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Theranostics for prostate cancer: A Canadian multidisciplinary expert report

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Appendix available at *cuaj.ca*

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INTRODUCTION

Prostate-specific membrane antigen (PSMA)-targeted imaging and therapy (theranostics) has significantly altered the management of advanced prostate cancer. In the proPSMA trial, PSMA positron emission tomography/computed tomography (PET/CT) imaging demonstrated superior accuracy compared with conventional imaging for staging high-risk prostate cancer and more frequently changed management.[1] In metastatic castration-resistant prostate cancer (mCRPC), lutetium-177-PSMA-617 (^{177}Lu-PSMA-617) improved radiographic progression-free survival (rPFS) and overall survival (OS) in the phase 3 VISION trial in patients previously treated with at least one androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy.[2] The PSMAfore trial demonstrated improved rPFS in taxane-naive patients following progression on an ARPI.[3] More recently, PSMAddition demonstrated improvement in rPFS in patients with metastatic castration-sensitive prostate cancer (mCSPC) when added to androgen deprivation plus ARPI therapy.[4]

Despite expanding evidence, uncertainty remains regarding the optimal use of theranostics in routine practice. A substantial proportion of the evidence guiding contemporary prostate cancer management was generated using conventional imaging modalities, creating challenges, as PSMA PET/CT detects disease that would previously have been occult. This stage migration complicates the application of historical trial data to patients staged with modern imaging techniques. The 2024 Advanced Prostate Cancer Consensus Conference (APCCC) highlighted areas of ongoing uncertainty and disagreement, including the interpretation of equivocal or discordant PSMA PET/CT findings, the implications of negative pelvic nodal imaging for salvage treatment decisions, and the role of PSMA PET/CT in patients with oligometastatic disease.[5] In addition, among clinicians there is a lack of familiarity with the indications for and interpretation of PSMA PET/CT imaging.

To address these uncertainties, a Canadian multidisciplinary panel with expertise in urologic oncology, medical oncology, radiation oncology, and nuclear medicine was convened to develop evidence- and expert-informed consensus recommendations for theranostics in prostate cancer. The objectives of this expert report were to: 1) identify appropriate scenarios for PSMA PET/CT imaging in prostate cancer; 2) develop best practices for patient management in the setting of novel imaging findings; and 3) provide guidance on the use of ^{177}Lu-PSMA-617 and related monitoring strategies across the disease course.

METHODS

This expert report was developed using a structured, modified Delphi consensus process conducted in accordance with the Canadian Urological Association Expert Report development principles. The methodology was designed to systematically refine and prioritize

KEY MESSAGES

- PSMA PET/CT should be used in high-risk or very high-risk localized prostate cancer, biochemical recurrence, and oligoprogression, particularly when findings are expected to change management.
- A negative PSMA PET/CT scan should not be used to omit otherwise indicated prostate bed or pelvic nodal treatment.
- A solitary PSMA-avid lesion without an anatomic or clinicopathologic correlate should not automatically define metastatic disease.
- Equivocal PSMA PET/CT findings require risk-adapted interpretation, with attention to lesion location, uptake pattern, clinical risk factors, tracer-specific pitfalls, and common benign mimics, such as rib fractures, degenerative changes, trauma, ganglia, and ureteric activity.
- ^{177}Lu-PSMA-617 for advanced prostate cancer should be guided by multidisciplinary decision-making, particularly when sequencing with ^{223}Ra or treating patients with impaired bone marrow reserve, renal dysfunction, or symptomatic metastases.
- Response assessment should integrate clinical response/progression, PSA testing, and imaging, including molecular imaging with PSMA PET/CT and/or post-therapy ^{177}Lu-PSMA SPECT/CT, in addition to contrast-enhanced CT of the thorax, abdomen, and pelvis.

clinically relevant statements informed by contemporary evidence and expert opinion.

The co-leads (AKL, MS, RR) developed the initial set of clinical questions based on key areas of uncertainty and controversy identified in the 2024 APCCC report.[5] Additional questions were developed with the co-leads based on clinical expertise, and most items were redrafted to reflect real-world clinical decision points within the Canadian healthcare system and areas where guidance would be most clinically relevant. The final question set addressed diagnostic and therapeutic issues relevant to contemporary prostate cancer management.

Draft questions were circulated electronically to the multidisciplinary panel consisting of three urologic oncologists, six medical oncologists, two radiation oncologists, and six nuclear medicine specialists to obtain structured feedback before the in-person meeting. Panelists were asked to assess clarity and wording, and to indicate whether individual questions should be retained, edited, or removed. They were also invited to suggest modifications, identify ambiguities, and propose additional content where relevant. Responses were collated and reviewed by the co-leads, and the question set was revised to improve clarity, reduce redundancy, and align with the intended clinical scope before presentation at the consensus meeting.

In addition, the co-leads developed a subset of 15 questions focused specifically on PSMA PET/CT findings to be addressed by nuclear medicine specialists. These questions were circulated separately to the six nuclear medicine specialists on the panel and were voted on prior to the consensus meeting. The voting results were then presented and discussed at the meeting.

A consensus meeting was conducted in person, with virtual participation available for panelists who were unable to attend physically. Two panel members (one urologic oncologist and one medical oncologist) provided feedback during question development but did not attend the meeting and did not participate in voting. Each question was presented individually, followed by open discussion to clarify its intent, scope, and clinical applicability. Unless otherwise specified, panelists were instructed to respond assuming unrestricted access to PSMA PET/CT imaging and ^{177}Lu-PSMA-617, such that recommendations reflected the panel's assessment of best clinical practice rather than current resource availability.

After discussion, panelists participated in anonymous voting, and the aggregated results were displayed to the group. Revoting was performed for selected questions following in-person discussion and when clarification of the question language was needed to remove ambiguity and more clearly reflect the intention of the clinical scenario. Consensus thresholds were predefined as ≥80% for consensus, 65–79% for near consensus, and <65% for lack of consensus. Consensus was calculated as the percentage of panelists selecting a given response among those who cast a vote. Panelists who abstained were not included in the calculation.

Following the meeting, the co-leads reviewed both the quantitative voting results and the qualitative feedback generated during discussion. Based on panel input, related questions were merged where appropriate, overlapping concepts were consolidated, and the remaining questions were restructured into affirmative consensus statements. This iterative process resulted in a refined series of consensus statements grounded in contemporary evidence and multidisciplinary expert input.

Following review of the draft manuscript by the expert panel, one additional statement was developed in response to panel feedback. As this statement was introduced after completion of the formal consensus process, it was reviewed and approved by the project leads but was not voted on by the full panel.

RESULTS

The 17 panel members, along with their geographic locations and disciplines, are listed in Supplementary Table 1 (available at *cuaj.ca*). Consensus was achieved for 59% (26/44) of the clinical questions and for 87% (13/15) of the nuclear medicine subsection questions (Supplementary Tables 2, 3; available at *cuaj.ca*).

Following voting and discussion, the clinical questions that met predefined consensus criteria were subsequently reformulated as consensus statements; these are presented in Table 1. Figure 1 presents a summary of the consensus guidance on PSMA PET/CT use by disease stage.

High-risk localized disease

■ STATEMENT 1

Clinical staging for high-risk and very high-risk localized prostate cancer should be performed with PSMA PET/CT, preferably with magnetic resonance imaging (MRI) (consensus achieved: 87%).

PSMA PET/CT provides more accurate disease localization than conventional imaging. In the phase 3 proPSMA trial, PSMA PET/CT was compared with conventional imaging (CT and bone scanning) in 302 men with high-risk prostate cancer undergoing first-line staging before curative-intent surgery or radiotherapy.[1] PSMA PET/CT had 27% higher accuracy than conventional imaging (92% vs. 65%), with higher sensitivity and specificity, fewer equivocal findings, and lower radiation exposure. It also changed treatment intent or modality in 28% of patients, compared with 15% staged with conventional imaging. Subsequent meta-analyses confirmed superior detection of metastatic disease, including bone metastasis.[6,7]

In one head-to-head meta-analysis, pooled sensitivity and specificity were 0.98 and 0.97 for PSMA PET/CT for bone metastases, compared with 0.85 and 0.70 for bone scan.[7] Additional comparative data also suggest that PSMA PET/CT changes treatment strategy in a clinically relevant minority of patients and may improve detection of both nodal and distant disease beyond CT plus bone scan.[8]

Improved staging accuracy must still be interpreted cautiously. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) appropriate-use criteria and the European Association of Nuclear Medicine (EANM)/SNMMI guideline note that existing treatment paradigms and prognostic frameworks were built using conventional imaging, while more sensitive molecular imaging introduces stage migration without yet showing improved long-term outcomes.[9,10]

The Canadian prospective PATRON study is evaluating whether PSMA PET-guided treatment intensification improves oncologic outcomes; results of this study are eagerly awaited.[11] Accordingly, while PSMA PET/CT has substantially advanced prostate cancer imaging and influences management in high-risk localized disease, conventional imaging still retains a complementary role as a baseline reference for longitudinal comparison and in settings where access to PSMA PET/CT remains limited.

■ STATEMENT 2

In patients with high-risk or very high-risk localized prostate cancer (National Comprehensive Cancer Network [NCCN] definition) who are candidates for definitive local therapy and have negative conventional imaging, PSMA PET/CT should be performed in all patients if feasible (consensus achieved: 86%).

The SNMMI appropriate-use criteria specifically state that PSMA PET/CT is appropriate in newly diagnosed unfavorable intermediate-, high-, and very high-risk prostate cancer with negative, equivocal, or oligometastatic conventional imaging, emphasizing that PSMA PET/CT may reveal sites of disease not identified on standard staging and may meaningfully influence clinical decision-making.[9] The joint EANM/SNMMI guideline similarly supports PSMA PET/CT for initial staging in patients with high-risk features.[10]

In practical terms, the value of PSMA PET/CT in this setting would be when management is uncertain, particularly when radical prostatectomy is under con-

Table 1. Statements that achieved consensus (≥80% agreement)

Disease stage	No.	Statement	Agreement n/N (%)
High-risk localized disease	1	Clinical staging for high-risk and very high-risk localized prostate cancer should be performed with PSMA PET/CT, preferably with MRI.	13/15 (87%)
	2	In patients with high-risk or very high-risk localized prostate cancer (NCCN definition) who are candidates for definitive local therapy and have negative conventional imaging, PSMA PET/CT should be performed in all patients if feasible.	12/14 (86%)
	3	In patients with high-risk or very high-risk localized prostate cancer and a single PSMA-avid bone lesion on PET/CT without a correlate on the CT component, correlative conventional imaging should be performed as the next investigation.	13/15 (87%)
	4	The planned approach to management of pelvic lymph nodes (lymph node dissection/radiotherapy to nodes) should not be altered based on a negative PSMA PET/CT (N0 M0) in patients with unfavorable intermediate-risk, high-risk, or very high-risk localized prostate cancer (NCCN definition) undergoing surgery or radiotherapy with curative intent.	11/11 (100%)
Biochemically recurrent disease	5	In patients with biochemical recurrence after radical prostatectomy, a negative postoperative PSMA PET/CT should not preclude salvage radiotherapy.	Post-consensus; not formally voted on
	6	In patients with PSA persistence or biochemical failure following radical prostatectomy (pN0 on extended or limited PLND, with or without high-risk factors) undergoing salvage radiotherapy, a negative postoperative PSMA PET/CT should not determine the decision to include pelvic lymph nodes in the radiotherapy treatment volume.	11/11 (100%)
	7	In patients with biochemical recurrence following primary radiotherapy, including those treated with radiotherapy plus systemic therapy (ADT ± ARPI), PSMA PET/CT should be performed as soon as biochemical recurrence is established according to the Phoenix definition (PSA ≥2.0 ng/mL above nadir), regardless of baseline risk features.	11/11 (100%)
Oligometastatic disease	8	In patients with high-risk or very high-risk prostate cancer being considered for radical therapy and found to have oligometastatic disease (1–5 lesions) on conventional imaging, PSMA PET/CT should be performed in selected patients who are candidates for metastasis-directed and/or primary tumor-directed therapy.	12/15 (80%)
Advanced disease	9	In patients with mCSPC receiving ADT plus an ARPI who develop biochemical progression without polymetastatic disease on conventional imaging, PSMA PET/CT should be performed when metastasis-directed therapy is considered.	12/14 (86%)
	10	In patients whose disease progresses on ADT plus ARPI and post-chemotherapy (triplet or sequential therapy), PSMA PET/CT should be performed when ^{177}Lu-PSMA-617 is considered.	14/14 (100%)
	11	Currently, ^{177}Lu-PSMA-617 is appropriate for patients with mCSPC only in the context of a clinical trial.	12/13 (92%)
	12	The use of ^{223}Ra following prior treatment with ^{177}Lu-PSMA-617 is feasible in appropriately selected patients with bone-dominant or bone-only metastatic disease.	12/14 (86%)
	13	The use of ^{177}Lu-PSMA-617 following prior treatment with ^{223}Ra is feasible in appropriately selected patients.	12/14 (86%)
	14	Routine continuation or re-introduction of a prior ARPI in combination with ^{177}Lu-PSMA-617 is not generally recommended for most patients with mCRPC, but can be used in special circumstances.	9/11 (82%)

^{177}Lu: lutetium-177; ^{223}Ra: radium-223: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; CT: computed tomography; HRR: homologous recombination repair; eGFR: estimated glomerular filtration rate; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; MRI: magnetic resonance imaging; N0 M0: node negative metastasis negative; NCCN: National Comprehensive Cancer Network; PET: positron emission tomography; PLND: pelvic lymph node dissection; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; SPECT: single-photon emission computed tomography.

sideration and imaging results would shift treatment toward radiotherapy and/or systemic intensification. This concern is supported by real-world data showing that PSMA PET/CT staging is associated with higher use of androgen deprivation therapy (ADT) and ARPI and lower rates of prostatectomy, suggesting that PSMA findings are already influencing frontline treatment selection.[12]

Table 1 (cont'd). Statements that achieved consensus (≥80% agreement)

Disease stage	No.	Statement	Agreement n/N (%)
Advanced disease (cont'd)	15	In patients with mCRPC (without HRR alteration) whose disease progresses on or after an ARPI and docetaxel, who have impaired bone marrow function due to extensive PSMA-avid bone marrow/skeletal involvement, and in whom ^{177}Lu-PSMA-617 is being considered, proceed with ^{177}Lu-PSMA-617 with transfusion support as needed, with consideration for dose reduction as clinically appropriate.	10/10 (100%)
	16	Re-treatment with ^{177}Lu-PSMA-617 in eligible patients who have previously responded to 6 cycles should not be routinely recommended.	9/11 (82%)
	17	In patients with mCRPC and impaired renal function (eGFR 30–49 mL/min) and no correctable causes, ^{177}Lu-PSMA-617 can be administered when clinically indicated.	9/11 (82%)
	18	In patients with mCRPC and stable/chronic renal impairment (eGFR <30 mL/min) and no correctable causes, in whom ^{177}Lu-PSMA-617 is being considered, treatment may be reasonable in carefully selected patients, most commonly with reduced administered activity on an individualized basis, and with multidisciplinary decision-making.	9/11 (82%)
Monitoring on ^{177}Lu-PSMA-617	19	In patients receiving ^{177}Lu-PSMA-617, imaging to monitor for response during treatment in the absence of clinical progression is supported in the majority of patients using molecular imaging (PSMA PET/CT and/or post-therapy SPECT/CT) in addition to contrast-enhanced CT of the thorax, abdomen, and pelvis.	12/14 (86%)
	20	In patients demonstrating a significant PSA, clinical, and/or radiographic response after 2–3 cycles of ^{177}Lu-PSMA-617, completion of the planned 6 cycles is appropriate for the majority of patients.	12/14 (86%)
	21	In patients with mCRPC planned for ^{177}Lu-PSMA-617 who have symptomatic metastases, referral for palliative radiotherapy is appropriate.	13/13 (100%)

^{177}Lu: lutetium-177; ^{223}Ra: radium-223: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; CT: computed tomography; HRR: homologous recombination repair; eGFR: estimated glomerular filtration rate; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; MRI: magnetic resonance imaging; N0 M0: node negative metastasis negative; NCCN: National Comprehensive Cancer Network; PET: positron emission tomography; PLND: pelvic lymph node dissection; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; SPECT: single-photon emission computed tomography.

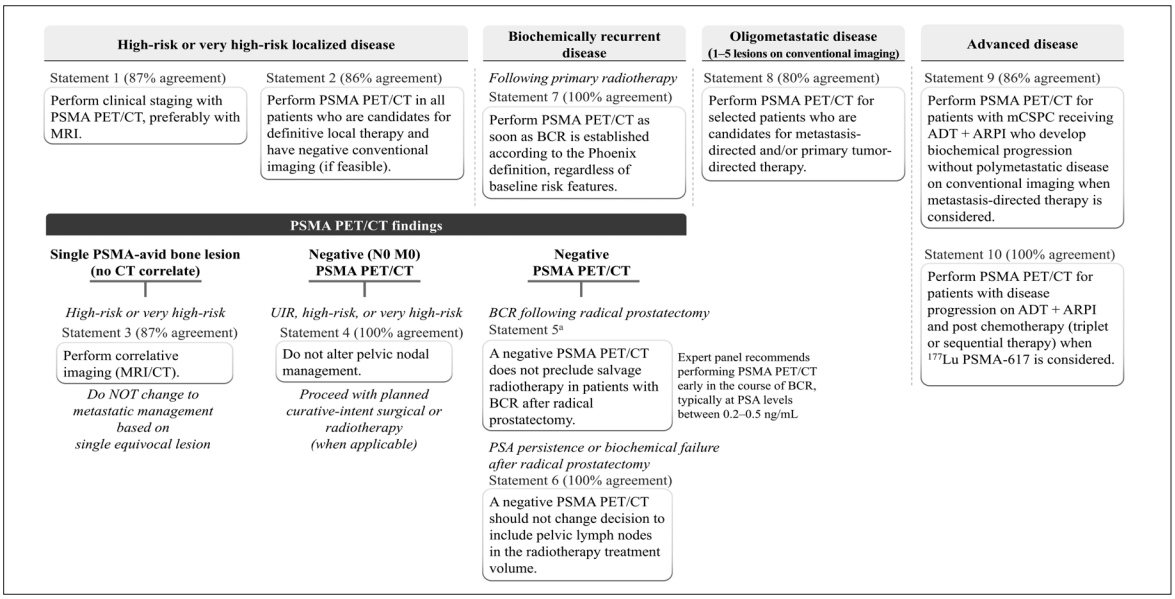

Figure 1. Consensus guidance on PSMA PET/CT use by disease stage. [a]Statement 5 was added post-consensus meeting following panel review and was not voted on by the full panel.
ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; BCR: biochemical recurrence; CT: computed tomography; MRI: magnetic resonance imaging; mCSPC: metastatic castration-sensitive prostate cancer; N0 M0: node negative metastasis negative; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; UIR: unfavorable intermediate-risk..

STATEMENT 3

In patients with high-risk or very high-risk localized prostate cancer and a single PSMA-avid bone lesion on PET/CT without a correlate on the CT component, correlative conventional imaging should be performed as the next investigation (consensus achieved: 87%).

In patients with high-risk localized or locally advanced prostate cancer, a solitary PSMA-avid bone lesion on PET/CT without a corresponding CT abnormality should prompt further evaluation with correlative conventional imaging rather than immediate classification as metastatic disease. Although PSMA PET/CT demonstrates high sensitivity for detecting bone metastases, focal uptake without a morphologic correlate remains a recognized limitation. False-positive and indeterminate lesions are occasionally observed, particularly in the ribs and pelvis.[13-15] In this setting, there is a risk of disease upstaging based on imaging alone.

Isolated PSMA-avid bone lesions should be interpreted with caution. The EANM/SNMMI procedure guideline recommends careful evaluation of indeterminate findings,[10] and the European Association of Urology (EAU) prostate cancer guidelines continue to support the use of conventional imaging modalities for staging in appropriate clinical settings.[16]

Tracer-related variability further contributes to diagnostic uncertainty, with higher rates of non-specific bone uptake reported for certain agents, particularly ^{18}F-PSMA-1007.[15] Standardized reporting systems, such as PSMA-RADS, reflect this uncertainty by classifying indeterminate bone lesions (PSMA-RADS-3B) as suspicious but not diagnostic of metastatic disease.[17] The Society of Prostate-specific Membrane Antigen Radiopharmaceuticals and Clinical Applications (SPARC) provides a recent PSMA PET/CT reporting and analysis consensus and recommends reporting imaging certainty in accordance with PSMA-RADS.[18]

Treatment should not be escalated based on a single equivocal lesion because there is no established benefit to treating patients as metastatic in the absence of confirmed metastases.[19] Targeted correlative imaging, with MRI or CT depending on lesion location, should be performed to further characterize the finding and guide management.[20] This approach balances the sensitivity of PSMA PET/CT with its known limitations and helps avoid inappropriate upstaging based on a single indeterminate lesion.

STATEMENT 4

The planned approach to management of pelvic lymph nodes (lymph node dissection/radiotherapy to nodes) should not be altered based on a negative PSMA PET/CT (N0 M0) in patients with unfavorable intermediate-risk, high-risk, or very high-risk localized prostate cancer (NCCN definition) undergoing surgery or radiotherapy with curative intent (consensus achieved: 100%).

PSMA PET/CT demonstrates high specificity but limited sensitivity for microscopic pelvic nodal metastases when compared with histopathology, with reported sensitivity of approximately 40%, despite specificity approaching 95%.[21,22] As a result, a negative PSMA PET/CT does not reliably exclude clinically meaningful occult nodal disease.

Pelvic lymph node dissection (PLND) remains the reference standard for pathologic nodal staging, and management decisions regarding PLND should continue to be based on established clinicopathologic risk stratification and validated nomograms rather than PSMA PET/CT findings alone.[16,23,24]

In patients with unfavorable intermediate-risk localized prostate cancer, the implications of a negative PSMA PET/CT differ by treatment modality. A negative PSMA PET/CT should not be used in isolation to omit PLND when surgery is otherwise indicated by baseline clinical risk. Pelvic nodal irradiation is not routinely recommended for this risk group, and its role remains less clearly established. The GETUG-01 trial did not demonstrate a significant OS or event-free survival benefit with pelvic nodal irradiation in the overall study population.[25] Early results from the phase 3 NRG/RTOG 0924 trial demonstrated no OS benefit with whole-pelvic radiotherapy compared with prostate-only radiotherapy in patients with unfavorable intermediate-risk or favorable high-risk prostate cancer, although biochemical failure rates were modestly reduced.[26]

Patients with high- and very high-risk localized prostate cancer have a higher baseline risk of occult nodal involvement. In this setting, using a negative PSMA PET/CT alone to exclude nodal management may lead to understaging and potential undertreatment. Randomized studies have suggested a benefit from pelvic nodal treatment in higher-risk populations. In NRG/RTOG 9413, whole-pelvic radiotherapy combined with neoadjuvant ADT improved PFS and biochemical control compared with prostate-only radiotherapy, despite no significant OS benefit and increased gastrointestinal toxicity.[27] Similarly, the phase 3 POP-RT trial demon-

strated that prophylactic pelvic irradiation with ADT significantly improved biochemical failure-free survival and disease-free survival compared with prostate-only radiotherapy in patients with node-negative high-risk or very high-risk disease, supporting consideration of pelvic nodal treatment in these patients.[28] Therefore, in patients with high-risk or very high-risk disease, a negative PSMA PET/CT should not justify omission of clinically indicated PLND or pelvic nodal radiotherapy.

Biochemically recurrent disease

■ STATEMENT 5

In patients with biochemical recurrence after radical prostatectomy, a negative postoperative PSMA PET/CT should not preclude salvage radiotherapy (added post-consensus meeting following panel review; not voted on by the full panel).

Biochemical recurrence develops in approximately 40% of patients following definitive treatment for prostate cancer, with most recurrences occurring within the first five years. After radical prostatectomy, biochemical recurrence is defined as a prostate-specific antigen (PSA) level ≥0.2 ng/mL measured at least six weeks after surgery. Prior to the introduction of PSMA PET/CT, salvage radiotherapy to the prostate bed was the standard treatment for biochemical recurrence, with conventional imaging generally omitted because of its poor sensitivity at low PSA levels.[29]

PSMA PET/CT has significantly improved the detection of recurrent disease, although its sensitivity remains highly dependent on PSA level. Detection rates are approximately 38% when PSA is <0.5 ng/mL, increasing to nearly 97% at PSA levels ≥5 ng/mL.[30] The Canadian PSMA-PET Registry for Recurrent Prostate Cancer (PREP) study similarly demonstrated increasing PSMA PET/CT positivity with rising PSA, reporting positive scans in approximately one-third of patients with PSA <0.2 ng/mL.[31] Additional predictors of a positive scan include higher Gleason score and a PSA doubling time of less than six months.

Although PSMA PET/CT detection rates improve as PSA rises, the likelihood of achieving durable disease control with salvage radiotherapy declines, particularly once PSA exceeds 0.5 ng/mL. Consequently, current expert consensus recommends performing PSMA PET/CT early in the course of BCR, typically at PSA levels between 0.2 and 0.5 ng/mL, when imaging can identify occult metastatic disease without compromising the opportunity for curative salvage treatment.

Importantly, a negative PSMA PET/CT should not be interpreted as the absence of local recurrence. At PSA levels where salvage radiotherapy remains potentially curative, approximately 40% of scans are negative because microscopic disease within the prostate bed often remains below the spatial resolution of current imaging. Patients with negative PSMA PET/CT who receive prostate bed salvage radiotherapy continue to achieve excellent outcomes, with the three-year freedom from progression (FFP) rate exceeding 80%.[32] Therefore, a negative PSMA PET/CT should not delay or exclude appropriately selected patients from receiving early salvage radiotherapy.

■ STATEMENT 6

In patients with PSA persistence or biochemical failure following radical prostatectomy (pN0 on extended or limited PLND, with or without high-risk factors) undergoing salvage radiotherapy, a negative postoperative PSMA PET/CT should not determine the decision to include pelvic lymph nodes in the radiotherapy treatment volume (consensus achieved: 100%).

While PSMA PET/CT has a high positive predictive value in patients with recurrent prostate cancer, false-negative findings remain possible, particularly for microscopic nodal disease, with potential causes including low or absent PSMA expression, limited lesion size, and proximity to urinary bladder activity.[10] Therefore, the absence of PSMA-avid pelvic lymph nodes should not be assumed to exclude occult nodal involvement.

The phase 3 NRG Oncology/RTOG 0534 (SPPORT) trial showed that adding salvage pelvic radiotherapy and short-term ADT to prostate bed radiotherapy improved the five-year rate of FFP to 87%, compared with 71% for prostate bed radiotherapy alone.[33] Guideline recommendations are consistent with these findings. For example, the joint American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (AUA/ASTRO/SUO) guideline advises that salvage prostate bed radiotherapy should not be withheld based on negative imaging.[34] Therefore, because small-volume residual or recurrent disease may remain undetectable after radical prostatectomy, along with the clinical benefit of salvage radiotherapy, imaging results should not override established principles, and a negative PSMA PET/CT does not justify omission of pelvic nodal irradiation when it is otherwise clinically indicated.

■ STATEMENT 7

In patients with biochemical recurrence following primary radiotherapy, including those treated with radiotherapy plus systemic therapy (ADT ± ARPI), PSMA PET/CT should be performed as soon as biochemical recurrence is established according to the Phoenix definition (PSA ≥2.0 ng/mL above nadir), regardless of baseline risk features (consensus achieved: 100%).

The Phoenix definition (PSA ≥2.0 ng/mL above nadir) remains the standard definition of biochemical recurrence in patients treated with primary radiotherapy, and provides a practical threshold for further investigation.[35]

At this PSA level, PSMA PET/CT has a high likelihood of localizing recurrent disease. Multiple studies have shown that PSMA PET/CT positivity increases with rising PSA, with reported detection rates approaching 95% at PSA levels ≥2.0 ng/mL.[36-39] In the Canadian PREP registry, 90% of patients meeting the Phoenix criteria for biochemical failure after primary radiotherapy had positive PSMA PET/CT findings;[31] however, the clinical utility of Phoenix is increasingly being questioned in the PSMA PET/CT era. Modern molecular imaging can detect recurrent disease at PSA levels well below the Phoenix threshold, enabling earlier risk stratification and salvage intervention.

The clinical value of PSMA PET/CT in this setting is to localize recurrence and distinguish local-only from regional or distant disease, thereby identifying patients who may still be candidates for salvage treatments (i.e., patients with pelvic failure).[16] Many studies have reported that prostate-only PET-positive disease is found in up to 60% of patients.[40,41] In patients with PSA >2 ng/mL, more than 50% could potentially benefit from salvage therapy.[41]

After primary radiotherapy, prostate biopsy is not routinely performed at biochemical recurrence and is generally reserved to confirm local recurrence when prostate-directed salvage therapy is being considered. In this context, PSMA PET/CT can be useful to localize recurrence and guide biopsy if indicated, and this approach is consistent with guideline recommendations supporting PSMA PET/CT imaging in patients fit for curative salvage treatment.[16] The need for correlative studies (biopsy or correlative MRI) could be considered on an individual basis, given the potential for f-lse positive PSMA uptake in the treated prostate.

Oligometastatic disease

■ STATEMENT 8

In patients with high-risk or very high-risk prostate cancer being considered for radical therapy and found to have oligometastatic disease (1–5 lesions) on conventional imaging, PSMA PET/CT should be performed in selected patients who are candidates for metastasis-directed and/or primary tumor-directed therapy (consensus achieved: 80%).

Conventional imaging may underestimate metastatic burden, with PSMA PET/CT identifying additional lesions in up to 67% of cases, and resulting in disease upstaging in approximately 20% of patients.[42] This stage migration has important therapeutic implications, as identification of more extensive disease may shift management away from finite metastasis-directed therapy (local treatment directed at individual metastatic lesions) and/or primary tumor-directed therapy toward broader systemic treatment without tumor-directed therapy. Accordingly, the SNMMI appropriate-use criteria endorse PSMA PET/CT in highrisk patients when imaging results are likely to inform management decisions.[9]

The de novo oligometastatic state may represent a distinct disease biology in which limited metastatic burden is amenable to localized treatment. Prospective randomized trials in the oligorecurrent setting (including STOMP, ORIOLE, and EXTEND) support the use of metastasis-directed therapy in carefully selected patients with low-volume metastatic disease.[43,44]

More recent phase 2 randomized evidence from PEACE V-STORM and RADIOSA have refined the optimal extent and intensity of treatment in the oligorecurrent setting. PEACE V-STORM demonstrated improved four-year metastasis-free survival with elective nodal radiotherapy (ENRT) plus six months of ADT compared with metastasis-directed therapy plus six months of ADT in patients with PET-detected pelvic nodal oligorecurrence (76% vs. 63%, respectively), while RADIOSA demonstrated that adding short-course ADT to stereotactic body radiotherapy (SBRT) improved clinical PFS compared with SBRT alone in oligorecurrent hormone-sensitive disease.[45,46]

The ongoing Canadian phase 3 PLATON trial is evaluating the addition of local ablative therapy to standard systemic therapy in de novo oligometastatic hormone-sensitive prostate cancer and will help clarify the role of metastasis-directed therapy in this population.[47] Given the heterogeneity of oligometastatic prostate cancer and the potential for imaging-driven changes

in therapeutic intent, treatment decisions in this setting should be guided by multidisciplinary evaluation.

Advanced disease

Figure 2 presents the consensus guidance on treatment sequencing with radium-223 (^{223}Ra), adjunctive treatment with palliative radiotherapy, specific patient populations, and monitoring and followup.

STATEMENT 9

In patients with mCSPC receiving ADT plus an ARPI who develop biochemical progression without polymetastatic disease on conventional imaging, PSMA PET/CT should be performed when metastasis-directed therapy is considered (consensus achieved: 86%).

Phase 2 studies have demonstrated a benefit of metastasis-directed therapy combined with ADT and an ARPI in patients with oligometastatic castration-resistant prostate cancer whose disease had progressed despite prior ADT.[48-50] The ARTO trial demonstrated improvements in biochemical response, biochemical PFS, and rPFS, while an unplanned survival analysis suggested

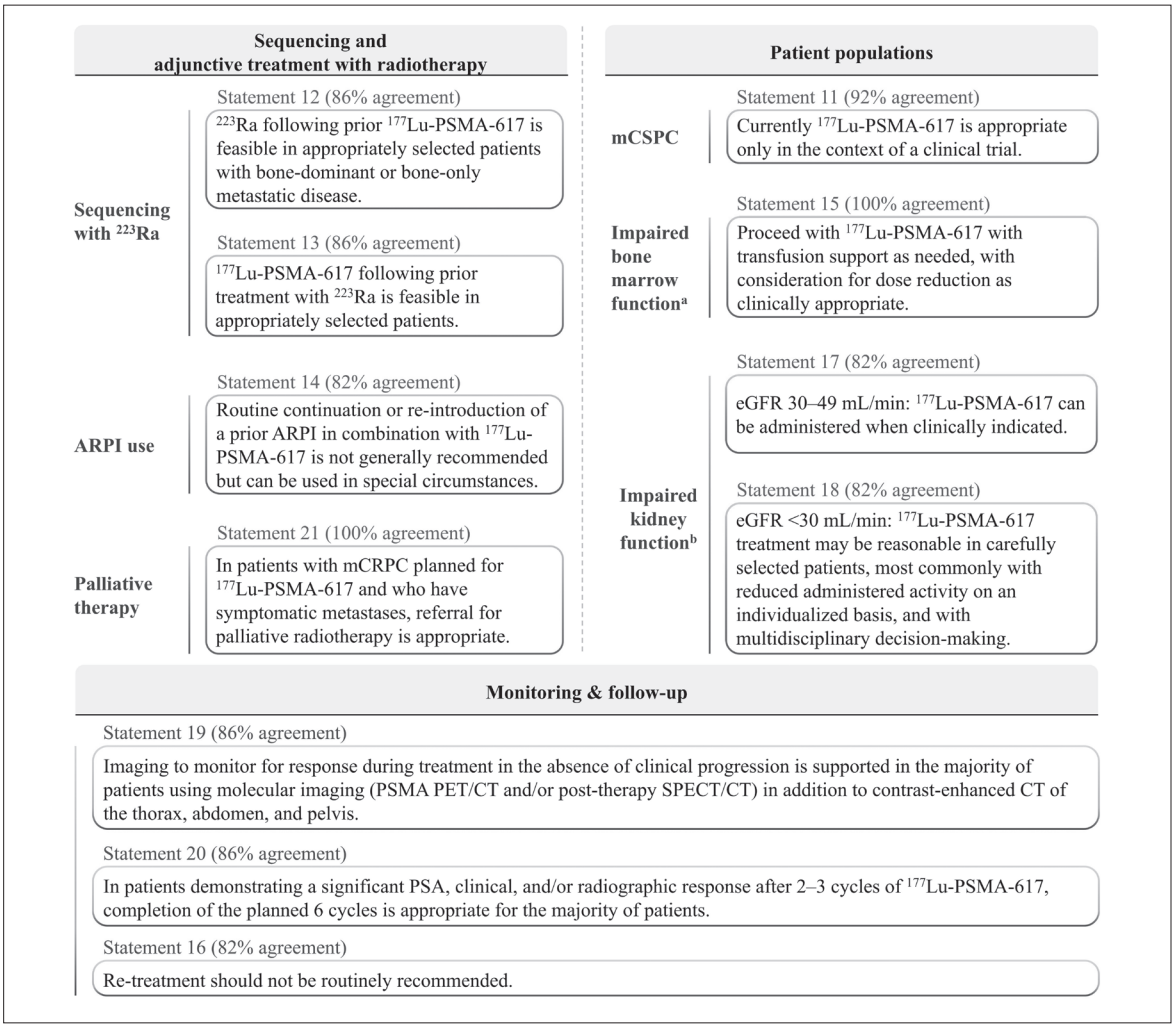

Figure 2. Consensus guidance for use of ^{177}Lu-PSMA-617 and monitoring. [a]In patients with mCRPC (without HRR alteration) whose disease progresses on or after an ARPI and docetaxel, who have impaired bone marrow function due to extensive PSMA-avid bone marrow/skeletal involvement. [b]With no correctable causes. ^{177}Lu: lutetium-177; ^{223}Ra: radium-223; ARPI: androgen receptor pathway inhibitor; CT: computed tomography; eGFR: estimated glomerular filtration rate; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; SPECT: single-photon emission computed tomography.

an OS benefit with the addition of SBRT to ADT plus abiraterone acetate.[48,49]

In the Prostate Cancer Study 9 (PCS-9), the addition of SBRT to ADT plus enzalutamide significantly improved median rPFS by 2.3 years compared with ADT plus enzalutamide alone, and delayed median time to subsequent antineoplastic therapy.[50] Although these studies were not conducted in patients with mCSPC, they highlight the clinical importance of accurately identifying patients without polymetastatic disease.

PSMA PET/CT frequently upstages disease compared with conventional imaging, and this may meaningfully alter management by identifying patients in whom metastasis-directed therapy should be avoided because disease is more extensive than initially appreciated.[51,52] In patients whose disease recurs, guideline-supported use of PSMA PET/CT can more accurately characterize disease extent.[9,10] Identification of polymetastatic disease on PSMA PET/CT may shift treatment intent from metastasis-directed therapy toward systemic therapy escalation.

■ STATEMENT 10

In patients whose disease progresses on ADT plus ARPI and post-chemotherapy (triplet or sequential therapy), PSMA PET/CT should be performed when ^{177}LuPSMA-617 is considered (consensus achieved: 100%).

In this setting, PSMA PET/CT can directly inform treatment planning by identifying patients eligible for ^{177}LuPSMA-617 and excluding those without sufficient PSMA-expressing disease. PSMA positivity is required under the regulatory approval indication, based on eligibility criteria used in clinical trials.[2,53] Moreover, these patients can also be candidates for metastasis-directed therapy, as described in Statement 9. For patients with advanced prostate cancer whose disease progresses on prior systemic therapy, international guidelines recommend PSMA PET/CT when imaging results are expected to inform subsequent management.[16,54] When feasible, PSMA PET/CT should be performed close to the time of disease progression, ideally within three months.

■ STATEMENT 11

Currently, ^{177}Lu-PSMA-617 is appropriate for patients with mCSPC only in the context of a clinical trial (consensus achieved: 92%).

Emerging phase 2/3 evidence in mCSPC has demonstrated improved PSA response with two cycles of ^{177}Lu-PSMA-617, followed six weeks later by docetaxel (UpFrontPSMA),[55] and improved rPFS with ^{177}Lu-PSMA-617 combined with ADT plus ARPI (PSMAddition interim analysis).[4] In the PSMAddition study, a positive trend in OS was observed, although crossover was allowed after progression, confounding the OS results.

As of July 31, 2026, the FDA approved ^{177}Lu-PSMA-617 for patients with PSMA-positive metastatic androgen pathway modulation-naive/sensitive prostate cancer in combination with an ARPI.[56] A submission has been made to Health Canada, although approval is still pending. Therefore, ^{177}Lu-PSMA-617 in mCSPC remains investigational in the Canadian context.

■ STATEMENT 12

The use of ^{223}Ra following prior treatment with ^{177}Lu-PSMA-617 is feasible in appropriately selected patients with bone-dominant or bone-only metastatic disease (consensus achieved: 86%).

The retrospective LuRa study evaluated the efficacy and safety of ^{223}Ra in patients with mCRPC previously treated with ^{177}Lu-PSMA-617.[57] Although the study only included 21 patients, the results support the feasibility of this sequencing approach in a heavily pretreated population. Median OS was 10.6 months, and following the first dose of ^{223}Ra, the six-month survival rate was 76%. After initiating ^{223}Ra, 42% of patients achieved a ≥30% reduction in alkaline phosphatase levels. Hematologic adverse events were notable, with grade ≥3 anemia and thrombocytopenia reported in 33% and 19% of patients, respectively, and 38% required transfusion support. These findings highlight bone marrow reserve as a key consideration of tolerability when sequencing ^{223}Ra after ^{177}LuPSMA617, rather than concerns regarding loss of radiopharmaceutical efficacy. When considering treatment with ^{223}Ra after ^{177}Lu-PSMA-617, careful patient selection is essential, with particular attention to baseline bone marrow function.

STATEMENT 13

The use of ^{177}Lu-PSMA-617 following prior treatment with ^{223}Ra is feasible in appropriately selected patients (consensus achieved: 86%).

Retrospective and real-world evidence support the use of ^{177}Lu-PSMA-617 after ^{223}Ra.[58-63] The prospective real-world study using the Frankfurt Metastatic Cancer database of the Prostate (FRAMCAP) registry demonstrated no significant differences in OS among patients with mCRPC who had received prior ^{223}Ra compared with patients who were ^{223}Ra treatment-naive (median OS was 17.9 vs. 14.8 months, respectively).[62]

The retrospective RALU study evaluated the safety and efficacy of treatment with ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T after ^{223}Ra in patients with bone-predominant mCRPC.[63] Among the 49 included patients, 67% had received ^{177}Lu-PSMA-617 and 33% had received ^{177}Lu-PSMA-I&T, 61% had received ≥4 life-prolonging therapies, and 91% had previously received taxane-based chemotherapy. Interim median OS was 12.6 months after starting ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T, and the incidence of grade 3/4 anemia and thrombocytopenia was 18% and 2%, respectively.[63] In addition, alkaline phosphatase levels were shown to be a significant predictor of mortality in ^{223}Ra-pretreated patients.[60]

Although hematologic adverse events reported in these studies are relevant to most later-line therapies, prior treatment with ^{223}Ra was not found to significantly contribute to hematotoxicity.[61] Patients with bone marrow suppression, including those with borderline suppression after ^{223}Ra, should receive supportive care as clinically indicated to allow recovery of bone marrow reserves before treatment initiation.[64] Complete blood count should be performed before starting ^{177}Lu-PSMA-617 and by week 4 of each cycle to inform decisions about proceeding with treatment two weeks later. In patients with myelosuppression, close monitoring every 2−3 weeks is warranted.

PSMA expression as a marker for treatment selection between ^{177}Lu-PSMA-617 and ^{223}Ra

PSMA PET/CT has demonstrated superior sensitivity for detecting visceral metastatic disease compared with conventional imaging, and is recommended to confirm bone-only metastatic disease in patients being considered for bone-targeted radionuclide therapy. Furthermore, the degree of PSMA expression may serve as an imaging biomarker to guide treatment selection. A subanalysis of the TheraP trial demonstrated that patients in the lowest quartile of mean standardized uptake value (SUVmean <6.9) had a poor PSA response to ^{177}Lu-PSMA-617 and derived greater benefit from cabazitaxel.[65] In addition, a retrospective analysis of 139 patients with mCRPC treated with ^{177}Lu-PSMA-617 showed that patients with a heterogeneity and intensity of tumors (HIT) score of 1, defined by a maximum standardized uptake value (SUVmax) <15, had no PSA response to treatment.[66] Notably, a similar SUVmax threshold was incorporated into the eligibility criteria of key Australian clinical trials, including the ENZA-p trial.[67]

Despite the lack of prospective data, PSMA PET/CT imaging may be useful to guide proper sequencing in patients, with patients with high PSMA expression possibly being more suitable for LuRa (^{223}Ra after ^{177}Lu-PSMA-617), and patients with low PSMA expression more suitable for a RALU treatment approach (^{177}Lu-PSMA-617 after ^{223}Ra).

STATEMENT 14

Routine continuation or re-introduction of a prior ARPI in combination with ^{177}Lu-PSMA-617 is not generally recommended for most patients with mCRPC but can be used in special circumstances (consensus achieved: 82%).

A phase 2 crossover trial demonstrated that, among patients with mCRPC whose disease had progressed on abiraterone acetate, treatment with enzalutamide resulted in PSA responses in approximately one-third of patients (36% vs. 4%) and prolonged the time to second PSA progression by approximately four months compared with the reverse sequence (enzalutamide followed by abiraterone acetate).[68] These findings suggest that optimal sequencing of ARPIs may provide clinical benefit in this setting. Furthermore, the randomized phase 2 ENZA-p trial demonstrated that the addition of ^{177}Lu-PSMA-617 to enzalutamide was associated with higher and deeper PSA response and significantly improved PSA PFS and OS in patients with early mCRPC disease.[67,69] Notably, 14% of patients in the investigational arm had previously received abiraterone acetate.

While these findings support combining an ARPI with ^{177}Lu-PSMA-617 in patients with early mCRPC, the efficacy of this strategy in patients with later-stage mCRPC following progression on multiple ARPIs and taxane chemotherapy remains uncertain.

A secondary analysis of the VISION trial demonstrated that patients who received ^{177}Lu-PSMA-617 with concomitant ARPI therapy had longer median

OS compared with those who did not (17.8 vs. 12.4 months, respectively);[70] however, interpretation is limited by baseline imbalances favoring the concomitant ARPI cohort, including younger age, better performance status, fewer prior taxane regimens, and lower PSA levels. No significant differences were observed for rPFS or other efficacy endpoints.

Findings from the PEACE-3 trial support the broader concept of combining ARPI therapy with radiopharmaceuticals in patients with mCRPC, with improvements in rPFS and OS observed with enzalutamide plus ^{223}Ra. More prospective data are needed to determine whether concurrent ARPI and ^{177}Lu-PSMA-617 confers a true clinical benefit.

Although concurrent treatment may be reasonable in selected patients because of minimal incremental toxicity and the biological heterogeneity of mCRPC, current evidence does not support the routine continuation or re-introduction of a prior ARPI with ^{177}Lu-PSMA-617. Treatment decisions should be individualized, and concurrent ARPI therapy may be considered in selected patients, particularly when prior ARPI therapy provided a meaningful clinical benefit.

STATEMENT 15

In patients with mCRPC (without homologous recombination repair [HRR] alteration) whose disease progresses on or after an ARPI and docetaxel, who have impaired bone marrow function due to extensive PSMA-avid bone marrow/skeletal involvement, and in whom ^{177}Lu-PSMA-617 is being considered, proceed with ^{177}Lu-PSMA-617 with transfusion support as needed, with consideration for dose reduction as clinically appropriate (consensus achieved: 100%).

The phase 3 VISION trial demonstrated improved rPFS and OS with ^{177}Lu-PSMA-617 in addition to standard of care compared with standard of care alone in patients with mCRPC whose disease progressed on prior ARPI and two taxane-based regimens, with more than 97% of patients having received prior docetaxel.[2] Study inclusion criteria, however, required patients to have adequate bone marrow function prior to enrollment, limiting data extrapolation to patients with preexisting cytopenias. One retrospective study in patients with diffuse bone marrow involvement showed that lower baseline levels of platelets and neutrophils were associated with a higher risk of grade 3/4 hematologic adverse events.[71] As a result, safety remains a key consideration when treating patients with impaired bone marrow function, with ideal candidates having stable blood counts.

Noting these risks, as well as the potential for bone marrow recovery following tumor response, risk-mitigation strategies should be individualized as clinically indicated.[61,72] These may include dose reduction, treatment delay, transfusion support, or a combination thereof, together with frequent hematologic monitoring (i.e., weekly bloodwork). There is no current role for primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) in this setting; however, for patients who develop grade ≥3 neutropenia, G-CSF is indicated and should be administered 72 hours after treatment.

STATEMENT 16

Re-treatment with ^{177}Lu-PSMA-617 in eligible patients who have previously responded to six cycles should not be routinely recommended (consensus achieved: 82%).

Robust prospective data on the safety and efficacy of re-treatment are lacking, with only limited evidence from mostly small, non-randomized, registry or retrospective studies.[73] One phase 2 prospective study in which a subset of 15 patients was re-administered ^{177}Lu-PSMA-617 demonstrated higher PSA response rates (73% vs. 19%) compared with the 21 patients who received other systemic therapies (i.e., abiraterone, enzalutamide, docetaxel, or cabazitaxel).[74] Responses following re-treatment, however, were less durable than following the initial treatment, with shorter durations of PSA PFS.

In addition, re-treatment raises concerns around the cumulative exposure to bone marrow and renal radiation. The ongoing RE-LuPSMA study is evaluating the efficacy and safety of re-treatment in patients with mCRPC with an initial good response to ^{177}Lu-PSMA-617 (i.e., PSA decline of ≥50%, no new prostate cancer lesions within two months of completing therapy) and subsequent disease recurrence.[75] Recruitment for this trial is currently ongoing. Until further evidence and funding are available, re-treatment should only be considered in highly selected cases (i.e., patients with durable response, ongoing PSMA-avid disease, and no major toxicity concerns), ideally within trials or registries.

■ STATEMENT 17

In patients with mCRPC and impaired renal function (estimated glomerular filtration rate [eGFR] 30–49 mL/min) and no correctable causes, ^{177}Lu-PSMA-617 can be administered when clinically indicated (consensus achieved: 82%).

Despite limited prospective data in patients with renal impairment, expert consensus supports consideration of ^{177}LuPSMA-617 in patients with mCRPC and an eGFR of 30–49 mL/min when clinically indicated. The joint EANM/SNMMI procedure guideline also supports treatment in patients with eGFR of ≥30 mL/min.[76]

The incidence of clinically significant acute renal toxicity during treatment with ^{177}Lu-PSMA-617 appears to be low. In the phase 3 VISION trial, grade 3 acute kidney injury was reported in two patients (0.4%).[2] In the REALITY study, patients with a mean baseline eGFR of 45 mL/min experienced no significant decline in renal function following treatment with ^{177}Lu-PSMA-617, with a non-significant increase in mean eGFR observed during followup.[77]

Although clinically significant nephrotoxicity appears uncommon in patients with eGFR ≥30 mL/min, caution during treatment remains warranted. Reduced glomerular filtration may delay radioligand excretion, increasing systemic radiation exposure and potentially elevating the risk of hematologic toxicity, particularly myelotoxicity.[76]

Patients with reduced baseline renal function, diabetes, hypertension, and chronic kidney disease may be at increased risk of renal toxicity and should be closely monitored during treatment. Data regarding delayed radiation-induced nephrotoxicity remain limited, particularly among patients with longer survival. Ongoing studies and longer-term followup from trials such as PSMAfore and PSMAddition may further clarify the long-term renal safety profile of ^{177}Lu-PSMA-617.

■ STATEMENT 18

In patients with mCRPC and stable/chronic renal impairment (eGFR <30 mL/min) and no correctable causes in whom ^{177}Lu-PSMA-617 is being considered, treatment may be reasonable in carefully selected patients, most commonly with reduced administered activity on an individualized basis, and with multidisciplinary decision-making (consensus achieved: 82%).

In patients with mCRPC and chronic renal impairment with eGFR <30 mL/min, treatment should be approached with heightened caution. Concerns persist regarding reduced renal clearance, prolonged whole-body radiation exposure, and an increased risk of cumulative toxicity. Dose modification, including reduced administered activity and individualized treatment planning, should be strongly considered. Decisions should be individualized and multidisciplinary, incorporating patient-specific factors, comorbidities, disease burden, expected clinical benefit, and applicable provincial reimbursement criteria. Renal function should be assessed before each treatment cycle to detect early changes that may require dose adjustment, intravenous fluids, or treatment discontinuation.[78]

Monitoring on ^{177}Lu-PSMA-617

■ STATEMENT 19

In patients receiving ^{177}Lu-PSMA-617, imaging to monitor for response during treatment in the absence of clinical progression is supported in the majority of patients using molecular imaging (PSMA PET/CT and/or post-therapy single-photon emission computed tomography [SPECT]/CT) in addition to contrast-enhanced CT of the thorax, abdomen, and pelvis (consensus achieved: 86%).

PSA is widely used as a biomarker of response; however, it does not characterize disease distribution and tumor biology and may at times be discordant with imaging or clinical response. Radiographic progression has been observed in approximately 25% of patients without a corresponding rise in PSA, supporting the need to complement biochemical assessment with imaging.[79,80]

Consistent with its established role in monitoring response to systemic therapies in metastatic prostate cancer, imaging remains critical during ^{177}LuPSMA-617. Serial imaging may detect new lesions, identify nonuniform response, determine etiology of myelosuppression, and differentiate responders from non-responders.[81,82]

Molecular imaging with PSMA PET/CT and/or post-therapy ^{177}Lu-PSMA SPECT/CT is recommended in combination with contrast-enhanced CT for detection of non-PSMA-avid disease. PSMA PET/CT after 2−3 cycles and at the end of treatment (e.g., 4−8 weeks post-treatment) is considered appropriate.[67,83] Post-therapy SPECT/CT is recommended after each cycle if feasible, which offers an alternative to interim and end-of-treatment PSMA PET/CT.[82] If post-therapy SPECT/CT is not feasible after each cycle due to limited resources, the panel suggested post-therapy SPECT/CT after the first, third, and sixth cycles.

Post-therapy SPECT/CT is routinely acquired 24 hours after treatment, but earlier acquisition, after approximately four hours, may be considered for logistical reasons (e.g., for patients who travel long distances for healthcare services). Importantly, consistency in the timing of imaging should be maintained across all cycles. In addition to molecular imaging with PSMA PET/CT or post-therapy SPECT/CT, contrast-enhanced CT of the thorax, abdomen, and pelvis should be performed every 8–12 weeks, as it is important for the detection of non-PSMA-avid disease.[84,85]

Interim PSMA PET/CT and post-therapy SPECT/CT imaging may provide valuable information to support discontinuing ineffective therapy or transitioning to alternative treatment strategies. In some cases, imaging may identify oligoprogressive disease that is amenable to metastasis-directed therapy.[86] Molecular imaging may also support a personalized approach to treatment based on early biologic response, although further validation of response-guided strategies is required.[87] Considerations for resource availability and coverage will influence the choice of monitoring modality, with practice varying by center.

■ STATEMENT 20

In patients demonstrating a significant PSA, clinical, and/or radiographic response after 2–3 cycles of ^{177}Lu-PSMA-617, completion of the planned six cycles is appropriate for the majority of patients (consensus achieved: 86%).

Complete molecular response on PSMA PET during Lu-PSMA-617 therapy is uncommon, and residual disease often persists.[88] Therefore, early treatment interruption risks potentially undertreating the patient. Treatment interruption in exceptional responders or treatment extension in patients with persistent responsive disease should be only considered in rare instances and on an individualized basis.

For example, a patient with no remaining PSMA uptake on imaging after four cycles may be considered for an extended treatment interval or discontinuation before completing six cycles, particularly if tolerability is a concern. In addition, in the first-line mCRPC setting, evidence is emerging for response-adapted treatment approaches. The phase 2 randomized ENZA-p trial evaluated ^{177}Lu-PSMA-617 in combination with enzalutamide and incorporated an adaptive dosing strategy in patients with mCRPC prior to taxane chemotherapy. Patients with no residual PSMA-avid disease after the second dose stopped ^{177}Lu-PSMA-617, and those with persistent PSMA-avid disease received up to four doses. The trial demonstrated significant improvements in PSA PFS and OS with the combination strategy; however, it was not designed to determine the independent effect of adaptive dosing.[67,69]

For most patients, even those with ongoing benefit, treatment according to regulatory guidance and clinical trials is advised.[2,76,89,90]

Routine practice considerations

In routine practice, ^{177}Lu-PSMA-617 is most commonly delivered according to the standard six-cycle paradigm at approximately six-week intervals, reflecting pivotal trial protocols and reimbursement criteria; however, real-world implementation may be affected by scheduling constraints, access limitations, or patient-specific factors, resulting in delays between cycles. Prolonged inter-cycle/treatment gaps, particularly beyond 10 weeks, may raise concerns related to reimbursement eligibility and treatment continuity in some jurisdictions.

At the same time, there is increasing clinical interest in adaptive treatment strategies for selected patients who demonstrate sustained response or clinical benefit. This includes consideration of modestly extended inter-cycle intervals (e.g., 8–10 weeks) or treatment pauses, particularly in good responders where toxicity, patient preference, or logistical considerations are relevant. In the absence of prospective data, such decisions remain individualized, and there is a need for clearer consensus guidance regarding clinically appropriate treatment delays or interval modifications.

The ReSPECT study demonstrated that response-adapted treatment strategies informed by early PSMA SPECT imaging and PSA response allowed approximately 35% of patients to pause therapy until subsequent biochemical progression, without apparent compromise in treatment efficacy.[87] Patients managed with a treatment pause strategy experienced longer PSA PFS compared with those treated continuously at fixed six-week intervals (12.1 vs. 6.1 months), with numerically longer OS (19.2 vs. 13.2 months). These findings support the feasibility of individualized treatment scheduling in carefully selected patients.

Following completion of six cycles in patients with a favorable clinical and biochemical response, it is important to closely monitor with ongoing clinical, laboratory, and imaging assessment until evidence of disease progression. There is currently limited evidence to support routine immediate transition to additional systemic therapy, such as ARPIs, in the absence of documented progression after ^{177}Lu-PSMA-617. Accordingly, deci-

sions regarding treatment pauses, interval extension, or initiation of subsequent therapy should remain individualized, multidisciplinary, and guided by disease progression, symptom burden, treatment tolerance, and patient preferences.

■ STATEMENT 21

In patients with mCRPC planned for ^{177}Lu-PSMA-617 who have symptomatic metastases, referral for palliative radiotherapy is appropriate (consensus achieved: 100%).

External beam radiotherapy (EBRT) is a standard treatment for patients with advanced prostate cancer and symptomatic metastases, particularly for painful bone metastases, where it provides effective palliation.[91] In patients with symptomatic metastases, EBRT and ^{177}Lu-PSMA-617 can serve complementary roles: radiotherapy addresses focal symptomatic disease and ^{177}Lu-PSMA-617 treats disseminated PSMA-avid disease.

Despite the lack of prospective evidence, retrospective studies showed that EBRT provided symptomatic relief when administered before, during, and after ^{177}Lu-PSMA-617, and was generally well tolerated.[92,93] Hematologic toxicities were common, but no significant differences in the rates of anemia, thrombocytopenia, neutropenia, or leukopenia were observed compared with ^{177}Lu-PSMA-617 alone; however, a shorter interval (≤3 months) between EBRT and ^{177}Lu-PSMA-617 was associated with higher rates of anemia and thrombocytopenia.[93] Prior taxane-based chemotherapy may have contributed to the development of cytopenias in these patients.

Clinical data supporting the use of metastasis-directed therapy, including SBRT, for oligopersistent or oligoprogressive disease during or following ^{177}Lu-PSMA-617 are currently lacking, and further investigation is needed. Patients with mCRPC and symptomatic metastases who are planned for ^{177}Lu-PSMA-617 should be assessed for referral to palliative radiotherapy on an individualized basis through multidisciplinary discussion.

Nuclear medicine subsection

Nuclear medicine interpretation is central to the safe implementation of PSMA PET/CT in prostate cancer. Although PSMA PET/CT improves the detection of nodal and distant disease, equivocal and false-positive findings remain clinically important, particularly when imaging results could alter eligibility for curative-intent therapy. The expert panel recognized the importance of identifying common causes of false-positive PSMA uptake and providing practical recommendations to support accurate image interpretation.

Particular emphasis was placed on avoiding inappropriate disease upstaging, which may adversely influence treatment selection and potentially deprive patients of curative-intent therapeutic options. The panel, therefore, focused on practical challenges in image interpretation, including solitary PSMA-avid lesions, benign patterns of uptake, common physiologic mimics, and the selective use of delayed imaging. Following voting and discussion, nuclear medicine questions meeting predefined consensus criteria were reformulated as consensus statements (Table 2).

It should be noted that several ^{68}Ga- and ^{18}F-labelled PSMA PET tracers are available, with differences in physiologic distribution and excretion that may affect image interpretation. Most undergo substantial urinary excretion, whereas ^{18}F-PSMA-1007 is predominantly hepatobiliary excreted, with relatively low urinary activity. These differences should be considered when interpreting lesions near sites of physiologic tracer uptake. In Canada, ^{68}Ga-PSMA-11 is currently the PSMA PET radiotracer approved by Health Canada for prostate cancer imaging.

The nuclear medicine consensus-based approach to PSMA PET/CT interpretation in prostate cancer is presented in Figure 3.

■ STATEMENT 22

A solitary PSMA-avid lesion without a CT or MRI correlate should generally be interpreted according to patient risk, lesion location, and uptake pattern (consensus achieved: 100%).

Interpretation of PSMA PET/CT requires integration of molecular imaging findings with anatomic imaging and clinical context. A solitary PSMA-avid lesion without a corresponding CT or MRI correlate represents an area of diagnostic uncertainty, particularly because PSMA expression is not specific to prostate cancer and uptake on PSMA PET/CT may be seen in benign bone processes, inflammatory conditions, and other malignancies.[94,95] The joint EANM/SNMMI PSMA PET/CT guideline recommends cautious interpretation of solitary lesions in the nabsence of a definite morphologic correlate, especially for isolated rib lesions.[10] Similarly, the E-PSMA standardized reporting guidelines emphasize cautious interpretation of solitary bone lesions without other metastatic sites, especially in patients undergoing preoperative staging.[96] More recently, the

Table 2. Nuclear medicine statements that achieved consensus (≥80% agreement)

No.	Statement	Agreement n/N (%)
22	A solitary PSMA-avid lesion without a CT or MRI correlate should generally be interpreted according to patient risk, lesion location, and uptake pattern.	6/6 (100%)
23	High PSA and grade group 3–5 disease, clinical stage ≥cT3, and a rapid PSA doubling time are clinical factors that increase suspicion for a solitary metastatic lesion.	6/6 (100%)
24	An elongated or fusiform pattern of PSMA uptake in the ribs is more suspicious for metastatic disease.	5/6 (83%)
25	An intramedullary ring- or arc-shaped pattern of sclerosis on CT favors a benign rib lesion.	6/6 (100%)
26	A solitary mild focal rib uptake on ^{68}Ga-PSMA-11 PET/CT without sclerosis, lytic change, or an anatomic correlate should be interpreted according to patient risk. In low-risk patients, it is likely post-traumatic or benign; however, in intermediate- or high-risk patients, it should be considered indeterminate, and followup is recommended.	5/6 (83%)
27	Bilateral elongated structures in typical anatomic locations best distinguish ganglia from nodal metastases.	6/6 (100%)
28	Ureteric activity is the physiologic variant that most commonly mimics nodal disease in the retroperitoneum and pelvis on PSMA PET/CT.	6/6 (100%)
29	Lesion size and location, the clinical likelihood of metastatic disease, and application of PROMISE V2 criteria all influence interpretation of equivocal lesions on PSMA PET/CT.	6/6 (100%)
30	Paget's disease, degenerative and post-traumatic changes, and enchondromas and non-aggressive fibro-osseous lesions are recognized benign or inflammatory processes that commonly cause false-positive PSMA uptake in bone.	6/6 (100%)
31	After 3 months post-treatment (radical prostatectomy or prostate radiotherapy) and in the presence of biochemical recurrence, any focal PSMA uptake within the prostate bed/prostate should generally be considered suspicious until proven otherwise.	6/6 (100%)
32	Delayed pelvic acquisition on PSMA PET/CT is not routinely indicated but may be reasonable in selected cases where additional clarification would meaningfully impact clinical decision-making.	6/6 (100%)

^{68}Ga: gallium-68; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen.

SPARC consensus further highlights the risk of upstaging associated with isolated PSMAavid rib lesions.[18]

No single PSMA PET/CT finding should be used in isolation to assign metastatic disease. Interpretation, therefore, should consider patient risk, lesion location, and uptake pattern and intensity. A solitary PSMAavid lesion is more likely to represent metastatic disease in patients with highrisk prostate cancer compared with patients with low-risk disease. An isolated PSMA-avid rib lesion is often found to be benign at initial staging and biochemical recurrence.[97,98]

While PSMA uptake pattern alone is insufficient for definitive classification of benign or malignant tumors, atypical uptake patterns, particularly when discordant with benign CT findings, should raise suspicion for metastatic disease. Uptake morphology can provide additional information to help determine the likelihood that a rib lesion is malignant. Assessment should include whether uptake patterns correspond to recognized benign patterns, such as physiologic structures, trauma-related change, or degenerative change.

Moreover, the updated PSMA expression scoring system incorporated within the published PROMISE V2 criteria provides a standardized framework for assessing the likelihood that a PSMA-avid lesion represents true metastatic disease.[99] By evaluating lesion uptake intensity relative to physiologic background activity in reference organs, the score supports more consistent interpretation of PSMA PET/CT findings and may help reduce diagnostic uncertainty in equivocal cases. The PRIMARY score is specific for intraprostatic lesions and does not apply in the context of metastatic disease.

Tracer type can also influence the interpretation of PSMA PET/CT, as ^{18}F-PSMA-1007 has a higher incidence of non-specific bone uptake compared with ^{68}Ga-PSMA-11.[100]

■ STATEMENT 23

High PSA and grade group 3–5 disease, clinical stage ≥cT3, and a rapid PSA doubling time are clinical factors that increase suspicion for a solitary metastatic lesion (consensus achieved: 100%).

High PSA, higher grade group, advanced clinical T stage, and rapid PSA doubling time are well-established markers of aggressive prostate cancer biology and increased risk of metastatic disease,[101-103] and, therefore, increase suspicion that a solitary lesion represents true metastasis rather than a benign or indeterminate finding.

In a retrospective study of 2193 patients with newly diagnosed prostate cancer, 87.5% of patients with PSA ≥100 ng/mL had metastatic disease (miN1-M1a-c). In addition, this study showed that clinical tumor stage ≥T2, grade group >3, and radiologic tumor stage ≥T3b were also associated with the presence of metastatic disease.[104] In biochemical recurrence, short PSA doubling time and higher grade group were also among the strongest predictors of metastatic progression and adverse outcomes, including mortality.[101,102]

Higher PSA levels were also independently associated with shorter metastasis-free survival. Moreover, large prospective studies have demonstrated a significant association between serum PSA levels and the diagnostic performance of PSMA PET/CT. Higher PSA

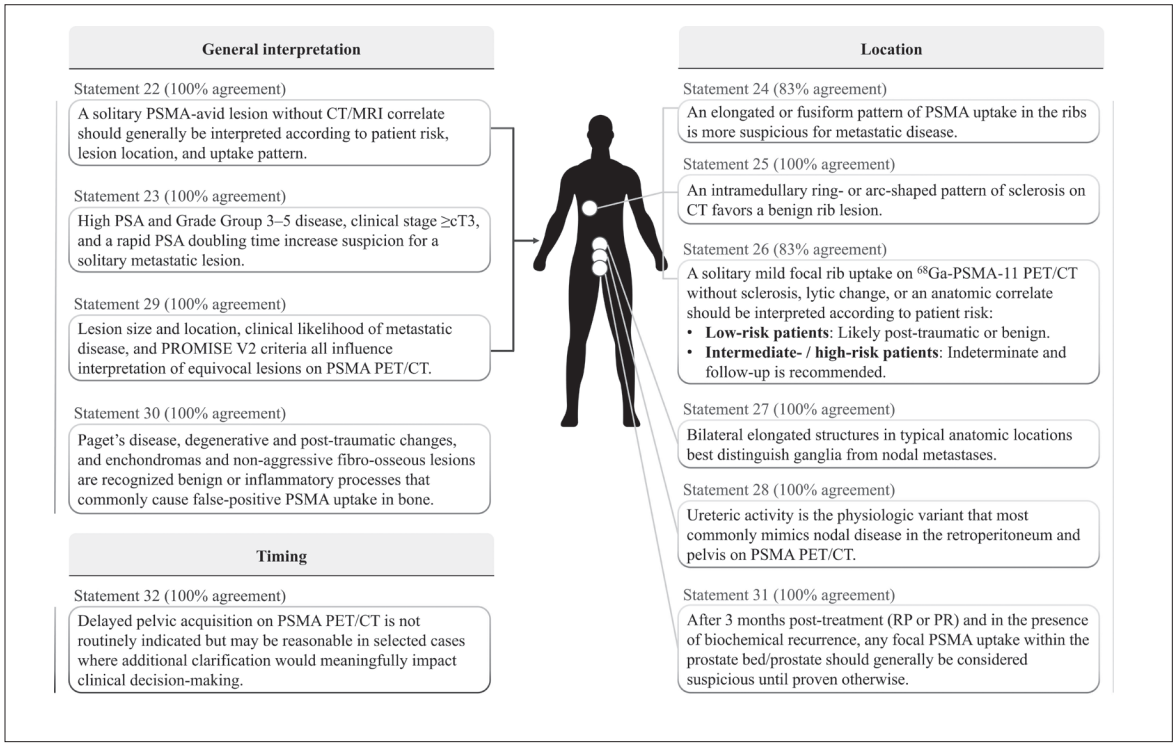

Figure 3. Nuclear medicine consensus-based approach to PSMA PET/CT interpretation in prostate cancer. 68Ga: gallium-68; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; PR: prostate radiotherapy; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; RP: radical prostatectomy.

levels are associated with increased detection rates, greater positive predictive value, and improved inter-reader agreement. These findings highlight the importance of considering PSA levels when interpreting PSMA PET/CT results.[30,31]

The 2022 AUA/ASTRO guideline supports the use of PSA, grade group, and clinical T stage for risk stratification, considering higher values are associated with increased risk of recurrence, metastasis, and prostate cancer-specific mortality.[103] Although these factors do not directly determine the nature of a solitary lesion (malignant vs. benign), they collectively increase the underlying risk of metastatic disease in an individual patient, and should be considered when interpreting solitary findings.

STATEMENT 24

An elongated or fusiform pattern of PSMA uptake in the ribs is more suspicious for metastatic disease (consensus achieved: 83%).

While there is a lack of prospective evidence supporting elongated or fusiform uptake morphology as an independent predictor of metastasis, this pattern may reflect underlying bone expansion and, therefore, raises suspicion. Although such appearances can still be benign—for example, in the context of fibrous dysplasia—they are considered more concerning for metastatic disease, particularly in the absence of corresponding benign anatomical findings on CT.

In contrast, linear uptake involving consecutive ribs is generally regarded as more likely benign, most commonly related to post-traumatic or degenerative changes, especially in patients with otherwise low clinical risk.

STATEMENT 25

An intramedullary ring- or arc-shaped pattern of sclerosis on CT favors a benign rib lesion (consensus achieved: 100%).

CT morphology plays an important complementary role in the characterization of PSMA-avid rib lesions. While sclerosis in isolation is non-specific, a well-defined intramedullary ring- or arc-shaped pattern, particularly when confined to the bone marrow, is highly suggestive of a benign rib lesion and should be interpreted in conjunction with other CT features and clinical context.[20] An intramedullary ring- or arc-shaped

pattern of mineralization is a wellrecognized feature of a chondroid matrix, reflecting calcification surrounding lobules of hyaline cartilage, and is most commonly seen in benign cartilaginous lesions, such as enchondroma.[105,106] In contrast, malignant lesions more likely demonstrate cortical destruction, soft-tissue extension, aggressive or expansile remodeling, or heterogeneous lytic-sclerotic patterns.[107-109]

■ STATEMENT 26

A solitary mild focal rib uptake on ^{68}Ga-PSMA-11 PET/CT without sclerosis, lytic change, or an anatomic correlate should be interpreted according to patient risk. In low-risk patients, it is likely post-traumatic or benign; however, in intermediate- or high-risk patients, it should be considered indeterminate, and followup is recommended (consensus achieved: 83%).

Solitary rib lesions detected during staging with PSMA PET/CT are frequently challenging to interpret due to the high prevalence of benign findings. In a retrospective study among men who underwent PSMA PET/CT for primary staging, 61 of 62 (98.4%) solitary PSMA-avid rib lesions were benign, and 17.7% of these had findings consistent with healed fractures on diagnostic CT scan.[97] Another study found that 85.2% of lesions were benign among 54 patients with exclusively PSMAavid rib lesions identified at initial staging or during biochemical recurrence, with PET imaging features alone lacking sufficient reliability to differentiate between benign and malignant lesions.[98] In addition, Woo et al found that among 175 men with PSMA-avid rib lesions, only 2.1% had isolated rib metastasis without any additional sites of metastatic disease.[100]

Even in intermediate- or high-risk patients, equivocal rib lesions are often clinically insignificant.[110,111] Findings are also tracer-dependent, with ^{18}F-PSMA-1007 associated with a higher rate of non-specific bone uptake, especially in the ribs, compared with ^{68}Ga-PSMA-11.[15,112]

In the ribs, benign findings tend to have characteristic features: they are more often solitary, of low intensity, and associated with fractures. On the other hand, malignant rib lesions typically occur in the presence of additional disease, have higher PSMA uptake, and show structural abnormality.[97,98,100]

Although isolated rib metastases are uncommon, the likelihood of metastatic disease increases with higher-risk clinical features. Accordingly, interpretation of solitary PSMA-avid rib lesions should be risk-adapted, as similar imaging findings may have different implications depending on the patient's overall risk of metastatic disease.[20]

In low-risk patients, a single rib lesion with mild focal uptake and no destructive CT features should be most often interpreted as benign or post-traumatic. In intermediate- or high-risk patients, however, the higher probability of metastatic disease warrants a more cautious classification, and such lesions should be generally considered indeterminate, with followup recommended. Serial imaging and followup can provide valuable information to resolve uncertainty because a single scan may be insufficient for definitive classification. Short-term followup imaging, preferably with a bone scan at approximately three months, is recommended to help clarify indeterminate rib findings.

A recent review further supports this risk-adapted approach, emphasizing that most solitary rib lesions are benign, particularly in low-risk patients, while factors such as multiple lesions, aggressive CT morphology, or higher-risk clinical context increase the likelihood of malignancy.[20] The clinical setting, including whether imaging is performed for initial staging or biochemical recurrence, may also influence interpretation, with greater caution warranted in patients who have a recurrence of prostate cancer.

■ STATEMENT 27

Bilateral elongated structures in typical anatomic locations best distinguish ganglia from nodal metastases (consensus achieved: 100%).

Physiologic PSMA tracer uptake is well described in ganglia of the sympathetic trunk and is commonly bilateral.[10,96,113,114] Non-pathologic PSMA uptake in ganglia has been identified in up to 98.5% of patients, and is typically located along the sympathetic chain in predictable regions, including the cervical, celiac, and sacral ganglia.[113] Ganglia differ morphologically from metastatic lymph nodes, most often demonstrating a linear or band-shaped configuration (71.2%) and only rarely appearing nodular (2.0%). In contrast, nodal metastases are predominantly nodular or rounded (58.6%) and are infrequently band-shaped (1.1%).[113] Accordingly, ganglia can usually be distinguished from nodal disease based on their characteristic elongated morphology and expected bilateral distribution in typical anatomic locations, features suggestive of a benign ganglionic origin.

STATEMENT 28

Ureteric activity is the physiologic variant that most commonly mimics nodal disease in the retroperitoneum and pelvis on PSMA PET/CT (consensus achieved: 100%).

Ureteric activity on PSMA PET/CT is a potential source of both falsepositive and falsenegative findings. Commonly used tracers (with the exception of ^{18}F-PSMA-1007) are excreted via the urinary tract, resulting in tracer accumulation within the ureters and bladder.[10,95] This high-intensity tracer activity can obscure or resemble PSMA-avid lesions. Ureteric uptake may appear focal or segmental and may localize adjacent to iliac vessels or nodal stations. Focal ureteric uptake adjacent to iliac vessels could be misinterpreted as small lymph node metastases.[29]

Diuretic administration or delayed imaging may improve lesion interpretation. Intravenous furosemide has been shown to reduce bladder and ureteral activity and thereby improve characterization of equivocal lesions on post-diuretic imaging;[115,116] however, diuretic use may be inappropriate in certain clinical settings, including for patients with urinary obstruction, incontinence, or furosemide hypersensitivity.[10] A combined approach using embedded contrast-enhanced CT and PSMA PET/CT may help differentiate pelvic lymph nodes from ureteric activity.[117]

STATEMENT 29

Lesion size and location, the clinical likelihood of metastatic disease, and application of PROMISE V2 criteria all influence interpretation of equivocal lesions on PSMA PET/CT (consensus achieved: 100%).

Interpretation of equivocal lesions on PSMA PET/CT is inherently multifactorial. Rather than relying on a single variable in isolation to interpret equivocal lesions, it is important to assess imaging features (size, location) together with a patient's risk of metastatic disease. The PROMISE V2 reporting criteria include lesion extent (miTNM) and location, and PSMA expression score based on uptake relative to physiologic reference organs.[99] Uptake intensity, lesions in typical metastatic regions, and the presence of additional sites of disease substantially increase the probability that an indeterminate lesion is malignant.[17,118]

One retrospective study showed that indeterminate softtissue lesions (PSMARADS3A) were more likely than indeterminate bone lesions (PSMARADS3B) to subsequently represent areas of prostate cancer on imaging (75% vs. 21%), emphasizing the importance of lesion location when interpreting equivocal findings.[17] Typical metastatic regions include the pelvis, lumbar spine, and thoracic spine.[119]

STATEMENT 30

Paget's disease, degenerative and post-traumatic changes, and enchondromas and non-aggressive fibro-osseous lesions are recognized benign or inflammatory processes that commonly cause false-positive PSMA uptake in bone (consensus achieved: 100%).

Recognition of differential diagnoses is critical to avoid false-positive interpretation and upstaging. In addition to location-based patterns, several benign and inflammatory bone processes are well-recognized causes of false-positive PSMA uptake.[120-123]

False-positive osseous PSMA uptake may occur in benign conditions, including Paget's disease, degenerative skeletal changes, healing fractures or other post-traumatic processes, and benign bone tumors such as enchondromas. Therefore, because PSMA tracer uptake is not tumor-specific within bone, correlation with CT-based morphologic features is essential to distinguish benign or inflammatory processes from metastatic bone lesions.[94]

STATEMENT 31

After three months post-treatment (radical prostatectomy or prostate radiotherapy) and in the presence of biochemical recurrence, any focal PSMA uptake within the prostate bed/prostate should generally be considered suspicious until proven otherwise (consensus achieved: 100%).

The prostate bed after radical prostatectomy and the prostate gland after primary radiotherapy represent the most common sites of recurrence following definitive local treatment; however, focal PSMA uptake in the prostate or prostate bed should be interpreted in the context of the interval from therapy. Early post-treatment inflammatory changes may result in non-specific PSMA uptake, typically within the first two months.[124,125]

While early uptake may be inflammatory, persistent focal uptake beyond the early post-treatment period remains clinically suspicious. In a prospective, multicenter study of patients with biochemically recurrent prostate cancer, false-positive findings on ^{68}Ga-PSMA-11 PET/CT or PET/MRI in the irradiated prostate or prostate bed were uncommon, occurring in 8% (17/217) of patients

(11 after radiotherapy and six after radical prostatectomy).[126] Among patients with suspected intraprostatic relapse after radiotherapy, the majority of lesions were confirmed as true-positive in 77% of patients (36/47). This demonstrates that focal PSMA uptake within the prostate beyond the early post-treatment period is more likely to represent persistent or recurrent prostate cancer than a benign post-treatment change, supporting the need for continued clinical suspicion of PSMA uptake after three months post-treatment in the presence of biochemical recurrence.

■ STATEMENT 32

Delayed pelvic acquisition on PSMA PET/CT is not routinely indicated but may be reasonable in selected cases where additional clarification would meaningfully impact clinical decision-making (consensus achieved: 100%).

The standard recommended time from tracer injection to image acquisition is approximately 60 minutes.[10] Delayed pelvic acquisition performed 2−3 hours after injection can help differentiate malignant uptake from urinary or inflammatory activity, particularly in the pelvis; however, the incremental diagnostic and clinical value of delayed imaging appears limited overall.[127,128] Logistical considerations, including scanner availability and time constraints, limit the feasibility of routine delayed imaging in many centers.

One prospective study demonstrated that delayed imaging impacted clinical management in 16% of patients with biochemical recurrence of prostate cancer after primary curative-intent treatment.[128] Accordingly, delayed pelvic acquisition may be useful for lesion characterization in selected scenarios, such as patients with negative initial imaging despite high clinical suspicion or patients with indeterminate or equivocal lesions adjacent to the ureter or the bladder, where clarification would possibly alter management.

Prior to performing delayed imaging, consideration should be given to adequate patient hydration and/or diuresis (e.g., with furosemide), as well as tracer selection (i.e., ^{68}Ga-PSMA-11 vs. ^{18}F-PSMA-1007), as these strategies may reduce urinary activity and may obviate the need for delayed acquisition.[10,116]

CONCLUSIONS

The rapid adoption of PSMA PET/CT and ^{177}Lu-PSMA-617 has created uncertainty regarding the optimal use of theranostics in many common clinical scenarios. This Canadian multidisciplinary expert report provides consensus-based recommendations to help guide decision-making in areas where evidence remains incomplete, including initial staging, biochemical recurrence, oligometastatic and advanced disease, interpretation of equivocal findings, treatment sequencing, and monitoring during ^{177}Lu-PSMA-617.

Several themes emerged from the panel's deliberations. First, PSMA PET/CT offers clear advantages over conventional imaging in many clinically relevant settings, including staging of high-risk and very high-risk localized prostate cancer; however, results must be interpreted within the clinical context: a negative scan does not exclude microscopic nodal disease, and a solitary PSMA-avid lesion without an anatomic correlate should not automatically define metastatic disease.

Second, theranostic treatment decisions should remain multidisciplinary, particularly when considering ^{177}Lu-PSMA-617 in patients with impaired bone marrow reserve, renal dysfunction, prior ^{223}Ra exposure, or symptomatic metastatic disease.

Third, response assessment during ^{177}Lu-PSMA-617 therapy should combine clinical evaluation, PSA response, and appropriate imaging, recognizing that PSA and imaging findings do not always align.

As additional evidence emerges, recommendations for PSMA PET/CT and ^{177}Lu-PSMA-617 will need to be revisited, particularly as trial data clarify the role of ^{177}Lu-PSMA-617 earlier in the disease course and as access to imaging and treatment evolves across Canada.

The present report focused on areas in which consensus was achieved. Areas not reaching the predefined consensus threshold were presented in the Appendix (available at *cuaj.ca*) and will be explored in a separate publication. In the meantime, the consensus statements in this expert report are intended to support consistent, patient-centered decision-making while preserving clinical judgment and local adaptability. The goal is not simply to adopt more sensitive imaging or newer therapies, but to use them thoughtfully to improve care for patients with prostate cancer.

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