Next Generation Imaging (PSMA) and Introduction to Theranostics

Presented by:

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Learning Objectives

- Characterize and compare current molecular imaging modalities.
- Discuss next generation PSMA PET imaging in the assessment of men with biochemical recurrence after failed local therapy.
- Understand the role, indications and techniques for imaging in patients with known or suspected metastatic prostate cancer.
- Identify patients and prescribe radionuclide therapy in appropriate patients with symptomatic mCRPC

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Conventional Imaging for Prostate Cancer Detection

- **Bone Scan**
- **Computed Tomography (CT) Scan**
- **Benefits:**
  - Widely available
  - Low Costs: $300–$1,500
  - Used in Clinical Trials for patient selection and stratification
    - CHAARTED High Vol: ≥4 bone mets, ≥1 outside vertebrae/pelvis, and/or visceral mets
    - LATITUDE High Risk: 2 or more of: Gleason ≥8, ≥3 bone mets, visceral mets

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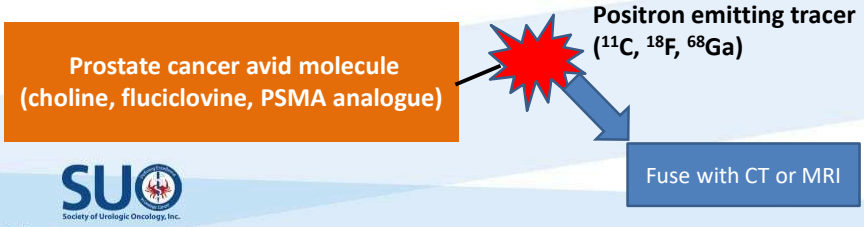
Positron Emission Tomography (PET)

- Guidelines have shifted from considering novel PET scans (fluciclovine, choline, PSMA) *as an alternative to conventional imaging* or in the setting of negative conventional imaging.
- Now: **PET** is preferentially recommended as an alternative to conventional imaging



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Approved Next Generation PET Imaging for Prostate Cancer

- C-11 choline PET
  - Used in cellular membrane synthesis, increased in prostate cancer cells
  - Short half life (20 minutes) need on site cyclotron
  - Limited Access
- F-18 Fluciclovine (Axumin)
  - Synthetic amino acid PET
  - Increased uptake in prostate cancer cells due to increased metabolism
  - Indicated for detection of recurrence, minimal urinary excretion
- PSMA Targeted PET
  - Transmembrane glycoprotein overexpressed on prostate cancer cells
  - F-18 piflufolastat (DCFPyL) PSMA
  - Ga-68 PSMA-11
  - Higher sensitivity than others

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FDA Approval PSMA PET

Approved 12/2020 Initially 2 sites in CA

For Recurrence and **Candidates for Initial Definitive Therapy**

^{68}GA-PSMA-11 PET

JAMA Oncology | Original Investigation

Assessment of ^{68}Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer
A Prospective Single-Arm Clinical Trial

Wolfgang P. Fendler, MD; Jeremie Calais, MD; Matthias Eiber, MD; Robert R. Flavell, MD, PhD; Ashley Mishoe, PharmD; Felix Y. Feng, MD; Hao G. Nguyen, MD, PhD; Robert E. Reiter, MD; Matthew B. Rettig, MD; Shozo Okamoto, MD; Louise Emmett, MD; Helle D. Zacho, MD; Harun Ilhan, MD; Axel Wetter, MD; Christoph Rischpler, MD; Heiko Schoder, MD; Irene A. Burger, MD, Jeannine Gartmann; Raven Smith; Eric J. Small, MD; Roger Slavik, PhD; Peter R. Carroll, MD, MPH; Ken Herrmann, MD; Johannes Czernin, MD; Thomas A. Hope, MD

JAMA Oncol. 2019;5(6):856-863.

Accuracy of 68Ga-PSMA-11 for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: A multicenter prospective phase III imaging study.

JCO 38, no. 15_suppl (2020) 5502

^{18}F-DCFPyL PSMA PET

A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with ^{18}F-DCFPyL in Prostate Cancer Patients (OSPREY)

Kenneth J. Pienta,* Michael A. Gorin,† Steven P. Rowe, Peter R. Carroll,‡ Frédéric Pouliot,§ Stephan Probst, Lawrence Saperstein, Mark A. Preston, Ajjai S. Alva,‖ Akash Patnaik, Jeremy C. Durack,¶ Nancy Stambler,** Tess Lin,** Jessica Jensen,** Vivien Wong,** Barry A. Siegel,**,†† Michael J. Morris,**,‡‡ and OSPREY Study Group

J Urol Vol. 206, 52-61, July 2021

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Diagnostic Performance of ^{18}F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study

Michael J. Morris[1], Steven P. Rowe[2], Michael A. Gorin[3], Lawrence Saperstein[4], Frédéric Pouliot[5], David Josephson[6], Jeffrey Y.C. Wong[7], Austin R. Pantel[8], Steve Y. Cho[9], Kenneth L. Gage[10], Morand Piert[11], Andrei Iagaru[12], Janet H. Pollard[13], Vivien Wong[14], Jessica Jensen[14], Tess Lin[14], Nancy Stambler[14], Peter R. Carroll[15], Barry A. Siegel[16], and CONDOR Study Group

Clin Cancer Res 2021;27:3674-82

Approved 5/2021

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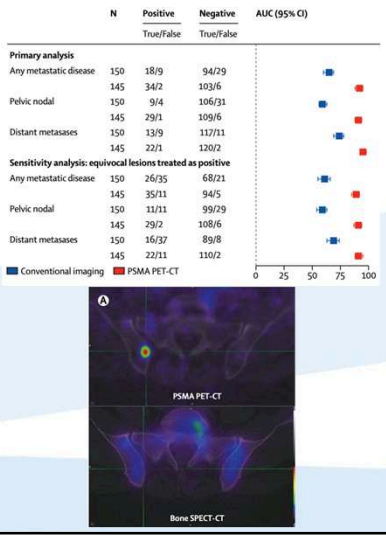
PSMA PET in High Risk Localized CaP: ProPSMA

- P3 trial of 302 men with high-risk CaP, randomized 1:1 to PSMA PET or conventional imaging
- Primary Endpoint: Accuracy of 1st line imaging to detect mets
- PSMA PET significantly greater accuracy (27%) with improved sensitivity and specificity
- PSMA PET had lower radiation exposure



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Lancet 2020; 395: 1208–16

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PSMA PET in High Risk BCR CaP: EMBARK Eligible

- Retrospective review of 182 patients who fulfilled the EMBARK Eligibility
- PSA >1 (RP) or >2 (XRT), PSAdt <9M
- Negative conventional imaging
- Ga-PSMA PET positive 84% overall
- PET detected pelvic nodal disease in 29%
- PET detected Distant Metastatic (M1) in 46%

Table 3. Metastatic Burden Classification by PSMA-PET/CT

	Patients, No. (%)			
Disease burden categorization	RP (n = 91)	dRT (n = 39)	SRT (n = 52)	Overall (N = 182)
Nonmetastatic	60 (65.9)	17 (43.6)	21 (40.4)	98 (53.8)
Oligometastatic (1 lesion)	10 (11.0)	7 (17.9)	16 (30.8)	33 (18.1)
Oligometastatic (2-4 lesions)	17 (18.7)	10 (25.6)	11 (21.2)	38 (20.9)
Polymetastatic (>≥5 lesions)	4 (4.4)	5 (12.8)	4 (7.7)	13 (7.1)

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JAMA Network Open. 2025;8(1):e2452971

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Clinically Localized Prostate Cancer: AUA/ASTRO Guideline (2022), Endorsed by SUO:

- Staging:

5. Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer. (Expert Opinion)
6. Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
7. In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion)

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Updates to Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline (2023):

- Biochemical Recurrence Without Mets After All Local Treatments:

5. **In patients with PSA recurrence after failure of local therapy who are at higher risk for the development of metastases (e.g., PSADT <12 months), clinicians should perform periodic staging evaluations consisting of cross-sectional imaging (CT, MRI) and technetium bone scan, and/or preferably PSMA PET imaging. (Clinical Principle)**
6. **Clinicians should utilize PSMA PET imaging preferentially, where available, in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging due to its greater sensitivity, or in the setting of negative conventional imaging. (Expert Opinion)**

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Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline (2024)

Treatment Decision-Making at the Time of Suspected Biochemical Recurrence After Primary Radical Prostatectomy (RP)

8. In patients with a BCR after local therapy, clinicians may obtain a prostate-specific membrane antigen (PSMA)-PET in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence. (Grade C)
9. For patients with BCR following RP in whom salvage radiation is being considered, the clinician should perform next generation molecular PET imaging. (Grade C)

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Updates to Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline (2023):

- Non-Metastatic Castration-Resistant Prostate Cancer:

21. Clinicians should assess nmCRPC patients for development of metastatic disease using conventional or PSMA PET imaging at intervals of 6 to 12 months. (Expert Opinion)

- Metastatic Castration-Resistant Prostate Cancer:

27. In mCRPC patients with disease progression (PSA or radiographic progression or new disease related symptoms) having previously received docetaxel and androgen pathway inhibitor, who are considering ^{177}Lu-PSMA-617, clinicians should order PSMA PET imaging. (Expert Opinion)

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2026 NCCN Guidelines

- PSMA PET can be considered as an alternative to conventional imaging for initial staging, evaluation of biochemically recurrent disease, and at the time of disease progression
- **Conventional imaging is not needed prior to PSMA PET and so PSMA PET can be considered equally or even more effective as front-line imaging at both initial staging and biochemical recurrence**
- C-11 choline or F-18 fluciclovine PET can be used to detect small-volume recurrence, however studies show that PSMA PET has higher sensitivity, especially at very low PSA levels

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2026 NCCN Guidelines

Intermediate[J]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[K]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive (eg, ≥6 of 12 cores)[K]	• Soft tissue imaging and consider bone imaging[g] ▸ If regional metastases are found, see PROS-7 ▸ If distant metastases are found, see PROS-14 for Low-Volume M1(Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC or PROS-15 for High-Volume M1 CSPC
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3–cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL			Bone and soft tissue imaging[g] ▸ If regional metastases are found, see PROS-7 ▸ If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC or PROS-15 for High-Volume M1 CSPC
Very high	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL			Bone and soft tissue imaging[g] ▸ If regional metastases are found, see PROS-7 ▸ If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC or PROS-15 for High-Volume M1 CSPC

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2026 NCCN Guidelines

- PSMA imaging should be done before initiation of ADT because ADT may affect detection sensitivity
- PET imaging may change treatment but may not change oncologic outcomes
- Consider the Will Rogers effect: moving patients with worse prognosis to a higher risk group appears to make the outcomes of both groups improve

PSMA PET Reporting Guidelines

1. No PSMA PET reporting Guidelines have been officially adopted among Radiological or Clinical Societies.
2. Several Exist: PROMISE v2.0 (miTNM), PRIMARY, and RECIP.
3. Available guidelines are directed more towards academic imaging

European Journal of Nuclear Medicine and Molecular Imaging (2024) 52:335–341

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EAU Guidelines 2026

Staging of Prostate Cancer

Recommendations	Strength rating
Any risk group staging	
Use prebiopsy magnetic resonance imaging (MRI) for local staging information.	Weak
Low-risk and favourable intermediate-risk localised disease	
Do not use additional imaging for staging purposes.	Strong
Unfavourable intermediate-risk disease	
Perform prostate-specific antigen positron emission tomography/computed tomography (PSMA PET/CT), if available, to increase accuracy, or at least cross-sectional abdominopelvic imaging and a bone scan.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening using PSMA PET/CT, if available, or at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

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EAU Guidelines 2026

Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) scan to males with a persistent prostate-specific antigen (PSA) and rising if the results will influence subsequent treatment decisions.	Weak

Evidence and guidelines for imaging in patients with biochemical recurrence

Recommendations	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions (i.e. EAU BCR risk groups).	Weak
PSA recurrence after radiotherapy	
Perform PSMA PET/CT in patients fit for curative salvage treatment.	Strong
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak

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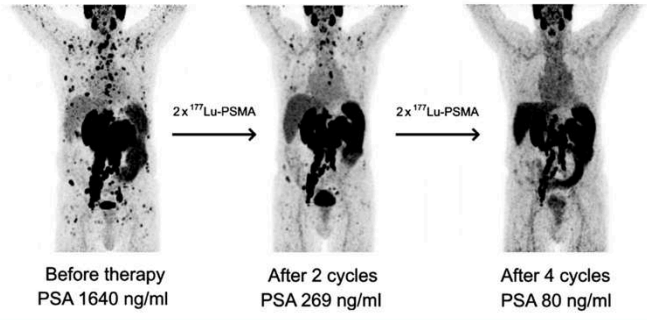
Theranostics

- Theranostics: combination of “therapy” and “diagnostics”
- Treatment using 2 radiolabeled ligands:
  1. Predictive biomarker
  2. Therapeutic agent
- A precision treatment option transitioning from conventional to personalized medicine



Clin Genitourin Canc 2021; **19**: e235–e247

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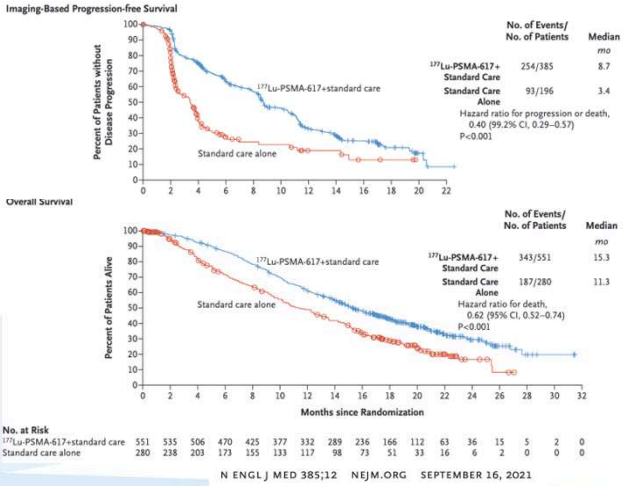
Approved 3/2022

First Theranostics Approval: Lutetium

- Lutetium-177 (177Lu)-PSMA is a β-particle radioligand therapy targeting PSMA-expressing cells
- VISION Trial: Phase III trial of Lutetium+SOC vs SOC
- Inclusion: At least 1 AR pathway inhibitor and 1 or 2 taxane regimens and 68Ga PSMA + PET scan
- Lutetium added to SOC improved PFS and OS compared to SOC alone
- Corresponding New Approval for Ga-68 PSMA-11 PET to identify candidates for targeted therapy
- FDA Approved: mCRPC, progression after docetaxel and androgen axis tx, with positive PSMA PET



N ENGL J MED 385;12 NEJM.ORG SEPTEMBER 16, 2021

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***NCCN Guidelines Support either Ga-68 PSMA-11 or F-18 PSMA PET for patient selection**

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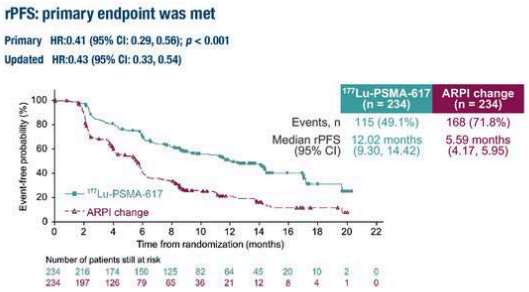
PSMAfore Trial: Earlier use of ^{177}Lu-PSMA-617

- Phase III Trial mCRPC post-ARPI, pre-chemotherapy
- Lutetium vs. Change in ARPI
- Primary EP: rPFS
  - HR 0.41 (95% CI: 0.29–0.56), p < 0.001
  - Median rPFS: 12M vs 5.6M
- 2025 FDA Approval:
  - mCRPC Post-APRI, Pre-chemo



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Sartor O, et al. Phase 3 trial of [177Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore). ESMO Congress 2023, LBA13

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ENZA-p: PSMA PET as Treatment Response Marker

- Phase 2 Trial of doce/APRI naïve mCRPC men (excluding Abi) at high risk for early progression
- 1:1 Enzalutamide +/- Lu-PSMA with adaptive-dosing (2/4 doses) based on PSMA PET at Day 92
- 11% received 2 doses, 81% received all 4 doses
- Combined treatment with imaging base adaptive-dosing significantly improved PSA PFS

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The Lancet Oncology: Volume 25, Issue 5, May 2024, Pages 563-571

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Conclusions

- CT and Tc-99m bone scan: standard imaging modalities, remain widely used, and continue to define disease states
- PSMA PET is more sensitive for PC (primary and recurrent) than CT and bone scan
  - However improved clinical outcomes are not clear
    - M0 CRPC Definition
    - High/Low Volume Mets
- Clinical trials assessing impact of new imaging on disease state definitions and outcomes of salvage therapy (efficacy, costs) are needed
- Lutetium is the first of a new drug class (Theranostics) that combines an image linked biomarker to a therapeutic agent that improves survival in patients with mCRPC

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