CUA Best Practice Report: PSMA PET/CT and PET/MR in Prostate Cancer

Bobby Shaygan*; Katherine Zukotynski*; François Bénard; Cynthia Ménard; Joda Kuk; Golmehr Sistani; Glenn Baumann; Patrick Veit-Haibach; Ur Metser

**Co-first authors*

Slides prepared by: Christine Cha

Background

- Prostate-specific membrane antigen (PSMA), is a transmembrane glycoprotein highly expressed in prostate cancer cells.
- PSMA expression increases with increased pathological Gleason grade and is thought to be upregulated with the emergence of androgen independence.
- The most commonly used PSMA-targeted positron emission tomography (PET) radiopharmaceuticals in Canada are ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, and ^{18}F-PSMA-1007.
- Hybrid PET/computed tomography (CT) and PET/magnetic resonance (MR) scanners with PSMA-targeted radiopharmaceuticals allow anatomical localization and characterization of PSMA-avid disease.

Integrated whole-body PET/CT and PET/MRI protocol

Table 1. Suggested injected dose of common PSMA tracers and optimal uptake time

Tracer	Injected dose*	Uptake time (min)
^{68}Ga-PSMA-11[1]	150±25 MBq	60–90
^{18}F-DCFPyL[2]	300±60 MBq	60–120
^{18}F-PSMA-1007[3]	300±60 MBq	60–120

*Calculated for 75 kg man: 4±0.8 MBq/kg for ^{18}F F-DCFPyL and ^{18}F-PSMA-1007 and 2±0.33 MBq/kg for ^{68}Ga -PSMA-11; and 5±1 MBq/kg for ^{18}F-FDG. These values can be adjusted according to body weight. PSMA: prostate-specific membrane antigen.

Integrated whole-body PET/CT and PET/MRI protocol

- After the suggested injected dose and uptake time, the patient is positioned supine on the imaging table, optimally with arms up.
- Routine image coverage is from the top of the skull to the mid-thighs. Usually, 5–9 bed positions are obtained, depending on the patient height (2–3 min/bed position).
- For PET/CT, attenuation correction maps are generated from CT data.
- For PET/MR, attenuation correction methods are MRI-based attenuation correction maps generated from a two-point Dixon Gradient-echo sequence for the entire scan field.
- The administration of IV Lasix (10–40 mg) and use of dual time-point imaging may be helpful.

Integrated whole-body PET/CT and PET/MRI protocol

- To enable localization of small metastases, an axial gadolinium-enhanced T1 sequence, such as the volumetric interpolated breath-hold examination (VIBE) sequence, has shown high lesion conspicuity and time-efficiency.
- Coronal T2-weighted turbo inversion recovery magnitude for bone lesions or diffusion-weighted imaging may be added.
- Dedicated MR imaging of the prostate gland or prostate bed may be needed in specific clinical situations
  - For instance, during the primary staging of high-risk prostate cancer with PET/MR or to confirm local recurrence of disease when PET images are obscured by activity from radiotracer in the bladder.
  - In these instances, routine MR protocols are used: multiplanar T2-weighted sequences and diffusion-weighted sequences, as well as pre- and post-dynamic contrast-enhanced MR.

Normal biodistribution of PSMA-targeted radiopharmaceuticals and common PSMA-avid benign entities

- Physiological, high PSMA-targeted radiopharmaceutical uptake is seen in PSMA-expressing organs, such as the lacrimal and salivary glands, as well as the kidneys.
- Moderate radiopharmaceutical uptake is seen in the spleen and nasopharynx, and variable uptake is seen in the vocal cords, trachea, and bronchi, as well as the proximal gastrointestinal tract (Figs. 1A, 1B).

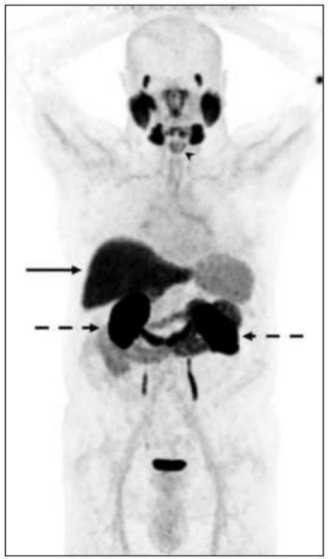

Fig. 1. Normal biodistribution of ^{18}F-DCFPyL (a common PSMA radiopharmaceutical). ***(A)*** Maximum Intensity Projection (MIP) image showing high uptake in lacrimal and salivary glands and kidneys (dotted arrows), moderate uptake in liver (solid arrow) and low to moderate uptake in the spleen and vocal cords (arrowhead).

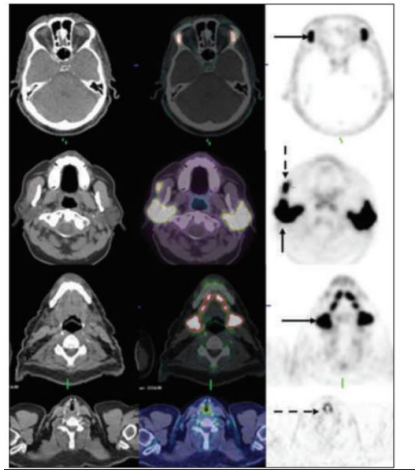

Fig. 1B. Axial CT, fused ^{18}F-DCFPyL PET/CT and PET images showing high uptake in lacrimal glands (arrow; top row), salivary glands (arrow; middle rows), accessory salivary gland (dotted arrow middle row) and moderate uptake in the larynx (dotted arrow; bottom row).

Normal biodistribution of PSMA-targeted radiopharmaceuticals and common PSMA-avid benign entities

- The degree of uptake in the liver and accumulation in the urinary tract and bladder varies depending on the clearance mechanism of the specific radiopharmaceutical.
  - Most PSMA-targeted radiopharmaceuticals are cleared via the genitourinary tract, with high accumulation in the urinary tract and bladder and moderate uptake in the liver.
  - ^{18}F-PSMA-1007 is an exception, with primarily hepatobiliary clearance, higher uptake in the liver, and little accumulation in the ureters and bladder.
  - Lack of renal clearance may aid in identifying disease sites adjacent to the bladder and ureters, such as local tumor recurrence after prostatectomy.
- Peripheral neural structures, including the ganglia and nerve roots, may show physiological increased radiopharmaceutical uptake.
- The celiac and stellate ganglia have been described as potential pitfalls for the assessment of retroperitoneal and supraclavicular lymph node disease spread, respectively.

Normal biodistribution of PSMA-targeted radiopharmaceuticals and common PSMA-avid benign entities

Despite its name, PSMA is not prostate-specific and there are numerous non-prostate malignancies, as well as benign processes, which have been reported to be PSMA-avid (Table 2).

Table 2. Benign processes which may be associated with increased PSMA uptake

	Origin	Subcategory	Entity
Benign tumors	Mesenchymal	Vascular/ perivascular	Hemangioma, angiomyolipoma
		Neural origin	Meningioma, peripheral nerve sheath tumors
		Connective tissue	Fibrous histiocytoma, dermatofibroma, aggressive fibromatosis, myxoma, pseudoangiomatous stromal hyperplasia (breast)
	Epithelial	Adenoma	Adrenal, thyroid, pancreatic serous cystadenoma
		Thymoma	
Infectious or inflammatory			Various infectious, sarcoidosis
Bone remodeling			Fracture, degenerative (osteophyte), Paget's disease
Other			Amyloidosis

Other (non-prostate) PSMA-avid malignancies

- Several malignancies are PSMA-avid and can have a range of PSMA intensity (Figs. 4, 5, 6).
- Additional non-prostatic malignancies that have been shown to be PSMA-avid include malignancies of the gastrointestinal tract, renal cell carcinoma, neuroendocrine malignancy, gliomas, and breast cancer, among others.

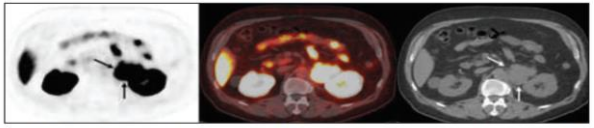

Fig. 4. Axial ^{18}F-DCFPyL PET, fused PET/CT, and CT images show intense uptake in a patient with a left adrenal leiomyosarcoma (arrows)..

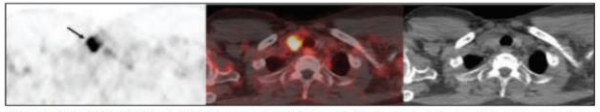

Fig. 5. Axial ^{18}F-DCFPyL PET, fused PET/CT and CT images show intense uptake in primary thyroid cancer of the right thyroid lobe (arrow).

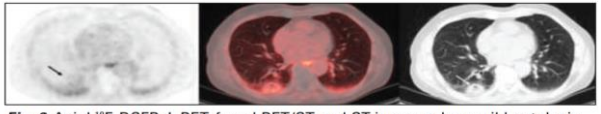

Fig. 6. Axial ^{18}F-DCFPyL PET, fused PET/CT and CT images show mild uptake in primary adenocarcinoma of the right lung (arrow).

In certain cases, the use of more than one radiopharmaceutical may be helpful for disease characterization (Fig. 7).

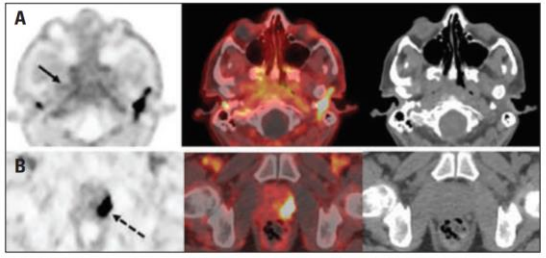

Fig. 7. (A) 58-year-old man with concurrent nasopharyngeal cancer and prostate cancer. Axial ^{18}F-DCFPyL PET, fused PET/CT, and CT images show mild uptake in the nasopharyngeal cancer (solid arrow top row) and intense uptake in the prostate cancer (dotted arrow bottom row). ***(B)*** Axial ^{18}F-FDG PET, fused PET/CT and CT images in the same 58-year-old man with concurrent nasopharyngeal cancer and prostate cancer show intense uptake in the nasopharyngeal cancer (solid arrow, top row) and mild uptake in the prostate cancer (dotted arrow; bottom row).

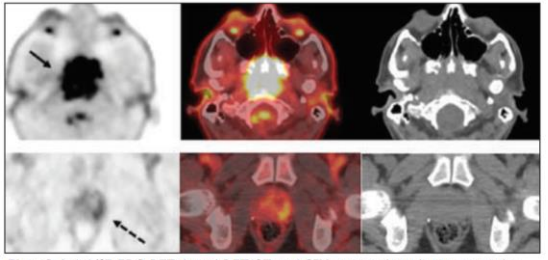

Fig. 7C. Axial ^{18}F-FDG PET, fused PET/CT and CT images show intense uptake in known nasopharyngeal cancer (solid arrow, top row) and a mild uptake in known prostate cancer (dotted arrow; bottom row).

Other (non-prostate) PSMA-avid malignancies

- It is important to remember that the intensity of PSMA uptake does not imply a diagnosis of prostate vs. non-prostatic malignancy.
  - Fig. 8 shows a case of an intensely PSMA-avid sternal metastasis related to prostate cancer in a patient with an intensely PSMA-avid hepatocellular carcinoma
- Ultimately, it is important to have the complete patient history, including any imaging prior to PSMA-targeted PET interpretation and even so, biopsy may be needed for pathological characterization in certain cases.

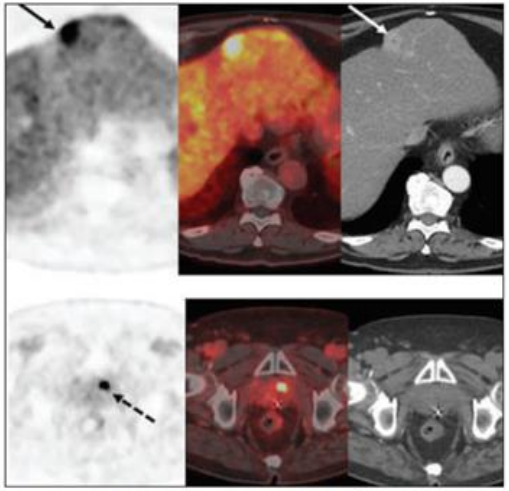

Fig. 8. Axial ^{18}F-DCFPyL PET, fused PET/CT, and CT images in a 76-year-old man show intense uptake in concurrent hepatocellular carcinoma (arrows, top row) and prostate cancer (dotted arrow bottom row).

Clinical indications for PSMA-targeted PET

While access to PSMA-targeted PET currently remains variable across Canada, Table 3 provides suggested indications, including the quality of supportive evidence and recommendation strength.

1. Staging of biochemical recurrence
2. Primary staging of high risk prostrate cancer
3. Primary detection of tumor as an adjunct to multiparametric MRI
4. Evaluation of men with metastatic prostrate cancer

Table 3. Suggested indications for PSMA-targeted PET

	Indication	Evidence quality	Recommendation strength	Current recommendation
Diagnosis	Primary diagnosis of prostate cancer	3	4	PSMA-targeted PET may be helpful to identify clinically significant prostate cancer when systematic biopsies and MRI are negative
Primary staging	Primary staging of high-risk prostate cancer	3	2	PSMA-targeted PET may be helpful if a change in management is contemplated
Castration-sensitive	Rising PSA after prostatectomy; locoregional salvage considered	1	1	PSMA-targeted PET may be helpful if locoregional salvage is considered
	Rising PSA after radiotherapy; locoregional salvage considered	2	2	PSMA-targeted PET may be helpful if locoregional salvage is considered
	Potentially oligometastatic, castration-sensitive prostate cancer	2	2	PSMA-targeted PET may be helpful to confirm oligometastatic vs. extensive disease
Castration-resistant	Non-metastatic	3	2	PSMA-targeted PET may be helpful if a change in management is contemplated
	Metastatic with PSA progression (stable on CI)	4	3	PSMA-targeted PET should not be routinely offered outside of a clinical trial
	Metastatic with radiographic progression on CI	4	2	PSMA-targeted PET should not be routinely offered outside of a clinical trial

Quality of evidence: 1=high; 2=intermediate; 3=weak; 4=insufficient. Strength of recommendation: 1=strong; 2=moderate; 3=weak. CI: conventional imaging (CT, bone scintigraphy). CI: conventional imaging; MRI: magnetic resonance imaging; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen.

Staging of biochemical recurrence

- The most common indication for PSMA-targeted PET is for the evaluation of disease in men with biochemical failure after primary prostate cancer therapy.
- PSMA-targeted PET may be useful in detecting disease sites even when the serum PSA is low.
  - Approximately 38% of PSMA-targeted PET scans show disease sites in men with PSA <0.5 ng/ml.
- A prospective trial of 635 patients showed a positive predictive value of 84–92% for ^{68}Ga-PSMA-11 PET in localizing disease, with PET-directed focal therapy alone leading to a PSA drop of ≥50% in 31/39 (80%) patients.
- Despite the strengths of PSMA-targeted PET, there are also limitations and pitfalls
  - Reasons for false-negative studies include: small tumor volume, such as may be seen in men with early-stage biochemical recurrence when the serum PSA is below 0.5 ng/ml or neuroendocrine differentiation of prostate cancer with downregulation of PSMA expression.

Primary staging of high-risk prostrate cancer

- Studies assessing the use of PSMA-targeted PET for staging men with prostate cancer are not numerous, although there is a growing body of supportive literature in patients with high-risk disease.
  - Pro-PSMA trial showed PET/CT performed better than conventional imaging with less equivocal findings and resulted in frequent management change.
  - PET/CT may identify nodes outside of the routine surgical field, as well as additional sites of distant disease (Fig. 16), although lymph node dissection may still be needed.

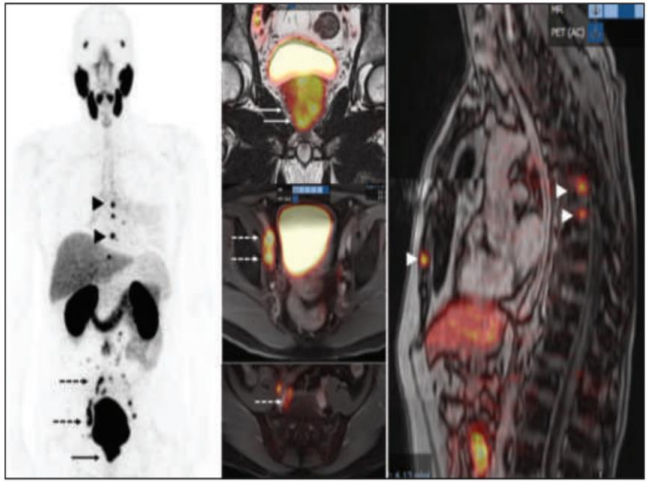

Fig. 16. A 58-year-old man with high-volume Gleason 9 (4+5) prostate cancer with seminal vesicle invasion (cT3b). Baseline serum PSA=217 ng/ml; negative conventional workup. Maximum intensity ^{18}F-DCFPyL PET image and select coronal, axial, and sagittal PET/MR images show extensive primary tumor (solid arrows), metastatic pelvic (miN), and common iliac lymph nodes (miM1a) (dotted arrows), as well as multiple bone metastases (miM1b) (arrowheads).

Primary detection of tumor as an adjunct to multiparametric MRI

- In recent years, multiparametric magnetic resonance imaging (mpMRI) has been incorporated in the work-up of men with suspected prostate cancer, showing considerable promise in detection, localization, risk stratification, and staging of prostate cancer.
  - A small series suggested PSMA-targeted PET identified histologically confirmed intraprostatic cancer sites[18] and may have performance comparable and complementary to mpMRI in the characterization of clinically significant (Gleason grade group >2) disease.
  - The role of PSMA targeted PET as an adjunct to mpMRI for primary detection of clinically significant prostate cancer is not well-established and is being investigated in a prospective trial (Fig. 17).

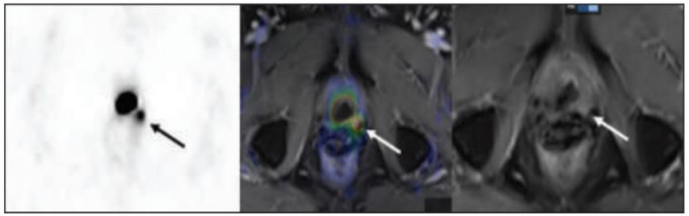

Fig. 17. A 65-year-old man with clinical suspicion of prostate cancer and prior negative systematic transrectal ultrasound-guided biopsies. Axial ^{18}F-DCFPyL PET, fused PET/MR and MR images shows focal intense uptake in the right peripheral zone in the mid gland, towards the apex. Biopsy revealed Gleason 7 (4+3) prostate cancer.

Evaluation of men with metastatic prostrate cancer

- PSMA-targeted PET can identify sites of metastatic disease at the time of initial staging, biochemical recurrence, and in the setting of castration-resistance in the absence of lesions on conventional imaging.
- While PET-based biomarkers offer the potential for quantitative evaluation of response, these metrics have yet to be validated in clinical populations and are not yet part of current decision-making pathways.
- The clinical importance of more comprehensive staging and PET-based response assessment remains to be defined, although PSMA-targeted PET may prove to be increasingly helpful as a diagnostic tool paired with PSMA-targeted therapy.
- Both ^{177}Lu and ^{225}Ac PSMA-targeted radioligand therapy are emerging as promising therapies for castration-resistant disease.

Conclusions

- While there are no PSMA-targeted PET radiopharmaceuticals approved by Health Canada for routine use in clinical care, it seems reasonable that PSMA-targeted PET will become part of routine clinical care in Canada in the near future.
- PSMA-targeted PET has high overall accuracy for the detection of prostate cancer and a growing role in determining patient management, particularly in men with high-risk disease at the time of staging and biochemical failure after primary therapy.
- Ongoing research will help clarify the long-term impact of PSMA-targeted PET on patient outcome, as well as to better define the relative strengths and weakness of the individual available PSMA-targeted PET radiopharmaceuticals.