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European Association of Urology

Platinum Priority – Prostate Cancer – Editor's Choice

Editorial by Rodney J. Hicks on pp. 61–62 of this issue

European Association of Nuclear Medicine Focus 5: Consensus on Molecular Imaging and Theranostics in Prostate Cancer

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Abstract

Background: In prostate cancer (PCa), questions remain on indications for prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging and PSMA radioligand therapy, integration of advanced imaging in nomogram-based decision-making, dosimetry, and development of new theranostic applications.
Objective: We aimed to critically review developments in molecular hybrid imaging and systemic radioligand therapy, to reach a multidisciplinary consensus on the current state of the art in PCa.
Design, setting, and participants: The results of a systematic literature search informed a two-round Delphi process with a panel of 28 PCa experts in medical or radiation oncology, urology, radiology, medical physics, and nuclear medicine. The results were discussed and ratified in a consensus meeting.
Outcome measurements and statistical analysis: Forty-eight statements were scored on a Likert agreement scale and six as ranking options. Agreement statements were analysed using the RAND appropriateness method. Ranking statements were analysed using weighted summed scores.
Results and limitations: After two Delphi rounds, there was consensus on 42/48 (87.5%) of the statements. The expert panel recommends PSMA PET to be used for staging the majority of patients with unfavourable intermediate and high risk, and for restaging of suspected recurrent PCa. There was consensus that oligometastatic disease should be defined as up to five metastases, even using advanced imaging modalities. The group agreed that [^{177}Lu]Lu-PSMA should not be administered only after progression to cabazitaxel and that [^{223}Ra]$RaCl_2$ remains a valid therapeutic option in bone-only metastatic castration-resistant PCa. Uncertainty remains on various topics, including the need for concordant findings on both [^{18F}]FDG and PSMA PET prior to [^{177}Lu]Lu-PSMA therapy.
Conclusions: There was a high proportion of agreement among a panel of experts on the use of molecular imaging and theranostics in PCa. Although consensus statements cannot replace high-certainty evidence, these can aid in the interpretation and dissemination of best practice from centres of excellence to the wider clinical community.
Patient summary: There are situations when dealing with prostate cancer (PCa) where both the doctors who diagnose and track the disease development and response to treatment, and those who give treatments are unsure about what the best course of action is. Examples include what methods they should use to obtain images of the cancer and what to do when the cancer has returned or spread. We reviewed published research studies and provided a summary to a panel of experts in imaging and treating PCa. We also used the research summary to develop a questionnaire whereby we asked the experts to state whether or not they agreed with a list of statements. We used these results to provide guidance to other health care professionals on how best to image men with PCa and what treatments to give, when, and in what order, based on the information the images provide.

1. Introduction

Globally, prostate cancer (PCa) is the second commonest male cancer [1,2]. Incidence rates are affected by prostate-specific antigen (PSA) testing availability, ageing populations, genetic, lifestyle factors, and varying (inter)national guidance on screening and diagnosis [3,4].

Modern imaging including the rapidly evolving PCa-dedicated positron emission tomography (PET) tracers, multiparametric magnetic resonance imaging (mpMRI) of the prostate, and whole-body magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) are existing management paradigms, traditionally based on conventional techniques. The concurrent use of these modalities in current practice creates a complex situation for health care professionals during initial staging and restaging of PCa. The role of theranostic applications is currently recognised for the advanced metastatic castration-resistant PCa (mCRPC), while potential indications for hormone-sensitive PCa are increasingly investigated. There are multiple uncertainties in the selection of radiopharmaceuticals, indications for radioligand therapy, dosimetry, clinical trial design in theranostics, and clinical implementation of new radioisotopes. Therefore, to consolidate and disseminate best clinical practice and judicious use of resources, the European Association of Nuclear Medicine (EANM) initiated the Focus 1 meeting dedicated to molecular imaging and theranostics in PCa, published in 2018 [5]. Five years later, to keep step with this rapidly evolving field, further consensus is required.

1.1. Aim

We aimed to define the role of advanced imaging techniques (ie, hybrid functional and anatomic PET/computed tomography [CT]/MRI, PET-CT/PET-MRI imaging, and whole-body MRI with DWI) in PCa diagnosis and therapy beyond existing guidelines, as well as to define knowledge gaps for future studies.

Within this overarching aim, we had a number of subaims organised in five thematic tracks: (1) imaging in intermediate- and high-risk PCa (histopathology proven), (2) imaging for biochemical recurrence of PCa, (3) imaging of advanced PCa, (4) therapy of advanced PCa, and (5) important factors to consider in PCa consensus statement projects. The aims of each track can be reviewed in the Supplementary material.

2. Materials and methods

We used a robust and transparent methodology to assess consensus within a multidisciplinary panel of experts and multiple research methods to meet our aims. First, we systematically searched the literature, guided by our thematic tracks, and appraised the quality of the evidence (see the Supplementary material). Based on this review, the Focus 5 meeting co-chairs and scientific programme advisor (D. O.L., R.D., and S.F.) created a list of statements that could be agreed or disagreed with, and for which the current evidence base provides no clear answers. We included these statements in a two-round modified Delphi process, whereby an expert panel members were asked to state their strength of agreement with each statement. Finally, we discussed these statements, exploring in detail the ones for which there was no consensus, at a face-to-face consensus meeting in Seville, Spain, on February 2–4, 2023.

The participants in the Delphi process comprised experts covering much of the spectrum of diagnostics and management of PCa, including molecular imaging and radionuclide therapy specialists, radiologists, medical oncologists, radiation oncologists, and urologists. Experts were identified via authorship of published research on PCa. Twenty-nine experts were invited to participate; one declined because of the feeling that the expertise was scientific rather than clinical. The remaining 28 completed both rounds. Their areas of expertise and country of practice can be seen in Table 1.

Table 1 – Expert panel field of expertise and country of practice

Name	Expertise	Country of practice
Daniela-Elena Oprea-Lager	Nuclear medicine	The Netherlands
Stefano Fanti	Nuclear medicine	Italy
Barbara Alicja Jereczek-Fossa	Radiation oncology	Italy
Anders Bjartell	Urology	Sweden
Alberto Briganti	Urology	Italy
Irene A. Burger	Nuclear medicine, Radiology	Switzerland
Igle de Jong	Urology	The Netherlands
Maria De Santis	Medical oncology	Germany
Rudi Dierckx	Nuclear medicine	The Netherlands
Uta Eberlein	Medical physics, nuclear medicine	Germany
Louise Emmett	Nuclear medicine	Australia
Karim Fizazi	Medical oncology	France
Silke Gillessen	Medical oncology	Switzerland
Ken Herrmann	Nuclear medicine	Germany
Andrei Iagaru	Nuclear medicine	USA
Jolanta Kunikowska	Nuclear medicine	Poland
Marnix Lam	Nuclear medicine	The Netherlands
Joe M. O'Sullivan	Clinical oncology	UK
Valeria Panebianco	Radiology	Italy
Evis Sala	Radiology	Italy
Oliver Sartor	Oncology	USA
Mike Sathekge	Nuclear medicine	South Africa
Roman Sosnowski	Urology	Poland
Derya Tilki	Urology	Germany
Bertrand Tombal	Urology	Belgium
Nina Tunariu	Radiology	UK
Jochen Walz	Urology	France
Derya Yakar	Radiology	The Netherlands

2.1. Systematic literature search

The PubMed database was searched from January 1, 2020 to August 10, 2022 for English-language publications regarding molecular imaging and therapy of PCa. Systematic reviews, meta-analyses, evidence-based guidelines, and consensus statements were included. Given that the area is evolving rapidly, review papers prior to 2020 were considered to be outdated and therefore were not used.

The quality of the retrieved systematic reviews was assessed using the AMSTAR 2 criteria (full search strategy and results are shown in the Supplementary material) [6]. The papers retrieved in the literature search were made available to the expert panelists alongside tables summarising the quality assessment.

2.2. Modified Delphi process

In round 1 of the modified Delphi process, participants were e-mailed a link to an online survey containing 44 agreement statements and six ranking questions organised in five thematic tracks (see the Supplementary material for the full questionnaire). For the 44 agreement statements, panelists were asked to state their strength of agreement with each statement on a 9-point Likert scale (1, strongly disagree; 5, neither agree nor disagree; and 9, strongly agree). Panelists were urged only to choose five if they felt that they truly neither agreed nor disagreed and to utilise the "unable to score" option if they did not have enough expertise to answer. For the ranking questions, participants were asked to rank their preferences in order or abstain if they felt that they did not have enough expertise to answer.

Participants could comment on any statement in round 1 and propose statements for consideration by the scientific committee that they believed should be added for round 2 scoring. Four agreement statements were added based on the panelists' suggestions, giving 48 agreement statements in total, and two questions were reworded for clarification (these are clearly flagged in the results tables).

In round 2 of the modified Delphi process, participants were reminded of their own round 1 scores for every question and shown the bar charts of the distribution of other panelists' scores for each agreement statement, as well as

the bar charts for the ranking preference questions. They were asked to rescore the original items and score the reworded and new items. REDCap was used to collect data and manage all aspects of the Delphi process [7,8].

2.3. Outcome measures and statistical analysis—Delphi

For the 48 agreement statements, the Research and Development Corporation (RAND) "appropriateness method" was followed [9]. For each statement, the median score and 30–70th interpercentile range (IPR) were calculated. Then, the IPR adjusted for symmetry (IPRAS) was calculated, using the following formula: (IPRAS = 2.35 + [asymmetry index × 1.5]). Asymmetry is the absolute difference between the central point of the IPR and 5 (ie, the scale centre point). If IPR is < IPRAS, this is interpreted as the range of scoring being narrowly dispersed around the median score and is defined as "consensus". Median scores in the range of 1–3 were categorised as "disagree", 4–6 as "uncertain", and 7–9 as "'agree". A worked example is shown in the Supplementary material. The number choosing "unable to score" was noted for each statement. A calculator in Microsoft Excel [10] was created and used for all consensus analyses.

For the six ranking statements, weighted scores were used to summarise the group preferences. The number of instances of each rank was calculated (eg, 1–5 on a question with five choices to rank), then the highest scoring choice was allocated the highest weight and the lowest given the lowest weighting. Each choice was then multiplied by the weighting, and the results were summed and then summarised in bar charts.

2.4. Consensus meeting

A face-to-face consensus meeting was held on February 2–4, 2023, in Seville, Spain. Thematic sessions were organised corresponding to the five tracks. In each session, up to eight presentations were given by different members of the expert panel, depending on their expertise. These were organised to provide expert interpretation in favour of or against the issues being discussed, and an overview of the evidence base. At the end of each track session, there was a question and answer session, chaired by the Focus 5 co-chair (D.O.L.) and different panel experts (S.F., A.I., J.O'S., S. G., A.B., and J.K.). This meeting provided an opportunity for the panel to explore the statements for which there was no consensus and to provide explanation and nuance for all statements. Importantly, there was no aim for the discussion to over-ride the Delphi results. The programme can be reviewed online at https://focusmeeting.eanm.org/programme/.

3. Results

3.1. Systematic literature search

The complete results of the systematic literature search and AMSTAR2 results are reported in the Supplementary material. Briefly, among 126 records retrieved, 62 were excluded (35 were not in the field of interest, 26 were published before 2020, and one was not in English). Sixty-four recent systematic reviews or meta-analyses and seven consensus statements or guidelines were included and provided to the panellists. In each track, there were systematic reviews rated at low, moderate, and high quality, with no discernible difference in quality between tracks.

3.2. Delphi

In round 1, there was consensus on 39/44 (88.8%) of the statements. After two Delphi rounds, there was consensus on 42/48 (87.5%) of the statements. The median number of panelists choosing unable to score was 2 in both rounds (range 1–11 in round 1 and 0–14 in round 2). The results for the agreement statements after two rounds are tabulated below, split by track, and the results of ranking statements are shown in bar charts. The full results of both Delphi rounds can be viewed in the Supplementary material.

The terms PSMA PET-CT and PET-MRI are "generically" used in this paper, irrespective of the type of isotope or ligand used.

In track 1, there was consensus for all 15 statements (see Table 2), indicating the scope and general agreement that mpMRI and PSMA PET-CT/PET-MRI have a clear role in initial staging and incorporation into nomograms for unfavourable intermediate- and high-risk PCa, even though the impact of imaging on patient management and survival outcomes is currently unknown.

For both ranking questions in track 1, PSMA PET-CT/PET-MRI was found to be the preferred imaging modality to assess nodal (Fig. 1) and distant metastases at initial diagnosis of high-risk PCa (Fig. 2). The panel agreed unanimously that PSMA PET-CT should replace conventional imaging in patients with high-risk PCa undergoing initial staging.

In track 2 (see the results in Table 3 and Fig. 3), there was consensus on ten of 14 (71%) statements. Panelists shared the view that mpMRI should not be the preferred choice of biochemical recurrence imaging, even at low PSA levels, and agreed that there is a clear preference for PSMA PET-CT/PET-MRI for recurrence imaging, depending on various PSA-based scenarios. No consensus was reached on whether mpMRI should be performed in patients with a suspicion of local recurrent disease, regardless of the PSA level.

In track 3 (see Table 4), there was consensus for all questions. Taken together, these statements indicate that there is a role for advanced imaging modalities in categorising and managing patients with metastatic castration-sensitive PCa, non-mCRPC (M0 CRPC), and oligo- or polymetastases. There was consensus on defining oligometastatic disease as five or fewer metastases, even using advanced imaging modalities.

In track 4, there was consensus on 14/16 (88%) agreement statements in favour of [^{177}Lu]Lu-PSMA, not only in terms of administration, maximum activity, and optimal number of cycles to be offered, but also regarding retreatment, bone marrow involvement, and extent of disease to be treated (Table 5, and Figs. 4 and 5). The group agreed that [^{177}Lu]Lu-PSMA should not be administered only after pro-

Table 2 – Delphi results after two rounds of scoring for track 1: imaging in intermediate- and high-risk PCa (histopathology proven)

	Median[a]	30th Pcentile	70th Pcentile	Consensus	Unable to score
1.1. mpMRI of the prostate is recommended for patients with a clinical suspicion of prostate cancer (ie, mpMRI in first detection setting).	9	9	9	Yes	2
1.2. mpMRI of the prostate is the most useful imaging method for local staging of intermediate- and high-risk prostate cancer.	9	9	9	Yes	2
1.3. PSMA PET-CT/PET-MRI for staging should be performed only after mpMRI of prostate and targeted biopsy.	9	8	9	Yes	1
1.4. PSMA PET-CT/PET-MRI should be used for staging of the majority of patients with favourable intermediate-risk prostate cancer.	1	1	3	Yes	1
1.5. PSMA PET-CT/PET-MRI should be used for staging of the majority of patients with unfavourable intermediate-risk prostate cancer (ie, primary Gleason pattern of 4, ≥50% percentage of prostate biopsy cores, or ≥2 NCCN intermediate-risk factors: clinical stage T2b or T2c, total Gleason score = 7 or PSA level = 10–20 ng/ml).	8	8	9	Yes	1
1.7. Modern nomograms, which incorporate PSMA PET-CT findings together with mpMRI findings and MRI-targeted biopsy, should be used to identify candidates for extended lymph node dissection (ie, dissection of presacral, obturator, external, internal, and common iliac nodes) at the time of radical prostatectomy, as opposed to classic nomograms using only clinical and biopsy findings (on random TRUS).	9	8	9	Yes	1
1.8. PSMA PET-CT/PET-MRI (skull base to midthigh) is preferred to pelvic or whole-body MRI for the detection of locoregional (N1) and distant (M1a) lymph node metastases in intermediate- and high-risk prostate cancer.	9	9	9	Yes	1
1.9. PSMA PET-CT should replace both bone scan and abdominopelvic CT in patients with high-risk prostate cancer, undergoing initial staging.	9	9	9	Yes	1
1.10. Choline PET-CT/PET-MRI is preferred to bone scan for staging of primary prostate cancer, when staging is indicated.	8	7	9	Yes	1
1.12. mpMRI of the prostate is useful for local treatment planning (eg, targeted biopsy, tumour delineation) in patients with intermediate- to high-risk prostate cancer.	9	9	9	Yes	1
1.13. Availability of ^{68}Ga/^{18}F-PSMA PET-CT is often limited to some nuclear medicine centres. Given that ^{99m}Tc-PSMA-SPECT-CT could be widely available, ^{99m}Tc-PSMA-SPECT-CT should be preferred to PSMA PET-CT.	1	1	2	Yes	4
1.14. ^{99m}Tc-MDP-SPECT bone scan and 99mTc-PSMA-SPECT scan share similar procedures and radiation exposures. ^{99m}Tc-PSMA-SPECT scan should replace ^{99m}Tc-MDP-SPECT bone scan.	8	7	9	Yes	7
1.15. Patients with distant metastases at diagnosis, detectable only with advanced imaging techniques (eg, PSMA PET-CT/PET-MRI or whole-body MRI), should be offered definitive local therapy along with metastasis-directed therapies, even though the impact of these techniques for prognosis and optimal patient management is unknown.	7.5	7	8	Yes	2

CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PCa = prostate cancer; Pcentile = percentile; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SPECT = single-photon emission computed tomography; TRUS = transrectal ultrasound.
[a] 1–3 = disagree; 4–6 = uncertain; 7–9 = agree.

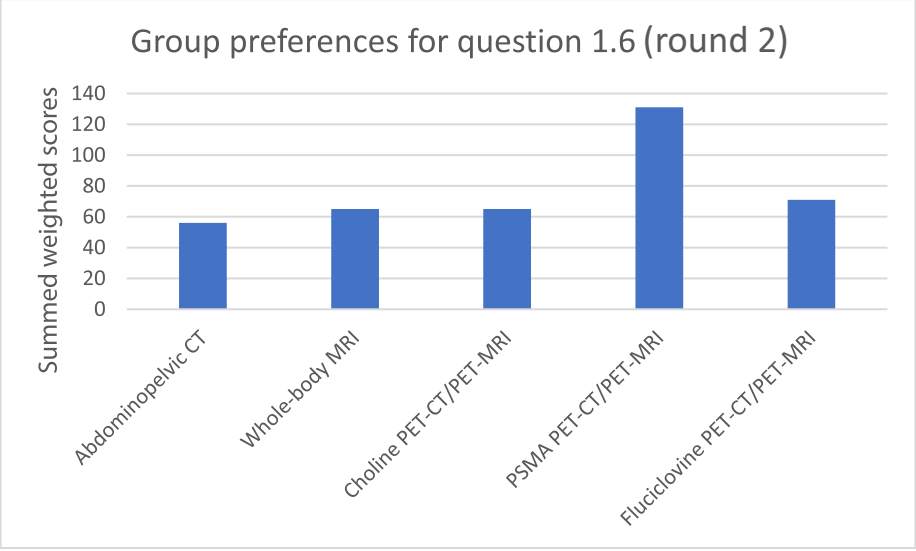

Fig. 1 – Group preferences for question 1.6: please rank the following methods to assess nodal metastases at initial diagnosis of high-risk prostate cancer, with 1 being your top preference, 2 your second, and so on. CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

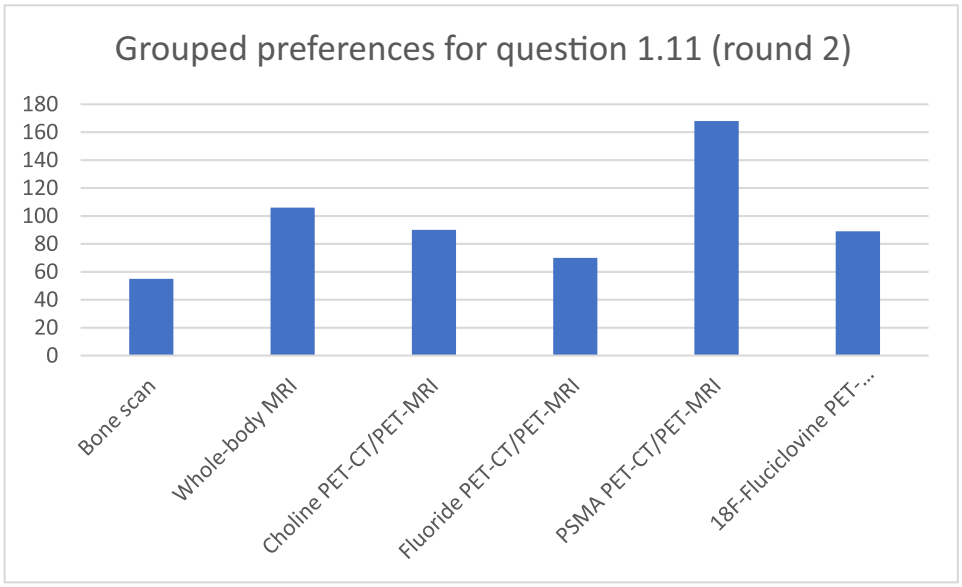

Fig. 2 – Group preferences for question 1.11: please rank the following methods to assess distant metastases at initial diagnosis of prostate cancer, with 1 being your top preference, 2 your second, and so on. CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Table 3 – Delphi results after two rounds of scoring for track 2: imaging for biochemical recurrence of prostate cancer

	Median[a]	30th Pcentile	70th Pcentile	Consensus	Unable to score
2.1. mpMRI of the prostate should be performed in patients with a suspicion of local recurrent disease (regardless of the PSA level).	5	3	8	No	1
2.2 A PSMA PET-CT/PET-MRI scan should be performed if mpMRI of the prostate is negative for recurrent prostate cancer.	9	9	9	Yes	1
2.3. mpMRI should not be used for local recurrences in the prostatic bed in patients with a low PSA level (<0.5 ng/ml, after prostatectomy).	8	7.8	9	Yes	1
2.4. PSMA PET-CT/PET-MRI should be performed in the majority of patients with a suspicion of recurrent prostate cancer.	9	9	9	Yes	1
New question 2.5a. A participant in round 1 commented that question 2.5 was unclear. Therefore, the Focus 5 chairs added the precursor question 2.5a. Please score it on the 1–9 scale: PSMA PET-CT/PET-MRI should always be performed as the only imaging modality in patients with (any level of risk or PSA) a suspicion of recurrent prostate cancer.	8	3	8	No	1
2.5. PSMA PET-CT/PET-MRI should always be performed in adjunct to mpMRI of the prostate in patients with (any level of risk or PSA) a suspicion of recurrent prostate cancer.	3	2	8	No	2
2.6. Choline PET-CT/PET-MRI is useful in biochemical recurrence setting after curative local treatment (ie, surgery or radiotherapy) of prostate cancer, with rising PSA above 4 ng/ml.	8	8	8	Yes	1
2.7. [^{18}F-]fluciclovine PET-CT/PET-MRI is the preferred imaging method for detecting metastases in the setting of local relapse after radical prostatectomy. [^{18}F-]fluciclovine is a radiolabelled amino acid analogue that functions based on amino acid transport upregulation in prostate cancer.	2	1	3	Yes	3
2.9. PSMA PET-CT/PET-MRI is the preferred imaging method for the detection of recurrent disease after radical prostatectomy, at PSA levels <0.5 ng/ml.	9	9	9	Yes	1
2.10. mpMRI of the prostate should be used for the detection of local recurrences after radiotherapy, at low PSA levels of <0.5 ng/ml.[b]	5	2	6	No	3
2.11. PSMA PET/CT should be used for the detection of local recurrences after radiation therapy, even at low PSA levels of <0.5 ng/ml.[b]	8	7	8	Yes	1
2.12. PSMA PET-CT/PET-MRI should be used to guide metastasis-directed therapy in patients with oligometastases relapsing after a local treatment. Note: some wording has been clarified in this question. Red text highlights the addition.	9	9	9	Yes	1
2.13. Men with persistent detectable PSA after radical prostatectomy (ie, PSA >0.1 ng/ml, >6 wk after radical prostatectomy, irrespective of the surgical margin status) should be investigated with PSMA PET-CT or PET-MRI.	9	9	9	Yes	1
2.14. [^{18}F-]fluoride PET-CT/PET-MRI should be preferred to bone scan for the detection of bone metastases at biochemical recurrence of prostate cancer.	9	7	9	Yes	1

CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; Pcentile = percentile; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

[a] 1–3 = disagree; 4–6 = uncertain; 7–9 = agree.

[b] Please note that PSA levels of <0.5 ng/ml after radiotherapy are below the ASTRO Phoenix definition of biochemical recurrence.

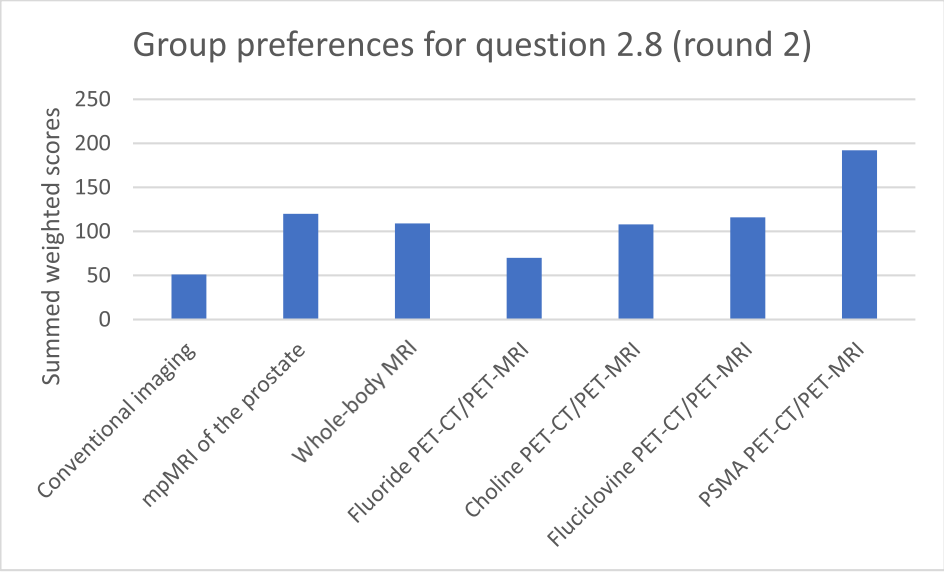

Fig. 3 – Group preference for question 2.8: please rank the following methods to assess recurrent prostate cancer, with 1 being your top preference, 2 your second, and so on. CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Table 4 – Delphi results after two rounds of scoring for track 3: imaging of advanced prostate cancer

	Median[a]	30th Pcentile	70th Pcentile	Consensus	Unable to score
3.1. Advanced imaging modalities (ie, PSMA PET-CT/PET-MRI, whole-body MRI) can be used to define high- and low-volume metastases (CHAARTED criteria) in metastatic hormone-sensitive prostate cancer.	8	7	8.5	Yes	2
3.2. Management of patients with nonmetastatic castration-resistant prostate cancer (by conventional imaging) is likely to be modified by advanced imaging techniques (eg, PSMA PET-CT/PET-MRI or whole-body MRI).	9	8	9	Yes	1
3.3. Oligometastatic prostate cancer should be defined as ≤5 metastases (detected on advanced imaging modalities, eg, PSMA PET-CT/PET-MRI or whole-body MRI).	9	8	9	Yes	1
3.4. PSMA PET-MRI is equivalent (in terms of diagnostic accuracy) to PET-CT, in the majority of patients with metastatic advanced prostate cancer.	8	8	8	Yes	4

CT = computed tomography; MRI = magnetic resonance imaging; Pcentile = percentile; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
[a] 1–3 = disagree; 4–6 = uncertain; 7–9 = agree.

gression to cabazitaxel and that [^{223}Ra]RaCl2 remains a valid therapeutic option in bone-only mCRPC. There was no consensus on the use of [^{177}Lu]Lu-PSMA only in patients with concordant findings on both [^{18}F]FDG PET and PSMA PET, assuming that metastases show adequate PSMA expression.

The expert panel agreed that patient advocates should be invited to review and comment on consensus statements (Table 6).

3.3. Limitations

Expert consensus, based on low-certainty evidence, is still low-certainty evidence [11]. Nonetheless, guidance is required, and where there is a diverse evidence base spanning a number of disciplines and rapidly evolving field, utilising the knowledge of a multidisciplinary group of experts is a sensible and efficient interim step. It also importantly allows for the identification of knowledge gaps to inform future research. We controlled for group processes and dominant voices through anonymised voting and controlled feedback in the Delphi process. This provided a framework for discussion at the face-to-face meeting, which offered some nuance and detail for interpreting the consensus statements.

A relatively large proportion of panelists chose unable to score for some statements. However, this is somewhat expected given wide-ranging disciplines from which we drew our expert panel, so for some questions, highly specialised knowledge was required, and it was better for the panelists to have the option to abstain rather than, for example, vote "5", potentially falsely skewing the median.

This study was conducted on behalf of the EANM, and the majority of panelists were from European centres, although experts from the USA, Australia, and South Africa were also invited and actively participated. It could be pro-

Table 5 – Delphi results after two rounds of scoring for track 4: therapy of advanced prostate cancer

	Median[a]	30th Pcentile	70th Pcentile	Consensus	Unable to score
4.1. [^{177}Lu]Lu-PSMA can be administered at the outpatient clinic (if allowed by local regulators).	9	8	9	Yes	4
4.4. Retreatment with another 4–6 cycles of [^{177}Lu]Lu-PSMA should be considered in patients with disease recurrence who received 6 injections of [^{177}Lu]Lu-PSMA (and had an initial good response, eg, progression-free survival of at least 6 mo).	8	6.2	8	Yes	13
4.5. In bone-only mCRPC, [^{223}Ra]$RaCl_2$ remains a valid therapeutic option despite the availability of [^{177}Lu]Lu-PSMA.	9	8	9	Yes	6
4.6. In mCRPC, patients should receive [^{177}Lu]Lu-PSMA only after progression to cabazitaxel.	1	1	1	Yes	5
4.7. [^{177}Lu]Lu-PSMA should be used before PARP inhibitors in patients with mCRPC. Note: based on the feedback from round 1 participants, we have added a clarification to question 4.7. The amended wording is in red text. Please score this amended question: 4.7. [^{177}Lu]Lu-PSMA should be used before PARP inhibitors in patients with BRCA 1– or 2–associated mCRPC.	5	5	5	Yes	6
4.8. [^{177}Lu]Lu-PSMA should be used only in patients with concordant findings on both [^{18}F]FDG PET and PSMA PET, assuming that metastases show adequate PSMA expression.	6	3	6.7	No	6
4.9. Patients with extensive bone metastases and bone marrow involvement are eligible for [^{177}Lu]Lu-PSMA therapy (assuming that the bone marrow function is adequate).	9	8	9	Yes	5
4.10. Patients with brain metastases are eligible for [^{177}Lu]Lu-PSMA therapy.	8	8	8	Yes	10
4.11. Kidney dysfunction (GFR <45) is a contraindication for [^{177}Lu]Lu-PSMA therapy. Note: based on the feedback from round 1 participants, we have added a clarification to question 4.11. The amended wording is in red text. Please score this amended question: 4.11. Kidney dysfunction (GFR <45) is a relative contraindication for [^{177}Lu]Lu-PSMA therapy.	3	3	6.2	No	11
4.12. WHO ECOG 3 patients can be considered for [^{177}Lu]Lu-PSMA therapy.	7	6	8	Yes	7
4.13. [^{177}Lu]Lu-PSMA-I&T and [^{177}Lu]Lu-PSMA-617 have similar efficacy in the treatment of mCRPC.	8	7	8.1	Yes	14
4.14. Therapy with [^{225}Ac]Ac-PSMA (if available) should be considered as an alternative to [^{177}Lu]Lu-PSMA, in patients with mCRPC being [^{177}Lu]Lu-PSMA naïve or progressing after [^{177}Lu]Lu-PSMA.	7	5	8	Yes	11
4.14a (new). Therapy with [^{225}Ac]Ac-PSMA (if available) should be considered as an alternative to [^{177}Lu]Lu-PSMA, in patients with mCRPC progressing after [^{177}Lu]Lu-PSMA. Note: based on the feedback from participants in round 1, a new question related to question 4.14 has been added. Please score this question on the same 1–9 scale.	8	7.1	8	Yes	10
4.15. In patients with metastatic advanced prostate cancer, the combinations of [^{177}Lu]Lu-PSMA with novel hormonal agents play a role outside of clinical trials. Note: in response to a comment from a participant in round 1, some text has been amended to clarify the question. The amended text is indicated in red.	8	6	8	Yes	4
New question 4.16. Administered activity in [^{177}Lu]Lu-PSMA therapy should be based on dosimetry.	7	6	7	Yes	10
New question 4.17. PSMA PET is mandatory before PSMA-targeted therapy.	9	9	9	Yes	1

ECOG = Eastern Cooperative Oncology Group; GFR glomerular filtration rate; mCRPC = metastatic castration-resistant prostate cancer; Pcentile = percentile; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; WHO = World Health Organization.
[a] 1–3 = disagree; 4–6 = uncertain; 7–9 = agree.

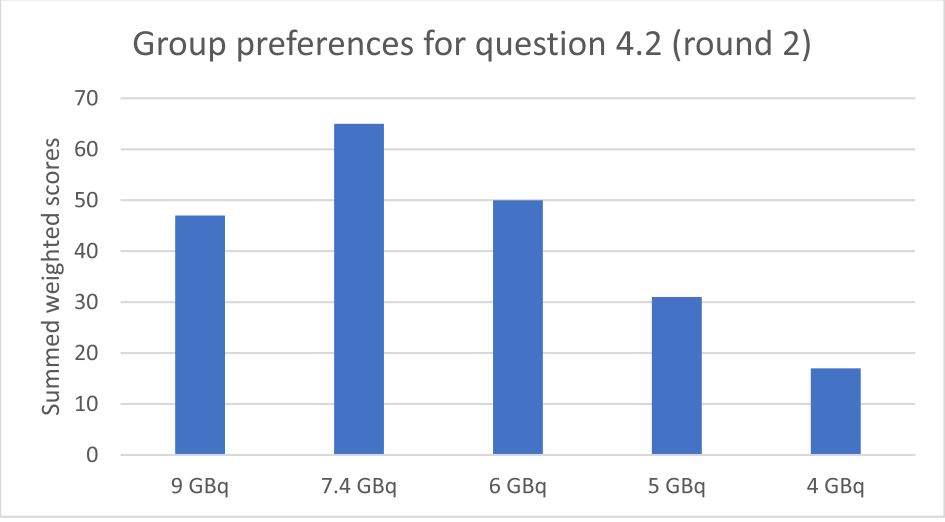

Fig. 4 – Group preferences for question 4.2: please rank the following options in order of the maximum activity of [^{177}Lu]Lu-PSMA that you think can be administered safely in mCRPC, with 1 being your top preference, 2 your second, and so on. mCRPC = metastatic castration-resistant prostate cancer; PSMA = prostate-specific membrane antigen.

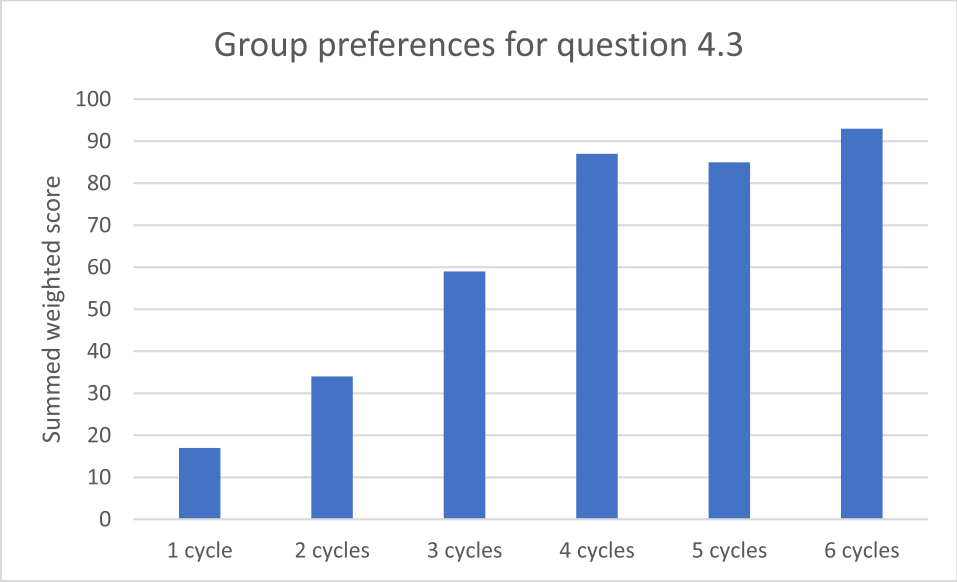

Fig. 5 – Group preferences for question 4.3: please rank the following options in order of the maximum number of cycles of [^{177}Lu]Lu-PSMA (7.4 GBq per cycle) that you think can be administered safely and efficiently in mCRPC, with 1 being your top preference, 2 your second, and so on. mCRPC = metastatic castration-resistant prostate cancer; PSMA = prostate-specific membrane antigen.

Table 6 – Delphi results after two rounds of scoring for track 5: important factors to consider in prostate cancer consensus statement projects

	Median[a]	30th Pcentile	70th Pcentile	Consensus	Unable to score
5.1. Consensus statements agreed by clinical experts should be shared with patient advocates who should be invited to review and comment on the statements.	9	9	9	Yes	0

Pcentile = percentile.
[a] 1–3 = disagree; 4–6 = uncertain; 7–9 = agree.

posed that the results are applicable mainly to Europe, but we encourage practitioners in other continents to assess the applicability of the results in their area of expertise.

4. Discussion

Given the rapid progress in PCa management, guidelines on screening, diagnosis, and treatment of clinically localised, relapsing, metastatic, and castration-resistant PCa are revised yearly [12,13]. The Advanced PCa Consensus Conference is organised regularly to supplement evidence-based guidelines for key dilemmas in clinical management of PCa [14,15]. The improvement of anatomicofunctional imaging modalities to (re)stage PCa and to characterise advanced disease, as well as the evolution of the theranostics field, continue to pose questions and deliver controversies. Therefore, to reach a multidisciplinary consensus on the current state of the art in PCa and to make expert recommendations on how to advance the field towards establishing clinical impact, a new EANM Focus 5 meeting in PCa was organised. Broadly, there was consensus within the panel. Although there was a reduction in consensus between Delphi rounds 1 and 2, this is an artefact of new statements being added, rather than a reflection of reduced consensus in the group.

To situate our interpretation within the wider literature, and offer a transparent link between the specific studies that the statements drew upon, we have clarified the statement numbers in brackets and signposted the relevant citations.

The panel agreed that mpMRI of the prostate is recommended for patients with clinical suspicion of PCa (1.1) and is the most useful imaging method for local staging of intermediate- and high-risk PCa (1.2) [16], aligning with the EAU guidelines [12].

In concordance with a recent meta-analysis of 23 studies [17], the panel concurred that PSMA PET-CT/PET-MRI is useful for staging PCa after mpMRI and targeted biopsy (1.3) in patients with unfavourable intermediate- (1.5) and high-risk (1.8) PCa.

All panelists agreed strongly in favour of replacing bone scan and abdominopelvic CT with PSMA PET/CT scans, for staging patients with high-risk PCa (1.10), which makes the results of a recent systematic review valid for use in routine clinical practice [18] and aligns these with a recent Dutch consensus statement [19].

The panel agreed that [^{18}F]fluciclovine PET-CT/PET-MRI is not the preferred imaging method for detecting metastases in the setting of local relapse after radical prostatectomy (2.7). There is still room for choline PET-CT/PET-MRI

[20], when PSMA either is not available or has limited availability, in case of PSMA-negative disease, in the biochemical recurrence setting, or after curative local treatment of PCa, with PSA rising above 4 ng/ml (2.6) [12].

There is initial evidence that mpMRI using a standardised scoring system, the Prostate Imaging for Recurrence Reporting, can identify local recurrence accurately, but further evidence is warranted [21]. There was consensus that PSMA PET-CT/PET-MRI should be used to guide metastasis-directed therapy in patients with oligometastases relapsing after a local treatment (2.12) [22].

No consensus was reached on whether mpMRI should be used for the detection of local recurrences after radiotherapy, at low PSA values under 0.5 ng/ml (2.10). On the contrary, there was consensus on the use of PSMA PET-CT for detecting local recurrences after radiation therapy, even at low PSA levels of <0.5 ng/ml (2.11). When these statements are considered against the current ASTRO Phoenix definition of biochemical recurrence after curative radiotherapy (which is defined as PSA nadir + 2 ng/ml) [23] and the National Comprehensive Cancer Network 2023 guidelines, which accept restaging at PSA levels below 2 ng/ml only in young patients with rapidly increasing PSA [24], there is a scope for refining currently used definitions.

The panel agreed that current management of patients with non-mCRPC (by conventional imaging) is likely to be modified by advanced imaging techniques (eg, PSMA PET-CT/PET-MRI or whole-body MRI; 3.2) [25,26].

All panellists agreed that the maximum number of metastases detected on advanced imaging modalities is up to 5. This is in line with other consensus statements showing that the number of oligometastases diagnosed by PSMA PET/CT ranged between 3 and 5 [19].

However, the time of metastatic presentation and disease volume are proved to be prognostic for patients with metastatic hormone-sensitive PCa treated with androgen deprivation therapy. This simple prognostic classification system can aid patient counselling and future trial design [27].

In patients with bone-only mCRPC, [^{223}Ra]$RaCl_2$ remains a valid therapeutic option despite the availability of [^{177}Lu]Lu-PSMA (4.5). There was consensus to disagree that patients with mCRPC should receive [^{177}Lu]Lu-PSMA only after progression to cabazitaxel (4.6) [28].

The panel agreed that in patients with metastatic advanced PCa, the combinations of [^{177}Lu]Lu-PSMA with novel hormonal agents play a role outside of clinical trials (4.15) [29–33]. Finally, there was consensus that the administered activity in [^{177}Lu]Lu-PSMA therapy should be based on dosimetry (4.16) and that PSMA PET is mandatory before PSMA-targeted therapy (4.17).

An important point must be highlighted when referring to PSMA PET in this consensus on molecular imaging and theranostics in PCa. The term "PSMA" was used generically, including all available types of ^{68}Ga- or ^{18}F-radiolabelled PSMA PET tracers. This has consequences on the confidence grade on the reporting of findings, especially in light of known nonspecific bone activity for some tracers (eg, ^{18}F-PSMA-1007). Nevertheless, to reduce the number of false positive and/or inconclusive results, different guidelines have been proposed for structured reporting of PSMA PET and harmonisation of interpretation criteria, and are successfully applied in clinical practice [34–37].

5. Conclusions

We systematically searched the literature to inform a panel of experts who participated in two modified Delphi rounds and a consensus meeting where consensus was sought and gained on several pressing issues, and knowledge gaps were identified. Consensus statements cannot replace high-certainty evidence, but what we have provided here is an expert recommendation of best practice from centres of excellence to guide the wider clinical community. These consensus statements should also be used as a basis to design prospective studies and clinical trials.

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Study concept and design: Oprea-Lager, MacLennan, Treglia, Dierckx, Fanti.
Acquisition of data: MacLennan, Treglia.
Analysis and interpretation of data: Oprea-Lager, MacLennan, Treglia, Dierckx, Fanti.
Drafting of the manuscript: Oprea-Lager, MacLennan, Treglia, Fanti.
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