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European Association of Urology



## EUO Priority Article

# EAU-EANM Consensus Statements on the Role of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography in Patients with Prostate Cancer and with Respect to [<sup>177</sup>Lu]Lu-PSMA Radioligand Therapy

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## Abstract

**Background:** Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) is useful for selected clinical indications in patients with prostate cancer (PCa) but it may have broader clinical utility owing to the emergence of lutetium-177-PSMA-617 ([<sup>177</sup>Lu]Lu-PSMA) therapy. However, robust data regarding the impact of PSMA PET/CT on patient management and treatment are lacking, and in many areas, the role of next-generation imaging has not been defined.

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**Objective:** To assess expert opinion on the use of PSMA-based imaging and therapy to develop interim guidance.

**Design, setting, and participants:** A panel of 21 PCa experts from various disciplines received thematic topics and relevant literature. A questionnaire to assess proposed guidance statements regarding PSMA PET/CT and [<sup>177</sup>Lu]Lu-PSMA therapy was developed for completion remotely in a first e-Delphi round. A subsequent panel discussion was conducted during a 1-d meeting, which included a second Delphi round.

**Outcome measurements and statistical analysis:** Panellists voted anonymously on statements using a nine-point Likert scale from 1 = strongly disagree to 9 = strongly agree. Median scores were calculated and consensus was assessed using methods proposed by the Research and Development (RAND) corporation.

**Results and limitations:** Statements were developed to cover the following topics: PSMA PET/CT utility, clinical use, and choice of tracer; patient selection; and management of patients receiving [<sup>177</sup>Lu]Lu-PSMA for metastatic PCa. Consensus was reached for 33/36 statements. In-group bias is a potential limitation, as some statements were rephrased during discussions at the 1-d meeting.

**Conclusions:** Adoption of PSMA PET/CT as an imaging tool to guide [<sup>177</sup>Lu]Lu-PSMA therapy should be supported by indications for appropriate use.

**Patient summary:** A panel of experts in prostate cancer reached a consensus for the majority of statements proposed regarding the role of prostate-specific membrane antigen (PSMA)-based imaging and therapy, particularly the use of PSMA-based imaging in patients suitable for [<sup>177</sup>Lu]Lu-PSMA therapy and the need to perform PSMA-based imaging before considering patients as candidates for this therapy.

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## 1. Introduction

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) (eg, [<sup>68</sup>Ga]Ga-PSMA-11, [<sup>18</sup>F]PSMA-1007, [<sup>18</sup>F]DCFPyL; hereafter referred to as PSMA PET/CT) is increasingly used for men with prostate cancer (PCa) in various clinical settings.

International guidelines, including those from the European Association of Urology (EAU) [1], have included PSMA PET/CT as an imaging tool and provided recommendations regarding its use in the management of PCa. For patients with biochemical recurrence (BCR) or persistently elevated prostate-specific antigen (PSA) after local therapy with curative intent, PSMA PET/CT is the recommended imaging modality after both radiotherapy and radical prostatectomy if the results will influence subsequent treatment decisions. PSMA PET/CT may also have a role in the primary staging of patients with high-risk PCa [2], although outcomes data are lacking. In addition, procedural guidelines for performing PSMA PET/CT have been endorsed by the European Association of Nuclear Medicine (EANM) [3].

Expression of the PSMA transmembrane protein on PCa cells makes it a suitable target for imaging as a diagnostic tool and for therapy as part of a theranostic approach. In recent years, several studies have reported promising results for lutetium-177-PSMA-617 ([<sup>177</sup>Lu]Lu-PSMA) use in patients with advanced PCa [4–6]. Procedural guidelines for radionuclide therapy with [<sup>177</sup>Lu]Lu-PSMA have been published by the EANM [7] but further exploration of the relationship between diagnostic PSMA PET and PSMA-based therapy is needed.

In recognition of the growing importance of PSMA-targeting radiopharmaceuticals in the diagnosis and treatment of PCa, the EAU in collaboration with the EANM

recruited a panel of international PCa experts from different specialties to assess the available evidence and provide their collective expert opinion regarding PSMA-based imaging and therapy, with the aim of developing interim guidance on PSMA PET/CT imaging in patients suitable for [<sup>177</sup>Lu]Lu-PSMA therapy until better evidence emerges [8].

## 2. Materials and methods

In August 2021, the EAU and EANM formed a collaboration to produce consensus statements intended as interim guidance on PSMA PET/CT imaging in patients suitable for [<sup>177</sup>Lu]Lu-PSMA therapy. A steering group (S. Fanti and A. Bjartell) identified and invited a panel of experts from different disciplines (urology, medical oncology, nuclear medicine, radiology, and radiation oncology) on the basis of their knowledge of PCa management and expertise on this specific topic. A PubMed literature search was performed by one author (S. Fanti) using the terms “PET imaging”, “PET/CT imaging”, and “Lu-PSMA”, with results limited to literature published in English between 2016 and 2021. On the basis of findings from this literature search, the steering group developed a series of proposed guidance statements regarding PSMA-based imaging and therapy.

A modified Delphi process was used for all panel members to assess the proposed statements. The first round was an e-Delphi process completed electronically 2 wk before the second Delphi round, which was scored in real time during a 1-d consensus meeting held in January 2022. This meeting was moderated by a specialist in consensus methodology (S. MacLennan).

Each panel member received the following thematic topics and relevant literature 1 mo before the start of the Delphi process: (1) appropriate indications for PSMA PET/

CT; (2) the role of PSMA imaging with respect to [<sup>177</sup>Lu]Lu-PSMA-based therapy; (3) the best tracer for performing PSMA PET/CT; (4) methodology for diagnostic and therapeutic PSMA use; (5) patient selection for [<sup>177</sup>Lu]Lu-PSMA therapy; (6) PET imaging in patients with PCa who are candidates for [<sup>177</sup>Lu]Lu-PSMA therapy; and (7) PET imaging in patients with PCa who are treated with [<sup>177</sup>Lu]Lu-PSMA. Panel members were asked if they wished to include any statements in addition to those proposed by the steering group. Each statement was phrased so that panel members could score their level of agreement, except for one descriptive statement (no. 19 in Table 1) that was not considered further for consensus purposes.

The round 1 e-Delphi was managed using Research Electronic Data Capture (RedCap), a web-based software platform [9]. Panellists voted on a nine-point Likert scale, ranging from 1 = strongly disagree to 9 = strongly agree (1–3, disagree; 4–6, uncertain; 7–9, agree). The panellists were then sent the results from the e-Delphi with the other panellists' anonymised scores and a reminder of their own scores.

During the 1-d meeting, results from the e-Delphi vote on each statement were conveyed to participants and the thematic topics were presented and discussed. The panellists were then asked to confirm the relevance of the statements and their wording. A second Delphi vote was then conducted only for statements for which consensus was not reached after the first Delphi vote and for statements for which rewording could result in a different score.

Statistical analysis of the Delphi voting focussed on the level of agreement (median score) for each statement and whether consensus was achieved (dispersion of scores around the median) based on the methods proposed by the Research and Development (RAND)/University of California, Los Angeles (UCLA) Appropriateness Method, which can be used in panels of any size [9]. For each statement, the median score and the 30th and 70th percentiles (which constitute the interpercentile range [IPR]) were calculated. The median score was used to determine the level of agreement: a median of 1–3 indicated that the panel disagreed with the statement, 4–6 indicated that the panel were uncertain, and 7–9 indicated that the panel agreed with the statement. The IPR was used to calculate the IPR adjusted for symmetry (IPRAS) using the formula:  $IPRAS = 2.35 + (\text{asymmetry index [AI]} \times 1.5)$ , where the AI is defined as the absolute difference between the central point of the IPR and 5 (ie, the central point on the 1–9 scale). If the IPR was less than the IPRAS, this indicated that there was no extreme dispersion of scores (ie, there was “consensus”).

### 3. Results

There were 21 panel members, all of whom participated in both Delphi rounds. In round 1, there was consensus for 80% (28/35) of the statements, which increased to 92% (33/36) after round 2. One statement was added during round 1 (Table 1, between statements 20 and 21). Fourteen statements were rephrased to improve clarity and precision during the discussion before the scoring in round 2. Despite

rephrasing, consensus was not reached for three statements (Table 1, statements 8, 10, and 35).

Statements included in the questionnaire, grouped into thematic topics, with the corresponding median scores and consensus results are reported in Table 1. In brief, the statements covered appropriate indications for PSMA PET/CT (statements 1–5; consensus reached for 5/5 statements); the role of PSMA imaging with respect to [<sup>177</sup>Lu]Lu-PSMA-based therapy (statements 6–7; consensus reached for 2/2 statements); the best tracer for performing PSMA PET/CT (statements 8–19; consensus reached for 9/11 statements; no voting was conducted for statement 19); the methodology for diagnostic and therapeutic PSMA use (statements 20–22; consensus reached for 4/4 statements); patient selection for [<sup>177</sup>Lu]Lu-PSMA therapy (statements 23–27; consensus reached for 5/5 statements); PET imaging in patients with PCa who are candidates for [<sup>177</sup>Lu]Lu-PSMA therapy (statements 28–31; consensus reached for 4/4 statements); and PET imaging in patients with PCa who are treated with [<sup>177</sup>Lu]Lu-PSMA (statements 32–36; consensus reached for 4/5 statements).

## 4. Discussion

### 4.1. Appropriate indications for PSMA PET/CT (statements 1–5)

Evidence regarding the value of PSMA PET/CT in terms of long-term outcomes and effects on clinical decision-making is not robust. During the panel discussion on the use of PSMA PET/CT, it was confirmed that such a novel approach should only be used if a change in clinical management is expected from the results, as already emphasised in the EAU guidelines [1]. For most statements, use of the words “in the majority of patients” rather than “every” or “any” was preferred simply because it is very unlikely that any statement could apply to all patients affected by PCa. This was the reason for the rephrasing of many statements (Table 1).

Significant concerns were raised regarding the management of patients with positive PSMA PET/CT and negative conventional imaging results, especially at initial staging, as it remains unclear if use of results from a more sensitive imaging tool to modify treatment has a demonstrable impact on meaningful outcomes, including survival. European Society for Medical Oncology guidelines suggest that patients with localised PCa according to conventional imaging should not be denied radical local treatment solely because metastatic lesions are identified via novel imaging techniques [10]. Nonetheless, there was clear agreement on the use of PSMA PET/CT in staging all high-risk patients and selected patients with unfavourable intermediate-risk disease. As already stated in the EAU guidelines, the panel strongly endorsed the use of PSMA PET/CT in patients with BCR.

Our results showed a consensus regarding the uncertainty of using PSMA PET/CT in patients with nonmetastatic castration-resistant PCa (nmCRPC), which may be because of several factors, including patient heterogeneity, lack of long-term data regarding the benefit of metastasis-directed therapy in CRPC (as a result of detecting distant

**Table 1 – Proposed statements and Delphi voting results regarding the role of PSMA-based imaging and therapy in prostate cancer <sup>a</sup>**

No.	Round 1 (original phrasing)	Round 1 (rephrased)	Round 1		Round 2	
			MS	CA	MS	CA
1	PSMA PET/CT should be performed in any high-risk PCa patient at staging		8	Yes		
2	PSMA PET/CT should be performed in some intermediate-risk PCa patients at staging	PSMA PET/CT should be <b>considered in unfavourable</b> intermediate-risk PCa patients at staging	7	Yes	8	Yes
3	PSMA PET/CT should be performed in any BCR patients	PSMA PET/CT should be performed in <b>the majority of</b> BCR patients	9	Yes	9	Yes
4	PSMA PET/CT should be performed in nmCRPC patients	PSMA PET/CT should be performed in <b>the majority of</b> nmCRPC patients	5.5	Yes	5	Yes
5	PSMA PET/CT should be performed in any mCRPC patient to evaluate disease progression	PSMA PET/CT should be performed in <b>the majority of</b> mCRPC patients to evaluate disease progression	3	No	3	Yes
6	PSMA PET/CT should be performed in any candidate for [ <sup>177</sup> Lu]Lu-PSMA		9	Yes		
7	PSMA-PET/CT should be performed in evaluation of response to [ <sup>177</sup> Lu]Lu-PSMA		7	Yes		
8	All PSMA tracers are equivalent for diagnostic purposes	All PSMA <b>PET</b> tracers are equivalent for diagnostic purposes ( <b>staging/BCR</b> )	4	No	4	No
9	PSMA tracers labelled with F-18 and Ga-68 are preferable for PET		8	Yes		
10	Data from trials with PSMA tracers can be extrapolated to any other tracers	Data from trials with PSMA <b>PET</b> tracers can be extrapolated to any other <b>PSMA PET</b> tracers <b>for diagnostic purposes</b>	3	No	3.5	No
11	All PSMA tracers are equivalent if PET is performed for selecting candidates for [ <sup>177</sup> Lu]Lu-PSMA		8	Yes		
12	The best PSMA PET tracer is [ <sup>68</sup> Ga]Ga-PSMA-11		8	Yes		
13	The best PSMA PET tracer is [ <sup>68</sup> Ga]Ga-PSMA I&T		5	Yes		
14	The best PSMA PET tracer is [ <sup>68</sup> Ga]Ga-PSMA R2		3.5	Yes		
15	The best PSMA PET tracer is [ <sup>18</sup> F]DCFPyL		7	Yes		
16	The best PSMA PET tracer is [ <sup>18</sup> F]PSMA-1007		4.5	Yes		
17	The best PSMA PET tracer is [ <sup>18</sup> F]rh PSMA 7		5	Yes		
18	The best PSMA PET tracer is [ <sup>64</sup> Cu]Cu-PSMA I&T		3	Yes		
19	If you feel another PSMA PET tracer not already listed above is best, please type your answer in here		NA	NA		
20	PSMA PET/CT should be performed and reported according to procedural guidelines		9	Yes		
New	–	<b>[<sup>177</sup>Lu]Lu-PSMA therapy should be performed according to guidelines</b>			9	Yes
21	PSMA PET/MRI is at least equivalent to PET/CT and thus is always acceptable	PSMA PET/MRI is equivalent to PET/CT and thus is acceptable <b>in the majority of cases</b>	8	Yes	8	Yes
22	Fully diagnostic CT with contrast media is mandatory as part of PSMA PET/CT	Fully diagnostic CT with contrast media is <b>recommended</b> as part of PSMA PET/CT <b>if not performed previously</b>	4.5	No	8	Yes
23	Only mCRPC patients can be considered for [ <sup>177</sup> Lu]Lu-PSMA	Only mCRPC patients can be considered for [ <sup>177</sup> Lu]Lu-PSMA <b>outside of clinical trials</b>	7	No	8.5	Yes
24	mHSPC with low-volume metastases can be considered for [ <sup>177</sup> Lu]Lu-PSMA	mHSPC with low-volume metastases can be considered for [ <sup>177</sup> Lu]Lu-PSMA <b>outside of clinical trials</b>	3	No	2	Yes
25	mHSPC with high-volume metastases can be considered for [ <sup>177</sup> Lu]Lu-PSMA	mHSPC with high-volume metastases can be considered for [ <sup>177</sup> Lu]Lu-PSMA <b>outside of clinical trials</b>	3.5	No	2	Yes
26	[ <sup>177</sup> Lu]Lu-PSMA outside of its approved indication should only be performed within a clinical trial		9	Yes		
27	Patients with parenchymal metastases (liver, lung) are <b>not suitable</b> for [ <sup>177</sup> Lu]Lu-PSMA	Patients with parenchymal metastases (liver, lung) are <b>suitable</b> for [ <sup>177</sup> Lu]Lu-PSMA	3	Yes	8	Yes
28	PSMA PET/CT should be performed in any candidate for [ <sup>177</sup> Lu]Lu-PSMA		9	Yes		
29	[ <sup>18</sup> F]FDG PET/CT should be performed in any candidate for [ <sup>177</sup> Lu]Lu-PSMA	[ <sup>18</sup> F]FDG PET/CT should be performed in any candidate for [ <sup>177</sup> Lu]Lu-PSMA	4.5	Yes	4	Yes
30	Choline/fluciclovine PET-CT have no role to select candidates for [ <sup>177</sup> Lu]Lu-PSMA		8.5	Yes		
31	No PET/CT scan is strictly mandatory to select patients to be treated with [ <sup>177</sup> Lu]Lu-PSMA	<b>Demonstration of PSMA expression by imaging is mandatory</b> to be treated with [ <sup>177</sup> Lu]Lu-PSMA	1	Yes	9	Yes
32	PSMA PET/CT should be performed after every cycle of [ <sup>177</sup> Lu]Lu-PSMA		1.5	Yes		
33	PSMA PET/CT should be performed only at the end of [ <sup>177</sup> Lu]Lu-PSMA therapy		6	Yes		
34	FDG PET/CT should be performed at the end of [ <sup>177</sup> Lu]Lu-PSMA therapy		2	Yes		
35	PET/CT with any tracer should not be performed to monitor response to [ <sup>177</sup> Lu]Lu-PSMA therapy	<b>PSMA PET/CT is necessary</b> to monitor <b>patients during follow-up after [<sup>177</sup>Lu]Lu-PSMA</b>	5	Yes	5	No
36	[ <sup>18</sup> F]FDG PET/CT should be performed after every cycle of [ <sup>177</sup> Lu]Lu-PSMA therapy		1	Yes		

BCR = biochemical recurrence; CA = consensus achieved; CRPC = castration-resistant prostate cancer; CT = computed tomography; FDG = fluorodeoxyglucose; HSPC = hormone-sensitive prostate cancer; m, metastatic; MS = median score (1–3 = disagreement, 4–6 = uncertainty, 7–9 = agreement); nm = nonmetastatic; PCa, prostate cancer; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

<sup>a</sup> Text in red indicates changes to the original proposed statement.



lesions via PSMA PET/CT), and a lack of data on appropriate sequencing of treatment.

Finally, there was a consensus against the systematic use of PSMA PET/CT to evaluate disease progression in patients with confirmed metastatic CRPC (mCRPC) based on a lack of data, possible lack of cost-effectiveness, and limited PSMA PET/CT availability in some countries.

#### 4.2. *The role of PSMA imaging with respect to [<sup>177</sup>Lu]Lu-PSMA therapy (statements 6–7)*

There was consensus regarding the need for PSMA PET/CT before considering patients as candidates for [<sup>177</sup>Lu]Lu-PSMA therapy (Table 1, statements 6 and 28–31) [11]. However, PSMA imaging is not perfect for selecting patients for [<sup>177</sup>Lu]Lu-PSMA treatment, as PSMA may be expressed but not detected; access to PSMA PET/CT may also be limited in some countries worldwide. Despite this, the consensus in favour of PSMA PET/CT use was strong.

Regarding PET/CT imaging (Table 1, statement 6), although PET tracers are used almost universally for imaging, the panel members noted that in exceptional circumstance (ie, when logistical issues may prevent the use of PET/CT) imaging with technetium-99m-labelled PSMA could be considered.

It was agreed that PSMA-based imaging should be used to evaluate the response to [<sup>177</sup>Lu]Lu-PSMA-based therapy. The use of lutetium-177 post-therapy imaging with single-photon emission computed tomography (SPECT)/CT was also suggested as an adjunct or potential alternative, which would permit dosimetry calculations [12].

#### 4.3. *The best tracer for PSMA PET/CT (statements 8–19)*

The choice of PSMA tracer to use in PET imaging depends on various factors, including diagnostic performance, logistics, regulatory approval, availability, and cost. Therefore, ranking of tracers was not possible; rather, the goal was to simply provide guidance regarding when tracers might be beneficial for clinical use. Furthermore, the list of tracers was not exhaustive; only those with relevant published data were included in the Delphi voting.

Our results showed a clear preference for the use of gallium-68- and fluorine-18-labelled radiotracers, particularly [<sup>68</sup>Ga]Ga-PSMA-11 and [<sup>18</sup>F]DCFPyL. However, for several statements a relevant number of panel members ( $n = 5, 6, 4, 6,$  and  $5$  for statements 13, 14, 15, 17, and 18, respectively) noted that they were unable to assign a score owing to the very limited data on these radiopharmaceuticals. It is worth noting that careful choice of the radiopharmaceutical and the aforementioned preferences were significant when considering a tracer for diagnostic purposes in potentially curative scenarios, whereas there was agreement on the equivalence between tracers for imaging undertaken to select candidates for [<sup>177</sup>Lu]Lu-PSMA therapy.

#### 4.4. *Methodology to use for diagnostic PSMA imaging (statements 20–22)*

As expected, there was strong agreement regarding the need to follow procedural guidelines for performing and reporting PSMA PET/CT.

PET/magnetic resonance imaging (MRI) has much lower availability worldwide in comparison to PET/CT, mainly because of costs and other limitations. However, the two imaging methods were considered equivalent [13] despite some acknowledged differences, such as for evaluation of the lungs and liver and for local staging [14].

After the second Delphi round there was agreement regarding the need to perform full diagnostic CT with intravenous contrast as part of the PET/CT examination, if not performed previously. Unsurprisingly, this statement was delicate and required careful articulation as it is influenced by multiple factors, including regulatory issues (in many countries, two different specialists are required to co-sign the imaging examination report), patient workflow (in many cases, a diagnostic CT would have been performed immediately before the referral for PET/CT), reimbursement issues, and other factors. Nevertheless, the panel reached a clear consensus on the usefulness of diagnostic contrast-enhanced PET/CT over low-dose non-enhanced PET/CT, if not performed previously.

#### 4.5. *Selection of patients for [<sup>177</sup>Lu]Lu-PSMA therapy (statements 23–27)*

All panel members emphasised that the topic of patient selection must be considered with particular care since it is related to approval registrations, which are changing rapidly and are different around the world. The theranostics concept was strongly endorsed in statement 26.

There was a strong consensus that, outside of clinical trials, only patients with mCRPC can be considered for [<sup>177</sup>Lu]Lu-PSMA therapy since this is the only setting for which [<sup>177</sup>Lu]Lu-PSMA therapy is supported by level 1 evidence after initial hormonal therapy and after taxane use. Therefore, it was agreed that patients with metastatic hormone-sensitive PCa (mHSPC), with either low-volume or high-volume metastases, should not be considered for [<sup>177</sup>Lu]Lu-PSMA therapy outside of a clinical trial.

The VISION trial reported a lower rate of success in patients with liver lesions [6]; however, there was agreement that patients with PCa and parenchymal lesions who are suitable for [<sup>177</sup>Lu]Lu-PSMA therapy should not be excluded from treatment since good results have been observed.

#### 4.6. *PET imaging in patients with PCa who are candidates for [<sup>177</sup>Lu]Lu-PSMA therapy (statements 28–31)*

There was a clear consensus that PSMA PET/CT must be performed in every patient who is a candidate for [<sup>177</sup>Lu]Lu-PSMA therapy, whereas PET/CT with [<sup>18</sup>F]F-choline [15] or [<sup>18</sup>F]F-fluciclovine has no role for this indication.

There was also consensus regarding the uncertain role of [<sup>18</sup>F]FDG PET/CT, which has been suggested in some trials (mainly those carried out in Australia [5]) but not used in others (including the VISION trial, in which CT with media contrast was used in addition to PSMA PET/CT [6]). While it may be desirable to develop a strategy to better select patients who will benefit from [<sup>177</sup>Lu]Lu-PSMA therapy, the added value of [<sup>18</sup>F]FDG imaging, which is associated with greater costs, radiation exposure, and patient discom-

fort, is unclear. There is also a possibility that such a strategy could inadvertently exclude some patients who might derive clinical benefit from [ $^{177}\text{Lu}$ ]Lu-PSMA therapy.

#### 4.7. PET imaging in patients with PCa treated with [ $^{177}\text{Lu}$ ]Lu-PSMA (statements 32–36)

The panel members agreed on the usefulness of dosimetric evaluation, eventually performed via SPECT/CT, although this is not strictly mandatory for patient selection before and during therapy. There was a consensus against performing PSMA PET/CT after every course of therapy and against [ $^{18}\text{F}$ ]FDG PET/CT after completion of treatment. There was also consensus regarding the uncertain role of performing additional PSMA PET/CT at the end of planned therapy. It is worth noting that there is a minor discrepancy between statements 33 and 7 regarding the use of PSMA PET/CT imaging to evaluate response to [ $^{177}\text{Lu}$ ]Lu-PSMA therapy. Unlike statement 33, which stipulates that PSMA PET/CT should be performed only at the end of [ $^{177}\text{Lu}$ ]Lu-PSMA therapy, statement 7 does not include a specific timing for imaging when evaluating the response, which is probably why consensus was achieved for this statement (in contrast to statement 33, which was scored as uncertain), as it is currently unclear when the response evaluation scan should be performed. Furthermore, a post-treatment scan could have different scopes or objectives: in cases where a PSMA PET/CT is performed when considering further PSMA therapy, this would be recommended (as per statement 28).

#### 4.8. Procedure to use for [ $^{177}\text{Lu}$ ]Lu-PSMA therapy

As with PSMA PET imaging, there was strong agreement regarding the need to follow procedural guidelines for performing [ $^{177}\text{Lu}$ ]Lu-PSMA therapy.

#### 4.9. Limitations

A full systematic review of the evidence base was not performed before the consensus process, so there is a possibility that some important literature was missed. However, given that this clinical area is relatively novel, with only a limited number of publications reported to date, and that the panel members are experts in this area, it is unlikely that any clinically relevant literature was missed.

A criticism of the RAND consensus methodology is that as the 30th and 70th percentiles are used to calculate consensus, outliers (ie, divergent views) may be dismissed. However, panel members were shown the anonymised scores given by all other panel members, and they all had an opportunity to voice their opinion during the 1-d meeting. Thus, in cases where divergent views existed, there was an opportunity for these to be considered.

## 5. Conclusions

The introduction of radiolabelled PSMA ligands has the potential to have an important impact on the management of patients with PCa, and the volume of data on PSMA-based imaging and therapy is growing rapidly. An increasing num-

ber of trials are being completed and reported, making the PSMA theranostic landscape very active.

For PSMA-based imaging, the major challenge is to demonstrate the real impact of this tool on major clinical outcomes such as overall and progression-free survival, and its potential use for successful selection of patients for life-prolonging systemic or local therapies. For PSMA therapy, major efforts are directed at optimal patient selection and sequencing, and at extending the current indication to earlier stages of PCa.

The EAU and EANM endorse and promote high quality standards in performing diagnostic and therapeutic procedures. In the absence of clinical trials clearly answering open research questions, high-level consensus events (including the Advanced Prostate Cancer Consensus Conference) are very important in providing expert opinion. With respect to the questions raised in this consensus meeting, our results provide indications and suggestions regarding the appropriate use of PSMA imaging and therapy in various clinical situations.

**Author contributions:** Stefano Fanti and Anders Bjartell had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Bjartell, Fanti, MacLennan.

*Acquisition of data:* MacLennan.

*Analysis and interpretation of data:* All authors.

*Drafting of the manuscript:* Bjartell, Fanti, MacLennan.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* MacLennan.

*Obtaining funding:* Bjartell, Witjes.

*Administrative, technical, or material support:* Witjes, MacLennan.

*Supervision:* Fanti, Bjartell.

*Other:* None.

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## References

- [1] Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2022. <https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2022.pdf>.
- [2] Hofman MS, Lawrentschuk N, Francis RJ, et al. 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. *Lancet* 2020;395:1208–16.
- [3] Fendler WP, Eiber M, Beheshti M, et al. <sup>68</sup>Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging* 2017;44:1014–24.
- [4] Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating <sup>177</sup>Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med* 2017;58:85–90.
- [5] Hofman MS, Emmett L, Sandhu S, et al. [<sup>177</sup>Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet* 2021;397:797–804.
- [6] Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021;385:1091–103.
- [7] Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with <sup>177</sup>Lu-labelled PSMA-ligands (<sup>177</sup>Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging* 2019;46:2536–44.
- [8] Vogl UM, Beer TM, Davis ID, et al. Lack of consensus identifies important areas for future clinical research: Advanced Prostate Cancer Consensus Conference (APCCC) 2019 findings. *Eur J Cancer* 2022;160:24–60.
- [9] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
- [10] Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:1119–34.
- [11] Herrmann K, Kraus BJ, Hadaschik B, et al. Nuclear medicine theranostics comes of age. *Lancet Oncol* 2021;22:1497–8.
- [12] Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of <sup>177</sup>Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med* 2019;60:517–23.
- [13] Kaufmann S, Kruck S, Gatidis S, et al. Simultaneous whole-body PET/MRI with integrated multiparametric MRI for primary staging of high-risk prostate cancer. *World J Urol* 2020;38:2513–21.
- [14] Martin O, Schaarschmidt BM, Kirchner J, et al. PET/MRI versus PET/CT for whole-body staging: results from a single-center observational study on 1,003 sequential examinations. *J Nucl Med* 2020;61:1131–6.
- [15] Schwenck J, Rempp H, Reischl G, et al. Comparison of <sup>68</sup>Ga-labelled PSMA-11 and <sup>11</sup>C-choline in the detection of prostate cancer metastases by PET/CT. *Eur J Nucl Med Mol Imaging* 2017;44:92–101.