches based on clinical scenario and patient preferences.

While a transrectal approach is conventionally a shorter procedure patients need more post procedure monitoring in clinic and follow up due to the increased risk of sepsis compared to a transperineal approach.

The benefit of a targeted biopsy to the patient is accurate early detection of prostate cancer, the increased risk of sepsis is a harm associated with the transrectal approach.

Preferences and values

The multidisciplinary Guideline Development Group including patient representatives recognises that finding clinically significant prostate cancer in a timely manner is of utmost importance. The transperineal and transrectal biopsy approaches realise that value. However, the transperineal biopsy has the benefit of a reduced risk of sepsis compared to a transrectal biopsy.

Resources, capacity and other considerations

One cost-effectiveness study was used to address this clinical question.

Venderink and colleagues (2017) developed a decision tree and Markov model to compare the cost-effectiveness of systematic TRUS guided prostate biopsy with direct in-bore MRI guided and MRI-TRUS fusion guided prostate biopsy. The time horizon for this analysis was 18 years. Unit costs were reported in Euros from a 2017 price based on Dutch cost data. All future costs were discounted to their present value by a rate of 4%.

The hypothetical population of this study consisted of biopsy-naive patients in whom clinically significant prostate cancer was suspected on the basis of an elevated serum PSA level or abnormal digital rectal examination finding. A strategy was deemed cost-effective if the costs of gaining one quality-adjusted life year (QALY) (incremental cost-effectiveness ratio (ICER)) did not exceed the willingness-to-pay threshold of €80,000 (≈\$85,000 in January 2017). A base case analysis was performed to compare systematic TRUS and image fusion-guided biopsies. Due to a lack of appropriate literature regarding the accuracy of direct in-bore MRI-guided biopsy, a threshold analysis was performed.

MRI-TRUS fusion is more effective than TRUS, having an incremental effect of 0.13 QALY. The ICER following a fusion-guided biopsy versus the systematic TRUS biopsy was €1386 (\$1470) per QALY gained. This indicates that a fusion-guided biopsy is cost-effective compared with TRUS-guided biopsy. An in-bore MRI guided biopsy would be cost-effective if its sensitivity for clinically significant prostate cancer is 11.8% higher than the sensitivity of MRI fusion-guided biopsy. Using a range of assumptions based on expert opinion, cost, and diagnostic accuracy parameters with realistic variations did not change this outcome.

This would suggest the recommendation will be cost-effective in the identification of clinically significant cancer.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Performing targeted biopsies

The Guideline Development Group highlighted that targeted biopsies are extremely operator dependant. To improve interoperator reproducibility all operators should be appropriately trained. Targeted biopsies should only be performed in a high volume centre by appropriately trained professionals.

Recommendation 3.3.1:

A targeted biopsy of focal lesions should be performed using either MRI (guided) transrectal/transperineal US fusion or cognitive registration biopsy.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

- Targeted biopsies are extremely operator dependant and should only be performed in a high volume centre by appropriately trained professionals.
- A minimum number of 12 cores should be taken for a systematic biopsy.

Clinical question 3.4

For men being investigated for prostate cancer without an MRI targetable lesion should they have a prostate biopsy?

Quality of Evidence

The evidence from a Cochrane review (Drost et al., 2019) and a meta-analysis (Sathianathen et al., 2020) addressed this clinical question. There is a lack of long term follow-up data available and therefore there is a high degree of uncertainty in this area.

For patients with a high clinical suspicion of prostate cancer (e.g. family history, PSA density >0.15 ng/ml/ml) as determined at the MDT, the Guideline Development Group recommends a systematic prostate biopsy. For those with a low clinical suspicion of prostate cancer omitting a prostate biopsy should be considered, following a shared decision-making model. The shared decision-making model should aim to identify how the patient individually values the benefits and harms. A meta-analysis (Sathianathen et al., 2020) emphasising the high negative predictive value (NPV) of a negative mpMRI (PI-RADS 1–2) in biopsy-naive men also supports this (90.8% (95% CI 88.1–93.1%) for Gleason score $\geq 3+4$, 97.1% (95% CI 94.9–98.7%) for Gleason score $\geq 4+3$).

Benefit and Harm

The benefits of shared decision-making to determine whether or not to biopsy a PI-RADS score of 1 or 2 centre around patients' autonomy, and clinicians' confidence that due diligence has been done to the individuality of each case.

In general, shared decision-making can give patients a measure of understanding and control over their treatment. In this particular context, clinicians will disclose the potential risks of having or not having a biopsy, as well as explain terms such as "clinically significant" and "clinically insignificant" cancer. Clinicians should help elicit patients' values regarding undergoing or not undergoing a biopsy. When done well this discussion has the benefit of improving patient trust. It also helps to assure clinicians that due diligence was done to each individual case regardless of whether or not a biopsy is taken.

Shared decision-making can be harmful when it is done poorly. When done poorly, shared decision-making can be coercive, undermine patient trust and/or leave patients confused.

It is worth noting, if shared decision-making leads to a biopsy for most PI-RADS scores of 1 or 2, then this practice would undo many of the benefits of using mpMRI as a first line test. This represents a risk of inefficiency.

Preferences and values

The multidisciplinary Guideline Development Group recognises the importance of ethical values, patient autonomy and clinical duty to patient individuality. The Guideline Development Group believes that patients as well as clinicians would prefer shared decision-making in the context of PI-RADS scores of 1 and 2.

(Driving value- clinical duty to patient individuality)

Resources, capacity and other considerations

There was no relevant cost-effectiveness literature found to address this clinical question.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Additional time for shared decision-making

In many institutions, there will be organisational hurdles that must be overcome before a shared decision-making framework can be put in place. Shared decision-making is time-consuming and requires skill. Resources to accommodate the time and to acquire the skills needed can be difficult to source. Such resources include Advanced Nurse Practitioners. When resources can be sourced, their application typically requires changes in practice and training that require dedication and coordination over time.

An audit of the number of men with a negative MRI (i.e. PI-RADS 1 or 2) who have a biopsy is recommended by the Guideline Development Group.

Recommendation 3.4.1 :

For patients with a negative MRI (i.e. PI-RADS 1 or 2) omitting a biopsy should be considered, following the shared decision-making model.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.4.2:

For patients with a negative MRI (i.e. PI-RADS 1 or 2) and a high clinical suspicion of prostate cancer the Guideline Development Group recommends a systematic prostate biopsy.

Quality of Evidence: High

Grade of recommendation: Strong

Recommendation 3.4.3:

For patients with a negative MRI (i.e. PI-RADS 1 or 2) who do not proceed to biopsy PSA should be monitored regularly at 6 months and then annually.

Quality of Evidence: Low

Grade of recommendation: Strong

Good practice point

- Advanced Nurse Practitioners should be available for shared decision-making with patients being investigated for prostate cancer.
- For patients at high risk of TRUS sepsis a transperineal approach is recommended (refer to [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#)).
- For timing of IV antibiotic prophylaxis refer to the [National Policy on the Prevention and Management of Infection Post TRUS Guided Biopsy, 2014](#).

Practical considerations around patient care

- Written information on the items relevant to shared decision-making, including the benefits and harms of proceeding to biopsy, should be provided to all patients being investigated for prostate cancer.
- Men should be allowed to have family members present during shared decision-making if they would like to.

Clinical question 3.5

In men with intermediate risk prostate cancer should staging investigations be performed?

Quality of Evidence

A meta-analysis (Suh et al., 2018) and a retrospective study (Eyrich et al., 2020) addressed this clinical question.

A meta-analysis based on 54 studies (n=50 retrospective studies) with 20,421 treatment naive prostate cancer patients demonstrated that the pooled proportions of positive bone scintigraphy examinations in patients with a PSA of <10, 10<PSA≤20, and PSA of >20 were 3.5%, 6.9%, and 41.8%, respectively, while the pooled proportions of positive bone scintigraphy examinations in patients with Gleason scores of <6, 7, and ≥8 were 4.1%, 10%, and 28.7%, respectively (Suh et al., 2018). Furthermore pooled proportions of positive bone scintigraphy examinations showed 3.4% in patients with a PSA of <10 and 3.3% in patients with 10 <PSA ≤20 regarding a Gleason score of ≤7 (Suh et al., 2018).

As all men with suspected prostate cancer are recommended to receive a pre-biopsy MRI (see Clinical question 3.2), a retrospective study investigated the benefit of additional staging in a cohort of men with low to high risk prostate cancer (Eyrich et al., 2020). Sensitivity of mpMRI for lymph node metastases was significantly higher than CT (65–73% vs 38%, $P < 0.005$), and specificity of mpMRI and CT were 97% to 99% and 99% ($P = 0.2–0.4$), respectively. For bone metastases, bone scintigraphy sensitivity was 68% as compared to 42% to 71% ($P = 0.02–0.83$) for mpMRI. Specificity for bone metastases was 95% to 99% across all modalities (Eyrich et al., 2020).

Evidence to support the use of CT and bone scans in men with intermediate risk prostate cancer is minimal. The evidence base with regard to the use of PSMA PET-CT in men with unfavourable risk prostate cancer is evolving (see Clinical question 3.7).

The guideline development group have formulated their recommendations for staging of men with intermediate risk prostate cancer based on their recommendation that all men will have undergone a pre-biopsy MRI (see Clinical question 3.2).

Benefit and Harm

The evidence suggests that in this patient population who have had a mpMRI scan prior to biopsy further imaging studies are unlikely to find any additional information that will change management. Refraining from additional imaging has the benefit of initiating treatment promptly, avoiding further studies for incidental findings and reducing patient anxiety. There will also be reduced exposure to unnecessary radiation for the patient.

Preferences and values

The multidisciplinary Guideline Development Group including patient representatives recognise that ethical and practical values are important. In this case we feel that it is in the best interests of the patient not to pursue further staging investigations as the benefits outweigh the harms, e.g. avoiding incidental findings, exposure to radiation and anxiety, without delay to treatment. Nonetheless, it is important that the benefits and harms of further staging investigations are communicated to the patient and the decision be made using a shared decision-making approach.

(Driving value- best interests of the patient)

Resources capacity and other considerations

There was no relevant cost-effectiveness literature found to address this clinical question.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Incorrect use of resources

Unnecessary staging investigations including CT and bone scans in men with intermediate prostate cancer is putting pressure on the availability of radiology resources in other areas of the health service. An audit of the volume of CT and bone scans performed in men with favourable and unfavourable intermediate risk prostate cancer is recommended by the Guideline Development Group.

Recommendation 3.5.1:

In men with favourable intermediate risk* prostate cancer who have had a pre-biopsy MRI the use of further staging scans is not recommended.

*Favourable intermediate risk is defined as having all of the following: one intermediate risk factor (cT2b–cT2c, Grade Group 2 or 3, PSA 10–20 µg/L), Grade Group 1 or 2 and <50% biopsy cores positive (e.g. <6 of 12 cores).

Quality of Evidence: Low

Grade of recommendation: Strong

Recommendation 3.5.2:

In men with unfavourable intermediate risk* prostate cancer who have had a pre-biopsy MRI the routine use of further staging scans is not recommended.

*Unfavourable intermediate risk is defined as having one or more of the following: two or three intermediate risk factors (cT2b–cT2c, Grade Group 2 or 3, PSA 10–20 µg/L), Grade Group 3, ≥ 50% biopsy cores positive (e.g. ≥6 of 12 cores).

Quality of Evidence: Low

Grade of recommendation: Weak

Recommendation 3.5.3:

PSMA PET-CT is not recommended for primary staging of low risk prostate cancer patients.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

- A clinician may decide to do further staging investigations if there are clinical features that may increase a patients individual risk following discussion at MDT.

Practical considerations around patient care

- The benefits and harms of further staging investigations should be communicated to all patients using a shared decision-making approach.
- Men should be allowed to have family members present during shared decision-making if they would like to.

Clinical question 3.6

In men with high risk prostate cancer what staging investigations should be performed?

Quality of Evidence

A randomised prospective trial, proPSMA, (Hofman et al., 2020) addressed this clinical question. Prior to this trial the evidence for PSMA PET-CT in the primary staging of prostate cancer was of low quality and based on retrospective or single-centre studies (Perera et al., 2020, von Eyben et al., 2018, Kim et al., 2019, Yaxley et al., 2019, Roach et al., 2018).

The proPSMA trial recruited men with high risk localised prostate cancer. Patients were classified as high risk if they had at least one of the following; a prostate-specific antigen (PSA) concentration of 20 µg/L or more within the 12 weeks prior to randomisation, International Society of Urothology (ISUP) grade group 3–5, or clinical stage T3 or worse (Hofman et al., 2020). 152 men were randomly assigned to conventional imaging and 150 men to ⁶⁸G PSMA-11 PET-CT. Conventional imaging was defined as the combined findings of CT and bone scanning.

This multicentre cross-over study found that PSMA PET-CT had a 27% (95% CI 23–31, p<0.0001) absolute greater AUC for diagnostic accuracy to detect pelvic nodal or distant metastatic disease than conventional imaging (92% [88–95] vs 65% [60–69]). Conventional imaging had a lower sensitivity (38% [24–52] vs 85% [74–96]) and specificity (91% [85–97] vs 98% [95–100]) compared with that of PSMA PET-CT. First-line PSMA PET-CT resulted in management change in 41 (28%) of 148 men, compared with 23 (15%) of 146 men who received firstline conventional imaging (p=0.008). This study cannot confirm if the information provided by PSMA PET-CT and any consequent change in management translates to improved patient survival (Hofman et al., 2020). Long term outcome data will be needed to address overall survival.

Benefit and Harm

The use of PSMA PET-CT staging for high risk patients has at least two patient benefits. Firstly, PSMA PET-CT can provide more accurate staging information for high risk patients than CT and bone scan imaging. This improved accuracy translates into greater certainty for patients about the extent of their prostate cancer. Greater certainty often gives patients more confidence to make decisions about their future. Secondly, more accurate staging can improve treatment decisions, which ultimately aim to reduce mortality and morbidity and improve patients' quality of life.

The use of PSMA PET-CT is associated with risk of harm. Firstly, as with any test or measure, the PSMA PET-CT is imperfect. This means that its use involves the risk of false positive and false negative results. Secondly, there are long wait lists for PSMA PET-CT, which reduces access to it. Consequently, patients may experience anxiety while waiting to hear if it is available for them or they may experience frustration if they learn it is not available. Patients who cannot access PSMA PET-CT will be offered conventional imaging. Thirdly, PSMA-PET-CT is associated with a radiation dose which may cause harm to the patient.

Due to long wait lists some high risk patients will not get the benefits of the PSMA PET-CT. The difference between patients who can and cannot access PSMA PET-CT is not based on risk stratification (they are all high risk) or clinical benefit, but rather chance events such as the timing of their request given the length of the wait list or the location of their referring hospital. Thus, one harm of using PSMA PET-CT in this patient population is the introduction of inequity into the diagnostic pathway.

Thirdly, the use of PSMA PET-CT must be tailored to high risk patients and may cause harm when used in the incorrect patient population. Lastly, although the aim is to improve patient outcomes

through more accurate staging and better treatment decisions, the effect of these changes in management on long term outcomes in this context is unknown.

Preferences and values

The multidisciplinary Guideline Development Group recognises that reliable and accurate knowledge about one's disease is an important patient value. The Guideline Development Group agreed that high risk prostate cancer patients would prefer the use of PSMA PET-CT in the primary staging of their cancer to CT or bone scans.

(Driving value – knowledge)

Resources capacity and other considerations

One cost-effectiveness study was used to address this clinical question.

de Feria Cardet et al., (2021) developed a cost-effectiveness analysis to assesses the costs and outcomes (diagnostic accuracy of nodal and distant metastases) associated with the use of PSMA PET-CT compared with conventional imaging in staging men with high-risk prostate cancer using data from the proPSMA study (Hofman et al., 2020). Unit costs were reported in Australian dollars (cost year not reported). The cost-effectiveness analysis was conducted from an Australian societal perspective.

A micro-costing approach was applied using pricing information provided by one site to derive the cost for ⁶⁸Ga-PSMA production and the associated PET-CT scan. Costs for conventional imaging were informed by the Australian Medicare Benefits Schedule. The costs associated with the production and delivery of both scanning modalities were included. The impact on the costs of variability in radiopharmaceutical generator prices, wages applied to time inputs, and the number of scans per ⁶⁸Ga-PSMA elution was tested in subsequent sensitivity analyses. Outcomes for the analysis were expressed in terms of accurate diagnoses at 6 months.

The authors found that the estimated cost per scan for PSMA PET-CT was AUD\$1203, which was less than the conventional imaging cost at AUD\$1412. This resulted in a cost of AUD \$959 saved per additional accurate detection of nodal disease, and AUD\$1412 saved for additional accurate detection of distant metastases. The results were most sensitive to variations in the number of men scanned for each ⁶⁸Ga-PSMA-11 production run.

This suggests that PSMA-PET CT when compared with conventional imaging will be cost-effective for the staging of men with high risk prostate cancer. However, further studies are required to assess the long term costs and benefits of PSMA PET-CT directed care.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Access to PSMA PET-CT

To enable all high risk prostate cancer patients to receive primary staging by PSMA-PET-CT, capacity for approximately 1,000 patients is required (Irish Prostate Cancer Outcomes Research (IPCOR), 2018, National Cancer Registry (NCRI), 2020). This will require capital and revenue investment.

Recommendation 3.6.1:

PSMA PET-CT should be considered for primary staging in high risk* prostate cancer patients who are suitable for definitive treatment.

*High risk is defined as having no very high risk features and having exactly one high risk feature: cT3a OR Grade Group 4 or Grade Group 5 OR PSA >20 µg/L.

Quality of Evidence: Moderate

Grade of recommendation: Strong

Good practice point

- If PSMA PET-CT is not available within 4 weeks then conventional imaging including an isotope bone scan, CT and MRI prostate (in those that have not had one to date) should be performed as an alternative with a view to proceeding to treatment.

Practical considerations around patient care

- All high risk prostate cancer patients should have access to a Clinical Nurse Specialist/Advanced Nurse Practitioner to explain their test and test results.

Clinical question 3.7

For men with biochemical recurrence of prostate cancer what is the role of PSMA PET-CT?

Quality of Evidence

Two meta-analyses (Hope et al., 2019, Perera et al., 2020), a systematic review (De Visschere et al., 2019), three prospective studies (Ceci et al., 2019, Roach et al., 2018, Witkowska-Patena et al., 2020) and one retrospective study (Giesel et al., 2019) addressed this clinical question.

The Guideline Development Group define a biochemical recurrence of prostate cancer post treatment as:

- Following radical prostatectomy, is two rising PSA levels above undetectable; and
- Following radiotherapy, a PSA value of 2 µg/L above the nadir after treatment.

The ⁶⁸Ga-PSMA-11 PET-CT detection rate for identifying the site of prostate cancer recurrence in a prospective, open label, single-center trial was 53.6% (CI 95% 48.1%–59.1%), with an incidence of distant lesions in 28.9% of cases (Ceci et al., 2019). The detection rate did however differ depending on the clinical stage of biochemical recurrence. The per patient positive predictive value (PPV) was 96.2% (95% CI, 95.6-96.7%). Comparison with other imaging procedures also found that when ⁶⁸Ga-PSMA-11 PET-CT was positive, correlative imaging using choline PET, MRI, CT and bone scintigraphy was negative in 83% of cases (108/130)(Ceci et al., 2019).

PSMA PET-CT is better than conventional imaging (bone scan, CT) in detecting extra pelvic metastases in patients with biochemical recurrence. MRI remains a useful tool for detection of local recurrence of pelvic metastatic disease however PSMA is also sensitive particularly at lower PSA levels (De Visschere et al., 2019). An updated systematic review and meta-analysis (Perera et al., 2020) also highlighted this, demonstrating that ⁶⁸Ga-PSMA PET-CT improved detection of metastases in men with biochemical recurrence at low PSA levels Table 1.

Table 1 The proportion of PSMA positivity separated by PSA level category in secondary staging (Perera et al., 2020)

	Overall recurrence staging Positivity rate	Staging- Mixed local definitive therapy * Positivity rate	Staging- Post radical prostatectomy Positivity rate
PSA >2.00 µg/L	95% (92–97%)	92% (88-95%)	97% (95-99%)
PSA 1.00–1.99 µg/L	75% (66–84%)	64% (50-78%)	82% (88-93%)
PSA 0.5–0.99 µg/L	59% (50–68%)	63% (47-78%)	57% (48-67%)
PSA 0.2-0.49 µg/L	45% (39-52%)	46% (37-56%)	46% (37-55%)
PSA ≤0.2 µg/L	33% (16– 51%)	44% (33-56%)	33% (14-54%)

*Mixed local definitive treatment includes both prostatectomy and other modalities that were not specified
Numbers presented in brackets are 95% confidence intervals (CI)

Furthermore a meta-analysis which included 256 patients across 15 studies with pathologic correlation, the sensitivity, specificity, PPV, negative predictive value (NPV), and accuracy of ⁶⁸Ga-PSMA PET-CT in detecting lesions was 0.99 (95% CI, 0.96–1.00), 0.76 (95% CI, 0.02–1.00), 0.99 (95% CI, 0.96–1.00), 0.76 (95% CI, 0.02–1.00), and 0.98 (95% CI, 0.94 –1.00), respectively (Hope et al., 2019). The detection rate was 0.63 (95% CI, 0.55–0.70) with a PSA of less than 2.0 µg/L and 0.94 (95% CI, 0.91– 0.96) with a PSA of more than 2.0 µg/L. It should be noted that the majority of studies included in this meta-analysis are low quality retrospective studies with small patient

populations. Furthermore, as it is not possible to biopsy numerous nodes in patients, the accuracy of PSMA PET-CT outside biopsied lesions is unknown (Hope et al., 2019).

In a prospective multicentre study of 323 men with biochemical recurrence of prostate cancer clinical management intent changed in 62% as a consequence of findings on the ⁶⁸Ga-PSMA PET-CT scans (Roach et al., 2018). The change in management intent remained high, even at low PSA values (<0.2 µg/L). There was a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs 19%, $p < 0.001$) and significant increases in the detection of presumed oligometastatic (10% vs 38%, $p < 0.001$) and polymetastatic disease (1% vs 19%, $p < 0.001$) (Roach et al., 2018). This highlights the importance of the findings in planning definitive treatment in this cohort of patients.

It should be noted that the term PSMA PET-CT generally refers to ⁶⁸Ga-PSMA-11 as it is the most studied radiopharmaceutical but technology is rapidly evolving and data has also been recently reported on ¹⁸F- labelled PSMA 1007 (Witkowska-Patena et al., 2020, Giesel et al., 2019). Although a majority of studies published on ¹⁸F- labelled PSMA have been retrospective and small numbers, ¹⁸F-PSMA-1007 PET-CT has demonstrated relatively high detection rates for patients with biochemical recurrence after radical prostatectomy and low, rising PSA levels (Giesel et al., 2019, Witkowska-Patena et al., 2020).

Imaging is only beneficial if it leads to a change in patient management that subsequently results in better outcomes. There is no body of evidence regarding the long-term patient outcomes on imaging in men with biochemical recurrence.

Benefit and Harm

In men with biochemical recurrence of prostate cancer the primary benefit of PSMA PET-CT over conventional imaging for the biochemical recurrence of prostate cancer is to hasten knowledge about the extent of a patient's prostate cancer, i.e. is it local or metastatic. Knowing sooner rather than later the extent of a patient's disease may increase the likelihood of improving treatment options and treatment decisions, with the aim of improving patients' mortality, morbidity and quality of life.

It is worth noting that there are long wait lists for PSMA PET-CT. Depending on the length of the wait list, some patients may not receive the benefit of hastened knowledge. Rather, some patients will see their PSA levels rise to a level that can be detected by conventional imaging while still on the wait list. These patients will receive conventional imaging instead of a PSMA PET-CT.

As with any test or measure, the PSMA PET-CT is imperfect. This means that its use involves the risk of false positive and false negative results. These results represent a possible harm to patients.

Preferences and values

The multidisciplinary Guideline Development Group recognises that knowledge is an important patient value. In the context of biochemical recurrence of prostate cancer improving the timeline of what you know about prostate cancer may help to improve treatment options open to patients. The Guideline Development Group agreed that the use of PSMA PET-CT in men with biochemical recurrence would be preferred over conventional imaging.

(Driving value- patient knowledge)

Resources, capacity and other considerations

There was no relevant cost-effectiveness literature found to address this clinical question.

The following resources, capacity and other considerations were discussed in detail by the Guideline Development Group:

Access to PSMA PET-CT

To enable all men with biochemical recurrence of prostate cancer receive a PSMA-PET-CT scan, capacity for approximately 1,011 patients is required (IPCOR, 2018, NCRI, 2020a, NCRI, 2020b). This will require capital and revenue investment.

Recommendation 3.7.1:

In men with a biochemical recurrence of prostate cancer following primary treatment (surgery or radiotherapy) PSMA PET-CT should be considered if it will influence patient management following discussion at a multidisciplinary team meeting.

Quality of Evidence: Moderate

Grade of recommendation: Strong

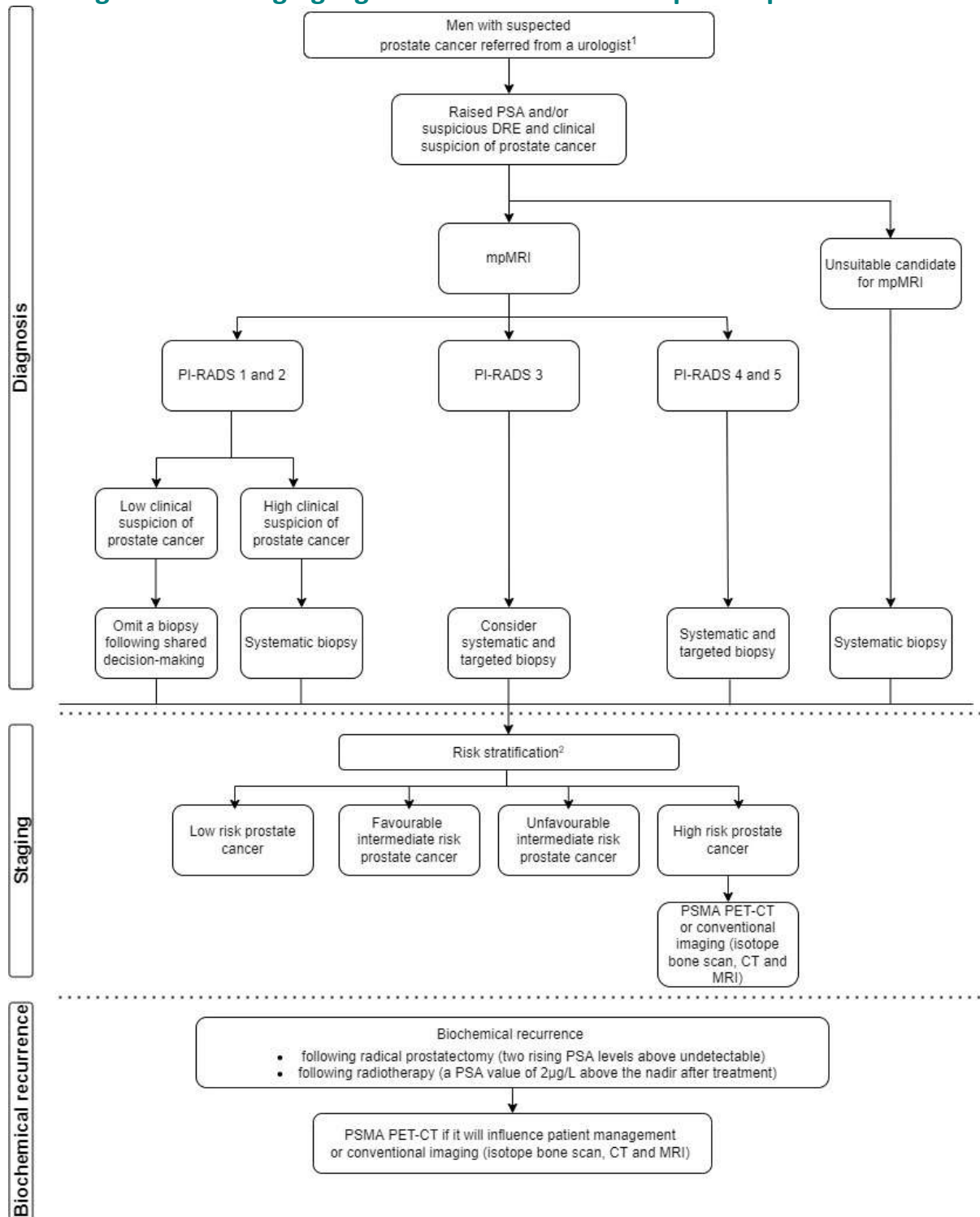
Good practice point

- The timeframe to PSMA PET-CT will vary with different clinical circumstances and should be determined by the multidisciplinary team.
- If PSMA PET-CT is not available within the timeframe recommended by the multidisciplinary team then conventional imaging including an isotope bone scan, CT and MRI should be performed as an alternative with a view to proceeding to treatment.

Practical considerations around patient care

- All men with biochemical recurrence of prostate cancer undergoing a PSMA PET-CT scan should have access to a Clinical Nurse Specialist/Advanced Nurse Practitioner to explain the PSMA PET-CT test and test results.
- All men with biochemical recurrence of prostate cancer undergoing any diagnostic test should have access to a Clinical Nurse Specialist/Advanced Nurse Practitioner to explain the test and test results.

4.0 Diagnosis and staging algorithm for men with suspected prostate cancer



¹ This algorithm should be interpreted in conjunction with the National Clinical Guideline 'Diagnosis and staging of prostate cancer' 2022

² Prostate cancer patients are risk stratified according to the National Comprehensive Cancer Network® (NCCN®) prostate cancer risk stratification (Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.3.2022. © National Comprehensive Cancer Network, 2022)

Figure 1: Diagnosis and staging algorithm for patients with suspected prostate cancer referred from a urologist recommended by the Guideline Development Group

5.0 References

- AHMED, H. U., EL-SHATER BOSAILY, A., BROWN, L. C., GABE, R., KAPLAN, R., PARMAR, M. K., COLLACOMORAES, Y., WARD, K., HINDLEY, R. G., FREEMAN, A., KIRKHAM, A. P., OLDROYD, R., PARKER, C. & EMBERTON, M. 2017. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*, 389, 815-822.
- CECI, F., CASTELLUCCI, P., GRAZIANI, T., FAROLFI, A., FONTI, C., LODI, F. & FANTI, S. 2019. 68Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy. *European Journal of Nuclear Medicine and Molecular Imaging*, 46, 31-39.
- DE FERIA CARDET, R. E., HOFMAN, M. S., SEGARD, T., YIM, J., WILLIAMS, S., FRANCIS, R. J., FRYDENBERG, M., LAWRENTSCHUK, N., MURPHY, D. G. & DE ABREU LOURENCO, R. 2021. Is Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Imaging Cost-effective in Prostate Cancer: An Analysis Informed by the proPSMA Trial. *European Urology*, 79, 413-418.
- DE VISSCHERE, P. J. L., STANDAERT, C., FÜTTERER, J. J., VILLEIRS, G. M., PANEBIANCO, V., WALZ, J., MAURER, T., HADASCHIK, B. A., LECOUVET, F. E., GIANNARINI, G. & FANTI, S. 2019. A Systematic Review on the Role of Imaging in Early Recurrent Prostate Cancer. *European Urology Oncology*. Netherlands: © 2018 European Association of Urology. Published by Elsevier B.V.
- DROST, F. H., OSSES, D. F., NIEBOER, D., STEYERBERG, E. W., BANGMA, C. H., ROOBOL, M. J. & SCHOOTS, I. G. 2019. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev*, 4, CD012663.
- EYRICH, N. W., TOSOIAN, J. J., DROBISH, J., MONTIE, J. E., QI, J., KIM, T., NOYES, S. L., MORIARITY, A. K. & LANE, B. R. 2020. Do patients who undergo multiparametric MRI for prostate cancer benefit from additional staging imaging? Results from a statewide collaborative. *Urologic Oncology*, 38, 636.e13-636.e19.
- FARIA, R., SOARES, M. O., SPACKMAN, E., AHMED, H. U., BROWN, L. C., KAPLAN, R., EMBERTON, M. & SCULPHER, M. J. 2018. Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). *European Urology*, 73, 23-30.
- GIESEL, F. L., KNORR, K., SPOHN, F., WILL, L., MAURER, T., FLECHSIG, P., NEELS, O., SCHILLER, K., AMARAL, H., WEBER, W. A., HABERKORN, U., SCHWAIGER, M., KRATOCHWIL, C., CHOYKE, P., KRAMER, V., KOPKA, K. & EIBER, M. 2019. Detection Efficacy of (18)F-PSMA-1007 PET/CT in 251 Patients with Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, 60, 362-368.
- GRADING OF RECOMMENDATIONS ASSESSMENT DEVELOPMENT AND EVALUATION (GRADE) WORKING GROUP 2013. GRADE Handbook.
- HOFMAN, M. S., LAWRENTSCHUK, N., FRANCIS, R. J., TANG, C., VELA, I., THOMAS, P., RUTHERFORD, N., MARTIN, J. M., FRYDENBERG, M., SHAKHER, R., WONG, L. M., TAUBMAN, K., TING LEE, S., HSIAO, E., ROACH, P., NOTTAGE, M., KIRKWOOD, I., HAYNE, D., LINK, E., MARUSIC, P., MATERA, A., HERSCHTAL, A., IRAVANI, A., HICKS, R. J., WILLIAMS, S. & MURPHY, D. G. 2020. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *The Lancet*, 395, 1208-1216.
- HOPE, T. A., GOODMAN, J. Z., ALLEN, I. E., CALAIS, J., FENDLER, W. P. & CARROLL, P. R. 2019. Metaanalysis of (68)Ga-PSMA-11 PET Accuracy for the Detection of Prostate Cancer Validated by Histopathology. *Journal of Nuclear Medicine*, 60, 1535-5667 (Electronic).
- IRISH PROSTATE CANCER OUTCOMES RESEARCH (IPCOR) 2018. Irish Prostate Cancer Outcomes Research (IPCOR), Annual Report.
- KASIVISVANATHAN, V., RANNIKKO, A. S., BORGHINI, M., PANEBIANCO, V., MYNDERSE, L. A., VAARALA, M. H., BRIGANTI, A., BUDAUS, L., HELLAWELL, G., HINDLEY, R. G., ROOBOL, M. J., EGGNER, S., GHEI, M., VILLERS, A., BLADOU, F., VILLEIRS, G. M., VIRDI, J., BOXLER, S., ROBERT, G., SINGH, P. B., VENDERINK, W., HADASCHIK, B. A., RUFFION, A., HU, J. C., MARGOLIS, D., CROUZET, S., KLOTZ, L., TANEJA, S. S., PINTO, P., GILL, I., ALLEN, C., GIGANTI, F., FREEMAN, A., MORRIS, S., PUNWANI, S., WILLIAMS, N. R., BREW-GRAVES, C., DEEKS, J., TAKWOINGI, Y., EMBERTON, M. & MOORE, C. M. 2018. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *New England Journal of Medicine*, 378, 1767-1777.
- KIM, S. J., LEE, S. W. & HA, H. K. 2019. Diagnostic Performance of Radiolabeled Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography for Primary Lymph Node Staging in Newly Diagnosed Intermediate to High-Risk Prostate Cancer Patients: A Systematic Review and Meta-Analysis. *Urology International*, 102, 27-36.

- NATIONAL CANCER REGISTRY (NCRI) 2020. Cancer in Ireland 19994-2018 with estimates for 2018-2020:Annual Report of the National Cancer Registry. NCRI, Cork, Ireland.
- NATIONAL CANCER REGISTRY IRELAND (NCRI) September 2020. NCRI unpublished analysis.
- PERERA, M., PAPA, N., ROBERTS, M., WILLIAMS, M., UDOVICICH, C., VELA, I., CHRISTIDIS, D., BOLTON, D., HOFMAN, M. S., LAWRENTSCHUK, N. & MURPHY, D. G. 2020. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *European Urology*, 77, 403-417.
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- ROACH, P. J., FRANCIS, R., EMMETT, L., HSIAO, E., KNEEBONE, A., HRUBY, G., EADE, T., NGUYEN, Q. A., THOMPSON, B. D., CUSICK, T., MCCARTHY, M., TANG, C., HO, B., STRICKER, P. D. & SCOTT, A. M. 2018. The Impact of (68)Ga-PSMA PET/CT on Management Intent in Prostate Cancer: Results of an Australian Prospective Multicenter Study. *Journal of Nuclear Medicine*, 59, 82-88.
- ROUVIÈRE, O., PUECH, P., RENARD-PENNA, R., CLAUDON, M., ROY, C., MÈGE-LECHEVALLIER, F., DECAUSSIN-PETRUCCI, M., DUBREUIL-CHAMBARDEL, M., MAGAUD, L., REMONTET, L., RUFFION, A., COLOMBEL, M., CROUZET, S., SCHOTT, A. M., LEMAITRE, L., RABILLOUD, M. & GRENIER, N. 2019. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *The Lancet Oncology*, 20, 100-109.
- SATHIANATHAN, N. J., OMER, A., HARRISS, E., DAVIES, L., KASIVISVANATHAN, V., PUNWANI, S., MOORE, C. M., KASTNER, C., BARRETT, T., VAN DEN BERGH, R. C., EDDY, B. A., GLEESON, F., MACPHERSON, R., BRYANT, R. J., CATTO, J. W. F., MURPHY, D. G., HAMDY, F. C., AHMED, H. U. & LAMB, A. D. 2020. Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in the Detection of Clinically Significant Prostate Cancer in the Prostate Imaging Reporting and Data System Era: A Systematic Review and Meta-analysis. *European Urology*. Switzerland: © 2020 European Association of Urology. Published by Elsevier B.V.
- SUH, C. H., SHINAGARE, A. B., WESTENFIELD, A. M., RAMAIYA, N. H., VAN DEN ABEELE, A. D. & KIM, K. W. 2018. Yield of bone scintigraphy for the detection of metastatic disease in treatment-naïve prostate cancer: a systematic review and meta-analysis. *Clinical Radiology*, 73, 158-167.
- TU, X., LIU, Z., CHANG, T., QIU, S., XU, H., BAO, Y., YANG, L. & WEI, Q. 2019. Transperineal Magnetic Resonance Imaging-Targeted Biopsy May Perform Better Than Transrectal Route in the Detection of Clinically Significant Prostate Cancer: Systematic Review and Meta-analysis. *Clinical Genitourinary Cancer*, 17, e860-e870.
- VAN DER LEEST, M., CORNEL, E., ISRAËL, B., HENDRIKS, R., PADHANI, A. R., HOOGENBOOM, M., ZAMECNIK, P., BAKKER, D., SETIASTI, A. Y., VELTMAN, J., VAN DEN HOUT, H., VAN DER LELIJ, H., VAN OORT, I., KLAVER, S., DEBRUYNE, F., SEDELAAR, M., HANNINK, G., ROVERS, M., HULSBERGEN-VAN DE KAA, C. & BARENTSZ, J. O. 2019. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *European Urology*, 75, 570-578.
- VENDERINK, W., GOVERS, T. M., DE ROOIJ, M., FÜTTERER, J. J. & SEDELAAR, J. P. M. 2017. Cost-Effectiveness Comparison of Imaging-Guided Prostate Biopsy Techniques: Systematic Transrectal Ultrasound, Direct In-Bore MRI, and Image Fusion. *American Journal of Roentgenology*, 208, 1058-1063.
- VON EYBEN, F. E., PICCHIO, M., VON EYBEN, R., RHEE, H. & BAUMAN, G. 2018. (68)Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis. *European Urology Focus*, 4, 686-693.
- WEGELIN, O., EXTERKATE, L., VAN DER LEEST, M., KUMMER, J. A., VREULS, W., DE BRUIN, P. C., BOSCH, J., BARENTSZ, J. O., SOMFORD, D. M. & VAN MELICK, H. H. E. 2019. The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. *European Urology*, 75, 582-590.

- WITKOWSKA-PATENA, E., GIŻEWSKA, A., DZIUK, M., MIŚKO, J., BUDZYŃSKA, A. & WALĘCKA-MAZUR, A. 2020. Diagnostic performance of 18F-PSMA-1007 PET/CT in biochemically relapsed patients with prostate cancer with PSA levels ≤ 2.0 ng/ml. *Prostate Cancer and Prostatic Diseases*, 23, 343-348.
- WOO, S., SUH, C. H., KIM, S. Y., CHO, J. Y. & KIM, S. H. 2017. Diagnostic Performance of Prostate Imaging Reporting and Data System Version 2 for Detection of Prostate Cancer: A Systematic Review and Diagnostic Meta-analysis. *European urology*, 72, 177-188.
- XIANG, J., YAN, H., LI, J., WANG, X., CHEN, H. & ZHENG, X. 2019. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. *World Journal of Surgical Oncology*, 17, 31.
- YAXLEY, J. W., RAVEENTHIRAN, S., NOUHAUD, F. X., SAMARATUNGA, H., YAXLEY, W. J., COUGHLIN, G., YAXLEY, A. J., GIANDUZZO, T., KUA, B., MCEWAN, L. & WONG, D. 2019. Risk of metastatic disease on (68) gallium-prostate-specific membrane antigen positron emission tomography/computed tomography scan for primary staging of 1253 men at the diagnosis of prostate cancer. *BJU Int*, 124, 401-407.
- ZHANG, L., TANG, M., CHEN, S., LEI, X., ZHANG, X. & HUAN, Y. 2017. A meta-analysis of use of Prostate Imaging Reporting and Data System Version 2 (PI-RADS V2) with multiparametric MR imaging for the detection of prostate cancer. *European radiology*, 27, 5204-5214.

