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Clinical and Translational Research in Radiotheranostics

Jeremie Calais

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Clinical and Translational Research in Radiotheranostics

Habilitation à diriger des recherches
de l'Université Paris-Saclay

présentée et soutenue à Paris, le 12 novembre 2024, par

Jeremie CALAIS

Composition du jury

Françoise KRAEBER-BODERE

Professeur des Universités - Praticien Hospitalier
CHU Nantes - Université de Nantes

Rapportrice

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Professeur des Universités - Praticien Hospitalier
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Rapporteur

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Professeur des Universités - Praticien Hospitalier
IUCT Oncopole - CHU Toulouse

Rapporteur

Irène BUVAT

Directeur de recherche CNRS
Institut Curie - Université Paris-Saclay

Examinatrice

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Professeur des Universités - Praticien Hospitalier
Institut Curie - Université Paris-Saclay

Examineur

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Professeur des Universités - Praticien Hospitalier
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Examineur

Pierre VERA

Professeur des Universités - Praticien Hospitalier
Centre Henri Becquerel – Université de Rouen

Examineur

ACKNOWLEDGEMENTS

I would like to express my gratitude to Irène Buvat and Philippe Dollfus for their kindness, help, guidance and support with this project of Accreditation to Supervise Research (Habilitation à Diriger des Recherches (HDR)).

I would also like to thank all the members of the Jury for their precious time and esteemed expertise.

Nothing of this work would have been possible without my colleagues, co-workers, co-authors, co-investigators, staff, students, residents, fellows, post-docs from UCLA and all over the world.

Thank you.

Words cannot express my gratitude to Johannes Czernin, my mentor for the past eight years, who offered me the opportunity of a new life in Los Angeles, and who gave me trust, support and deep friendship.

And above all, I want to thank my wife Camille, my son Oscar and my daughter Nina, for their support and the strength they give me in my life.

I love you.

MANUSCRIPT PRESENTATION

This manuscript of Accreditation to Supervise Research (Habilitation à Diriger des Recherches (HDR)) aims at presenting my scientific contributions since joining the University of California, Los Angeles (UCLA) with a focus on selected publications in which I served as supervisor.

As the Director of the Theranostics and Clinical Research Programs of the Ahmanson Translational Theranostics Division at the David Geffen School of Medicine, University of California Los Angeles (UCLA), I had the opportunity to supervise multiple students, residents, PhD, post-doctoral fellows, and physicians for research projects related to cancer imaging and theranostics.

The manuscript is divided in 3 parts. In the first part are summarized my credentials, career track, and scientific productions. The second part provides an overview of my work as research supervisor through a selection of published articles in which I served as supervisor. In the third part, I briefly describe my future research perspective and projects.

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BIO

I am a physician-scientist specialized in nuclear medicine and oncology working at UCLA (University of California, Los Angeles). I serve as the Director of the Theranostics and Clinical Research Programs of the Ahmanson Translational Theranostics Division and as an Associate Professor in the Department of Molecular and Medical Pharmacology at the David Geffen School of Medicine, University of California Los Angeles (UCLA).

I completed my training in France: I earned my medical degree at the University of Paris VII Diderot (2010), completed my residency at the Henri Becquerel Cancer Center, University of Rouen (2014) and my Fellowship at the Xavier Bichat University Hospital in Paris (2016). I also obtained my Master of Sciences (MSc) at the University of Paris-Saclay (2016).

I went abroad to experience academic research in the Ahmanson Translational Theranostics Division at UCLA (University of California, Los Angeles) in 2016. It has now been 8 years since I have had the chance to work at UCLA, in a very stimulating academic environment. I became responsible for several programs within the nuclear medicine department: director of the clinical Theranostics program and director of the clinical research program. I lead a team dedicated to clinical research which is made up of research MDs (n= 3 to 5), clinical research assistant coordinators (n=10), and students (n= 3 to 8). I work in close collaboration with the clinical hospital teams but also with the pre-clinical research teams investigating pre-clinical and in-vitro models, as well as with the doctoral school of biomedical physics.

My research focuses on radiotheranostics, an approach combining targeted imaging and therapeutic radiopharmaceuticals binding to the same molecular target. My goal is to improve the outcome of patients with cancer through theranostic approaches by applying knowledge gained from preclinical models and clinical studies. I have worked extensively on PSMA, a protein overexpressed by prostate cancer cells. Diagnostic and therapeutic applications using PSMA are now implemented in clinical routine here at UCLA. I had the opportunity to conduct the initial research, then the pivotal studies that led to FDA approval and finally to supervise the routine clinical implementation of PSMA PET imaging and Lu177-PSMA therapy. Multiple other molecular targets (FAP, CA-IX, SSTR, GRPR, GPC3) and applications (dosimetry, artificial intelligence) are also being studied.

Taking advantage of the resources of the American academic research system, and of the rise of radiotheranostics, I had the opportunity to lead as principal investigator numerous clinical and translational research studies (from phase 0 to phase 3) using targeted radionuclide imaging and/or therapy and to collaborate with many academic and industrial partners, national and international. I became a certified principal investigator by the ACRP (Association of Clinical Research Professionals).

I obtained the Doctorate in Science (PhD) from the University of Paris-Saclay (Physics and Medical Imaging Specialty) by Accreditation of Prior Learning (Validation of Acquired Experience (VAE)) in December 2023 using the work conducted at UCLA over the past 8 years.

CURRICULUM VITAE - JEREMIE CALAIS - MD PhD

Current Position: **Associate Professor**, Department of Molecular and Medical Pharmacology
Director, Theranostics Program, Ahmanson Translational Theranostics Division
David Geffen School of Medicine at UCLA

Work address: **Ahmanson Translational Theranostics Division**,
Clinic Office, UCLA Nuclear Medicine, 200 Medical Plaza, Suite B114-69
Research Office, Department of Molecular & Medical Pharmacology, CHS AR-255
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Social Media: <https://twitter.com/CalaisJeremie>
<https://www.linkedin.com/in/jeremie-calais/>

EDUCATION

1995-2002 Middle School and High School
Lycée Carnot, Paris, France.

2002-2003 Biology, Chemistry, Physics, and Earth Sciences (CPGE BCPST)
Lycée Chaptal, Paris, France.

2003-2010 **Medical School (MD)**
Xavier Bichat Faculty of Medicine, University of Paris-Diderot, France.

2010-2014 **Nuclear Medicine Specialty (DES de Medecine Nucleaire)**
Henri Becquerel Cancer Center, University of Rouen, France.

October 2014 **Doctor of Medicine**
University of Rouen, France.
Medical Thesis Defense Date: October 14, 2014. <https://dumas.ccsd.cnrs.fr/dumas-01083363>

2014-2016 **Oncology Imaging Specialty (DESC Cancerologie, option Imagerie)**
University of Rouen, France.

2015-2017 **Master of Science (MSc)**
Biomedical Imaging
University Paris-Sud, France.

December 2023 **Doctor of Science (PhD)** by Accreditation of Prior Learning (VAE),
Medical Physics and Imaging
Institut Curie, University Paris-Saclay, France.
PhD defense date: December 18, 2023. <https://theses.fr/s356616>

April 2024 **Certified Principal Investigator (CPI)**
Association of Clinical Research Professionals (ACRP), USA.

ACADEMIC CAREER TRACK

- 2010-2014 **Residency (Nuclear Medicine Specialty)**
Department of Nuclear Medicine
Henri Becquerel Cancer Center at University of Rouen, France.
- 2014-2016 **University Assistant - Clinical Fellow**
Department of Nuclear Medicine and Biophysics
Xavier Bichat Hospital and Faculty of Medicine at University of Paris-Diderot, France.
- 2016-2017 **Post-doctoral Research Fellow**
Ahmanson Translational Theranostics Division
Department of Molecular and Medical Pharmacology
David Geffen School of Medicine at University of California Los Angeles, USA.
- 2017-2018 **Assistant Adjunct Professor**
Ahmanson Translational Theranostics Division
Department of Molecular and Medical Pharmacology
David Geffen School of Medicine at University of California Los Angeles, USA.
- 2018-2021 **Assistant Professor**
Ahmanson Translational Theranostics Division
Department of Molecular and Medical Pharmacology
David Geffen School of Medicine at University of California Los Angeles, USA.
- 2021 - Present **Associate Professor**
Ahmanson Translational Theranostics Division
Department of Molecular and Medical Pharmacology
David Geffen School of Medicine at University of California Los Angeles, USA.

PROGRAM DIRECTOR

- 2018 - Present **Director, Clinical Research Program**
Ahmanson Translational Theranostics Division
Department of Molecular and Medical Pharmacology
David Geffen School of Medicine at University of California Los Angeles, USA.
- 2021 – Present **Director, Theranostics Program**
Ahmanson Translational Theranostics Division
Department of Molecular and Medical Pharmacology
David Geffen School of Medicine at University of California Los Angeles, USA.

MEDICAL PROFESSIONAL EXPERIENCE: See details in full CV pages 183-185

BIOPHARMA INDUSTRY CONSULTANT: See details in full CV pages 199-201

OTHER PROFESSIONAL MEMBERSHIPS: See details in full CV page 187

RESEARCH TRACK

CLINICAL RESEARCH TRIAL INVESTIGATOR: (detailed list of trials in full CV pages 193-197)

	Investigator Initiated Trial (IIT)		Industry Sponsored Clinical Trials	
	Imaging	Therapy	Imaging	Therapy
Principal Investigator (PI)	14	2	1	5
Co-Investigator	5	2	4	11

GRANTS, FUNDING AND SUPPORT (as of Sept 2024)

- 2016-2017 **ARC Foundation International Mobility Award SAE20160604150**
Title: Development and translation of a new nuclear imaging probe for theranostics in cancer patients: 68Ga-Pentixafor
Supporting Agency: ARC French foundation for Cancer Research (ARC-France)
Level of funding: **30,000€**
- 2016-2017 **Philippe Foundation Exchange Program Grant**
Title: Development and translation of a new nuclear imaging probe for theranostics in cancer patients: 68Ga-Pentixafor
Supporting Agency: Philippe Foundation, NYC, USA.
Level of funding: **\$10,000**
- 2017-2018 **Philippe Foundation Exchange Program Grant**
Title: Preclinical and clinical exploration of theranostics pairs 68Ga-/177Lu-DOTATATE and 68Ga-/177Lu-PSMA
Supporting Agency: Philippe Foundation, NYC, USA.
Level of funding: **\$10,000**
- 2019-2021 **ERF-SNMMI [USA], Molecular Imaging Research Grant for Junior Academic Faculty**
Title: Imaging tumor stroma with 68Ga-PSMA-11 and 68Ga-FAPI-46 in patients with non-prostate cancers: an exploratory PET biodistribution study with histopathology validation.
Supporting Agency: Society of Nuclear Medicine and Molecular Imaging
Level of Funding: **\$105,000**
<https://newsroom.ucla.edu/dept/faculty/grant-expands-new-imaging-techniques-that-target-tumor-environment>
<https://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=35505>
<https://clinicaltrials.gov/study/NCT04147494>
- 2020-2023 **PCF Young Investigator Award 20YOUN05**
Title: Validating a PET imaging biomarker for targeting fibroblast activation protein in prostate cancer stroma.
Supporting Agency: Prostate Cancer Foundation
Level of Funding: **\$225,000**
<https://newsroom.ucla.edu/dept/faculty/jeremie-calais-young-investigator-award-prostate-cancer>
<https://clinicaltrials.gov/study/NCT04457232>
- 2020-2024 **Investigator Initiated trial Protocol #PSMA-dRT IRB#20-000378 NCI-2020-03445**
Title: Phase 3 Randomized Trial of PSMA PET Prior to Definitive Radiation Therapy for Unfavorable Intermediate-Risk or High-Risk Prostate Cancer [PSMA dRT]
Supporting Agency: Progenics Pharmaceuticals, Inc
Level of Funding: **\$270,000**
<https://clinicaltrials.gov/study/NCT04457245>
- 2021-2023 **Department of Defense (DoD) Health Program, FY19 Prostate Cancer Research Program (PCRP), Clinical Trial Award W81XWH2010351 Subgrant**
Title: Measuring Patient-Reported Outcomes Related to Radiopharmaceuticals for Prostate Cancer
Supporting Agency: H. Lee Moffitt Cancer Center & Research Institute (PI: Brian Gonzalez)
Level of Funding: **\$124,806**

- 2020-2024 **Progenics Sponsored trial Protocol #1095-2301**
Title: A Multicenter, Randomized, Controlled Phase 2 Study: Efficacy and Safety of I-131-1095 Radiotherapy in Combination with Enzalutamide in Metastatic Castration-Resistant prostate Cancer (mCRPC) Patients Who are 18F-DCFPyL Prostate-Specific Membrane Antigen (PSMA)-avid, Chemotherapy-Naïve, and Progressed on Abiraterone (ARROW)
Supporting Agency: Progenics Pharmaceuticals, Inc
Level of Funding: **\$1,115,693**
<https://clinicaltrials.gov/study/NCT03939689>
- 2023-2026 **Novartis Sponsored trial Protocol # CAAA617C12301**
Title: An International Perspective Open-label Randomized, Phase III Study Comparing 177Lu-PSMA-617 in Combination with Standard of Care, Versus Standard of Care Alone, in Adult Male Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) (PSMAddition)
Supporting Agency: Novartis Pharmaceuticals (Novartis AG)
Level of Funding: **\$425,740**
<https://clinicaltrials.gov/study/NCT04720157>
- 2023-2026 **POINT Biopharma/Lilly Sponsored trial Protocol #PBP-301**
Title: SPLASH: Study Evaluating Prostate Cancer Treatment Using Lutetium After Second-Line Hormonal Treatment
Supporting Agency: POINT Biopharma, a wholly owned subsidiary of Eli Lilly and Company
Level of Funding: **\$502,610**
<https://clinicaltrials.gov/study/NCT04647526>
- 2024-2028 **Investigator Initiated trial Protocol #CAAA617A1US04T**
Title: Flexible dosing schedule of LuPSMA molecular radiotherapy in mCRPC patients: a randomized phase 2 trial (FLEX-MRT)
Supporting Agency: Novartis Pharmaceuticals Corporation
Level of Funding: **\$2,679,387**
<https://clinicaltrials.gov/study/NCT06216249>
- 2024-2028 **Investigator Initiated trial Protocol #CAAA617A1US03T**
Title: Re-Treatment with Lu177-PSMA molecular Radiotherapy for Metastatic castration resistant Prostate Cancer: a Prospective Phase 2 Trial (RE-LuPSMA)
Supporting Agency: Novartis Pharmaceuticals Corporation
Level of Funding: **\$1,675,767**
<https://clinicaltrials.gov/study/NCT06288113>

CONTRIBUTIONS TO SCIENCE

The summary of my peer-reviewed publications and the most-cited key papers are presented below. The full list of publications is provided in full CV pages 214-235 and can be accessed online here: <https://www.webofscience.com/wos/author/record/AAG-7119-2020>, <https://pubmed.ncbi.nlm.nih.gov/?term=jeremie+calais>.

These include pillar work on the clinical development of PET and molecular radiotherapy targeting PSMA and has benefited from recognition from the international scientific community with publications in oncology (*The Lancet Oncology*, *JAMA Oncology*, *Clinical Cancer Research*), nuclear medicine and radiology (*The Journal of Nuclear Medicine*, *Radiology*) or urology (*European Urology*, *Nature Reviews Urology*, *The Journal of Urology*) major journals.

This research work has been presented at multiple major international scientific congresses over the years in the USA (ASCO, AACR, ASTRO, AUA, SNMMI, RSNA) and in Europe (ESMO, UAE, ESTRO, EANM): total of **237** selected oral communications and poster abstracts as of Sept 1st 2024 (see full list of selected abstracts in full CV pages 236-258).

	H-index (as of Sept 1 st 2024)	Citations (as of Sept 1 st 2024)
Google Scholar	43	7323
Web of Science	36	4490

Total Publications (as of Sept 1 st 2024)						
	Co-author	First or Co-First Author	Second Author	Second to Last Author	Last or Co-Last Author	Supervision Role
Original Research	88	15	6	8	25	22
Meta-Analysis	6			1	1	1
Guidelines	11		1	1		
Review	17		1	3	3	4
Case Report	24	5	2	3	11	14
Editorial	25	5	3	3	13	
Total	171	25	13	19	53	41

Publications in Journals of High Impact Factor (IF)							
	IF 2023	Co-author	First or Co-First Author	Second Author	Second to Last Author	Last or Co-Last Author	Supervision Role
<i>The Lancet Oncology</i>	IF 41.6	4	2	1			
<i>European Heart Journal</i>	IF 37.6	1	1				
<i>European Urology</i>	IF 25.3	8				3	1
<i>JAMA* Oncology</i>	IF 22.5	3		1		2	
<i>Journal of Thoracic Oncology</i>	IF 21	2	2				
<i>Annual Review of Medicine</i>	IF 15.1	1				1	1
<i>Nature Reviews Urology</i>	IF 12.1	1		1			
<i>Radiology</i>	IF 12.1	3			1		
<i>JAMA* Network Open</i>	IF 10.5	1			1		
<i>Clinical Cancer Research</i>	IF 10	1					
<i>Clinical Nuclear Medicine</i>	IF 9.6	4			1	3	4
<i>Cancer Treatment Reviews</i>	IF 9.6	1	1				
<i>The Journal of Nuclear Medicine</i>	IF 9.1	77	12	6	7	29	20
<i>EJNMMI**</i>	IF 8.6	14	2	1	2	4	4
<i>European Urology Oncology</i>	IF 8.2	4			2	1	1
<i>The Journal of Urology</i>	IF 7.45	6			2		1
<i>Circulation Cardiovascular Imaging</i>	IF 6.7	1	1				
<i>IJROBP***</i>	IF 6.4	1			1		

IF: impact factor; *JAMA: The Journal of the American Medical Association; **EJNMMI: European Journal of Nuclear Medicine and Molecular Imaging; ***IJROBP: International Journal of Radiation Oncology, Biology, Physics

KEY PUBLICATIONS – MOST CITED PAPERS: (as of Sept 1st 2024)

1. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial.
Fendler WP, **Calais J**, Eiber M, Flavell RR, Mishoe A, Feng FY, Nguyen HG, Reiter RE, Rettig MB, Okamoto S, Emmett L, Zacho HD, Ilhan H, Wetter A, Rischpler C, Schoder H, Burger IA, Gartmann J, Smith R, Small EJ, Slavik R, Carroll PR, Herrmann K, Czernin J, Hope TA.
JAMA Oncol. 2019 Jun 1;5(6):856-863. PMID: 30920593
➔ **624 citations by Google Scholar, 492 citations by Web of Science**
2. PROstate cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT.
Eiber M, Herrmann K, **Calais J**, Hadaschik B, Giesel FL, Hartenbach M, Hope TA, Reiter R, Maurer T, Weber WA, Fendler WP.
J Nucl Med. 2018 Mar;59(3):469-478. PMID: 29123012.
➔ **506 citations by Google Scholar, 368 citations by Web of Science**
3. 18F-Fluciclovine and 68Ga-PSMA-11 PET/CT in patients with biochemical recurrence after prostatectomy at PSA levels of ≤ 2.0 ng/ml: a prospective single-center, single-arm, comparative imaging trial
Calais J, Ceci F, Eiber M, Hope T, Hofman M, Rischpler C, Bach-Gansmo T, Nanni C, Savir-Baruch B, Elashoff D, Grogan T, Dahlbom M, Slavik R, Gartmann J, Nguyen K, Lok V, Jadvar H, Kishan A, Rettig M, Reiter R, Fendler W, Czernin J.
Lancet Oncol. 2019 Sep; 20: 1286–94 PMID: 31375469
➔ **399 citations by Google Scholar, 327 citations by Web of Science**
4. 68Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: Impact on Salvage Radiotherapy Planning.
Calais J, Czernin J, Cao M, Kishan AU, Hegde JV, Shaverdian N, Sandler KA, Chu FI, King CR, Steinberg ML, Rausher I, Schmidt-Hegemann NS, Poeppel T, Hetkamp P, Ceci F, Herrmann K, Fendler WP, Eiber M, Nickols NG.
J Nucl Med. 2018 Feb;59(2):230-237. PMID: 29123013.
➔ **274 citations by Google Scholar, 207 citations by Web of Science**
5. Prostate-specific membrane antigen ligand positron-emission tomography in men with non-metastatic castration-resistant prostate cancer.
Fendler W, Weber M, Irvani A, Hofman M, **Calais J**, Czernin J, Ilhan H, Saad F, Small E, Smith M, Perez P, Hope T, Rauscher I, Londhe A, Lopez-Gitlitz A, Cheng S, Maurer T, Herrmann K, Eiber M, Hadaschik B.
Clin. Cancer Res. 2019 Dec 15;25(24):7448-7454. PMID: 31511295
➔ **237 citations by Google Scholar, 185 citations by Web of Science**
6. Diagnostic Accuracy of 68Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection: A Multicenter Prospective Phase 3 Imaging Trial.
Hope TA, Eiber M, Armstrong WR, Juarez R, Murthy V, Lawhn-Heath C, Behr SC, Zhang L, Barbato F, Ceci F, Farolfi A, Schwarzenböck SM, Unterrainer M, Zacho HD, Nguyen HG, Cooperberg MR, Carroll PR, Reiter RE, Holden S, Herrmann K, Zhu S, Fendler WP, Czernin J, **Calais J**.
JAMA Oncol. 2021 Nov 1;7(11):1635-1642. doi: 10.1001/jamaoncol.2021.3771. PMID: 34529005
➔ **220 citations by Google Scholar, 172 citations by Web of Science**
7. Radiation dosimetry and biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients.
Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, Czernin J, Haberkorn U, **Calais J**.
J Nucl Med. 2020 Aug;61(8):1171-1177. PMID: 31836685
➔ **176 citations by Google Scholar, 145 citations by Web of Science**
8. Nomograms to predict outcomes after 177Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study.
Gafita A, **Calais J**, Grogan TR, Hadaschik B, Wang H, Weber M, Sandhu S, Kratochwil C, Esfandiari R, Tauber R, Zeldin A, Rathke H, Armstrong WR, Robertson A, Thin P, D'Alessandria C, Rettig MB, Delpassand ES, Haberkorn U, Elashoff D, Herrmann K, Czernin J, Hofman MS, Fendler WP, Eiber M.
Lancet Oncol. 2021 Aug;22(8):1115-1125. doi: 10.1016/S1470-2045(21)00274-6. PMID: 34246328
➔ **159 citations by Google Scholar, 129 citations by Web of Science**

SCIENTIFIC RECOGNITION

My research activity has allowed me to benefit from local, national and international recognition. The list of my research and global recognition honorary awards is provided below.

I have been invited to give lectures and presentations at major international scientific congresses (ASCO, ASTRO, AUA, SNMMI, RSNA, EANM, PCF), in multiple universities in the US (USC, Scripps MD Anderson Cancer San Diego, Mount Sinai New York, Mallinckrodt Institute of Radiology, Washington University, Henry Ford Cancer Institute, Detroit, Ohio University) or international (CHUV Lausanne (Lausanne, Suisse), APHM CHU Timone (Marseille, France), CHU de Québec-Université Laval (Quebec City, Canada), CHUM (Montreal, Canada), McGill (Montreal, Canada)) for biopharmaceutical manufacturers (Novartis, Astellas, Janssen, Pfizer, GE Healthcare, Sanofi, Telix) as well as for patient associations (see full list of invited lectures and presentations in full CV pages 202-206).

I was given the opportunity to work for leading scientific journals.

I have been an *Associate Editor* for *The Journal of Nuclear Medicine* since 2020.

I have conducted more than 115 peer-reviews for multiple international journals including *Nature Reviews Clinical Oncology*, *The Journal of Clinical Oncology*, *The Lancet Oncology*, *European Urology*, *Radiology*, *Cancer Research* or *PNAS Proceedings of the National Academy of Sciences* (cf Peer review section in <https://www.webofscience.com/wos/author/record/AAG-7119-2020> and in full CV page 213).

I have received mainstream (*The New York Times*, *San Francisco KPIX CBS Local TV*, *Medscape*) and specialized (*Diagnostic Imaging Europe*, *Onclive*, *Urology Times*, *Oncology Central*, *Oncology Times*, *Urotoday*, *DocWire News*, *GU Oncology Now*, *eCancer*, *Endpoints News*) media exposure in press articles and videos (see full list of in full CV pages 207-212).

I have had the opportunity to collaborate with multiple industrial partners as a consultant, key opinion leader, member of the scientific committee, medical speaker, blinded independent reader (*Advanced Accelerator Applications*, *Amgen*, *Astellas*, *Bayer*, *Blue Earth Diagnostics Inc.*, *Curium Pharma*, *DS Pharma*, *Fibrogen*, *GE Healthcare*, *Isoray*, *IBA RadioPharma*, *Janssen Pharmaceuticals*, *Monrol*, *Lightpoint medical*, *Lantheus*, *Novartis*, *Nucleus Radiopharma*, *Pfizer*, *POINT biopharma*, *Progenics*, *Radiomedix*, *Radiopharm Theranostics*, *Sanofi*, *Siemens-Varian*, *SOFIE*, *Telix Pharmaceuticals*). Cf full list of consulting activities in CV page 199-201). My exposure to the biopharmaceutical industry contributes significantly to my understanding of pre-clinical and clinical research.

AWARDS

- 2016 **Achard-Medecine Award, National Academy of Medicine (France)**
Development of a new nuclear imaging probe in oncology: ⁶⁸Ga-Pentixafor
- 2017 **Best Oral Abstract Award, WRSNM annual meeting 2017 (Vancouver, Canada)**
⁶⁸Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning.
- 2018 **Best Article of the Month (February 2018 Cover Page), The Journal of Nuclear Medicine**
⁶⁸Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning.
- 2018 **Best Clinical Article of the Month (November 2018), The Journal of Nuclear Medicine**
Potential impact of (⁶⁸Ga-PSMA-11 PET/CT on prostate cancer definitive radiation therapy planning.
- 2018 **Top 1 Research Story, PCF Annual Scientific Retreat**
Elucidating mechanisms of effectiveness and resistance to ¹⁷⁷Lu-PSMA-617
<https://www.pcf.org/blog/top-5-from-the-pcf-scientific-retreat/>
- 2019 **Best Manuscript of the Year (2018), The Journal of Nuclear Medicine.**
⁶⁸Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning.
- 2019 **Walter Wolf Young Investigator Award, SNMMI Correlative Imaging Council, SNMMI annual meeting 2019 (Anaheim, CA)**
⁶⁸Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to ¹⁸F-Fluciclovine PET/CT in a prospective head to head comparative phase 3 study

- 2019 **Early Career Abstract Award (Clinical Science), SNMMI Early Career Professionals Committee, SNMMI annual meeting 2019 (Anaheim, CA)**
68Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to 18F-Fluciclovine PET/CT in a prospective head to head comparative phase 3 study
- 2019 **Best Article of the Month (September 2019 Cover Page), The Journal of Nuclear Medicine**
111In-pentetreotide scintigraphy vs. 68Ga-DOTATATE PET: Impact on Krenning Scores and effect of tumor burden.
- 2020 **« Ones to Watch » 2020 Selection , SNMMI early career professionals**
 Nominated in the list of 30 early career professionals for the « Ones to Watch » 2020 Campaign Selection
<https://jnm.snmiournals.org/content/inumed/61/5/14N.full.pdf>
- 2022 **Hal O'Brien Rising Star Award, High Country Nuclear Medicine Conference 2022 (Sun Valley, Idaho)**
for outstanding leadership in Nuclear Medicine Science
<https://cancer.ucla.edu/Home/Components/News/News/1836/>
- 2022 **Best Article of the Month (June 2022 Cover Page), The Journal of Nuclear Medicine**
Head-to-head comparison of 68Ga-PSMA-11 PET/CT and mpMRI with histopathology gold-standard in the detection, intra-prostatic localization and local extension of primary prostate cancer: results from a prospective single-center imaging trial.
- 2022 **SNMMI Cancer Cooperative Group Junior Faculty Mentorship Award**
 SWOG Cancer Research Network – UCLA JCCC
- 2023 **Best Article of the Month (July 2023 Cover Page), The Journal of Nuclear Medicine**
PSMA PET Tumor-to-Salivary Gland Ratio to Predict Response to [177Lu]PSMA Radioligand Therapy: An International Multicenter Retrospective Study.
- 2023 **Best Article of the Month (November 2023 Cover Page), The Journal of Nuclear Medicine**
Do Bone Scans Overstage Disease Compared with PSMA PET at Initial Staging? An International Multicenter Retrospective Study with Masked Independent Readers.
- 2023 **SS. Gambhir Distinguished Scientist Award, WRSNM annual meeting 2023 (Vancouver, Canada)**
for significant contributions to the Clinical Science of Nuclear Medicine or Molecular Imaging.
<https://wrsnm.org/jeremie-calais-md-msc-to-receive-western-region-snm-distinguished-scientist-award/>
- 2024 **Distinguished Investigator of Theranostics, Xcancer TheranosticTrials.org**
<https://www.theranostictrials.org/distinguished-investigators/qt0e9xe7yvdchxi1xsamino4>

APTITUDE FOR SUPERVISION

During these 8 years of work at UCLA, I had the opportunity to supervise many retrospective and prospective research projects with a wide range of management levels: laboratory technicians, clinical staff, biology students, medical students, medical physics students, medical interns, clinical research assistants, post-doctoral fellows or senior physicians.

I am responsible for providing guidance and oversight to medical students, residents and physicians seeking for research projects. I am also affiliated with the doctoral school of physics and medical biology (Physics and Biology In Medicine, formerly known as Biomedical Physics, <https://pbm.ucla.edu/index.jsp>) which allows me to supervise doctoral students in medical physics working on topics related to our research program: radiation protection, image acquisition, image reconstruction, image processing, and dosimetry of radiopharmaceuticals.

This research project supervision and mentoring activities led to more than 90 oral communications and poster abstracts presentations at conferences and more than 40 publications with more than 30 different mentees (see summary of publications in page 12). Publications and presentations associated with direct supervision role (1-1) of students, interns and fellows are marked in yellow in full CV pages 214-258.

Some of these supervised research projects gained attention, awards, and recognition as shown below.

- 2019 **Best Poster Award - ICIS Verona 2019, International Cancer Imaging Society Annual Teaching Course**
K Pomykala, M Jardon, J Czernin, J Williams, TR Grogan, **J Calais**.
Total-body 68Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients
- 2021 **SNMMI Alavi-Mandell Award**
Pomykala K, Czernin J, Grogan T, Armstrong W, Williams J, **Calais J**.
Total-body 68Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients: Potential Impact on bone scan guidelines.
J Nucl Med. 2020 Mar;61(3):405-411. PMID: 31541035
<https://www.auntminnie.com/index.aspx?sec=sup&sub=mol&pag=dis&ItemID=126662>
- 2021 **SNMMI Alavi-Mandell Award**
Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, Czernin J, Haberkorn U, **Calais J**.
Radiation dosimetry and biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients.
J Nucl Med. 2020 Aug;61(8):1171-1177. PMID: 31836685
- 2021 **Oncology, Basic Science Poster Award Winner, 2nd place - SNMMI Annual Meeting**
CE Mona, M Benz, F Hikmat, TG Grogan, K Lueckerath, AA Razmaria, R Riahi, R Slavik, MD Grigis, G Carlucci, KA Kelly, J Czernin, DW Dawson, **J. Calais**.
Validation of FAPI PET biodistribution by immunohistochemistry in patients with solid cancers: A prospective exploratory study.
- 2021 **Early-Career Professionals Abstract Award Winner, 1st Place Basic Science Oncology - SNMMI Annual Meeting**
CE Mona, M Benz, F Hikmat, TG Grogan, K Lueckerath, AA Razmaria, R Riahi, R Slavik, MD Grigis, G Carlucci, KA Kelly, J Czernin, DW Dawson, **J. Calais**.
Validation of FAPI PET biodistribution by immunohistochemistry in patients with solid cancers: A prospective exploratory study.
- 2022 **Featured Article of the Month (June), The Journal of Nuclear Medicine**
Sonni I, Felker ER, Lenis AT, Sisk AE, Bahri S, Allen-Auerbach MS, Armstrong WR, Suvannarerg V, Tubtawee T, Grogan T, Elashoff D, Eiber M, Raman SS, Czernin J, Reiter R, **Calais J**.
Head-to-head comparison of 68Ga-PSMA-11 PET/CT and mpMRI with histopathology gold-standard in the detection, intra-prostatic localization and local extension of primary prostate cancer: results from a prospective single-center imaging trial.
J Nucl Med. 2022 Jun;63(6):847-854. doi: 10.2967/jnumed.121.262398. PMID: 34649942
<https://www.urologytimes.com/view/psma-and-mri-for-early-prostate-cancer-detection>

- 2022 **1st Place Winner Abstract Competition - AdMeTech 6th Global Summit on Precision Dx and Tx of Prostate Cancer**
I Sonni, A Dal Pra, D O'Connell, M Benz, K Nguyen, S Yoon, J Deng, CP Smith, NG Nickols, M Cao, AU Kishan, **J Calais**.
PSMA PET/CT–Based Atlas for Prostatic Bed Recurrence of Prostate Cancer after Radical Prostatectomy: Clinical Implications for Salvage Radiation Therapy
- 2022 **SNMMI Alavi–Mandell Award**
Armstrong WR, Gafita A, Zhu S, Thin P, Nguyen K, Alano RM, Lira S, Booker K, Gardner L, Grogan T, Elashoff D, Allen-Auerbach MS, Dahlbom MS, Czernin J, **Calais J**.
The impact of monosodium glutamate on 68Ga-PSMA-11 biodistribution in men with prostate cancer: a prospective randomized, controlled, imaging study.
J Nucl Med. 2021 Jan 28. doi: 10.2967/jnumed.120.257931. PMID: 33509974
- 2022 **Oncology: Clinical Therapy & Diagnosis Poster Award Winner, 2nd place - SNMMI Annual Meeting**
M Hotta, A Gafita, J Czernin, **J Calais**.
Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy: a multicenter retrospective analysis
- 2022 **Oncology: Clinical Therapy & Diagnosis Poster Award Winner, 3rd place - SNMMI Annual Meeting**
M Hotta, A Gafita, V Murthy, MR. Benz, I Sonni, I Burger, M Eiber, L Emmett, A Farolfi, WP Fendler, MS Hofman, TA Hope, C Kratochwil, J Czernin, **J Calais**.
PSMA PET tumor-to-Salivary Glands ratio (PSG score) to predict response to Lu-177 PSMA radioligand therapy: an international multicenter retrospective study
- 2023 **Featured Article of the Month (March), The Journal of Nuclear Medicine**
Hotta M, Gafita A, Murthy V, Benz MR, Sonni I, Burger IA, Eiber M, Emmett L, Farolfi A, Fendler WP, Weber MM, Hofman MS, Hope TA, Kratochwil C, Czernin J, **Calais J**.
PSMA PET Tumor-to-Salivary Gland Ratio to Predict Response to [177Lu]PSMA Radioligand Therapy: An International Multicenter Retrospective Study.
J Nucl Med. 2023 Mar 30;jnumed.122.265242. doi: 10.2967/jnumed.122.265242. PMID: 36997329
<https://www.miragenews.com/new-psg-score-improves-patient-selection-for-989556/>
<https://www.snmml.org/NewsPublications/NewsDetail.aspx?ItemNumber=43729>
https://www.vjncology.com/video/bum_hgsrfgu-psma-pet-ratio-predicts-response-to-177lupsma-radioligand-therapy-a-multicenter-study/
<https://www.miragenews.com/new-psg-score-improves-patient-selection-for-989556/>
- 2024 **General Clinical Specialties Poster Award Winner, 2nd place – SNMMI Annual Meeting**
M Hotta, G Kim, V Rerkpichaisuth, G Fishbein, J Czernin, E Volkmann, S Weigt, **J Calais**
Correlation of FAPI PET signal with immunohistochemistry in explanted lung tissue from transplanted patients with refractory interstitial lung diseases: preliminary results of a prospective exploratory study

DOCTORAL COMMITTEE

Doctor of Medicine - Medical Thesis

<i>Name</i>	<i>Date of Thesis Defense</i>	<i>Institution</i>
Anne Chaput	September 30 2016	University of Brest, France

Title: Correlation between fluorodeoxyglucose hotspots on pretreatment positron emission tomography/CT and preferential sites of local relapse after chemoradiotherapy for head and neck squamous cell carcinoma.

<https://hal.archives-ouvertes.fr/hal-01643973>

Committee Chair: Pierre Yves Salaun MD PhD

Committee Members: Ronan Abgral MD PhD, **Jeremie Calais** MD, Ulrike Schick, MD, PhD, Solene Querellou MD

Main Supervisor: Ronan Abgral MD PhD

Supervision: Ronan Abgral **60%**, **Jeremie Calais 40%**

Associated Publications:

1. Chaput A*, **Calais J*** (co-first author), Robin P, Thureau S, Bourhis D, Modzelewski R, Schick U, Vera P, Salaün PY, Abgral R. Correlation between (18)F-FDG hotspots on PET/CT and preferential sites of local relapse after chemoradiotherapy for head and neck squamous cell carcinoma. *Head Neck*. 2017 Jun;39(6):1155-1165. PMID: 28263422.
2. Truffault B, Bourhis D, Chaput A, **Calais J**, Robin P, Le Pennec R, Lucia F, Leclère JC, Gujral DM, Vera P, Salaün PY, Schick U, Abgral R. Correlation Between FDG Hotspots on Pre-radiotherapy PET/CT and Areas of HNSCC Local Relapse: Impact of Treatment Position and Images Registration Method *Front. Med*. 2020 Jun 4;7:218. PMID: 32582727

Associated Conference Abstracts:

1. A. Chaput, **J. Calais**, P. Robin, S. Thureau, D. Bourhis, R. Modzelewski, U. Schick, P. Vera, P.Y. Salaün, R. Abgral Recherche d'une corrélation entre les zones les plus hypermétaboliques en TEP/TDM au ¹⁸F-FDG préthérapeutique (hotspots) et les sites préférentiels de récurrence locale après radiothérapie des cancers des VADS JFMN Grenoble 2016 – Journées francophones de médecine nucléaire.
 2. A. Chaput, **J. Calais**, P. Robin, S. Thureau, D. Bourhis, R. Modzelewski, U. Schick, P. Vera, P-Y. Salaün, R. Abgral Correlation between areas of high FDG uptake on pre-treatment PET/CT and preferential sites of local relapse after chemoradiotherapy for head and neck squamous cell carcinoma. SNMMI San Diego 2016 - Society of Nuclear Medicine and Molecular Imaging
 3. A. Chaput, **J. Calais**, P. Robin, S. Thureau, D. Bourhis, R. Modzelewski, U. Schick, P. Vera, P. Salaün, R. Abgral. High ¹⁸F-FDG uptake on pre-radiotherapy PET/CT and preferential sites of local relapse after chemoradiotherapy for locally advanced head and neck cancer. EANM Barcelona 2016 - Annual Congress of the European Association of Nuclear Medicine
-

Doctor of Sciences - PhD Thesis

Name	Date of Thesis Defense	Institution
Catherine Meyer	May 18 2022	University of California, Los Angeles

Program Specialty: **Physics and Biology in Medicine**

Title: Advancements in Prostate-Specific Membrane Antigen Targeted Radionuclide Therapy Through Dosimetry
<https://escholarship.org/uc/item/4dn4r0h4>

Committee Chair: Magnus Dalhbom PhD

Committee Members: **Jeremie Calais** MD, Johannes Czernin MD, Keisuke S Iwamoto PhD, Nicholas G Nickols MD PhD, Roger Slavik PhD.

Main Supervisor: Magnus Dalhbom PhD

Supervision: Magnus Dalhbom **50%**, **Jeremie Calais 30%**, Roger Slavik **20%**.

Associated Publications:

1. Stuparu AD, Capri JR, Meyer C, Le TM, Evans-Axelsson SL, Current K, Lennox M, Mona CE, Fendler WP, **Calais J**, Eiber M, Dahlbom M, Czernin J, Radu CG, Lücknerath K, Slavik R.
Mechanisms of Resistance to Prostate-Specific Membrane Antigen-Targeted Radioligand Therapy in a Mouse Model of Prostate Cancer.
J Nucl Med. 2021 Jul 1;62(7):989-995. doi: 10.2967/jnumed.120.256263. PMID: 33277393.
2. Urbán S, Meyer C, Dahlbom M, Farkas I, Sipka G, Besenyi Z, Czernin J, Pávics L, **Calais J**.
Radiation dosimetry of Tc99m-PSMA I&S: a single-center prospective study.
J Nucl Med. 2021 Aug 1;62(8):1075-1081. doi: 10.2967/jnumed.120.253476. PMID: 33277398
1. Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, Czernin J, Haberkorn U, **Calais J**.
Radiation dosimetry and biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients.
J Nucl Med. 2020 Aug;61(8):1171-1177. PMID: 31836685
3. Meyer C, Prasad V, Stuparu A, Kletting P, Glatting G, Miksch J, Solbach C, Lueckerath K, Nyiranshuti L, Zhu S, Czernin J, Beer AJ, Slavik R, **Calais J**, Dahlbom M.
Comparison of PSMA-TO-1 and PSMA-617 labeled with gallium-68, lutetium-177 and actinium-225.
EJNMMI Res. 2022 Oct 1;12(1):65. doi: 10.1186/s13550-022-00935-6. PMID: 36182983
4. Meyer C, Stuparu A, Lueckerath K, **Calais J**, Czernin J, Slavik R, Dahlbom M.
Tandem Isotope Therapy with 225Ac- and 177Lu-PSMA-617 in a Murine Model of Prostate Cancer.
J Nucl Med. 2023 Nov;64(11):1772-1778. doi: 10.2967/jnumed.123.265433. PMID: 37797974

Associated Abstracts Presentations:

1. C Meyer, M Dahlbom, J Czernin, S Vauclin, T Lindner, U Haberkorn, **J Calais**.
Biodistribution and radiation dosimetry study of 68Ga-FAPI-46 PET imaging in patients with various cancers.
EANM Barcelona 2019 - Annual Congress of the European Association of Nuclear Medicine
2. C Meyer, D Mirando, T Adams, D Ranganathan, R Esfandiari, E Delpassand, J Czernin, **J Calais**, M Dahlbom
Patient-specific kidney absorbed doses in mCRPC patients treated with 177Lu-PSMA-617: a post-hoc analysis of a prospective phase 2 study
EANM 2020 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-772
3. C. Meyer, A. Stuparu, L. Wei, C. Radu, **J Calais**, J. Czernin, M. Dahlbom, R. Slavik.
A combination isotope approach towards improved PSMA-targeted radioligand therapy in a murine model of prostate cancer
SNMMI Virtual Meeting 2020 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting

4. Patient-specific tumor dosimetry in mCRPC patients treated with ¹⁷⁷Lu-PSMA-617
C Meyer, D Mirando, T Adams, J Czernin, **J Calais**, M Dahlbom
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
 5. C Meyer, A Stuparu, K Lueckerath, L Nyiranshuti, J Czernin, M Dahlbom, **J Calais**, R Slavik
Preclinical evaluation of PSMA-TO1- a PSMA-targeting ligand with increased circulating half-life
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
 6. C. Meyer, V. Prasad, A. Stuparu, G. Glatting, P. Kletting, J.Miksch, C. Solbach, K. Lueckerath, L. Nyiranshuti, S. Zhu, J.Czernin, M. Dahlbom, **J. Calais**, A. Beer, R. Slavik.
Comparison of PSMA-TO-1 and PSMA-617 labelled with ⁶⁸Ga, ¹⁷⁷Lu and ²²⁵Ac: a first in-human translational study
EANM 2021 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-0113
 7. Extrapolating organ and tumor doses for ²²⁵Ac-PSMA-I&T radionuclide therapy in patients with mCRPC
C Meyer, A Allmann, J Allmann, M Eiber, J Czernin, M Dahlbom, **J Calais**.
SNMMI Vancouver 2022 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
 8. Kidney and tumor radiation absorbed doses in mCRPC patients treated with ¹⁷⁷Lu-PSMA-617: a preliminary analysis of the RESIST-PC phase 2 trial
C Meyer, D Mirando, J Czernin, **J Calais**, M Dahlbom,
SNMMI Vancouver 2022 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
-

Doctor of Sciences - PhD Thesis

Name	Date of Thesis Defense	Institution
Zachary Ells	2025-2026	University of California, Los Angeles

Program Specialty: **Physics and Biology in Medicine**

Title: Lu177-PSMA Dosimetry for Radionuclide Therapy

Committee Chair: Magnus Dalhbom PhD

Committee Members: **Jeremie Calais** MD, Johannes Czernin MD, Keisuke S Iwamoto PhD, Amar U Kishan MD, Catherine Meyer PhD.

Main Supervisor: Magnus Dalhbom PhD

Supervision: Magnus Dalhbom **50%**, **Jeremie Calais 40%**, Johannes Czernin **10%**.

Associated Publications:

1. Ells Z, Grogan TR, Czernin J, Dahlbom M, **Calais J**.
Dosimetry of [177Lu]Lu-PSMA-Targeted Radiopharmaceutical Therapies in Patients with Prostate Cancer: A Comparative Systematic Review and Metaanalysis.
J Nucl Med. 2024 Jul 3:jnumed.124.267452. doi: 10.2967/jnumed.124.267452. PMID: 38960712

Associated Abstracts Presentations:

- 1- Z Ells, A Farolfi, RE Reiter, NM Donin, JD Shirk, JJ H Zhang, AB Weiner, **J Calais**, M Dahlbom.
Potential value of 3D Volume Rendering using PSMA PET/CT to improve surgical planning for salvage lymph node resection: the UCLA initial experience
JCCC 2023 Annual Retreat of UCLA Jonsson Comprehensive Cancer Center – Lushkin Center
- 2- Z Ells, A Farolfi, RE Reiter, NM Donin, JD Shirk, JJ H Zhang, AB Weiner, **J Calais**, M Dahlbom.
Potential value of 3D Volume Rendering using PSMA PET/CT to improve surgical planning for salvage lymph node resection: the UCLA initial experience
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
- 3- Z Ells, C Meyer, M Dahlbom, A Farolfi, JJ H Zhang, A Gafita, G Carlucci, JD Shirk, J Czernin, RE Reiter, **J Calais**.
Determining the optimal time interval between 99mTc-PSMA-I&S administration and radioguided pelvic lymph node dissection in patients with prostate cancer pelvic lymph node metastasis: results from a prospective exploratory study
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
- 4- Z. Ells, L. Unterrainer, D. Sennung, R. Alano, K. Booker, C. Felix, A. Daley, A. Farolfi, J. Czernin, M. Dahlbom, A. Kishan, **J. Calais**
Dosimetry estimates of 177Lu-PNT2002 in oligorecurrent prostate cancer: preliminary dosimetry results from a randomized phase 2 trial (LUNAR)
EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
- 5- Z Ells, T Grogan, J Czernin, M Dahlbom, **J Calais**
Dosimetry of lutetium-177 PSMA-targeted radiopharmaceutical therapies for prostate cancer patients: A comparative systematic review and meta-analysis.
ASCO Chicago 2024- American Society of Clinical Oncology Annual Meeting
- 6- Z Ells, T Grogan, J Czernin, M Dahlbom, **J Calais**
Dosimetry of Lutetium-177 PSMA-targeted radiopharmaceutical therapies for prostate cancer patients: a comparative systematic review and meta-analysis
SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
- 7- Z Ells, V Ludwig, A Weiner, C Meyer, D Sennung, G Carlucci, A Farolfi, J Czernin, M Dahlbom, R Reiter, **J Calais**
99mTc-PSMA-I&S radioguided salvage lymphadenectomy for prostate cancer: preliminary clinical results from a prospective trial
SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting

Selected Supervised Research Projects.

In the following part of the manuscript, I provide a selection of research projects that I supervised and for which I provided oversight to guide the junior first author. The articles are presented in their final publication format preceded by a short background introduction.

For this manuscript, these were arbitrarily grouped in 3 research topics:

- 1- Clinical Translation of FAP-PET imaging
- 2- Randomized Trials of PSMA PET imaging trials powered for clinical outcome.
- 3- Exploring Beyond the approved use of PSMA theranostics

First Topic: Clinical Translation of FAP-PET imaging

Papers provided:

1- ***FAP: the next billion dollar nuclear theranostics target ?***

Calais J.

J Nucl Med. 2020 Feb;61(2):163-165 PMID: 31924719

2- ***Radiation dosimetry and biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients.***

Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, Czernin J, Haberkorn U, **Calais J.**

J Nucl Med. 2020 Aug;61(8):1171-1177. PMID: 31836685

3- ***Correlation of 68Ga-FAPi-46 PET biodistribution with FAP expression by immunohistochemistry in patients with solid cancers: interim analysis of a prospective translational exploratory study.***

Mona CE, Benz MR, Hikmat F, Grogan TR, Lückerrath K, Razmaria A, Riahi R, Slavik R, Girgis MD, Carlucci G, Kelly KA, French SW, Czernin J, Dawson DW, **Calais J.**

J Nucl Med. 2021 Nov 5;jnumed.121.262426. doi: 10.2967/jnumed.121.262426. PMID: 34740953

First Topic: Clinical Translation of FAP-PET imaging

Article 1:

Title: ***FAP: the next billion dollar nuclear theranostics target ?***

Authors: **Calais J.**

Reference: *J Nucl Med.* 2020 Feb;61(2):163-165 PMID: 31924719

Brief Outline:

This article provides an overview of the potential of the use of the fibroblast activation protein (FAP) as a target for PET imaging and radiopharmaceutical therapy.

FAP: The Next Billion Dollar Nuclear Theranostics Target?

Jeremie Calais¹⁻⁴

¹Ahmanson Translational Theranostics Division, Department of Molecular & Medical Pharmacology, University of California Los Angeles, Los Angeles, California; ²Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, California; ³Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; and ⁴Institute of Urologic Oncology, University of California Los Angeles, Los Angeles, California

The recent successful clinical translation of nuclear theranostics (1,2) fueled industry investment in the radiopharmaceutical market (3). Among other examples, Novartis invested \$6 billion to acquire Endocyte (¹⁷⁷Lu-PSMA-617) and Advanced Accelerator Applications (AAA; ¹⁷⁷Lu-DOTATATE [Lutathera]) and Bracco S.p.A. obtained Blue Earth Diagnostics (radiohybrid PSMA [prostate-specific membrane antigen]-targeted technology) for \$500 million. Thus, investors have recognized the potential clinical benefits and substantial financial upside of nuclear theranostics and are now in hot pursuit of the next relevant nuclear theranostics target. Fibroblast activation protein (FAP) has emerged as the front-runner, and the next gold rush appears to be around the corner.

WHY IS FAP A PROMISING TARGET?

FAP, also known as seprase or prolyl-endopeptidase-FAP, is a type II membrane-bound glycoprotein enzyme with peptidase activity (substrates can be, among others, gelatin or collagen). FAP is highly expressed on the cell surface of activated but not quiescent fibroblasts (4,5). Expression in normal adult tissues is absent or low (6). Expression increases in remodeling processes such as wound healing, inflammation, or fibrosis when fibroblasts become activated (7). Importantly FAP is highly expressed by cancer-associated fibroblasts (CAFs), a major constituent of tumor stroma (4,7,8).

WHAT ARE CAFs?

Tumor masses consist of cancer cells but also vascular structures, inflammatory cells, fibroblasts, and collagen that together make up the tumor stroma that can account for up to 90% of the mass in highly desmoplastic cancers (4,7,8). Cancer cells induce the fibroblast activation via TGFβ. CAFs have a supporting function on cancer growth and invasion. They contribute to the remodeling of the extracellular matrix (collagenolysis) and promote invasiveness and angiogenesis and, via growth factors and cytokine secretion, can induce epithelial to mesenchymal transition (6). CAFs are also involved in the immunologic interactions between the tumor and the host (9).

WHY IS FAP-TARGETED THERAPY ATTRACTIVE?

FAP-positive CAFs are found in more than 90% of epithelial cancers, therefore representing a potential pan-cancer target (6). Targeting FAP to deplete stromal CAFs may disrupt cancer-supportive functions and inhibit cancer growth (10–12). Furthermore, by breaking the stroma barrier, the effectiveness of other pharmacologic, immunologic, radiation- or cell-based systemic therapies may thus be enhanced (4–6).

FAP-targeted molecular radiotherapy (MRT) can deliver ionizing radiation to CAFs directly and also to cancer cells, via crossfire effects. Combining α- and β-emitters may improve these dual antitumor effects via short-range α-radiation to CAFs and mid- to long-range β-radiation to cancer cells. As another potential application, combining FAP-targeted with PSMA-targeted MRT may increase radiation doses in stroma-rich prostate cancer lesions (13,14).

WHY IS FAP-TARGETED IMAGING ATTRACTIVE?

Tumor lesions exceeding 1–2 mm in size require the formation of a supporting stroma (15). As stroma volume can be larger than cancer cell volume, stroma-targeted PET imaging may be more sensitive than glucose metabolic PET imaging for detecting small lesions if FAP is expressed sufficiently (Fig. 1). FAP-targeted PET [Fig. 1] imaging may also be attractive for detecting tumor lesions with low or heterogeneous glucose metabolism or those located in close vicinity to highly glycolytic normal tissues (16–18). Additional potential advantages include early imaging at 10 min after injection and the absence of required fasting. Finally and most importantly, FAP-targeted PET imaging could serve as a precise predictive biomarker of response to any FAP-targeted treatments across most cancers.

As a limitation, FAP expression is not cancer-specific due to its expression in many tissue-remodeling processes. This may, for instance, render the differentiation between chronic pancreatitis and pancreatic ductal adenocarcinoma difficult (19). Conversely, FAP-targeted PET imaging may be useful for many non-oncologic imaging applications such as myocardial infarction (20–22), chronic inflammatory diseases (23), and lung, liver or kidney fibrosis (24).

FAP-TARGETED RADIOPHARMACEUTICALS

Molecular Imaging

The Heidelberg group has recently developed quinolone-based FAP inhibitors (FAPI) with a DOTA-chelator moiety to enable radiolabeling. One early derivative, FAPI-02, was near completely internalized after 1 h of incubation. First-in-human PET/CT studies of ⁶⁸Ga-FAPI-02 PET/CT scans demonstrated high-contrast tumor imaging across various cancers (Fig. 1) (7,16,25). To optimize

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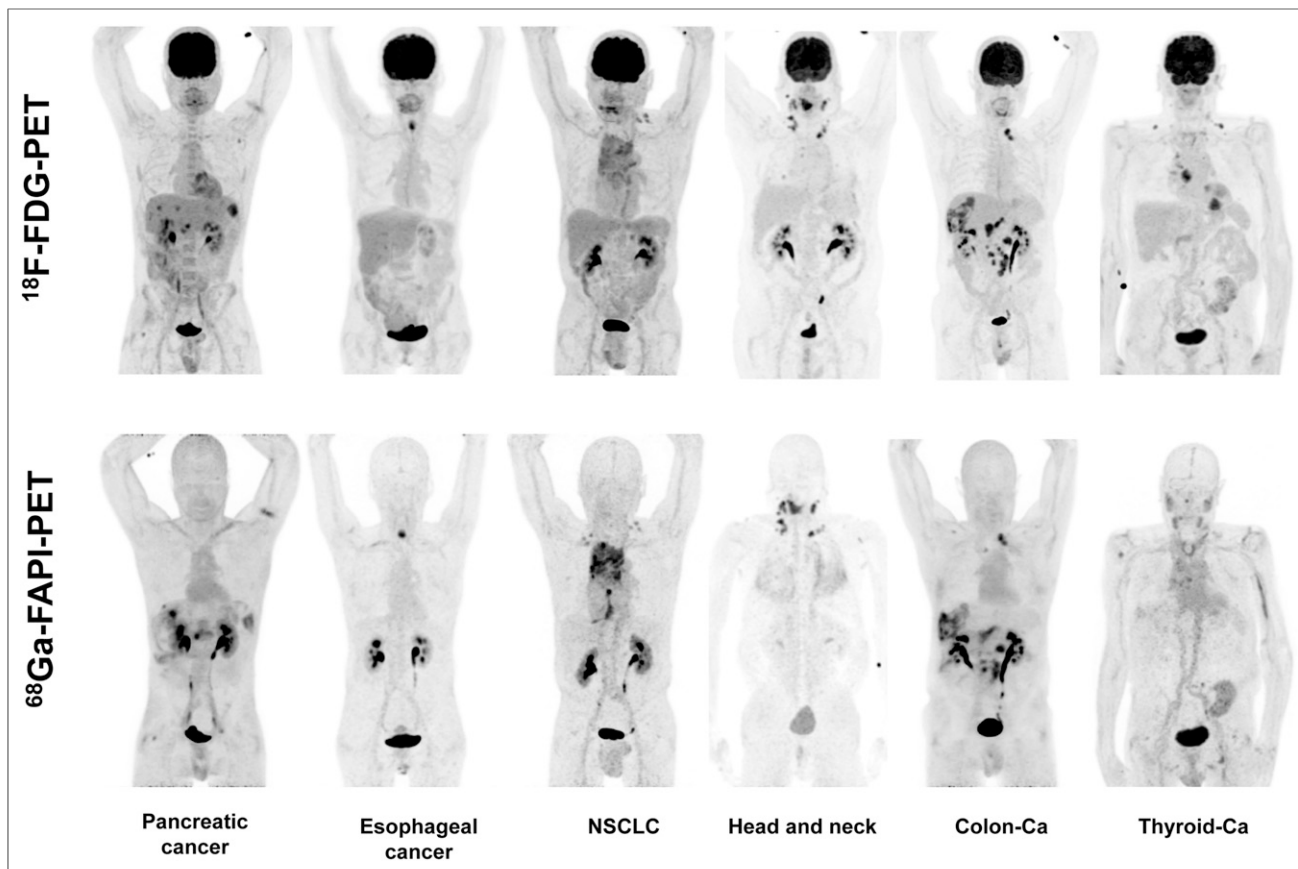


FIGURE 1. ^{68}Ga -FAPI and ^{18}F -FDG PET images in patients with various cancers. (Reprinted with permission of (16).)

tracer uptake and retention, a series of subsequent derivatives was developed (25). ^{68}Ga -FAPI-04 showed the most favorable properties for PET imaging (low nanomolar affinity to FAP, near-complete internalization of radioactivity bound to FAP, and rapid blood clearance) with impressive lesion-to-background ratios in patients with a broad range of cancers (26). ^{18}F -labeled compounds (FAPI-74, RPS-301) are being developed to improve potential commercial distribution (27–29).

Molecular Radiotherapy

Although imaging probes are clinically highly relevant, the market interest arises from potential therapeutic applications that generate an order of magnitude greater return on investment. There is no published report of FAP-targeted MRT except a single case of a late-stage breast cancer patient with bone metastases treated with ^{90}Y -labeled FAPI-04 (25). A single administration of 2.9 GBq of ^{90}Y -FAPI-04 led to symptomatic improvement without significant toxicity. However, further optimization steps are needed. For instance, the physical half-life of the therapeutic isotope needs to be matched to the tumor retention time. FAPI-04 clears relatively rapidly from tumor tissue, limiting the achievable radiation dose delivery. A therapeutic isotope with a shorter physical half-life may be more effective than ^{90}Y . The radiation type (α vs. β) also requires optimization. In a preclinical study, a single administration of ^{225}Ac -FAPI-04 resulted in tumor growth retardation in mice bearing PANC-1 xenografts (30).

Further modifications to the FAPI compounds were performed to improve tumor retention while retaining the imaging contrast

obtained with FAPI-02 and FAPI-04 (6,17,31). A further increase of tumor retention time was achieved with FAPI-46 (17,31). ^{68}Ga -FAPI-46 PET/CT imaging had a favorable dosimetry profile and showed high tumor-to-background ratios increasing over time, suggesting more favorable kinetics for potential therapeutic applications (31).

IS THE INDUSTRY INVESTING IN FAP-TARGETED NUCLEAR THERANOSTICS?

3B-Pharmaceuticals developed a new class of FAP-targeted radiolabeled peptidomimetics (FAP-3BP-2286) that have been licensed to Clovis Oncology for \$12 million. Sofie Biosciences, Inc. (SOFIE) signed a \$5 million exclusive global license agreement with the University of Heidelberg for the small-molecule FAPI compounds. Both companies are planning to file investigational new drug applications for their FAP-targeted radiopharmaceuticals in 2020. Even when no diagnostic or therapeutic data are yet available, these acquisitions underscore the high industry interest in FAP-targeted nuclear theranostics compounds.

Challenges

To streamline research and development of FAP-targeted compounds, the nuclear medicine community (industry and academia) can learn from the National Oncologic PET Registry successes for FDG and the successful translation of ^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, ^{18}F -fluciclovine, and, more recently, the PSMA imaging agents. Strategies for translating FAP-targeted imaging agents may range from phase 3 diagnostic efficacy studies for each cancer

type to pan-cancer diagnostic or predictive biomarker applications, respectively. Prospective exploratory studies have been registered and initiated (NCT04147494).

The effectiveness of FAP-targeted MRT is also unknown, and it may not be sufficiently effective as a single agent. Thus, combination therapy approaches including, among others, immunotherapy and MRT with α -/ β -combination or multitargeted MRT should be a priority for research at least in preclinical models.

In summary, FAP is a promising target for imaging and therapy. Industry has embraced nuclear theranostics targeting FAP. The next gold rush has begun early.

DISCLOSURE

Jeremie Calais is a consultant for Blue Earth Diagnostics, Janssen Pharmaceuticals, Progenics Radiopharmaceuticals, and Radiomedix, outside of the submitted work. He is the recipient of grants from the ERF-SNMMI (2019–2021 Molecular Imaging Research Grant for Junior Academic Faculty), the Philippe Foundation Inc. (New York, USA) and the ARC Foundation (France) (International Mobility Award SAE20160604150). No other potential conflict of interest relevant to this article was reported.

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First Topic : Clinical Translation of FAP-PET imaging

Article 2:

Title: *Radiation dosimetry and biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients.*

Authors: Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, Czernin J, Haberkorn U, Calais J.

Reference: *J Nucl Med.* 2020 Aug;61(8):1171-1177. PMID: 31836685

Brief Outline:

As a required step for clinical translation and approval by regulatory agencies, the primary objective of this study was to provide the radiation dosimetry and organ biodistribution of 68Ga-FAPI-46 PET imaging in cancer patients.

The junior first author was Catherine A Meyer, who was beginning her PhD in medical physics. This work was included in her PhD dissertation. It was presented as an oral communication at the EANM annual congress 2019 in Barcelona.

The paper was highly cited (176 citations by Google Scholar, 145 citations by Web of Science as of Sept 1st 2024) and received the SNMMI Alavi–Mandell Award in 2021.

Radiation Dosimetry and Biodistribution of ^{68}Ga -FAPI-46 PET Imaging in Cancer Patients

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Key Words: FAPI; PET/CT; ^{68}Ga ; dosimetry; biodistribution

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Targeting cancer-associated fibroblasts (CAFs) has become an attractive goal for diagnostic imaging and therapy because they can constitute as much as 90% of a tumor mass. The serine protease fibroblast activation protein (FAP) is overexpressed selectively in CAFs, drawing interest in FAP as a stromal target. The quinoline-based FAP inhibitor (FAPI) PET tracer ^{68}Ga -FAPI-04 has been previously shown to yield high tumor-to-background ratios (TBRs) in patients with various cancers. Recent developments toward an improved compound for therapeutic application have identified FAPI-46 as a promising agent because of an increased tumor retention time in comparison with FAPI-04. Here, we present a PET biodistribution and radiation dosimetry study of ^{68}Ga -FAPI-46 in cancer patients. **Methods:** Six patients with different cancers underwent serial ^{68}Ga -FAPI-46 PET/CT scans at 3 time points after radiotracer injection: 10 min, 1 h, and 3 h. The source organs consisted of the kidneys, bladder, liver, heart, spleen, bone marrow, uterus, and remainder of body. OLINDA/EXM software, version 1.1, was used to fit and integrate the kinetic organ activity data to yield total-body and organ time-integrated activity coefficients and residence times and, finally, organ-absorbed doses. SUVs and TBR were generated from the contoured tumor and source-organ volumes. Spheric volumes in muscle and blood pool were also obtained for TBR (tumor SUV_{max} /organ SUV_{mean}). **Results:** At all time points, average SUV_{max} was highest in the liver. Tumor and organ SUV_{mean} decreased over time, whereas TBRs in all organs but the uterus increased. The organs with the highest effective doses were bladder wall ($2.41\text{E}-03$ mSv/MBq), followed by ovaries ($1.15\text{E}-03$ mSv/MBq) and red marrow ($8.49\text{E}-04$ mSv/MBq). The average effective total-body dose was $7.80\text{E}-03$ mSv/MBq. **Conclusion:** ^{68}Ga -FAPI-46 PET/CT has a favorable dosimetry profile, with an estimated whole-body dose of 5.3 mSv for an administration of 200 MBq (5.4 mCi) of ^{68}Ga -FAPI-46 (1.56 ± 0.26 mSv from the PET tracer and 3.7 mSv from 1 low-dose CT scan). The biodistribution study showed high TBRs increasing over time, suggesting high diagnostic performance and favorable tracer kinetics for potential therapeutic applications.

Targeting the stroma in the tumor microenvironment has become an attractive goal for diagnostic imaging and therapy (1–3). Cancer-associated fibroblasts (CAFs) are the predominant component of the stroma surrounding epithelial cancer cells, and they can compose up to 90% of the total tumor mass in desmoplastic cancers (4–7). These reactive stromal cells selectively produce fibroblast activation protein (FAP), a serine protease that is scarcely expressed within the stroma of healthy tissues (1,4,5). FAP-positive CAFs are reported to promote and enhance protumorigenic characteristics such as angiogenesis, neoplastic progression, metastatic invasion, and migration (4,8–14). FAP expression is high in CAFs but low in normal adult tissues, except for sites of active tissue damage, remodeling, and inflammation (4).

The specificity of FAP for CAFs in the tumor microenvironment provided the motivation to develop FAP-specific small-molecule inhibitors. Several quinoline-based FAP inhibitors (FAPIs) labeled with positron emitters have been developed (15–17). FAPI-04 labeled with ^{68}Ga provided PET images with high tumor-to-background ratios (TBRs) in patients across a wide array of cancers, suggesting high potential for FAP-targeted diagnostics and possibly molecular radiotherapy (17–20). Because the stroma can represent up to 90% of the total tumor mass, stroma-targeted PET imaging may be more sensitive than glucose metabolism PET imaging for tumor detection in some cancers (16,18,21,22). In the context of stroma-targeted radionuclide therapy, breaking the tumor stroma barrier may increase tumor cell accessibility for pharmacologic, immunologic, or cell-based therapies (10–12). Additionally, delivery of ionizing radiation to the cancer cells may also be possible by crossfire effect.

In an effort to increase FAPI tumor uptake and retention for therapeutic applications, related FAPI-04 derivatives were developed and assessed preclinically and in cancer patients (17). From these studies, FAPI-46 emerged as the most promising tracer for therapeutic clinical application because of its high tumor uptake and retention and its decreased uptake in normal organs compared with FAPI-04.

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As a required step for further translation and approval by regulatory agencies, the primary objective of this study was to provide the radiation dosimetry analysis in cancer patients who underwent ^{68}Ga -FAPI-46 PET imaging. The secondary aim was to describe the organ biodistribution, SUV metrics, and temporal changes in TBRs (tumor $\text{SUV}_{\text{max}}/\text{organ SUV}_{\text{mean}}$).

MATERIALS AND METHODS

Study Design and Patients

This was a retrospective study of radiation dosimetry and biodistribution of a novel PET imaging probe. The imaging data were acquired at the Heidelberg University Hospital in Germany. The analysis was conducted at UCLA. Six patients (4 men, 2 women; age range, 56–81 y) with different cancer types were included. All 6 patients were referred for an unmet diagnostic challenge that could not be solved sufficiently with standard diagnostic imaging. The patient characteristics are summarized in Table 1. All patients gave written informed consent to undergo FAPI PET/CT. Following the regulations of the German Pharmaceuticals Act §13(2b), indication and labeling of the FAPI tracers were under the direct responsibility of the applying physician. The data were analyzed retrospectively with the approval of the local ethics committee (approval S016/2018).

Radiopharmaceutical Synthesis

The radiotracer synthesis was conducted as previously described (15–17). Briefly, radiolabeling was performed by adjusting a mixture of 20 nmol of FAPI-46, 10 μL of ascorbic acid solution (20% in water), and 1 mL of ^{68}Ga -solution (0.6–2 GBq in 0.6 M HCl in water) to pH 3.3–3.6 with sodium acetate (2.5 M in water). After being heated to 95°C for 20 min, the product was isolated by solid-phase extraction (Oasis Light HLB; Waters) using 0.5 mL of ethanol as the eluent. After dilution with 5 mL of sodium chloride solution (0.9%), the pH was adjusted to 7 by the addition of phosphate buffer.

PET/CT Image Acquisition

Injected activity was limited to 100–370 MBq per examination based on previous dosimetry estimates of related FAPIs with an effective whole-body dose of 1.6 mSv/100 MBq as well as count rate considerations (21). Each patient underwent PET/CT imaging scans at 3 time points after radiotracer injection: 10 min (before voiding), 1 h, and 3 h. No bladder voiding model was used, and thereby the calculated bladder dose will be the maximum dose assuming no voiding. All imaging was performed on a Biograph mCT Flow scanner (Siemens). After non-contrast-enhanced low-dose CT had been performed (130 keV, 30 mAs, CareDose; reconstructed with a soft-tissue kernel to a slice thickness of 5 mm, increment of 3–4 mm), PET images were acquired in 3-dimensional mode (matrix, 200 \times 200) using FlowMotion (Siemens) with 0.7 cm/min continuous bed motion. The emission

data were corrected for randoms, scatter, and decay. Reconstruction was performed using ordered-subset expectation maximization with 2 iterations and 21 subsets and Gauss-filtering to a transaxial resolution of 5 mm in full width at half maximum. Attenuation correction was performed using the nonenhanced low-dose CT data.

Radiation Dosimetry

Mean absorbed radiation doses were estimated using the source and target organ framework outlined by the MIRD Committee (23,24). Organ delineation and activity accumulation at each imaging time point was determined using PLANET Dose internal dosimetry software (DOSIsoft SA). Time-activity curve fitting and subsequent dose calculation was performed using OLINDA/EXM, version 1.1. The source organs consisted of the kidney parenchyma, urinary bladder, liver, heart contents, spleen, bone marrow, uterus, and remainder of body. Source organs were chosen on the basis of highest tracer uptake and previously published work (21).

Source organ volumes of interest were contoured manually at the first time point and propagated to later-time-point scans on the basis of automatic deformable registration between each scan. Propagated organ volumes were then manually adjusted when necessary. Organ volume differences that arose because of elastic propagation between time points were accounted for by calculating the mean volume for organ mass input for dose calculation in OLINDA/EXM. Kidney volumes included left and right renal parenchyma, excluding the urinary activity in renal calyces, as shown in Figure 1. The urinary activity (Fig. 1B) was delineated using SUV thresholding and subsequently subtracted from the entire kidney volume to yield only kidney parenchyma (Fig. 1C). Activity in the bone marrow was determined by contouring 2 lumbar vertebrae and scaling on the basis of the proportion of total-body bone marrow mass, with each vertebra assumed to contain 2.5% (25).

In all cases, tumor lesion activity was excluded from normal-organ source volumes by Boolean subtraction operations and incorporated in the body remainder term. Tumors were contoured using patient-specific SUV thresholding with manual adjustment (SUV threshold ranged from 2.5 to 3.5). The body remainder volume was determined by subtracting all source organs from a whole-body contour.

After tumor and organ contouring, the non-decay-corrected percentage injected activity accumulated in the organs at each time point per patient was then used as input for OLINDA/EXM software.

TABLE 1
Patient Characteristics

Patient no.	Sex	Age (y)	Diagnosis	Injected activity (MBq)
1	F	63	Cholangiocellular carcinoma	246
2	M	81	Pancreatic cancer with peritonitis carcinomatosa	240
3	F	78	Breast cancer	234
4	M	56	Oropharynx carcinoma	239
5	M	78	Head and neck cancer	214
6	M	62	Gastric cancer	243

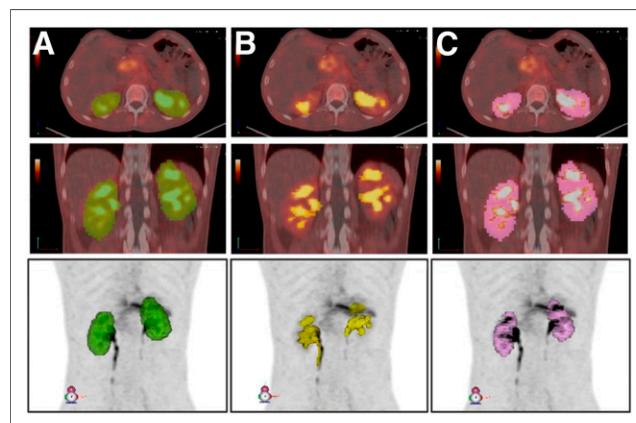


FIGURE 1. Delineated volumes used for determination of renal cortex volume: entire kidney volume (A) from which urine, including in renal calyces, is subtracted (B) to yield renal cortex volume (C). Images are shown for patient 6 and are representative of method applied for all patients. All volumes are shown in axial (top), coronal (middle), and maximum-intensity-projection views (bottom).

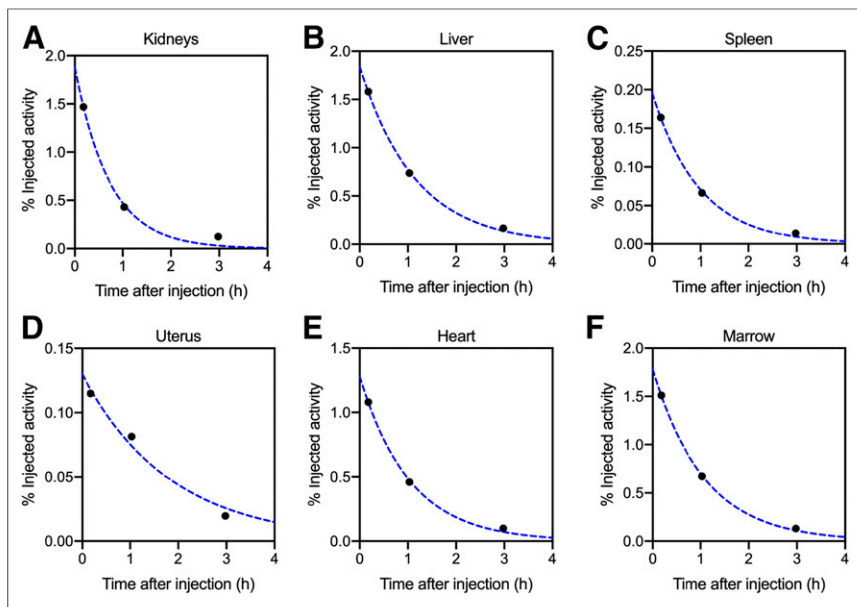


FIGURE 2. Percentage injected activity curves for patient 3 are shown for various source organs. Solid circles are measured values, and dotted lines are monoexponential functions fit to data.

Patient-specific masses were used for the liver, kidneys, spleen, uterus, and total body. The organ and total-body/remainder activity kinetic data were then fitted with a monoexponential decay function using OLINDA/EXM. Representative percentage injected activity curves for various source organs for 1 patient are shown in Figure 2. The functions are integrated to obtain time-integrated activity coefficients, and S values are applied

according to MIRD methodology from standard adult phantoms to yield absorbed and effective radiation doses. Radiation weighting factors from International Commission on Radiological Protection publication 60 were applied for calculation of effective doses (26). The calculated doses based on individual patient inputs were then reported as mean \pm SD to more accurately represent the general population risk associated with this imaging scan.

Biodistribution

In addition to the contoured tumor and source organ volumes drawn for dosimetry, spheric volumes in the gluteal muscle (range, 7–20 cm³) and blood pool in the ascending aorta (range, 4–5 mL) were created and automatically propagated to later time points for biodistribution analysis. SUV_{mean} and SUV_{max} were generated for all previously contoured organs and spheric muscle and blood volumes of interest to compute TBRs (tumor SUV_{max}/organ SUV_{mean}).

RESULTS

PET/CT Imaging

The injected activity of ⁶⁸Ga-FAPI-46 ranged from 214 to 246 MBq (5.8–6.6 mCi) (Table 1). Images were acquired at 12 \pm 2.5 min, 1.2 \pm 0.3 h, and 3.3 \pm 0.3 h after intravenous administration of ⁶⁸Ga-FAPI-46. The tracer injection was well tolerated without any side effects in all 6 patients. No adverse events were observed during the 3 h after injection. Maximum-intensity projections and organ volumes used for activity quantification are shown for patient 3 (female) and patient 5 (male) in Figures 3 and 4, respectively. The other patients' images and SUV kinetics are available in supplemental Figures 1–4 (supplemental materials are available at <http://jnm.snmjournals.org>).

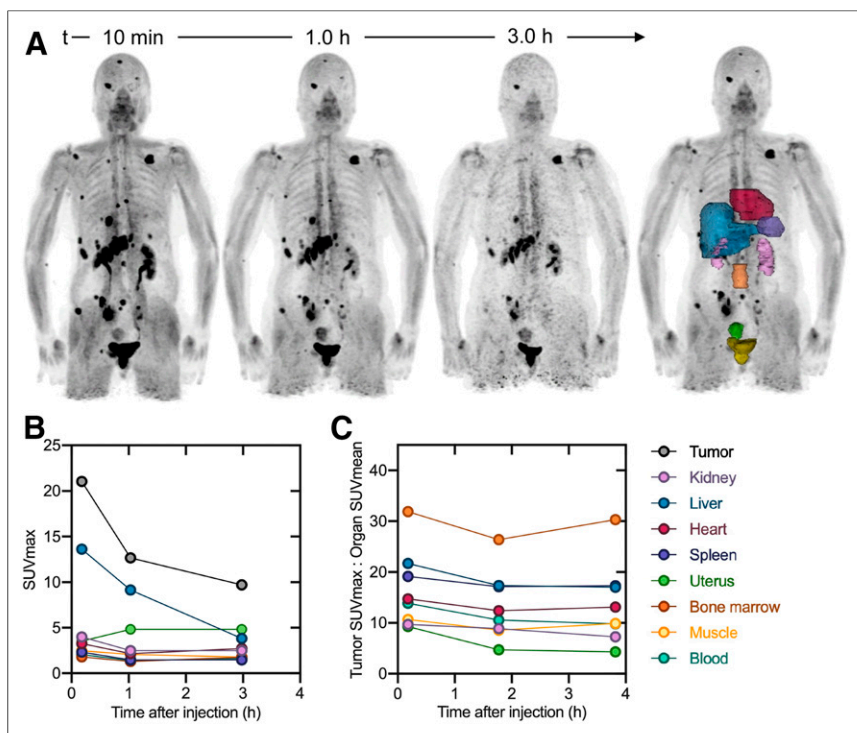


FIGURE 3. Patient 3 (female). (A) ⁶⁸Ga-FAPI-46 maximum-intensity projections and delineated organs for dose calculations. (B) SUV_{max} at 3 time points after tracer injection. (C) TBR at 3 time points after tracer injection. SUV_{max} and TBR for bladder are excluded from plot. Data values are available in Supplemental Table 1.

Radiation Dosimetry

The monoexponential curve-fitting parameters and time-integrated activity coefficients (residence times) for each source organ are summarized in Table 2. The pooled patient dosimetry reports from OLINDA/EXM are shown in Table 3.

The organ with the highest absorbed dose was the urinary bladder wall, with 4.83E–02 mGy/MBq, followed by the kidneys (1.60E–02 mGy/MBq), the heart wall (1.11E–02 mGy/MBq), the liver (1.01E–02 mGy/MBq), and the uterus (9.54E–03 mGy/MBq). The remaining organ-absorbed doses were all below 6.96E–03 mGy/MBq. Organs with the highest effective doses were the bladder wall (2.41E–03 mSv/MBq), followed by the ovaries (1.15E–03 mSv/MBq) and red marrow (8.49E–04 mSv/MBq). The average total-body absorbed dose was 5.82E–03 mGy/MBq, and the effective dose was 7.80E–03 mSv/MBq—similar to,

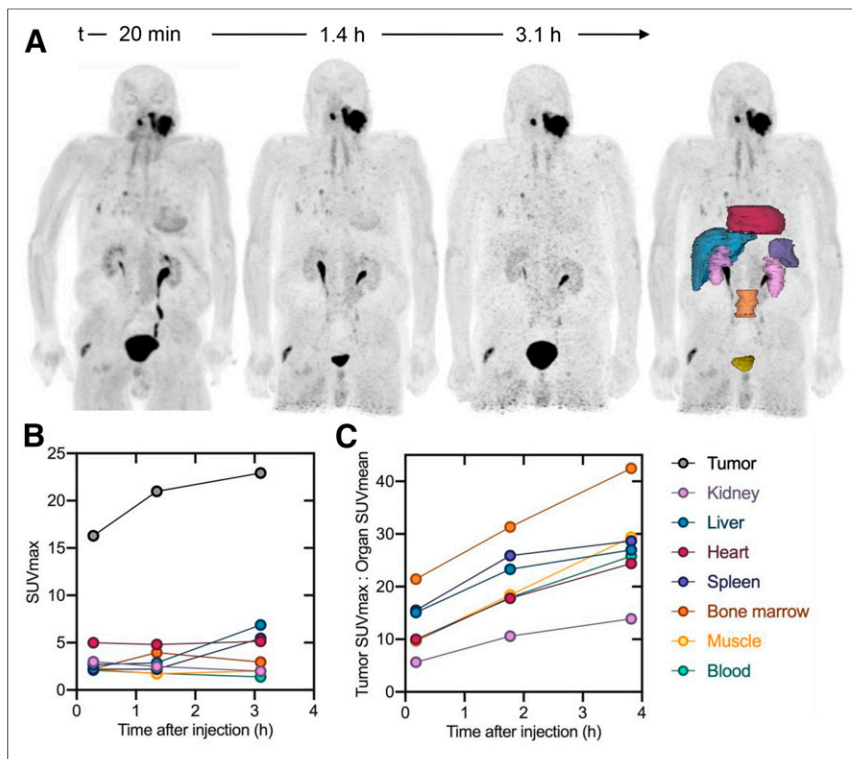


FIGURE 4. Patient 5 (male). (A) ^{68}Ga -FAPI-46 maximum-intensity projection and delineated organs for dose calculations. (B) SUV_{max} at 3 time points after tracer injection. (C) TBR at 3 time points after tracer injection. SUV_{max} and TBR for bladder are excluded from plot. Data values are available in Supplemental Table 1.

though lower than, the reported values for related FAPIs (21). Thus, for administration of 200 MBq (5.4 mCi) of ^{68}Ga -FAPI-46, the total-body effective dose was 1.56 ± 0.26 mSv. Together with approximately 3.7 mSv from 1 low-dose CT attenuation scan (27), this results in an estimated total effective dose of 5.3 mSv. The reported SDs

TABLE 2

Monoexponential Function Fitting Parameters and Time-Integrated Activity Coefficients (Residence Times) for ^{68}Ga -FAPI-46 in Various Organs

Organ	A (%IA)	λ (h^{-1})	TIAC (h)
Liver	3.49 (2.26)	0.88 (0.12)	0.0378 (0.0198)
Kidney	2.07 (0.65)	1.08 (0.26)	0.0195 (0.0062)
Bladder	6.82 (2.32)	1.47 (0.91)	0.0595 (0.0319)
Heart	1.69 (0.30)	0.94 (0.06)	0.0182 (0.0035)
Spleen	0.71 (0.62)	0.96 (0.12)	0.0074 (0.0066)
Marrow	2.61 (0.63)	2.05 (2.97)	0.0250 (0.0114)
Uterus ($n = 2$)	0.13 (0.004)	0.50 (0.07)	0.0027 (0.0005)

A = activity, expressed as %IA = percentage injected activity; %IA = $A \times \exp(-\lambda t)$; λ = rate constant; TIAC = time-integrated activity coefficient.

Data are mean followed by SD in parentheses for 6 patients. Representative percentage injected activity curves with monoexponential curve fits overlaid are available in Supplemental Figure 1. Per-patient coefficients and TIACs are available in Supplemental Table 2.

arise from calculating the mean OLINDA/EXM dosimetry profile from 6 patients and do not account for any possible errors involved in organ delineation.

Biodistribution

Biodistribution data assessed by SUV kinetics for patients 3 (female) and 5 (male) are shown in Figures 3 and 4, respectively. Pooled SUV_{max} and TBR for all 6 patients are summarized in Figure 5; SUV_{mean} is listed in Table 4. The highest average normal-organ SUV_{max} at all time points was observed in the liver, decreasing from an average SUV_{max} of 7.4 at 10 min to 5.0 by 3.3 h (decline of 32%). Tracer uptake in the tumor was rapid, with greater retention than in normal organs: an average SUV_{max} of 15.5 at 10 min and 13.4 at 3.3 h (decrease of 14%).

Tumor and organ mean SUVs decreased in all patients from the first to last time points, whereas TBRs increased with time (with the exception of the uterus TBR). The highest TBR at all time points was observed in the marrow, with a ratio of 31 at 3.3 h. The tumor-to-muscle ratio of 10.7 at 10 min increased more than 2-fold at 3.3 h to 22.8. At 3.3 h, the next highest TBRs were observed in the heart (19.1), spleen (18.9), and liver (16.8).

In summary, the tracer rapidly accumulated in the primary tumors and metastases, with high SUV_{max} and low tracer uptake in normal tissue. The radioactivity was cleared steadily from the blood pool and was excreted via the kidneys, producing high-contrast images.

DISCUSSION

Herein we describe the biodistribution of ^{68}Ga -FAPI-46 and its estimated radiation dose deposition in the organs of 6 cancer patients who underwent ^{68}Ga -FAPI-46 PET/CT imaging at 3 time points. These data are required for clinical translation and approval by regulatory agencies. The average effective whole-body dose for administration of 200 MBq of ^{68}Ga was 1.56 ± 0.26 mSv ($7.80\text{E}-03 \pm 1.31\text{E}-03$ mSv/MBq). This estimate is slightly lower than the prior reported effective total-body effective doses of other ^{68}Ga -FAPI PET tracers: $1.80\text{E}-02$ and $1.64\text{E}-02$ mSv/MBq with ^{68}Ga -FAPI-02 and ^{68}Ga -FAPI-04, respectively (21). As a comparison, the reported effective dose for ^{68}Ga -PSMA-11 ranges from $1.08\text{E}-02$ to $2.46\text{E}-02$ mSv/MBq (28,29), whereas the effective total-body dose of both ^{68}Ga -DOTATOC and ^{68}Ga -DOTATATE is $2.10\text{E}-02 \pm 3.00\text{E}-03$ mSv/MBq (30).

Despite collection of patient-specific time-activity curves, the dose calculation was based on the stylized phantoms provided in OLINDA/EXM. These estimates provide generalizable population mean absorbed dose values to organs by means of standard phantoms with selected customized organ masses. The reported SD for the dosimetry estimates (Table 3) arise from taking the average of 6 sets of OLINDA/EXM patient reports. There are, however, sources of uncertainty not included in the analysis that are inherent in

TABLE 3

⁶⁸Ga-FAPI-46 Dosimetry Summary of Mean Absorbed and Effective Doses Using OLINDA/EXM

Organ	Dose per injected activity (mGy/MBq)	Effective dose per injected activity (mSv/MBq)
Adrenals	5.60E-03 (8.12E-04)	2.80E-05 (4.04E-06)
Brain	4.59E-03 (6.12E-04)	2.29E-05 (3.06E-06)
Breasts	4.55E-03 (6.47E-04)	2.28E-04 (3.23E-05)
Gallbladder wall	5.62E-03 (8.53E-04)	—
Lower large intestine wall	5.72E-03 (6.96E-04)	6.86E-04 (8.33E-05)
Small intestine	5.48E-03 (6.37E-04)	2.74E-05 (3.20E-06)
Stomach wall	5.32E-03 (7.25E-04)	6.38E-04 (8.69E-05)
Upper large intestine wall	5.47E-03 (6.97E-04)	2.74E-05 (3.50E-06)
Heart wall	1.11E-02 (1.26E-03)	—
Kidneys	1.60E-02 (4.60E-03)	7.98E-05 (2.29E-05)
Liver	1.01E-02 (7.96E-03)	5.05E-04 (4.00E-04)
Lungs	5.02E-03 (7.09E-04)	6.02E-04 (8.48E-05)
Muscle	4.96E-03 (6.54E-04)	2.48E-05 (3.27E-06)
Ovaries	5.76E-03 (6.91E-04)	1.15E-03 (1.38E-04)
Pancreas	5.69E-03 (8.49E-04)	2.84E-05 (4.24E-06)
Red marrow	7.08E-03 (1.00E-03)	8.49E-04 (1.20E-04)
Osteogenic cells	9.38E-03 (1.30E-03)	9.38E-05 (1.30E-05)
Skin	4.41E-03 (6.33E-04)	4.41E-05 (6.33E-06)
Spleen	6.96E-03 (2.76E-03)	3.48E-05 (1.39E-05)
Testes	4.88E-03 (6.69E-04)	1.15E-03 (1.38E-04)
Thymus	5.10E-03 (6.40E-04)	2.55E-05 (3.21E-06)
Thyroid	4.84E-03 (5.72E-04)	2.42E-04 (2.85E-05)
Urinary bladder wall	4.83E-02 (8.55E-03)	2.41E-03 (4.27E-04)
Uterus	9.54E-03 (5.36E-03)	4.76E-05 (2.67E-05)
Total body	5.82E-03 (1.18E-03)	7.80E-03 (1.31E-03)
Total body dose for 200 MBq	1.16 mGy (0.24 mGy)	1.56 mSv (0.26 mSv)

Data are mean followed by SD in parentheses for 6 patients. Effective doses in ovaries and testes are equivalent because of use of hermaphroditic adult phantom weighting. Gallbladder wall and heart wall effective doses are not available based on ICRP radiation weighting factors. Nonpooled OLINDA/EXM reports, including β and photon contribution to total dose, are available in Supplemental Table 3.

the dose calculation process and propagate to the final dose result. One of the most significant contributing sources of uncertainty is the organ volume delineation itself (31,32). Interpatient variability is also

seen within Table 2, which shows a relatively high SD for time–activity curve-fitting parameters, most prominently observed in the liver.

Although tumor dosimetry was not addressed directly in this study, the trend in biodistribution observed up to 3.3 h after tracer administration demonstrates rapid tumor uptake and satisfactory retention. FAPI-46 biodistribution and dosimetry (including tumor dosimetry) using longer-lived isotopes for therapeutic applications remain to be studied. Such studies are essential to evaluate longer-term tracer kinetics and thereby determine rational therapeutic isotope conjugates with a well-matched physical half-life. The promising trend observed thus far of increasing TBRs over time seems to be favorable for therapeutic applications. Given the high achieved TBRs even at 10 min, early-time-point imaging with ⁶⁸Ga-FAPI becomes possible; however, it should be considered that the contrast ratio improves with time.

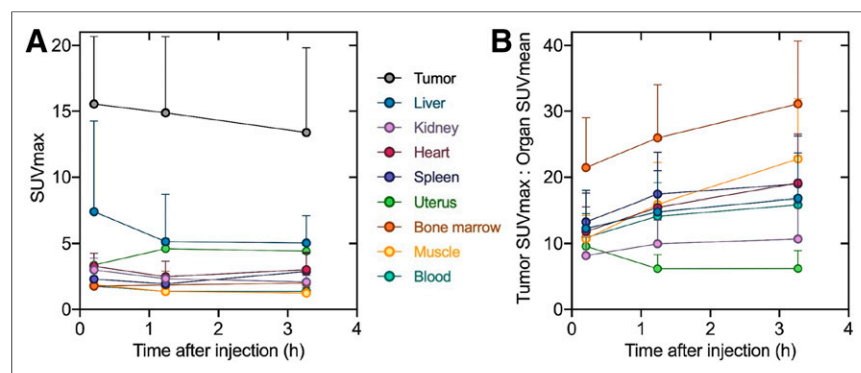


FIGURE 5. Pooled tumor and organ SUV_{max} (A) and TBR (B) at 3 time points after tracer injection (excluding bladder). Results are shown as mean and SD for 6 patients. Data values are available in Table 4.

TABLE 4
Pooled Tumor-to-Organ SUV Ratio, SUV_{max}, and SUV_{mean} at 3 Time Points After ⁶⁸Ga-FAPI-46 Administration

Parameter	10 min	1.2 h	3.3 h
SUV_{max}-to-SUV_{mean} ratio			
Tumor-to-liver	12.28 (5.75)	14.79 (6.22)	16.80 (6.90)
Tumor-to-kidney	8.17 (2.76)	9.96 (3.64)	10.68 (5.34)
Tumor-to-blood	10.89 (3.61)	14.15 (5.02)	15.87 (7.30)
Tumor-to-muscle	10.71 (3.56)	15.91 (6.33)	22.77 (9.15)
Tumor-to-heart	11.78 (3.76)	15.48 (5.49)	19.11 (7.44)
Tumor-to-spleen	13.27 (4.31)	17.44 (6.36)	18.99 (7.27)
Tumor-to-marrow	21.46 (7.56)	25.96 (8.09)	31.13 (9.52)
Tumor-to-uterus (<i>n</i> = 2)	9.60 (0.46)	6.19 (2.12)	6.20 (2.70)
SUV_{max}			
Tumor	15.54 (5.13)	14.89 (5.77)	13.39 (6.44)
Liver	7.42 (6.84)	5.15 (3.56)	5.04 (2.07)
Kidney	3.00 (0.89)	2.33 (0.26)	2.08 (0.49)
Blood	1.77 (0.35)	1.38 (0.26)	1.37 (0.31)
Muscle	1.87 (0.49)	1.37 (0.45)	1.24 (0.56)
Heart	3.28 (1.00)	2.48 (1.17)	3.02 (1.31)
Spleen	2.30 (0.23)	1.94 (0.42)	2.88 (1.38)
Marrow	1.77 (0.34)	1.85 (1.05)	2.00 (0.59)
Uterus (<i>n</i> = 2)	3.37 (0.23)	4.61 (0.32)	4.42 (0.58)
SUV_{mean}			
Tumor	3.87 (1.30)	3.37 (1.11)	2.81 (1.44)
Liver	1.51 (0.96)	1.10 (0.58)	0.81 (0.34)
Kidney	1.92 (0.34)	1.47 (0.17)	1.25 (0.22)
Blood	1.43 (0.25)	1.03 (0.15)	0.83 (0.15)
Muscle	1.48 (0.41)	0.96 (0.32)	0.61 (0.24)
Heart	1.32 (0.21)	0.95 (0.15)	0.68 (0.15)
Spleen	1.17 (0.20)	0.85 (0.17)	0.69 (0.16)
Marrow	0.73 (0.12)	0.56 (0.11)	0.41 (0.10)
Uterus (<i>n</i> = 2)	2.08 (0.27)	2.53 (0.24)	1.97 (0.42)

Data are mean followed by SD in parentheses for 6 patients.

This analysis was limited to 6 cancer patients (4 men and 2 women) and no healthy subjects. The basal FAP expression profile of a greater variety of cancers, as well as in healthy subjects, remains to be quantitatively assessed. It is, however, known that FAP is expressed at sites of arthritis, wound healing and active tissue remodeling, bone marrow mesenchymal cells, and cirrhotic liver (5,18,33,34). The extent of this expression and its impact on imaging and potential therapies require further clinical study. Implementation of FAP-targeted therapies thereby necessitates a better understanding of the comprehensive role of FAP, not only in the tumor microenvironment and carcinogenesis of different cancer types but also in widespread bodily fibrotic mechanisms. Evaluation of ⁶⁸Ga-FAPI-46 diagnostic accuracy was outside the study scope.

CONCLUSION

⁶⁸Ga-FAPI-46 PET/CT imaging is shown to have a favorable dosimetry profile. For administration of 200 MBq (5.4 mCi) of

⁶⁸Ga-FAPI-46, the effective whole-body dose of a PET scan is 1.56 ± 0.26 mSv. When including a low-dose CT scan (3.7 mSv), the dose of a ⁶⁸Ga-FAPI-46 PET/CT scan is approximately 5.3 mSv in total. The biodistribution study showed high TBRs increasing over time, suggesting high diagnostic performance and favorable tracer kinetics for potential therapeutic applications. Long-term tracer biodistribution and dosimetry for longer-lived therapeutic isotope applications remain to be studied. Further work is needed to better identify indications for FAPI PET/CT and its diagnostic accuracy.

DISCLOSURE

Jeremie Calais is consultant for Blue Earth Diagnostics, Progenics Radiopharmaceuticals, and Radiomedix, outside the submitted work. Johannes Czernin is a cofounder and holds equity in Sofie Biosciences and Trethera Therapeutics. Intellectual property patented by the University of California has been

licensed to Sofie Biosciences and Trethera Therapeutics. This intellectual property was not used in the current study. Sebastien Vauclin is an employee of DOSIsoft SA (Cachan, France). Uwe Haberkorn and Thomas Lindner are coauthors on a patent application for FAP agents. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the biodistribution and radiation dosimetry profile of ^{68}Ga -FAP-46, a new PET tracer targeting tumor stroma with high potential for theranostic applications?

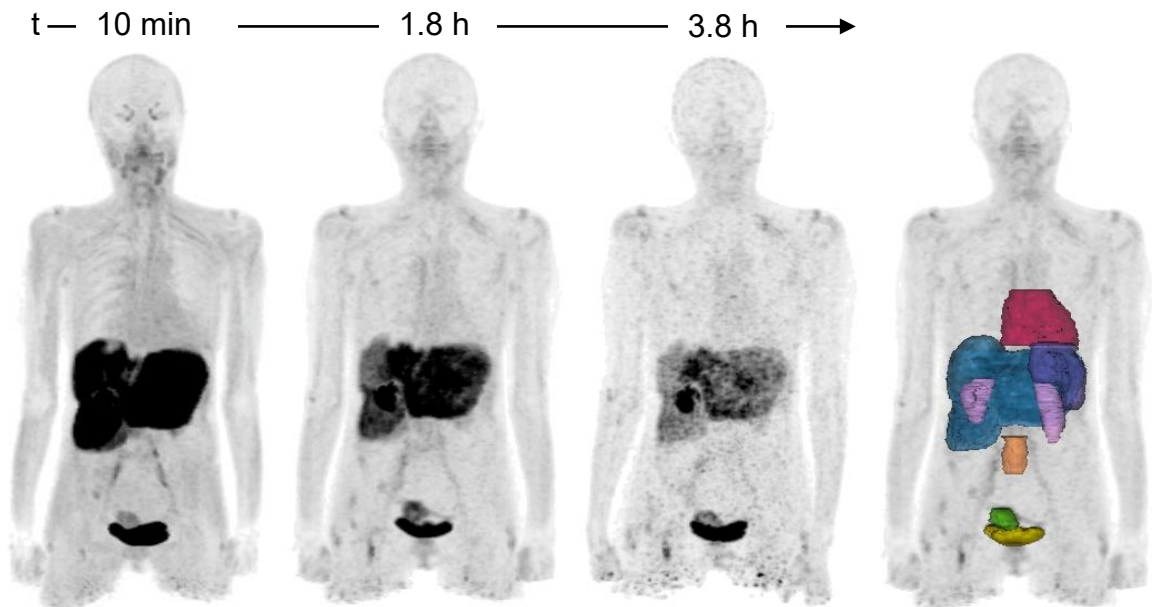
PERTINENT FINDINGS: Based on 3 serial ^{68}Ga -FAP-46 PET/CT scans acquired in 6 cancer patients, the average effective whole-body dose estimation for administration of 200 MBq of ^{68}Ga -FAP-46 was 1.56 mSv, which is lower than with other ^{68}Ga PET tracers (^{68}Ga -PSMA-11 or ^{68}Ga -DOTATATE). The biodistribution study showed high TBRs increasing over time.

IMPLICATIONS FOR PATIENT CARE: This study confirms the high potential of ^{68}Ga -FAP-46 for theranostic applications and provides required data for translation and approval by regulatory agencies.

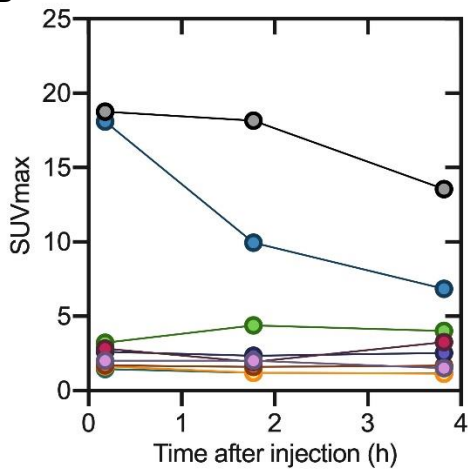
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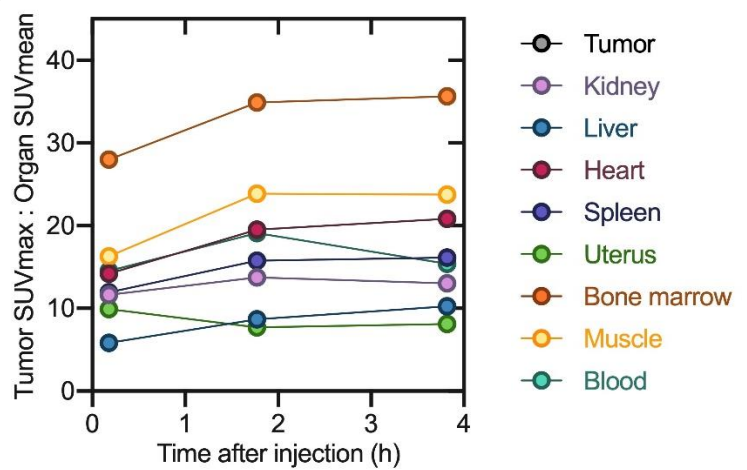
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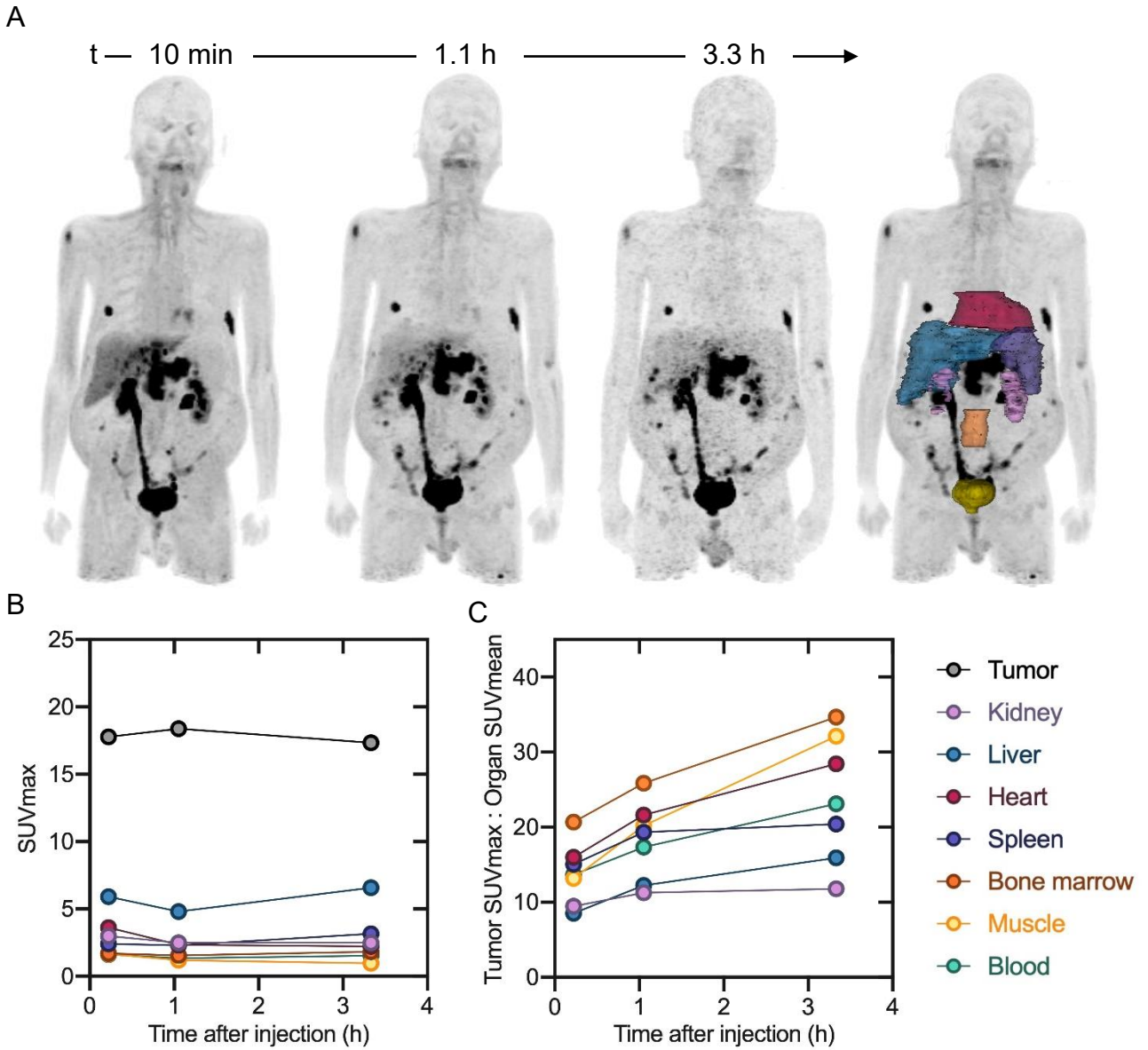
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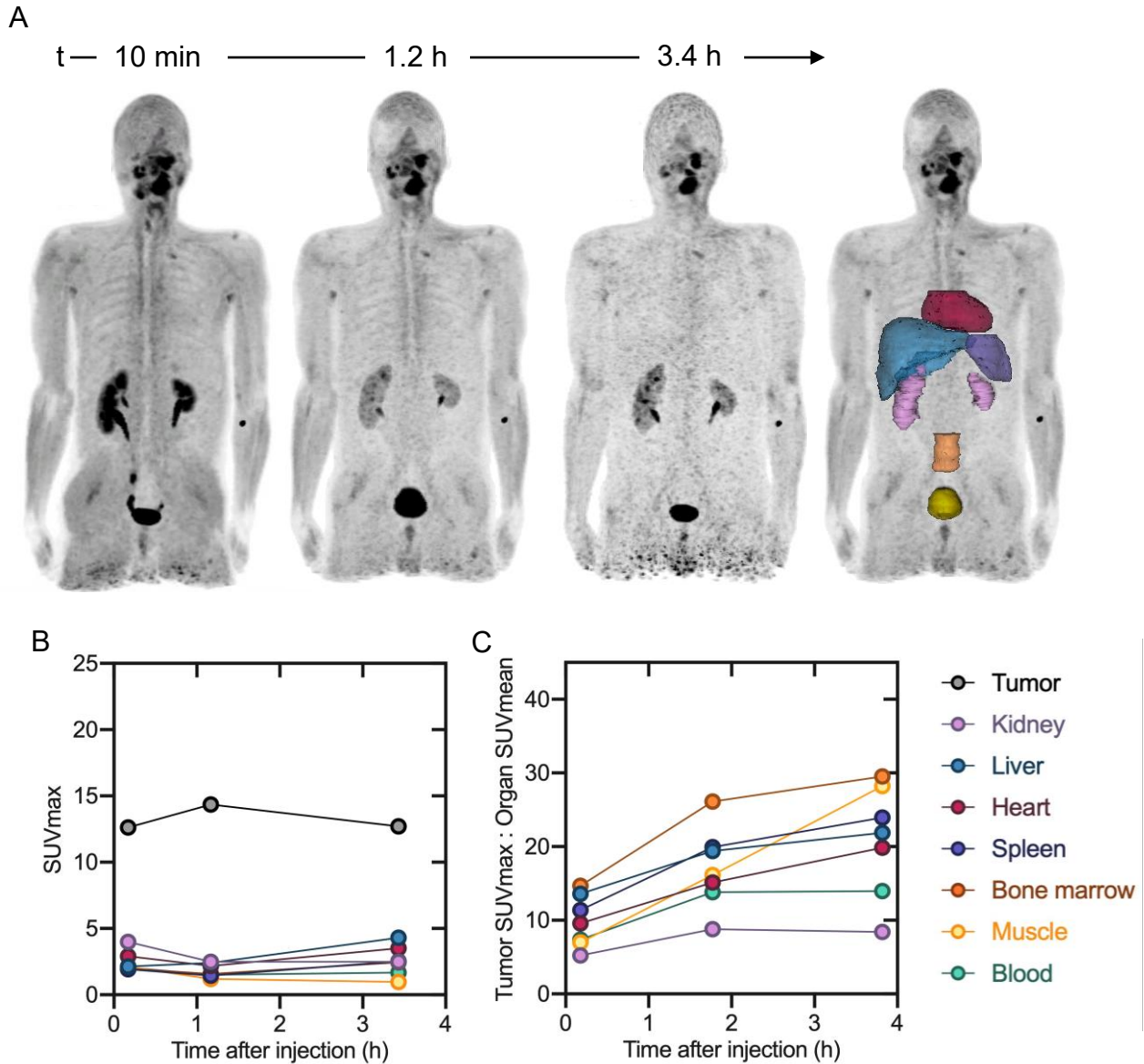
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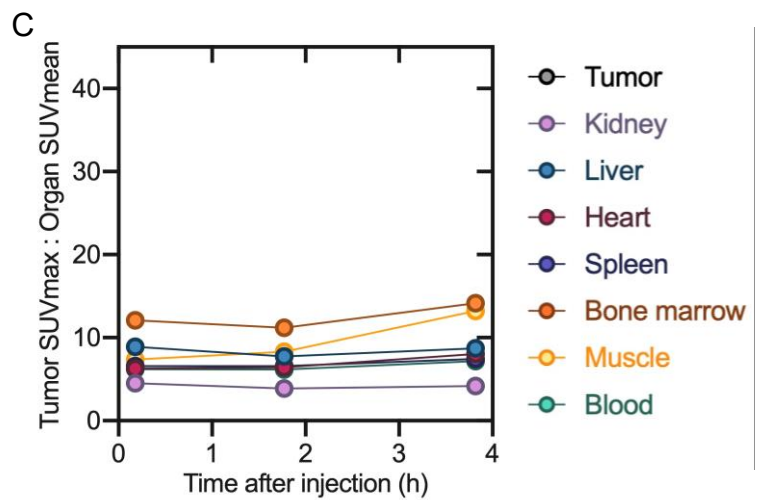
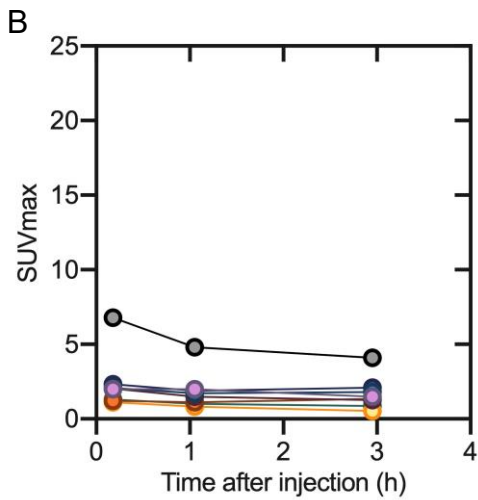
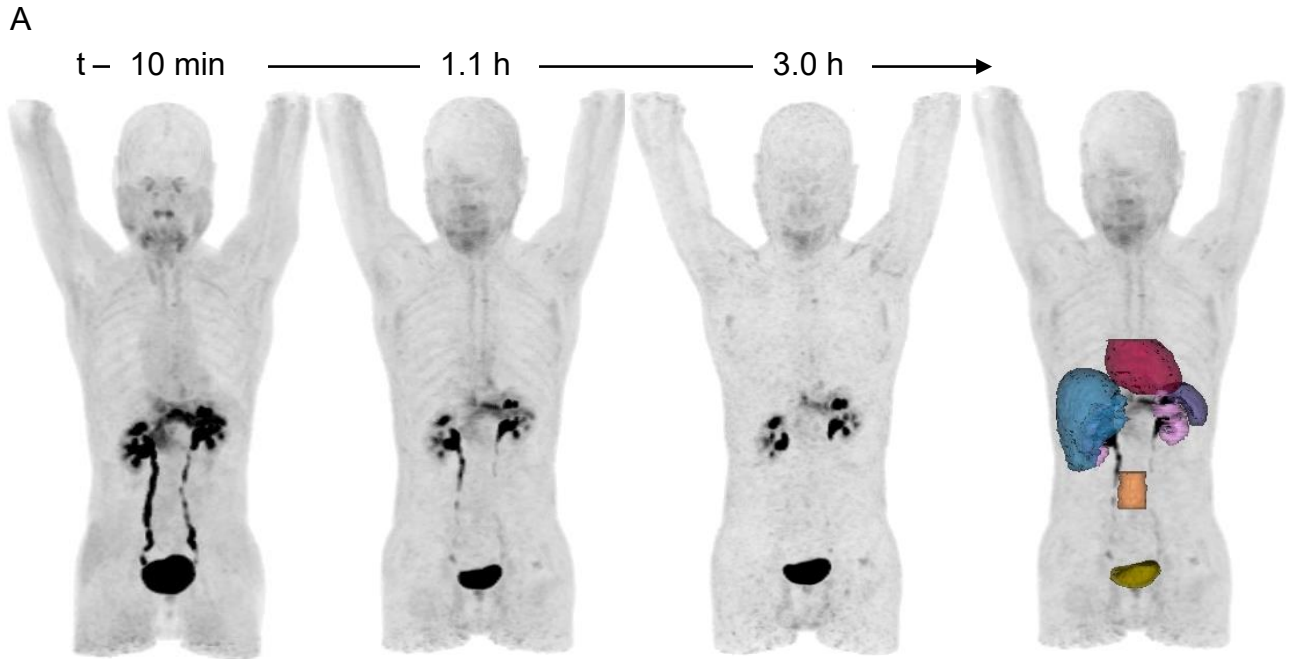
Supplemental Figure 1 | Patient 1 A) ^{68}Ga -FAPI-46 MIP and delineated organs for dose calculations, B) SUVmax at three timepoints following tracer injection and C) TBR at three timepoints following tracer injection. SUVmax and TBR for the bladder are excluded from the plot. Data values available in Supplemental Table 1.



Supplemental Figure 2 | Patient 2 A) ^{68}Ga -FAPI-46 MIP and delineated organs for dose calculations, B) SUVmax at three timepoints following tracer injection and C) TBR at three timepoints following tracer injection. SUVmax and TBR for the bladder are excluded from the plot. Data values available in Supplemental Table 1.



Supplemental Figure 3 | Patient 4 A) ^{68}Ga -FAPI-46 MIP and delineated organs for dose calculations, B) SUVmax at three timepoints following tracer injection and C) TBR at three timepoints following tracer injection. SUVmax and TBR for the bladder are excluded from the plot. Data values available in Supplemental Table 1.



Supplemental Figure 4 | Patient 6 A) ^{68}Ga -FAPI-46 MIP and delineated organs for dose calculations, B) SUVmax at three timepoints following tracer injection and C) TBR at three timepoints following tracer injection. SUVmax and TBR for the bladder are excluded from the plot. Data values available in Supplemental Table 1.

Supplemental Table 2 | Time-integrated activity coefficients (TIACs) per patient

	$%IA = A * \exp(-\lambda t)$						
	Heart	Bladder	Spleen	Marrow	Uterus	Kidney	Liver
Patient 1							
A (%)	1.590	7.550	1.480	2.220	0.136	1.140	6.740
λ (h ⁻¹)	0.840	1.720	0.812	0.720	0.447	0.776	1.010
TIAC (h)	0.019	0.044	0.018	0.031	0.003	0.015	0.067
Patient 2							
A (%)	2.020	3.720	1.510	3.620	N/A	2.830	6.030
λ (h ⁻¹)	0.965	0.316	1.160	8.100	N/A	0.969	1.020
TIAC (h)	0.021	0.118	0.013	0.004	N/A	0.029	0.059
Patient 3							
A (%)	1.280	4.400	0.196	1.780	0.130	1.880	1.840
λ (h ⁻¹)	0.965	0.992	1.020	0.932	0.544	1.380	0.868
TIAC (h)	0.013	0.044	0.002	0.019	0.002	0.014	0.021
Patient 4							
A (%)	1.540	9.800	0.291	2.920	N/A	2.250	1.970
λ (h ⁻¹)	0.960	2.900	0.947	0.940	N/A	1.400	0.827
TIAC (h)	0.016	0.034	0.003	0.031	N/A	0.016	0.024
Patient 5							
A (%)	2.050	8.170	0.260	2.560	N/A	1.620	1.970
λ (h ⁻¹)	0.893	1.950	0.873	0.716	N/A	0.857	0.726
TIAC (h)	0.023	0.042	0.003	0.036	N/A	0.019	0.027
Patient 6							
A (%)	1.680	7.290	0.520	2.540	N/A	2.700	2.380
λ (h ⁻¹)	0.989	0.964	0.958	0.891	N/A	1.100	0.821
TIAC (h)	0.017	0.076	0.005	0.029	N/A	0.025	0.029

First Topic: Clinical Translation of FAP-PET imaging

Article 3:

Title: *Correlation of 68Ga-FAPi-46 PET biodistribution with FAP expression by immunohistochemistry in patients with solid cancers: interim analysis of a prospective translational exploratory study.*

Authors: Mona CE, Benz MR, Hikmat F, Grogan TR, Lückerrath K, Razmaria A, Riahi R, Slavik R, Girgis MD, Carlucci G, Kelly KA, French SW, Czernin J, Dawson DW, **Calais J.**

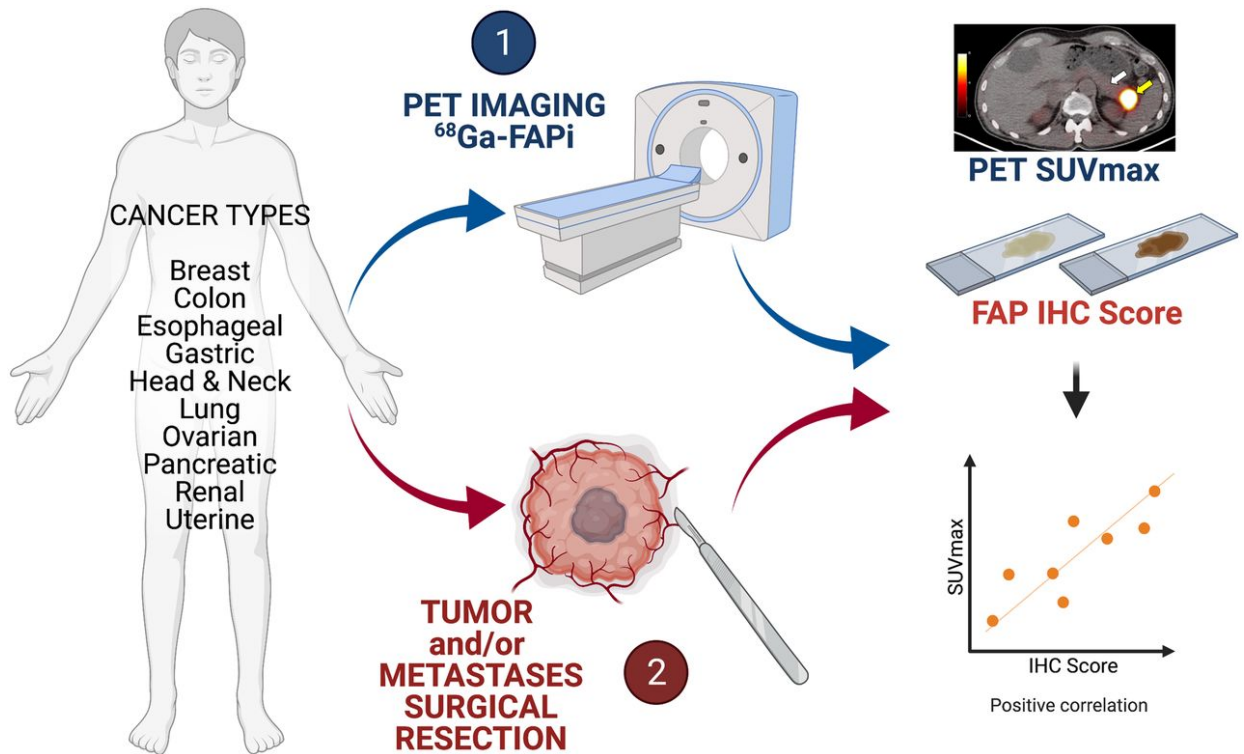
Reference: *J Nucl Med.* 2021 Nov 5;jnumed.121.262426. doi: 10.2967/jnumed.121.262426. PMID: 34740953

Brief Outline:

In this translational study, we first surveyed tissue microarrays (TMAs) of 141 patients with 14 cancer types for the presence and degree of FAP expression by immunohistochemistry. A cohort of surgical patients representing 10 of those cancer types was then tested to determine the correlation between 68Ga-FAPi-46 PET biodistribution and FAP immunohistochemistry expression in excised tumor tissue.

The first author was Christine Mona PhD, who was working as Post-Doctoral Research Associate after a PhD in Pharmacology. This work was presented at the AACR and ASCO in 2021 and received 2 awards at the SNMMI annual meeting : 1st place in the Early-Career Professionals Abstract Award and 2nd place in the Oncology, Basic Science Poster Award.

The paper has 95 citations by Google Scholar and 65 citations by Web of Science as of Sept 1st 2024 and was highlighted in Autminnie: <https://www.auntminnie.com/index.aspx?sec=sup&sub=mol&pag=dis&ItemID=133969>.



Correlation of ^{68}Ga -FAPi-46 PET Biodistribution with FAP Expression by Immunohistochemistry in Patients with Solid Cancers: Interim Analysis of a Prospective Translational Exploratory Study

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Fibroblast activation protein (FAP)-expressing cancer-associated fibroblasts confer treatment resistance and promote metastasis and immunosuppression. Because FAP is overexpressed in many cancers, radiolabeled molecules targeting FAP are studied for their use as pancancer theranostic agents. This study aimed to establish the spectrum of FAP expression across various cancers by immunohistochemistry and to explore whether ^{68}Ga FAP inhibitor (FAPi)-46 PET biodistribution faithfully reflects FAP expression from resected cancer and non-cancer specimens. **Methods:** We conducted a FAP expression screening using immunohistochemistry on a pancancer human tissue microarray (141 patients, 14 different types of cancer) and an interim analysis of a prospective exploratory imaging trial in cancer patients. Volunteer patients underwent 1 whole-body ^{68}Ga -FAPi-46 PET/CT scan and, subsequently, surgical resection of their primary tumor or metastasis. ^{68}Ga -FAPi-46 PET SUV_{max} and SUV_{mean} was correlated with FAP immunohistochemistry score in cancer and tumor-adjacent non-cancer tissues for each patient. **Results:** FAP was expressed across all 14 cancer types on tissue microarray with variable intensity and frequency, ranging from 25% to 100% (mean, $76.6\% \pm 25.3\%$). Strong FAP expression was observed in 50%–100% of cancers of the bile duct, bladder, colon, esophagus, stomach, lung, oropharynx, ovary, and pancreas. Fifteen patients with various cancer types (colorectal [$n = 4$], head and neck [$n = 3$], pancreas [$n = 2$], breast [$n = 2$], stomach [$n = 1$], esophagus [$n = 2$], and uterus [$n = 1$]) underwent surgery after their ^{68}Ga -FAPi-46 PET/CT scan within a mean interval of 16.1 ± 14.4 d. ^{68}Ga -FAPi-46 SUVs and immunohistochemistry scores were higher in cancer than in tumor-adjacent non-cancer tissue: mean SUV_{max} 7.7 versus 1.6 ($P < 0.001$), mean SUV_{mean}

6.2 versus 1.0 ($P < 0.001$), and mean FAP immunohistochemistry score 2.8 versus 0.9 ($P < 0.001$). FAP immunohistochemistry scores strongly correlated with ^{68}Ga -FAPi 46 SUV_{max} and SUV_{mean} : $r = 0.781$ (95% CI, 0.376–0.936; $P < 0.001$) and $r = 0.783$ (95% CI, 0.379–0.936; $P < 0.001$), respectively. **Conclusion:** In this interim analysis of a prospective exploratory imaging trial, ^{68}Ga -FAPi-46 PET biodistribution across multiple cancers strongly correlated with FAP tissue expression. These findings support further exploration of FAPi PET as a pancancer imaging biomarker for FAP expression and as a stratification tool for FAP-targeted therapies.

Key Words: cancer; PET/CT; fibroblast activation protein; immunohistochemistry; ^{68}Ga -FAPi-46

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DOI: 10.2967/jnumed.121.262426

Fibroblast activation protein (FAP) is strongly expressed on cancer-associated fibroblasts and is a key player in tumor progression (1). High FAP expression is restricted almost exclusively to cancer-associated fibroblasts and serves as an independent negative prognostic factor for multiple types of cancer (2). In vivo depletion of FAP-positive stromal cells inhibits tumor growth by decreasing cancer support, increasing antitumor immunity, and limiting stromal barrier effects (3–5). However, targeting the enzymatic activity of FAP with antibodies does not yield beneficial clinical effects (6,7). Recently, FAP inhibitor (FAPi)-targeting ligands labeled with radioisotopes for PET imaging (e.g., ^{68}Ga and ^{18}F for PET) and therapy (e.g., ^{177}Lu and ^{90}Y) have been introduced (8,9). The high tumor uptake that was observed with FAPi PET imaging in various cancers suggests that radiolabeled FAPi compounds have promising potential for diagnostic and therapeutic applications (10).

In this prospective translational, exploratory study, we aimed at assessing the utility of FAPi PET imaging as a pancancer imaging biomarker for FAP expression. We first surveyed tissue microarrays (TMAs) of 141 patients with 14 cancer types for the presence

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Guest Editor: Barry A. Siegel, Mallinckrodt Institute of Radiology

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and degree of FAP expression by immunohistochemistry (11). A cohort of surgical patients representing 10 of those cancer types was then tested to determine the correlation between ^{68}Ga -FAPi-46 PET biodistribution and FAP immunohistochemistry expression in excised tumor tissue.

MATERIALS AND METHODS

TMA Screening

FAP expression in human tumor tissue was assessed using a pan-cancer TMA obtained from the University of Virginia. This TMA included 141 patients with 14 different types of cancer (bile duct, bladder, breast, colon, esophagus, stomach, liver, lung, ovary, oropharynx, pancreas, prostate, kidney, and uterus; 6–14 tumors per tissue type). Normal tissues present on the TMA were also evaluated (5–8 samples per tissue type). After deparaffinization and rehydration, heat-induced antigen retrieval (sodium citrate, 0.05% polysorbate 20, pH 6.0) was performed for 20 min using a vegetable steamer followed by quenching of endogenous peroxidase activity (3% hydrogen peroxide, 10 min). Primary antibody incubation with a 1:50 dilution of rabbit monoclonal anti-FAP α -[EPR20021] (ab207178; Abcam) was performed overnight at 4°C. Detection was performed using the ultraView Universal DAB Detection Kit (K3467; DAKO) per the manufacturer's instructions. An experienced surgical pathologist (DWD) confirmed the histologic diagnoses and performed a immunohistochemistry analysis using a semiquantitative visual scoring system (0, negative staining; 1, weak staining; 2, strong staining).

Clinical Study Design and Participants

We conducted a prospective exploratory biodistribution study of ^{68}Ga -FAPi-46 PET imaging under the Radioactive Drug Research Committee Program (title 21 of *Code of Federal Regulations*, section 361.1). The primary objective was to define the biodistribution of ^{68}Ga -FAPi-46 PET in normal and cancer tissues and further correlate with tissue expression as determined by FAP immunohistochemistry. Volunteer cancer patients scheduled to undergo surgical resection of a primary tumor or metastasis were eligible (the inclusion and exclusion criteria are in Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>). The type of surgery depended on the location and disease as determined by clinical standard-of-care explorations. ^{68}Ga -FAPi-46 PET/CT imaging findings did not impact the therapy plan, and surgery was performed independently of the results of the scan findings. The study was approved by the UCLA Institutional Review Board (approval 19-000756) and registered on ClinicalTrials.gov (NCT04147494). All patients provided oral and written informed consent.

We present here the results of an interim analysis that was mandated by the UCLA Jonsson Comprehensive Cancer Center Internal Scientific Peer Review Committee and Data Safety Monitoring Board after completed enrollment of 15 patients.

FAPi PET/CT Image Acquisition

^{68}Ga -FAPi-46 was used as the FAP-targeted radioligand (8). The mean injected activity was 184 ± 3 MBq (range, 174–185 MBq). The mean uptake time was 63 ± 10 min (range, 54–96 min). Images were acquired using 64-detector PET/CT scanners (Biograph 64 mCT [$n = 7$] or Biograph 64 TruePoint [$n = 8$]; Siemens Healthcare). Unenhanced CT (120 kV, 80 mAs) was performed for attenuation correction and anatomic correlation of the PET findings. PET images were acquired from vertex to mid thigh, using an emission time of 2–4 min per bed position, depending on patient body weight. All PET images were reconstructed using correction for attenuation, dead time, random events, and scatter. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization).

FAPi PET/CT Image Analysis

Images were analyzed in consensus by 2 readers (MRB, JCa) blinded to the histopathology and immunohistochemistry results. The readers had access to all medical records and other imaging modality results available to facilitate tumor localization. Image analysis was performed with OsiriX (Pixmeo) (12). The readers quantified the ^{68}Ga -FAPi-46 PET uptake in cancer tissue and tumor-adjacent non-cancer tissue by placing volumes of interest in the tumor lesions and the surrounding normal tissue in the same organ. The readers adapted the size of the volume of interest visually to best encompass the structure of interest and to preclude overlapping of activity between the cancer and non-cancer volumes of interest. Anatomic CT information was used to avoid activity spillover from other organs. SUV_{mean} , SUV_{max} , and lesion size by CT were recorded.

Histopathology and Immunohistochemistry Analysis

Clinical pathology reports were used to collect final pathology diagnoses and pathologic TNM staging. Representative sections of normal and tumor tissue from surgical resection specimens were obtained from the UCLA Department of Pathology through the UCLA Translational Pathology Core Laboratory. FAP immunohistochemistry staining was performed as described above.

All hematoxylin and eosin slides from each surgical pathology case were evaluated to select representative sections consisting of normal and tumor tissue for immunohistochemistry evaluation. One representative section that best reflected the overall tumor histology (i.e., histologic type and grade, relative stroma and tumor cell component), that included sampling of both the edge and the central portions of the tumor mass, and that contained surrounding adjacent normal tissue (>5 mm distance from malignant cells) was selected for each patient. Immunohistochemistry stains were independently scored by 2 pathologists (DWD, SWF) who did not know each other's scores, the clinical information, or the PET imaging results. A semiquantitative approach adapted from a prior study was used (13). Briefly, FAP expression was assessed globally across the entire cross-sectional area of tumor and adjacent nonmalignant tissue without any specific focus on invasive fronts or areas of active tumor growth. The tumor compartment was defined on the basis of morphologic assessments as the geographic area where malignant cells were present, as well as the immediately adjacent area of intratumoral and peritumoral stromal response. A score of 0 was defined as complete absence of staining or weak staining in less than 10% of the area under assessment. A score of 1 was defined as weak expression in greater than 10% of the area under assessment. A score of 2 was defined as moderate or strong expression in 10%–50% of the area under assessment. A score of 3 was defined as moderate or strong expression in more than 50% of the area under assessment.

Cross-Sectional Correlation Analysis of the FAPi PET Signal and FAP Immunohistochemistry Staining

The ^{68}Ga -FAPi-46 PET SUV and the FAP immunohistochemistry score of cancer and tumor-adjacent non-cancer tissue were evaluated for correlation on a per-patient basis: for each tumor lesion, the ^{68}Ga -FAPi-46 PET SUV of the lesion was evaluated for correlation with the immunohistochemistry score of the tumor compartment on the selected pathology slide, and the ^{68}Ga -FAPi-46 PET SUV of the normal tissue surrounding the tumor lesion was evaluated for correlation with the immunohistochemistry score of the tumor-adjacent non-cancer tissue available on the same pathology slide as that containing the tumor lesion.

Statistics

Patient characteristics and study variables were summarized using mean, SD, ranges, or frequency (%) as appropriate. To test for differences in expression levels of both immunohistochemistry and PET measures between cancer and non-cancer tissues, the 2 groups were compared using *P* values from a generalized-estimating-equation model (to properly account for the repeated-measures design of the

study) (14). For assessing the association between immunohistochemistry and PET findings, we computed repeated-measures correlation coefficients. Interreader agreement for the immunohistochemistry scoring was assessed using Cohen κ -statistics. *P* values of less than 0.05 were considered statistically significant. Analyses were performed using SAS (version 0.4; SAS Institute) and R (version 3.6.1, Rmcrr package; www.r-project.org). Because of the exploratory nature of this study and the Radioactive Drug Research Committee-mandated limit of 30 patients, with an interim analysis after 15 patients mandated by the UCLA Institutional Review Board, a power analysis for sample size was not performed.

RESULTS

TMA Analysis

Representative FAP immunohistochemistry scoring by cancer type performed in the TMA is shown in Figure 1. FAP expression was present in 80.9% (114/141) of tumors. Of the 114 positive tumors, FAP expression was stromal in 108, epithelial in 1, and mixed in 5 (lung cancer [*n* = 1], ovarian cancer [*n* = 1], oropharynx [*n* = 1], pancreatic [*n* = 1], and uterine cancer [*n* = 1]). No stroma was present for evaluation in 1 case of ovarian cancer (0.7%).

Although there was variability in the intensity and frequency of FAP expression, FAP was positive in more than 50% of cases from 11 of 14 cancer types. Strong FAP expression was observed in 50%–100% of cancers from the bile duct, bladder, colon,

esophagus, stomach, lung, oropharynx, ovary, and pancreas. Liver, prostate, and renal cell cancer were the 3 tumor types with the lowest FAP expression.

This TMA survey provided a rationale for the design of the subsequent clinical PET imaging study.

PET Imaging Study Cohort

Between December 2019 and May 2020, 15 patients (8 men and 7 women; mean age, 60.7 ± 10.5 y) with 7 different cancer types (colorectal [*n* = 4], head and neck [*n* = 3], pancreatic [*n* = 2], breast [*n* = 2], gastric [*n* = 1], esophageal [*n* = 2], and uterine [*n* = 1] cancer) were enrolled. Supplemental Table 2 summarizes the demographics and clinical characteristics of the study population. All 15 patients underwent ^{68}Ga -FAPi-46 PET/CT and subsequent surgery within 16.1 ± 14.4 d (range, 1–50 d) after the scan. Two patients had tumors deemed unresectable at the time of surgery (gastric linitis plastica with duodenal extension, patient 3; pancreatic cancer with venous involvement, patient 14).

^{68}Ga -FAPi-46 PET Biodistribution in Cancer Lesions, Normal Organs, and Non-Cancer Tissues

The ^{68}Ga -FAPi-46 biodistribution as determined by SUV_{mean} in normal organs is described in Supplemental Table 3 and Supplemental Figure 1. The ^{68}Ga -FAPi-46 SUVs and the size of the cancer lesions are provided in Supplemental Tables 4 (primary tumors) and 5 (metastases).

Normal Organs and Non-Cancer Tissues.

The highest normal-organ ^{68}Ga -FAPi-46 PET signals were in the urinary bladder (because of urinary excretion) and the uterus (because of normal myometrial FAP expression). Other organs with notable ^{68}Ga -FAPi-46 uptake included the submandibular glands, Waldeyer ring, pancreas, and kidneys (average $\text{SUV}_{\text{mean}} < 2.5$). ^{68}Ga -FAPi-46 uptake higher than in normal tissues was noted in 3 lesions (SUV_{max} of 4.4, 2.4, and 2.6) that subsequently revealed a benign pathology, including an elastofibroma dorsi (patient 3) and 2 areas of fibrosis or scarring in breast tissue (patient 11).

Cancer Tissues. The average ^{68}Ga -FAPi-46 SUV_{mean} and SUV_{max} was 7.2 ± 4.4 (range, 1.5–15.2) and 8.6 ± 5.2 (range, 1.7–19), respectively, in primary tumors (*n* = 15) and 4.3 ± 2.9 (range, 2.1–8.8) and 5.3 ± 3.6 (range, 2.7–10.8), respectively, in metastases (*n* = 6). The cancer types with the highest uptake were those of the pancreas, stomach, colon, and uterus. The lowest uptake was in 2 patients with a complete response to neoadjuvant therapy (patients 13 and 15) and thus low FAP expression

Immunohistochemistry Findings

Histologic sections from 13 patients who underwent tumor resection were analyzed. Normal tissue adjacent to tumors and tumor tissue from individual histologic sections were available for immunohistochemistry in 13 of 15 (87%) and 11 of 15

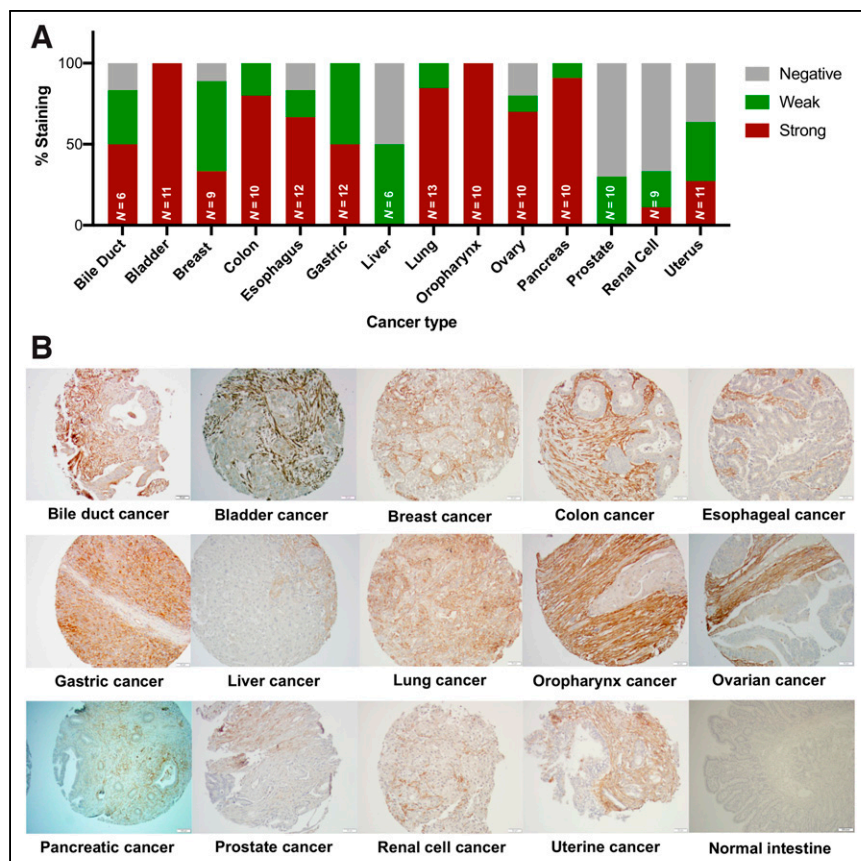


FIGURE 1. FAP expression by immunohistochemistry in 14 cancer types and normal tissues (TMA analysis). (A) Quantification of FAP expression per cancer type. FAP intensity was evaluated using semiquantitative visual scoring system that accounts for staining intensity (0, negative; 1, weak; 2, strong). (B) FAP immunohistochemistry expression on representative tissue core from indicated cancer or normal tissue type.

patients (73%), respectively. Primary tumor, metastasis, or both primary tumor and metastasis were evaluated in 7 of 11 (63%), 2 of 11 (18%), and 2 of 11 (18%) cases, respectively. The FAP scoring between the 2 pathologists was in almost perfect agreement ($\kappa = 0.89$).

Primary Tumors. The highest FAP immunohistochemistry scores were observed in pancreatic, esophageal, and breast cancer. FAP staining was confined exclusively to the tumor-associated stromal compartment in most patients (12/13; 92.3%) and ranged from weak to strong expression (1–3). The staining intensity was the greatest in stromal areas within and immediately adjacent to (peritumoral) the malignant epithelial compartment of tumors as shown in a case example in Figure 2 (patient 10).

Metastatic Lesions. All 4 evaluated metastatic lesions (3 lymph nodes and 1 liver metastasis) were positive for FAP, including stromal staining in 3 of the 4 and malignant epithelial cell staining in 1 of the 4 (uterine squamous cell carcinoma involving a left pelvic lymph node, patient 8). FAP staining was equivalent between primary and metastatic lesions in 2 patients with tissue available for comparative analysis (patients 6 and 15, Supplemental Fig. 2).

Tumor-Adjacent Non-Cancer Tissues. Staining was absent or weak in most normal tissues (71.4% negative, 25% weak, 3.6% moderate) and observed primarily in capillary and small-vessel endothelium. FAP expression was moderate in a concurrently resected benign elastofibroma dorsi (patient 3) and was moderate to strong in 2 areas of radial scarring and biopsy site changes in benign breast tissue without cancer (patient 11, Supplemental Fig. 3).

Correlation of ^{68}Ga -FAPi-46 PET Signal and FAP Immunohistochemistry Staining in Cancer and Tumor-Adjacent Non-Cancer Tissues (Per-Patient Analysis)

Supplemental Figures 4–16 depict each patient case with an available cross-sectional correlation analysis of the ^{68}Ga -FAPi-46 PET signal and FAP immunohistochemistry staining score.

^{68}Ga -FAPi-46 SUV_{max} and SUV_{mean} , and the FAP immunohistochemistry score, were higher in cancer tissue than in

tumor-adjacent non-cancer tissue: mean SUV_{max} was 7.7 (95% CI, 5.1–10.3) versus 1.6 (95% CI, 0.9–2.2; $P < 0.001$), respectively; mean SUV_{mean} was 6.2 (95% CI, 4.0–8.3) versus 1.0 (95% CI, 0.7–1.3; $P < 0.001$), respectively; and mean FAP immunohistochemistry score was 2.8 (95% CI, 2.6–3.0; $P < 0.001$) versus 0.9 (95% CI, 0.4–1.4; $P < 0.001$), respectively (Fig. 3).

The FAP immunohistochemistry score correlated positively both with ^{68}Ga -FAPi-46 SUV_{max} across cancer and tumor-adjacent non-cancer tissues ($r = 0.781$ [95% CI, 0.376–0.936], $P < 0.001$) and with SUV_{mean} ($r = 0.783$ [95% CI, 0.379–0.936], $P < 0.001$) (Fig. 4). FAP immunohistochemistry scores of 0, 1, 2, and 3 corresponded to a mean ^{68}Ga -FAPi-46 SUV_{max} of 1.2 (95% CI, 0.8–1.6), 1.9 (95% CI, 0.4–3.3), 3.9 (95% CI, 2.8–4.9), and 7.4 (95% CI, 4.5–10.3), respectively. CT size tended to correlate positively with SUV_{max} (Spearman $r = 0.57$; $P = 0.054$) and SUV_{mean} (Spearman $r = 0.54$; $P = 0.068$).

DISCUSSION

In this translational study, we aimed to establish the spectrum of FAP expression across various cancers by immunohistochemistry and to explore whether ^{68}Ga -FAPi-46 PET biodistribution faithfully reflects FAP expression in cancer patients. We report here the results of a TMA analysis from 141 patients with 14 different types of cancer and of an interim analysis of a prospective exploratory imaging trial that included 15 patients. FAP was expressed across all cancer types with variable intensity and frequency. We established a positive and significant correlation between FAP-target expression and FAPi PET SUVs.

Cancer-associated fibroblasts are key constituents of the tumor stroma that can support an immunosuppressive microenvironment and tumor cell growth, progression, and metastatic potential (1). Depleting the stroma can improve delivery of drugs or systemically applied radiation and enhance cancer immune responses (15). Thus, FAP expressed by cancer-associated fibroblasts is an attractive diagnostic and therapeutic target (16). Target specificity

and tumor-specific uptake are critical determinants of the accuracy and efficacy of PET probes for diagnosis and therapy (17). FAP frequently is strongly expressed in solid tumors, with only limited expression in normal tissues, making it an attractive theranostic target (10).

FAPi PET imaging has reported high tumor-to-background characteristics (10). However, FAPi PET human biodistribution in cancer has not been validated against tumor FAP expression as assessed by immunohistochemistry in a pancancer approach. Recently, a study showed a strong association between tumor ^{68}Ga -FAPi-46 PET uptake intensity and histopathologic FAP expression in sarcoma tumors (18). Here, we first screened TMAs from 14 cancers for FAP expression to guide patient selection for the exploratory imaging trial. Guided by our initial TMA screening, we intentionally selected multiple cancer types to validate the pancancer approach. In the interim analysis of this prospective exploratory trial, the biodistribution of ^{68}Ga -FAPi-46 PET correlated

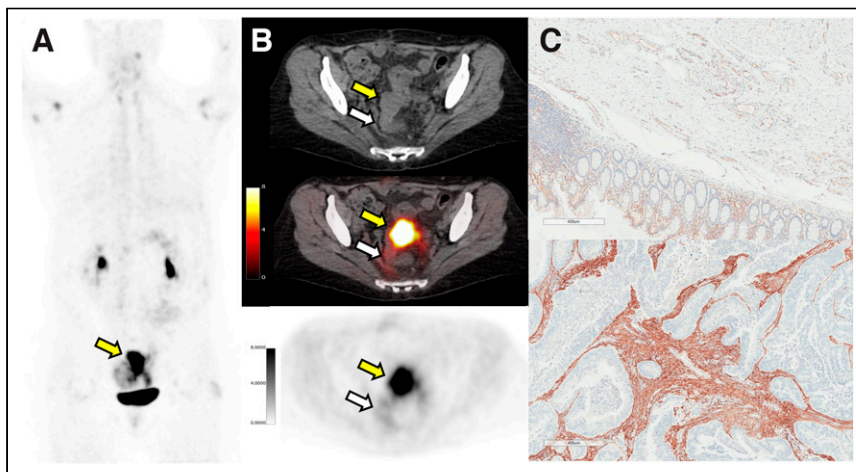


FIGURE 2. Matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry results for patient 10, 56-y-old woman with sigmoid colon adenocarcinoma who underwent colorectal anterior resection (ypT4b N0 M0). In area corresponding to resected mass as shown by yellow arrows (PET maximum-intensity projection [A], axial CT [B, top], axial PET/CT [B, middle], and axial PET [B, bottom]), ^{68}Ga -FAPi-46 PET/CT showed intense uptake (SUV_{max} , 15.9; SUV_{mean} , 12.8). FAP immunohistochemistry on representative histologic sections demonstrated absent to weak FAP expression seen predominantly as vessel endothelial cell staining in normal tissue (C, top) and strong FAP expression in intratumoral and peritumoral stromal (C, bottom). White arrows depict normal region resected.

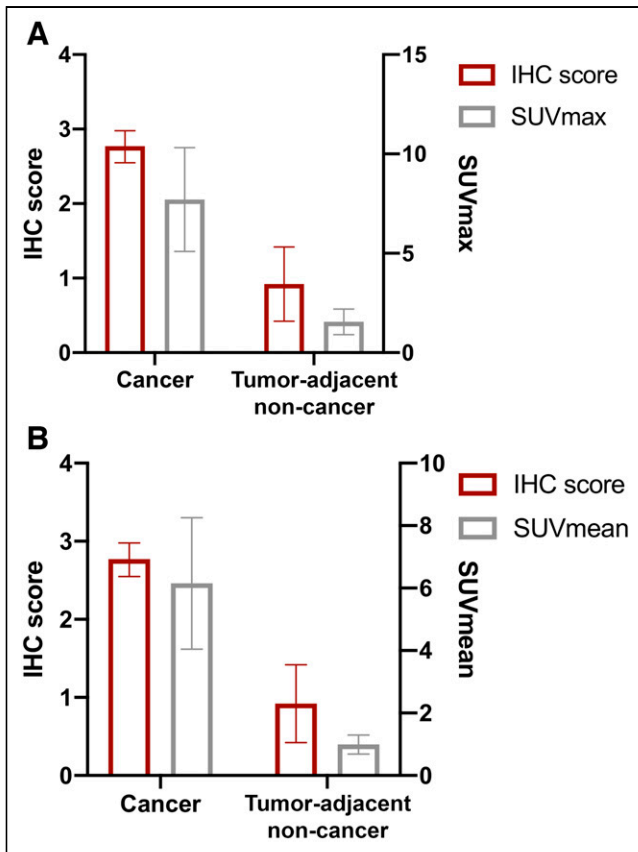


FIGURE 3. FAP immunohistochemistry (IHC) score with ⁶⁸Ga-FAPi-46 PET SUV_{max} (A) and SUV_{mean} (B) in cancer and tumor-adjacent non-cancer tissues. Each bar represents mean with SD.

strongly with FAP expression in cancer versus normal tissues across 7 different cancer types, supporting its potential role as a pancancer predictive biomarker for FAP-targeted therapies. In a subset of patients, the ⁶⁸Ga-FAPi-46 SUV_{max} of metastasis was also comparable to that of their primary tumor, suggesting that FAP expression may be consistent across primary and metastatic lesions within individual patients, which has important implications for its role as a theranostic in the setting of advanced disease (19).

These findings support further exploration of ⁶⁸Ga-FAPi-46 as a potential pancancer imaging biomarker for FAP expression. This use could find application as an enrichment biomarker or patient selection tool for clinical trials and as a potential predictor of treatment response in the clinic. Extensive emerging data implicate FAP-positive cells as important accomplices involved in cancer progression and metastases. Evaluating FAP-targeting small-molecule inhibitors, antibodies, bispecific T-cell engagers, and radioligand therapy requires a means for verifying whole-body target expression (20).

The main limitation of the study was the small sample size. This was an exploratory study, and local oversight committees (Internal Scientific Peer Review Committee, Data Safety Monitoring Board) mandated an interim analysis after the first 15 patients. This interim analysis revealed a strong correlation between immunohistochemistry and PET findings in 14 patients, which provided the motivation to publish the data.

Another major limitation was the intratumor heterogeneity and sampling bias inherent in the histopathology and immunohistochemistry analysis. Unfortunately, autoradiography was not possible in

this exploratory study because a second administration of ⁶⁸Ga-FAPi-46 just before surgery was not practical. We performed an evaluation of all hematoxylin and eosin slides from each surgical pathology case to select the section best representing the overall tumor histology or its surrounding tumor-adjacent non-cancer tissue.

A perfect anatomic match between tumor SUV measurements and immunohistochemistry scores was unfortunately not possible because tumors were not resected in a defined orientation (unlike in prostate cancer). Therefore, we collected the SUV_{max} and SUV_{mean} of the whole tumor lesion.

Another limitation is that visual immunohistochemistry scoring by pathologists is semiquantitative only, is subjective, and produces ordinal rather than continuous variable data. Computer-aided analysis with automatic immunohistochemistry scoring may overcome these limitations. However, even with semiquantitative ordinal data, the correlation of immunohistochemistry scoring with SUV was strong. Furthermore, the interreader scores between the 2 pathologists was in near-perfect agreement.

CONCLUSION

In this interim analysis of a prospective exploratory imaging trial, ⁶⁸Ga-FAPi-46 PET biodistribution correlated strongly with FAP expression in cancer and tumor-adjacent non-cancer tissues across multiple cancer types. These data support the use of ⁶⁸Ga-FAPi-46 PET as a pancancer predictive biomarker and stratification tool for FAP-targeted therapeutic approaches and lay the foundation for future evaluation of FAPi ligands labeled with therapeutic isotopes in clinical trials.

DISCLOSURE

This was an investigator-initiated trial with support from the Society of Nuclear Medicine and Molecular Imaging (2019 Molecular Imaging Research Grant for Junior Academic Faculty 20194491 [principal investigator, Jeremie Calais]) and the Prostate Cancer Foundation (2019 Challenge Award 19CHAL02 [principal investigator, Johannes Czernin] and 2020 Young Investigator Award 20YOUN05 [principal investigator, Jeremie Calais]). Johannes Czernin is a founder, holds equity in, and is a board member of Sofie Biosciences and Momentum Biosciences, which have licensed intellectual property of FAPi compounds from the University of Heidelberg. He is also a cofounder of Trethera Therapeutics and serves on the Medical Advisory Boards of Point Pharma and Actinium Pharmaceuticals. Jeremie Calais reports

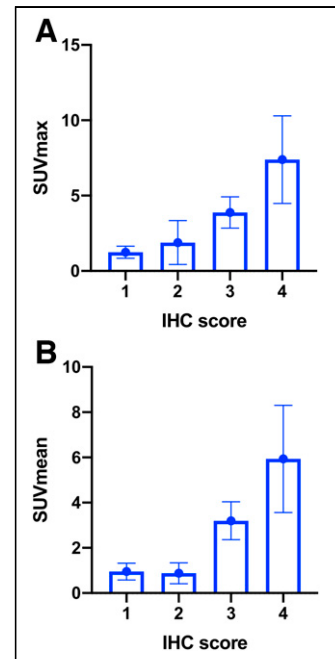


FIGURE 4. Correlation between FAP immunohistochemistry (IHC) score and ⁶⁸Ga-FAPi-46 PET SUV_{max} (A) and SUV_{mean} (B) across cancer and tumor-adjacent non-cancer tissues. $r = 0.781$ in A (95% CI, 0.376–0.936; $P < 0.001$) and $r = 0.783$ in B (95% CI, 0.379–0.936; $P < 0.001$).

prior consulting activities for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, Janssen Pharmaceuticals, Progenics Radiopharmaceuticals, Radiomedix, and Telix Pharmaceuticals, outside the submitted work. Christine Mona and Katharina Lueckerath report consulting activities for Sofie Biosciences/iTheragnostics outside the submitted work. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

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KEY POINTS

QUESTION: Is FAPi PET imaging a reliable biomarker of FAP expression in cancer and tumor-adjacent non-cancer tissues?

PERTINENT FINDINGS: In this translational study using TMA and an interim analysis of a prospective exploratory imaging trial in 15 surgical oncology patients, the FAPi PET uptake and FAP expression per immunohistochemistry correlated strongly in cancer and tumor-adjacent non-cancer tissue.

IMPLICATIONS FOR PATIENT CARE: FAPi PET uptake correlates strongly with FAP expression in cancer patients, and FAPi PET may thus serve as a predictive biomarker for FAP-targeted therapeutic approaches.

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Supplemental Table 1: Inclusion and exclusion criteria of the clinical trial NCT04147494

Inclusion criteria

Patients with the following cancer types:

- Breast cancer
- Colon cancer
- Esophageal cancer
- Gastric cancer
- Head and Neck cancer
- Lung cancer
- Ovarian cancer
- Pancreatic cancer
- Renal cancer
- Uterus Cancer

Patients who are scheduled to undergo surgical resection of the primary tumor and/or metastasis.

Patients are ≥ 18 years old at the time of the radiotracer administration.

Patient can provide written informed consent.

Patient is capable of complying with study procedures.

Patient is able to remain still for duration of imaging procedure (up to one hour).

Exclusion criteria

Patient is pregnant or nursing.

Patient has underlying disease which, based on the judgment of the investigator, might interfere with the collection of high-quality data.

Supplemental Table 2: Study population demographics and clinical characteristics

Patient ID#	Age	Gender	Race	Cancer type	Organ	Histologic type	Surgical Procedure	pTNM
#001	51	M	Hispanic	Head and Neck	Oral mucosa left mandible	Squamous cell carcinoma	Left Composite Mandibulectomy With Left Neck Dissection	pT4a N0 M0
#002	71	M	Caucasian	Esophageal	Distal and mid esophagus	Squamous cell carcinoma	Esophagogastrectomy	pT1b N0 M0
#003	69	F	Caucasian	Gastric	Gastroesophageal junction	Adenocarcinoma	Not performed	NA
#004	57	M	Caucasian	Head and Neck	Left piriform sinus + cervical lymph nodes	P16+ squamous cell carcinoma	Left partial glossectomy and left neck dissection	pTx N2b M0
#005	76	M	NA	Colon	Cecum	Medullary Carcinoma	Right hemicolectomy	pT2 N0 M0
#006	55	M	African American	Colon	Cecum	Mucinous Adenocarcinoma	Right hemicolectomy	pT3 N1b M0
#007	68	F	African American	Head and Neck	Right retromolar trigone	Verrucous Squamous Cell Carcinoma	Right mandibulectomy	pT2 N0 M0
#008	36	F	Latino	Uterus	Uterus and lymph nodes	Squamous Cell Carcinoma	Bilateral Salpingectomy + left pelvic lymphadenectomy	pTx N1 M0
#009	65	M	Caucasian	Pancreatic	Pancreas, Tail	Adenocarcinoma	Partial pancreatectomy, pancreatic tail	pT2 N1 M0
#010	56	F	Caucasian	Colon	Sigmoid Colon	Adenocarcinoma	Colo-rectal anterior resection	ypT4b N0 M0
#011	65	F	Caucasian	Breast	Bilateral breasts	Invasive ductal adenocarcinoma	Bilateral Mastectomy	pT1c Nx
#012	61	M	Caucasian	Esophageal	Gastroesophageal junction	Adenocarcinoma	Esophagogastrectomy	pT3 pN2
#013	51	F	other	Breast	Right breast	Invasive ductal carcinoma	Right mastectomy and lymphadenectomy	ypT0 N0 M0
#014	73	M	Caucasian	Pancreatic	Pancreas, head	Adenosquamous carcinoma	Not performed	NA
#015	56	F	Latino	Colon	Left colon + solitary liver metastasis	Adenocarcinoma	Left hemicolectomy	ypT3 N1b M1a

Supplemental Table 3: ⁶⁸Ga-FAPi-46 PET biodistribution in normal organs quantified by SUVmean (n=15 patients)

Organ	⁶⁸ Ga-FAPi-46 uptake SUVmean Average ±SD (range)
1. Brain	0.03±0.04 (0-0.1)
2. Parotid	1.3±0.3 (0.8-2.0)
3. Submandibular gland	2.5±0.5 (1.5-3.3)
4. Waldeyer's ring	2.0±0.8 (1.1-4.0)
5. Thyroid	1.8±0.6 (1.0-3.5)
6. Blood pool	1.2±0.2 (0.9-1.5)
7. Heart	1.1±0.5 (0.6-2.8)
8. Lung	0.5±0.2 (0.2-1.2)
9. Liver	0.8±0.2 (0.6-1.2)
10. Gallbladder	0.7±0.2 (0.5-1.1)
11. Pancreas	2.0±1.4 (0.6-6.0)
12. Spleen	0.9±0.2 (0.6-1.2)
13. Adrenal	1.0±0.3 (0.4-1.5)
14. Kidney	2.0±0.6 (1.4-3.9)
15. Small bowel	0.8±0.2 (0.5-1.2)
16. Colon	0.8±0.4 (0.3-1.6)
17. Urinary bladder	51.9±28.4 (13.9-108.7)
18. Uterus (n=7)	6.3±3.7 (2.3-13.4)
19. Prostate (n=8)	1.2±0.4 (0.5-1.9)
20. Ovary (n=6)	1.7±0.4 (1.2-2.2)
21. Testis (n=8)	1.6±0.3 (1.2-2.1)
22. Bone marrow	0.7±0.3 (0.4-1.5)
23. Muscle	1.3±0.3 (0.9-2.2)
25. Fat	0.3±0.1 (0.2-0.7)
25. Breast (n=7)	1.4±0.8 (0.7-2.5)

Supplemental Table 4: ⁶⁸Ga-FAPi-46 uptake in primary tumors (n=15 patients)

Patient	Cancer type	Histologic type	Size (mm)	SUVmax	SUVmean
001	Head/Neck	Carcinoma cuniculatum	13	7.7	6.3
002	Esophagus	Squamous cell carcinoma	13	5.4	4.3
003*	Gastric	Adenocarcinoma	32	7.4	6.0
004	Head/Neck	P16+ squamous cell carcinoma	12	7.4	6.3
005	Colon	Medullary Carcinoma	30	8.1	6.8
006	Colon	Mucinous Adenocarcinoma	16	6.3	5.2
007	Head/Neck	Verrucous Squamous Cell Carcinoma	18	4.7	3.9
008	Uterus	Squamous Cell Carcinoma	38	19.0	15.2
009	Pancreas	Adenocarcinoma	26	15.7	12.5
010*	Colon	Adenocarcinoma	39	15.9	12.8
011	Breast	Invasive ductal adenocarcinoma	10	4.6	4.0
012*	Esophagus	Adenocarcinoma	52	9.1	7.3
013*	Breast	Invasive ductal carcinoma	-	1.7	1.4
014*	Pancreas	Adenosquamous carcinoma	13	13.4	10.6
015*	Colon	Adenocarcinoma	-	2.5	2.0
Average±SD			24±13	8.6±5.2	7.2±4.4

- = no anatomic correlation

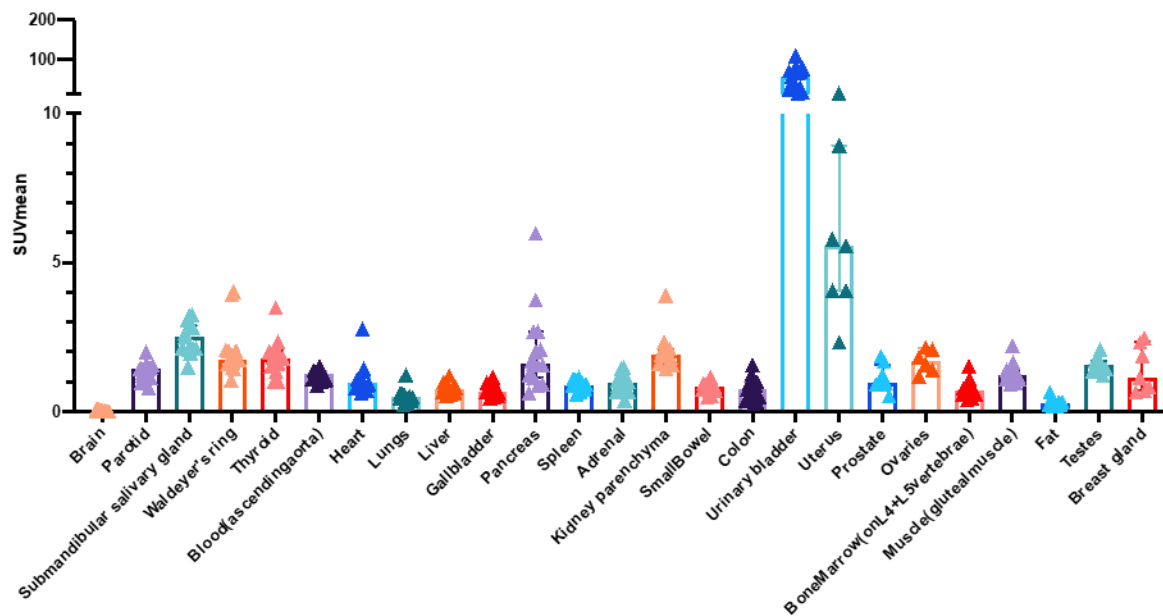
* = Neo-adjuvant therapy

Supplemental Table 5: ⁶⁸Ga-FAPi-46 uptake in metastases (n= 3 patients)

Patient	Metastasis Site	Primary Histologic type	Size (mm)	SUVmax	SUVmean
004	Lymph node	SCC (Head/Neck)	20	5.6	4.6
004	Lymph node	SCC (Head/Neck)	20	6.8	5.5
004	Lymph node	SCC (Head/Neck)	19	7.7	6.3
008	Lymph node	SCC (uterus)	21	10.8	8.8
009	Liver	Adenocarcinoma (pancreas)	11	3.5	3.0
015	Liver	Adenocarcinoma (colon)	12	2.7	2.1
Average±SD			17.1±4.1	5.3±3.6	4.3±2.9

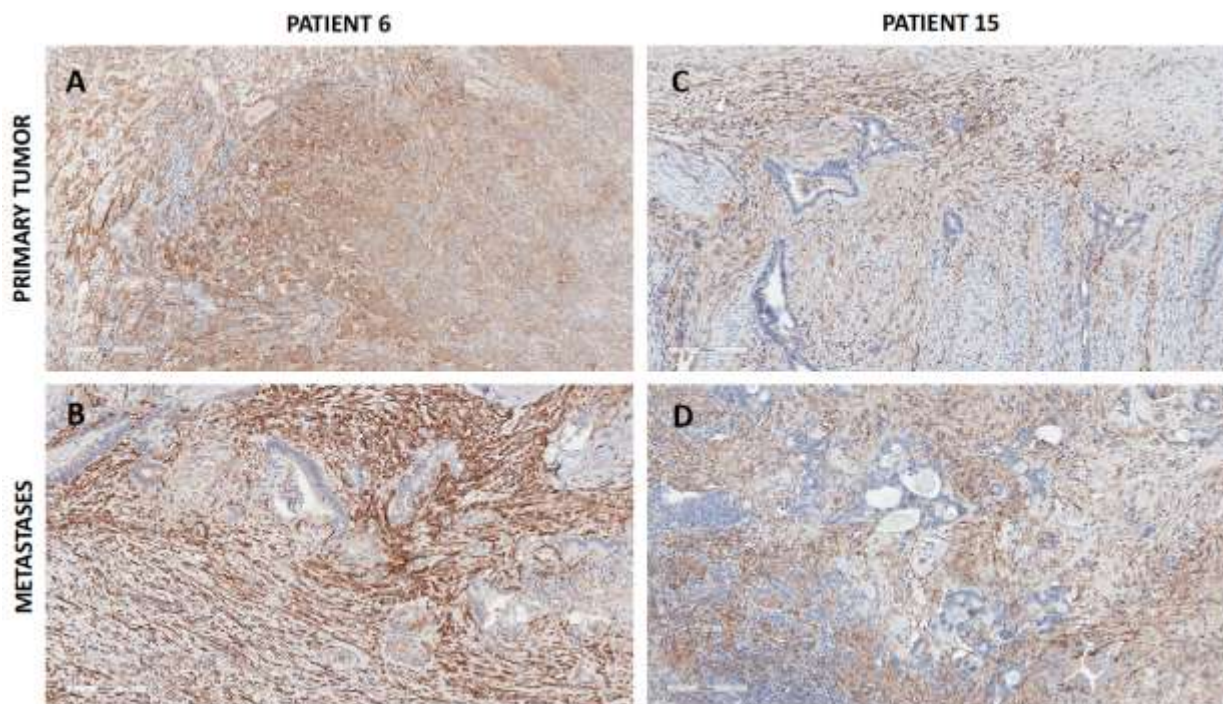
SCC: Squamous Cell Carcinoma

Supplemental Figure 1: ⁶⁸Ga-FAPi-46 PET biodistribution in normal organs quantified by SUVmean (n=15 patients)



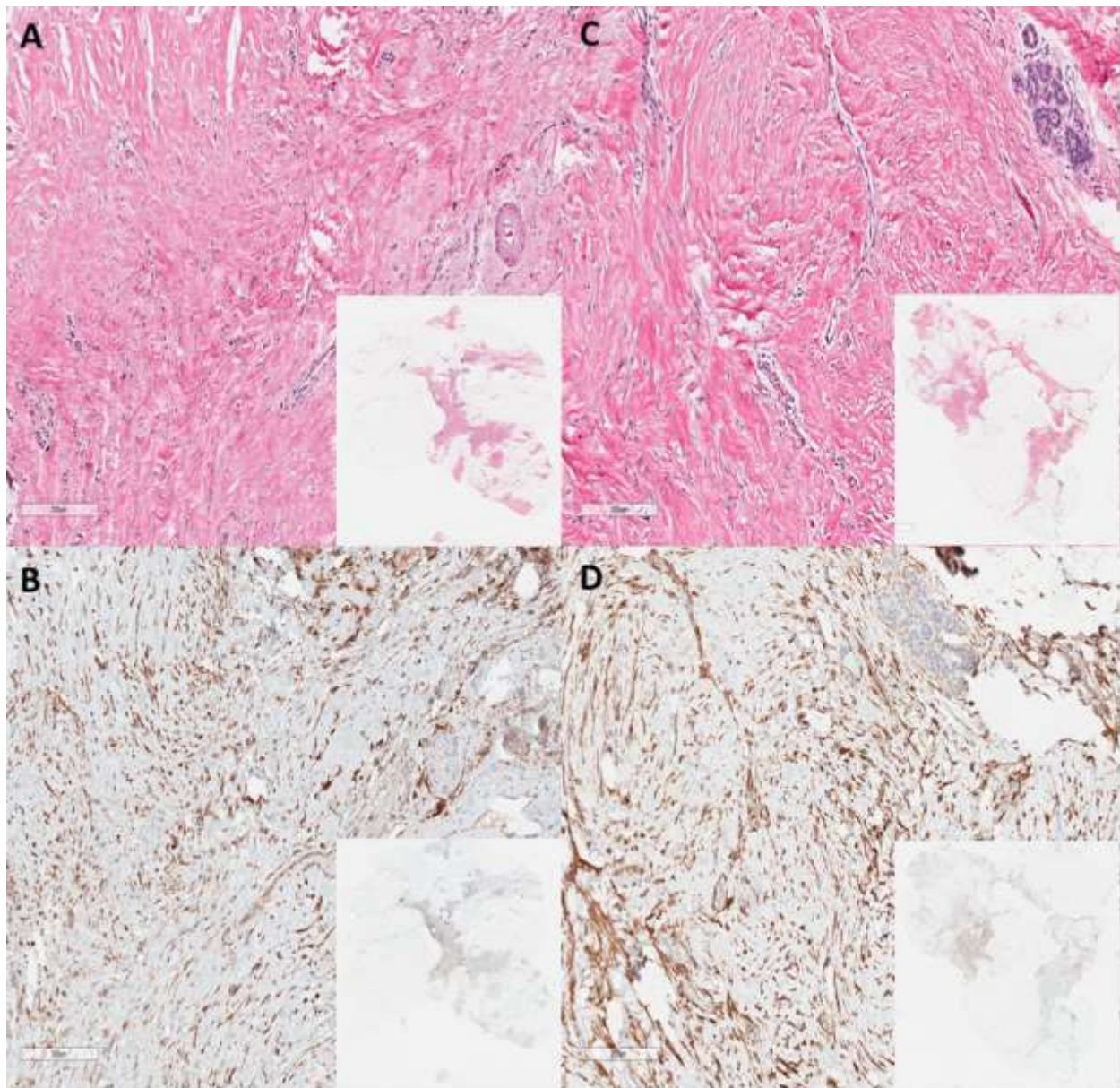
Each bar represents the average SUVmean with standard deviation error bars

Supplemental Figure 2. Matched IHC in primary tumor and metastases in patient #006 and #015



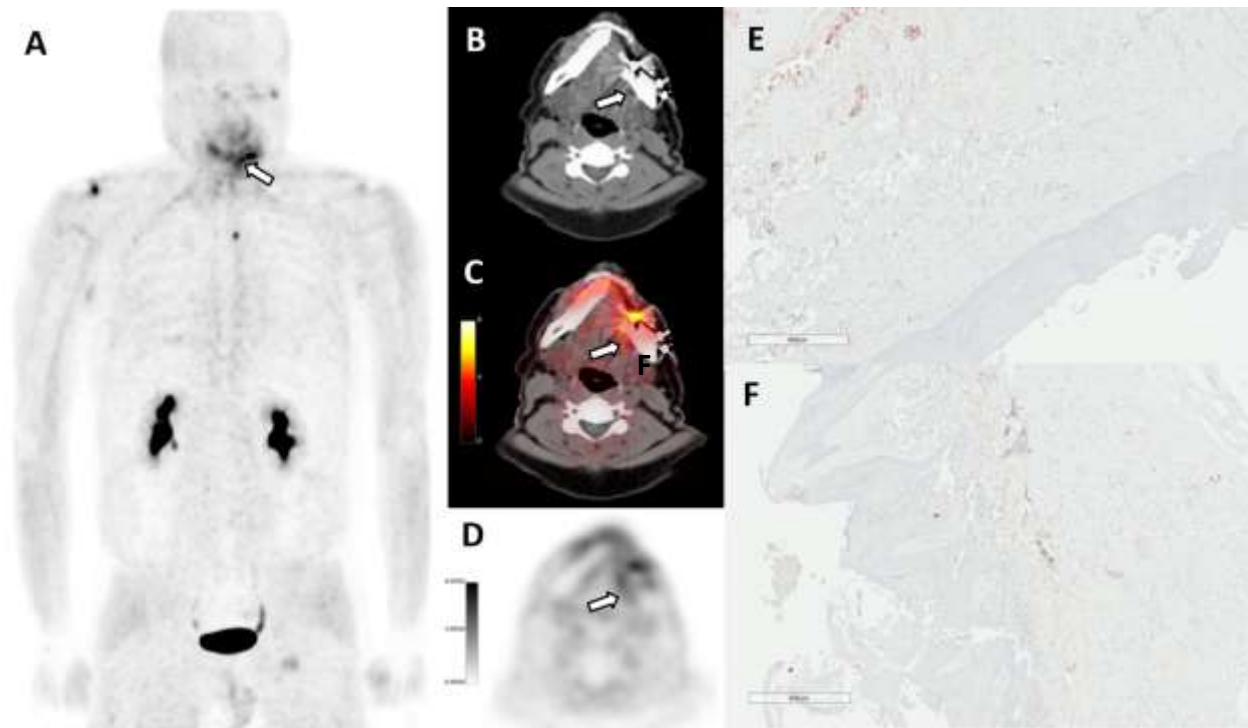
Concordance between IHC score in primary tumor (A, top left) and metastatic lesion (B, bottom left) from patient #006 showing moderate to strong FAP expression. Concordance between IHC score in primary lesion (C, top right) and metastatic lesion (D, bottom right) from patient #015 showing moderate FAP expression.

Supplemental Figure 3: Patient #011 Breast Biopsies immunohistochemistry



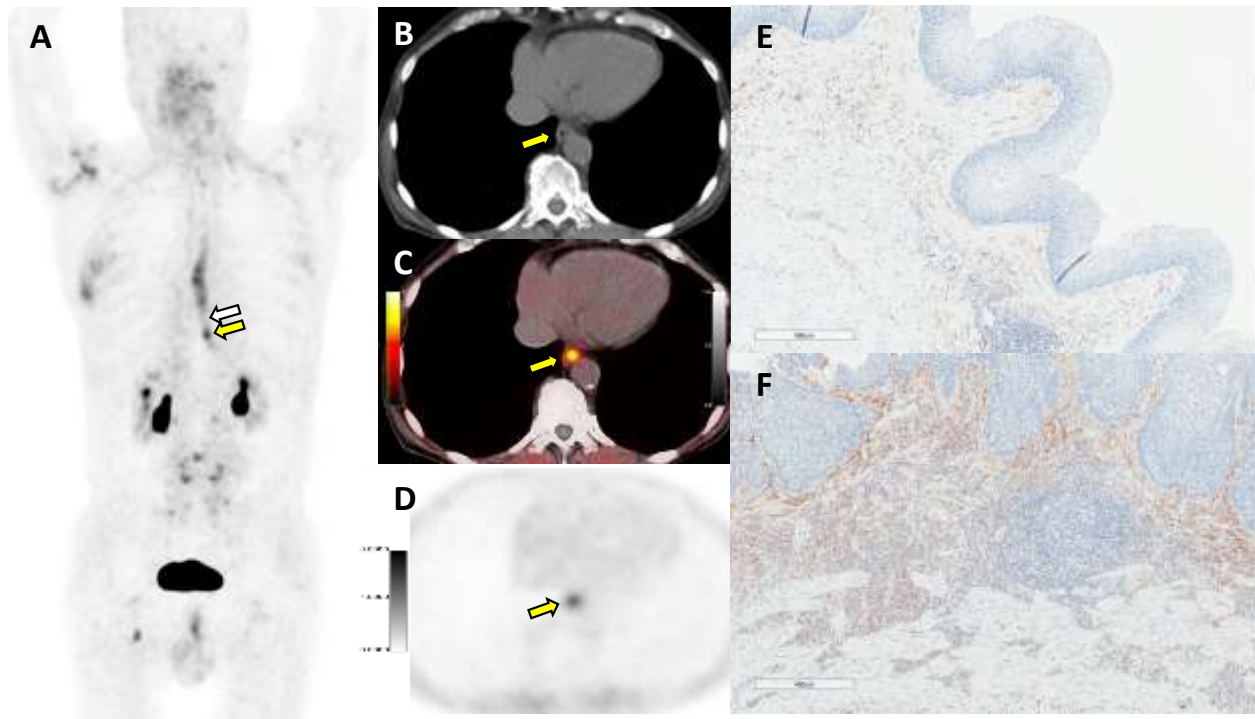
A 65-year-old female patient with 65-year-old female patient with bilateral breast invasive ductal adenocarcinoma. H&E and FAP IHC of histologic sections of left (**A** and **B**) and right (**C** and **D**) demonstrated weak to moderate FAP expression in radial scar tissues.

Supplemental Figure 4: Patient #001 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



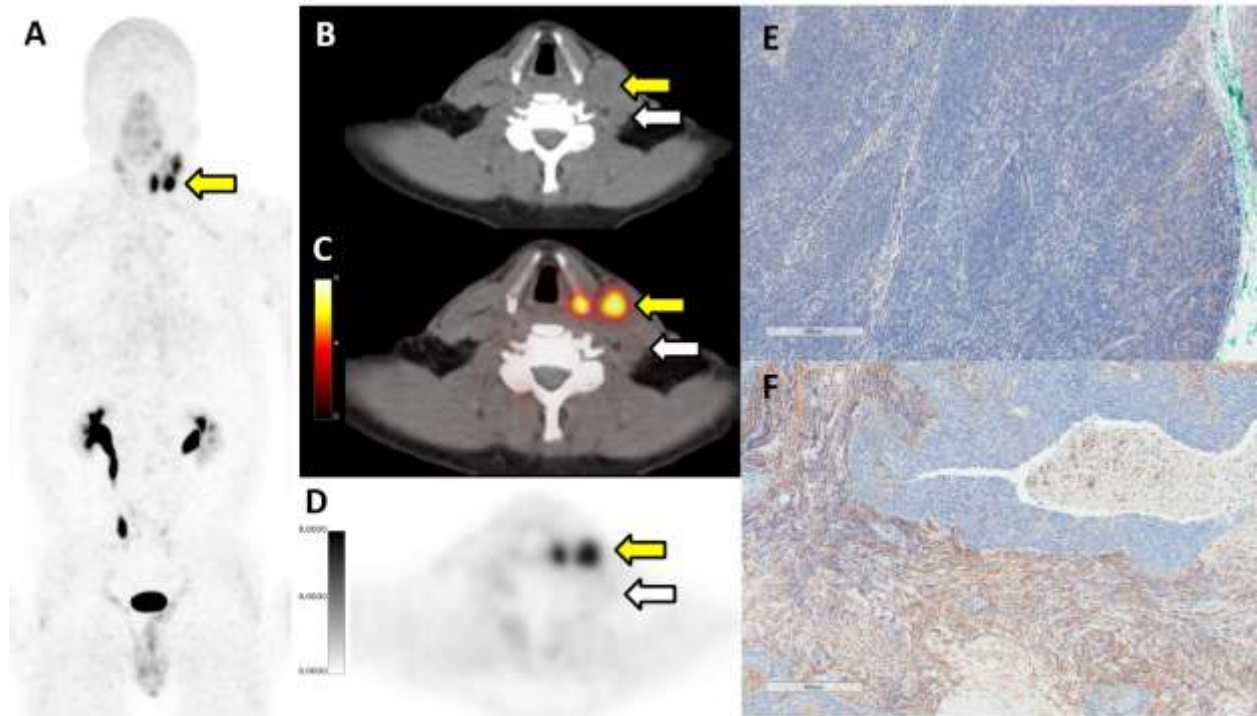
51-year-old male patient with squamous cell carcinoma (carcinoma cuniculatum) of the oral mucosa who underwent left composite mandibulectomy with left neck dissection (pT4a N0 M0). In correspondence of the resected lesion as shown by the white arrows, ^{68}Ga -FAPi-46 PET/CT showed moderate diffuse increased signal (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 7.7 and SUVmean 6.3, respectively). FAP IHC on representative histologic sections of normal (**E**) and tumor (**F**) tissue demonstrated absent FAP expression in both, indicative of either a histologic sampling bias or PET overcorrection artefact from dense material.

Supplemental Figure 5: Patient #002 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



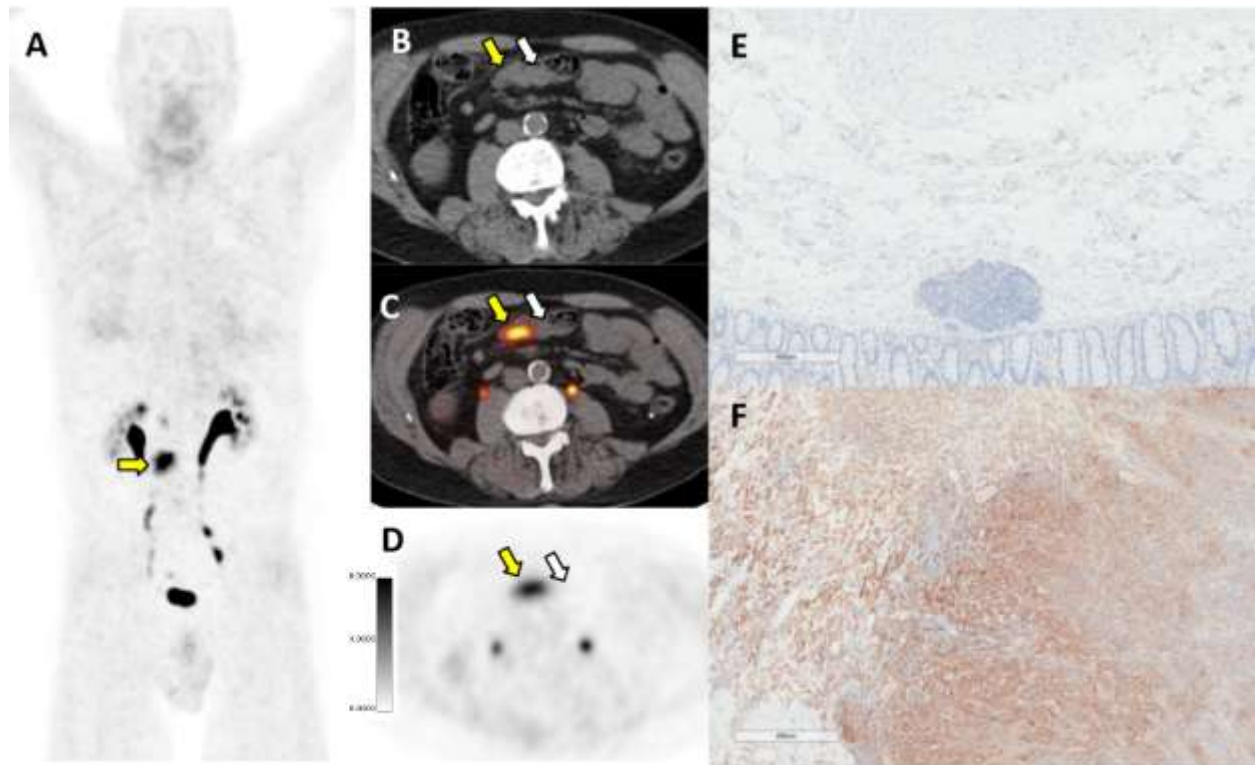
71-year-old male patient with esophageal adenocarcinoma who underwent esophagogastrectomy (pT1b N0 M0). In correspondence of the resected lesion as shown by the yellow arrows, ^{68}Ga -FAPi-46 PET/CT showed moderate focal uptake (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 5.4 and SUVmean 4.3, respectively). FAP IHC on representative histologic sections demonstrated absent to patchy and weak FAP expression for normal tissue (**E**) and weak to moderate FAP expression for tumor tissue (**F**). White arrow depicts resected non-cancer esophagus region.

Supplemental Figure 6: Patient #004 matched ⁶⁸Ga-FAPi-46 PET/CT and immunohistochemistry



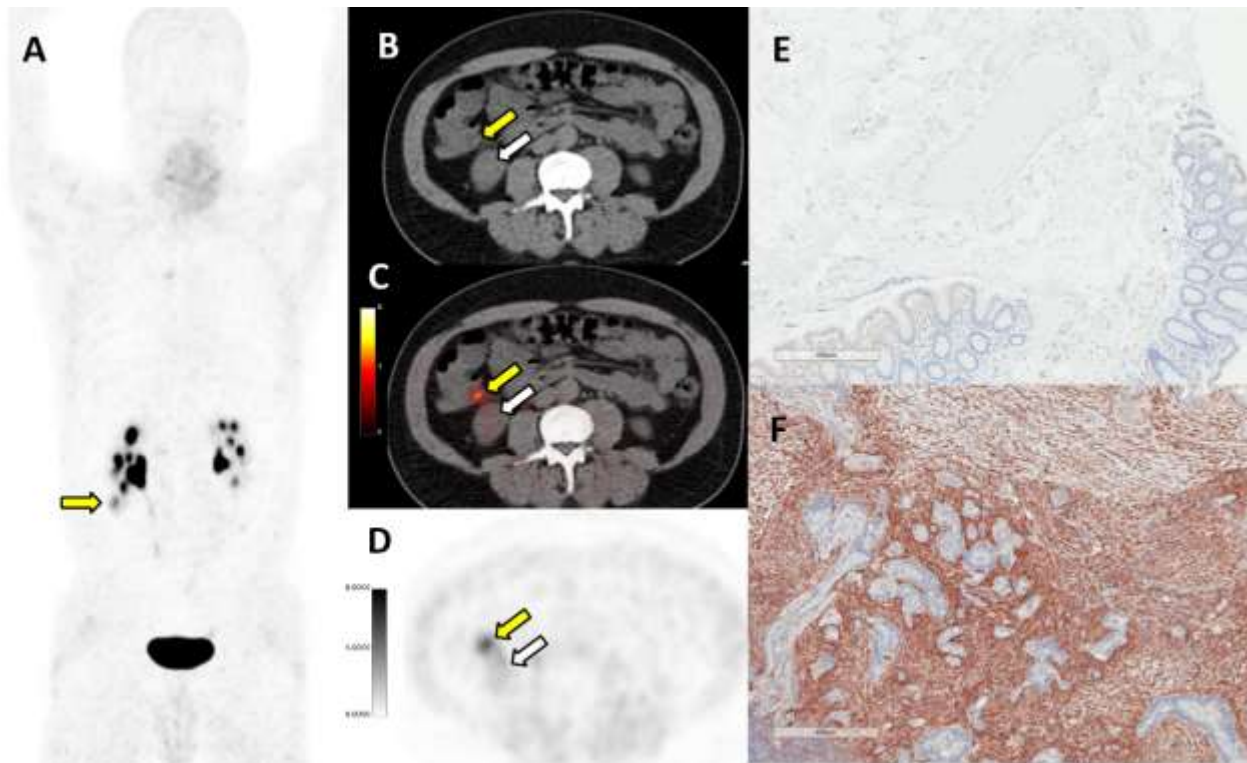
57-year-old male patient with head-and-neck squamous cell carcinoma cancer who underwent left partial glossectomy and left neck dissection (pTx N2b M0). In correspondence of the resected enlarged neck lymph nodes as shown by the yellow arrows ⁶⁸Ga-FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and CT, SUVmax 7.4 and SUVmean 6.3, respectively). FAP IHC on representative histologic sections demonstrated no FAP expression in normal tissue (**E**) and moderate to strong FAP expression in tumor tissue (**F**). White arrows depict resected normal lymph node.

Supplemental Figure 7: Patient #005 matched ⁶⁸Ga-FAPi-46 PET/CT and immunohistochemistry



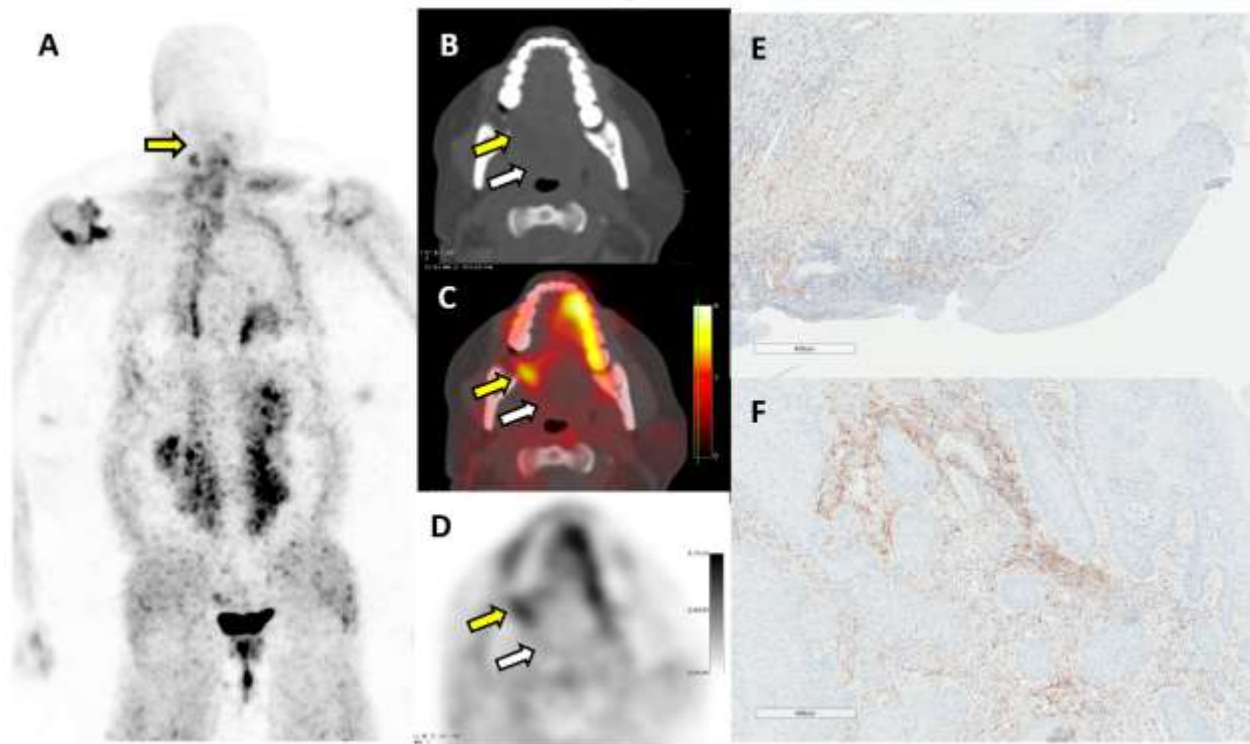
57-year-old male patient with medullary adenocarcinoma of the cecum who underwent right hemicolectomy (pT2 N0 M0). In correspondence of the resected lesion as shown by the yellow arrows ⁶⁸Ga-FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and CT, SUVmax 8.1 and SUVmean 6.8, respectively). FAP IHC on representative histologic sections demonstrated no FAP expression in normal tissue (**E**) and moderate to strong FAP expression in tumor tissue (**F**). White arrows depict resected normal colon region.

Supplemental Figure 8: Patient #006 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



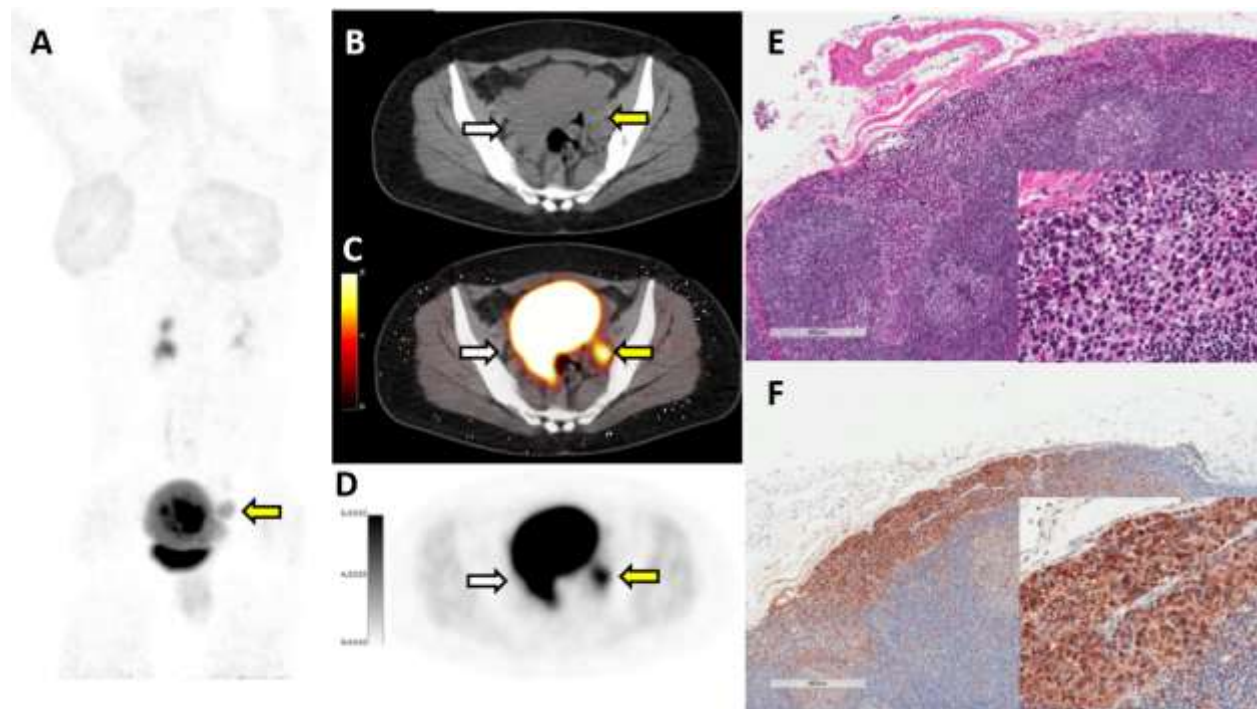
55-year-old male patient with mucinous adenocarcinoma of the cecum who underwent right hemicolectomy (pT3 N1b M0). In correspondence of the resected lesion as shown by the yellow arrows, ^{68}Ga -FAPi-46 PET/CT showed increased focal uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 6.3 and SUVmean 5.2, respectively). FAP IHC on representative histologic sections demonstrated no FAP expression in normal tissue (**E**) and strong FAP expression in tumor tissue (**F**). White arrows depict normal region resected.

Supplemental Figure 9: Patient #007 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



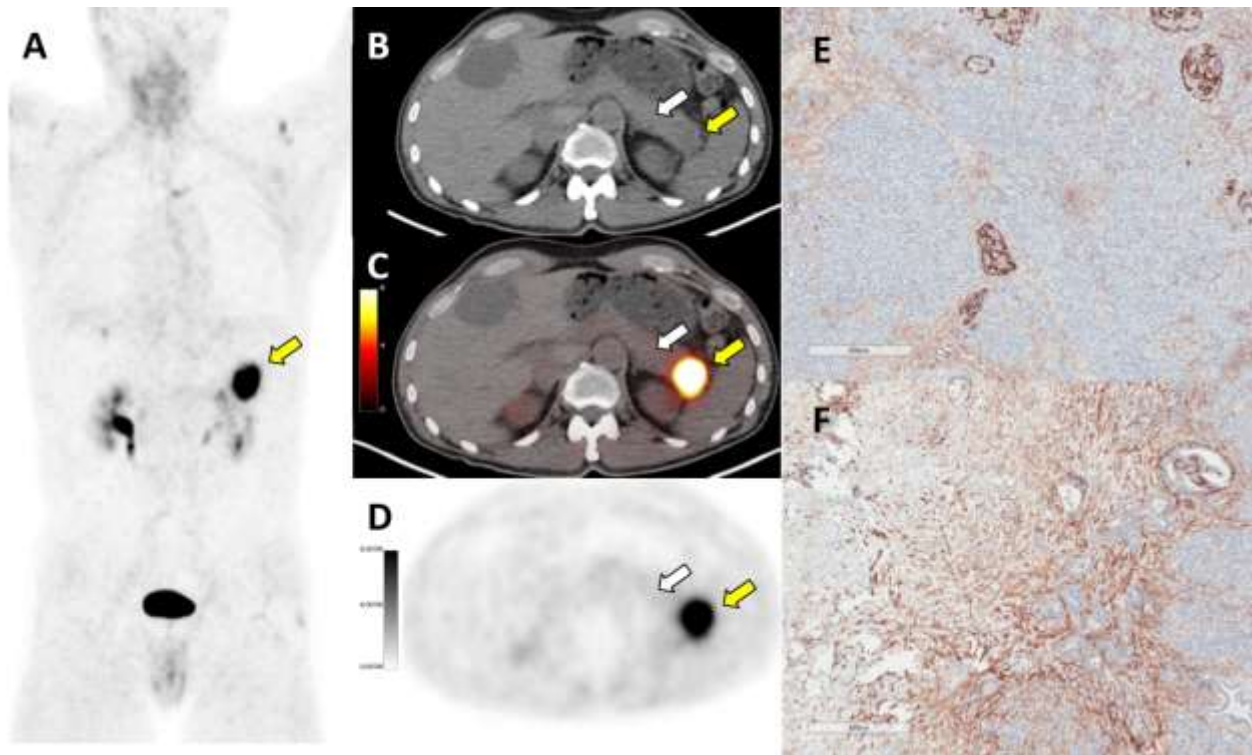
68-year-old female patient with verrucous squamous cell carcinoma of the right retromolar trigone who underwent right mandibulectomy (pT2 N0 M0). In correspondence of the resected lesion as shown by the yellow arrows, ^{68}Ga -FAPi-46 PET/CT showed moderate uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 4.7 and SUVmean 3.9, respectively). FAP IHC on representative histologic sections demonstrated variable negative to weak FAP expression in normal tissue in an area notable for ulceration (**E**) and moderate FAP expression for tumor tissue (**F**). White arrows depict resected normal mucosa region.

Supplemental Figure 10: Patient #008 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



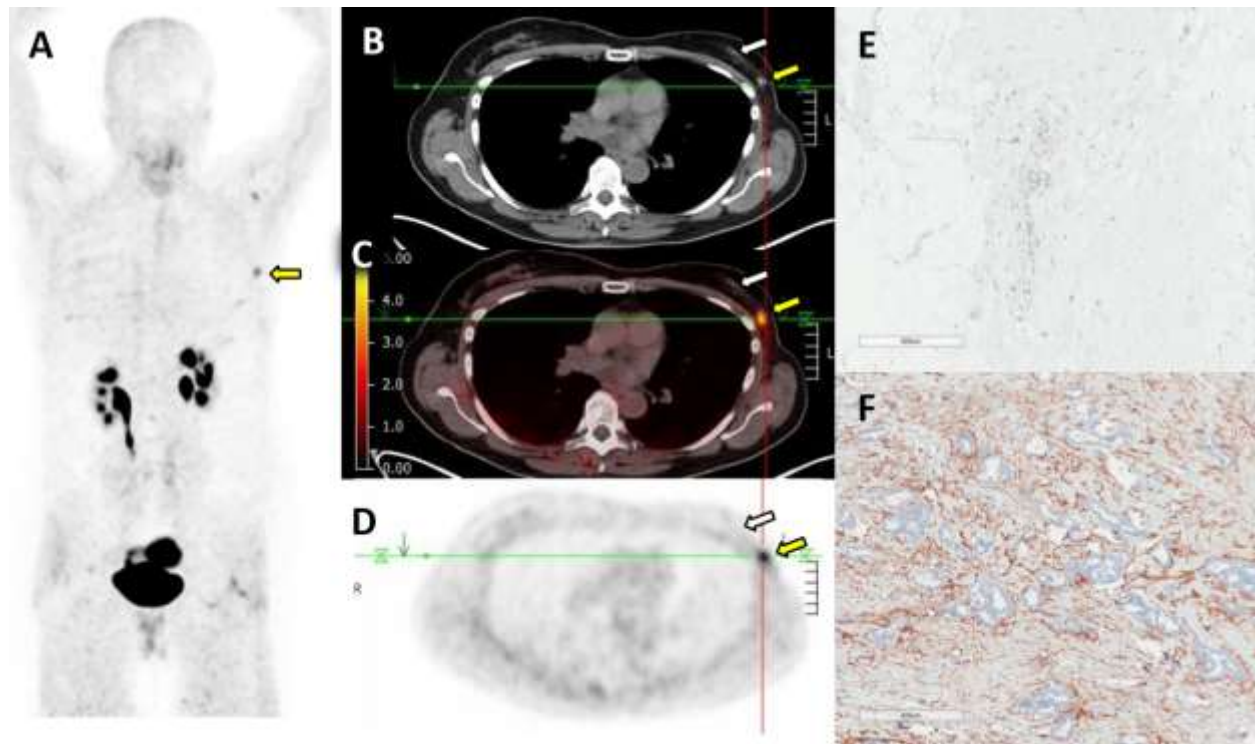
36-year-old female patient with uterine squamous cell carcinoma who underwent Bilateral Salpingectomy + left pelvic lymphadenectomy (pTx N1 M0). In correspondence of the uterus lesion and the enlarged left pelvic lymph node involved by metastatic squamous cell carcinoma as shown by the yellow arrows, ^{68}Ga -FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 19 and SUVmean 15.2, respectively). H&E (**E**) and FAP IHC staining (**F**) on histologic section of a representative lymph node revealed moderate to strong FAP staining of tumor cells metastasizing to the lymph node. White arrows depict resected normal contralateral lymph node.

Supplemental Figure 11: Patient #009 matched ⁶⁸Ga-FAPi-46 PET/CT and immunohistochemistry



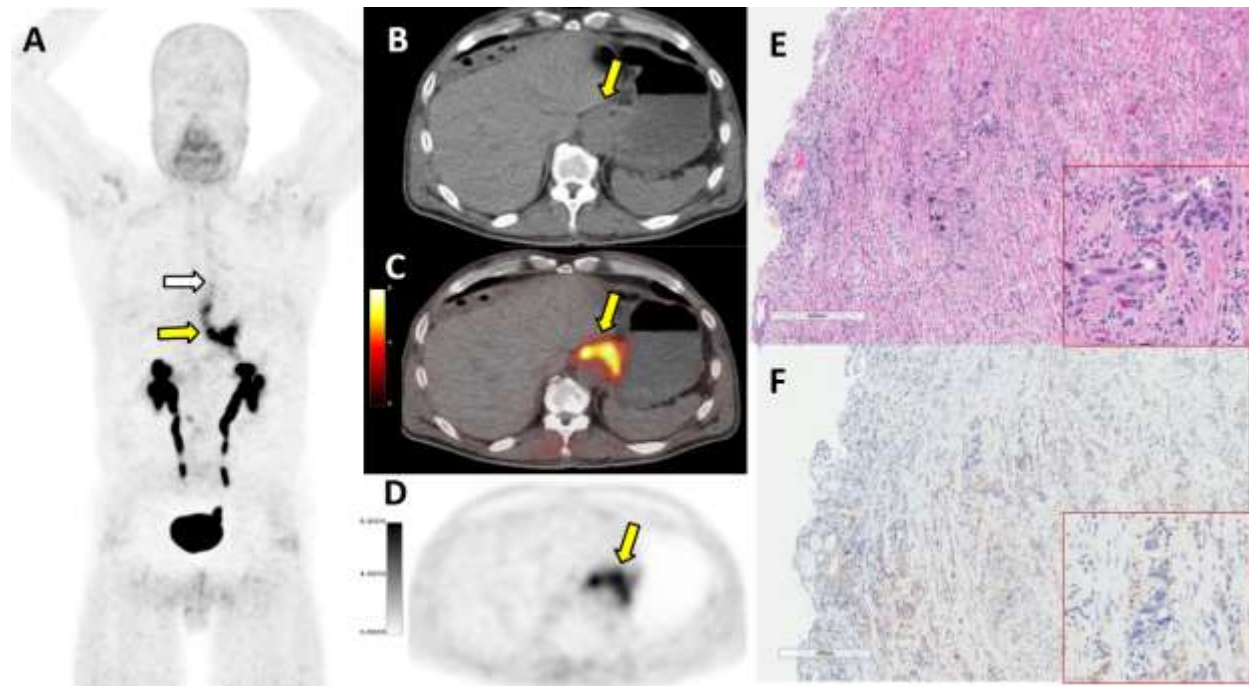
65-year-old male patient with pancreatic ductal adenocarcinoma who underwent partial pancreatectomy, of the pancreatic tail (pT2 N1 M0). In correspondence of the resected lesion as shown by the yellow arrows, ⁶⁸Ga-FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 15.7 and SUVmean 12.5, respectively). FAP IHC on representative histologic sections demonstrated variable negative to weak FAP expression in normal pancreatic parenchyma with a subpopulation of cells in normal islets consistently showing strong FAP expression (**E**). Moderate to strong FAP expression was noted for tumor tissue (**F**). White arrows depict resected normal pancreas region.

Supplemental Figure 12: Patient #011 matched ⁶⁸Ga-FAPi-46 PET/CT and immunohistochemistry



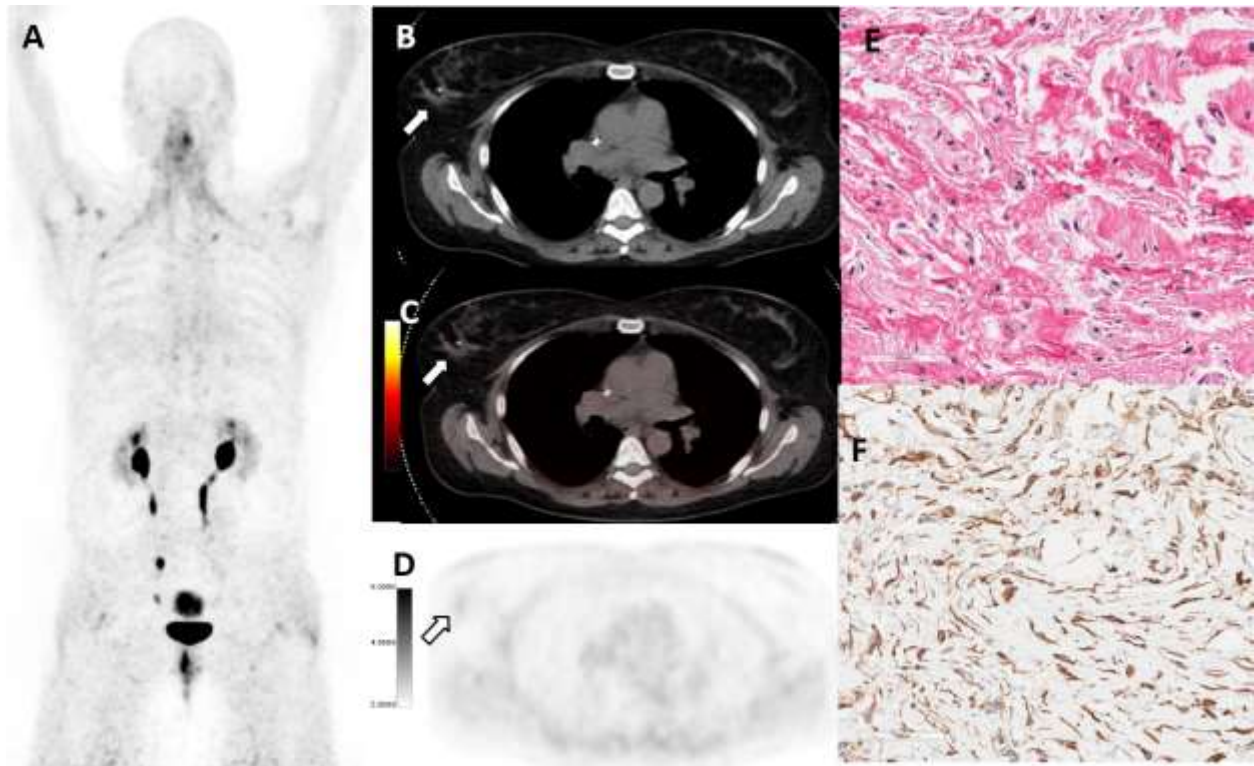
65-year-old female patient with bilateral breast invasive ductal adenocarcinoma who underwent bilateral mastectomy (pT1c Nx M0). In correspondence of the resected lesion as shown by the yellow arrows, ⁶⁸Ga-FAPi-46 PET/CT showed moderate uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 4.6 and SUVmean 4.0, respectively). FAP IHC on representative histologic sections demonstrated absent to weak FAP expression for normal tissue (**E**) and moderate to strong FAP expression for tumor tissue (**F**). White arrows depict resected normal breast region.

Supplemental Figure 13: Patient #012 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



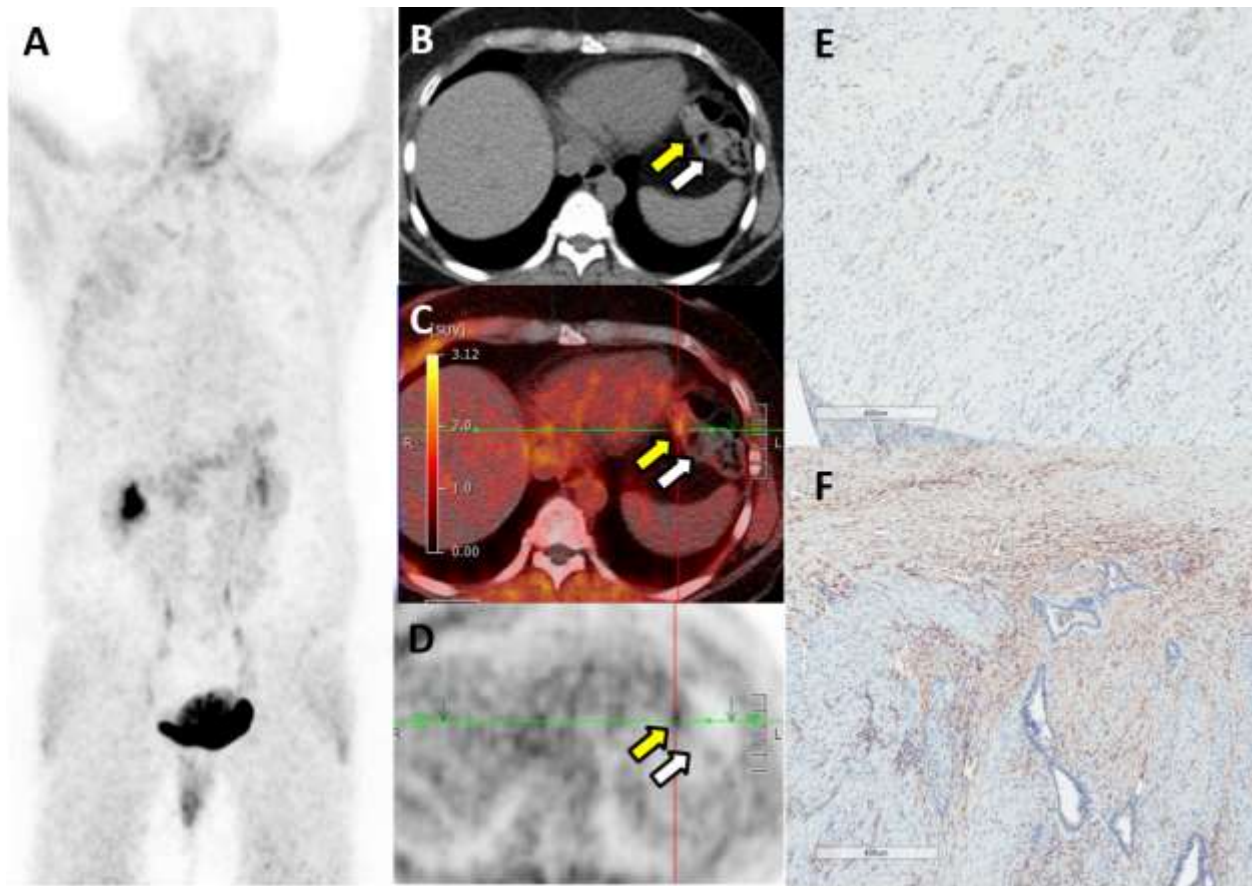
61-year-old male patient with adenocarcinoma of the gastroesophageal junction who underwent esophagogastrectomy (pT3 pN2). In correspondence of the resected lesion as shown by the yellow arrows, ^{68}Ga -FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 9.1 and SUVmean 7.3, respectively). H&E (**E**) and FAP IHC staining (**F**) on histologic section of the residual small focus of adenocarcinoma revealed weak FAP staining of stroma and vessel endothelium immediately adjacent to and more distant from the tumor cells. White arrow depicts resected normal esophagus region.

Supplemental Figure 14: Patient #013 matched PET/CT and immunohistochemistry



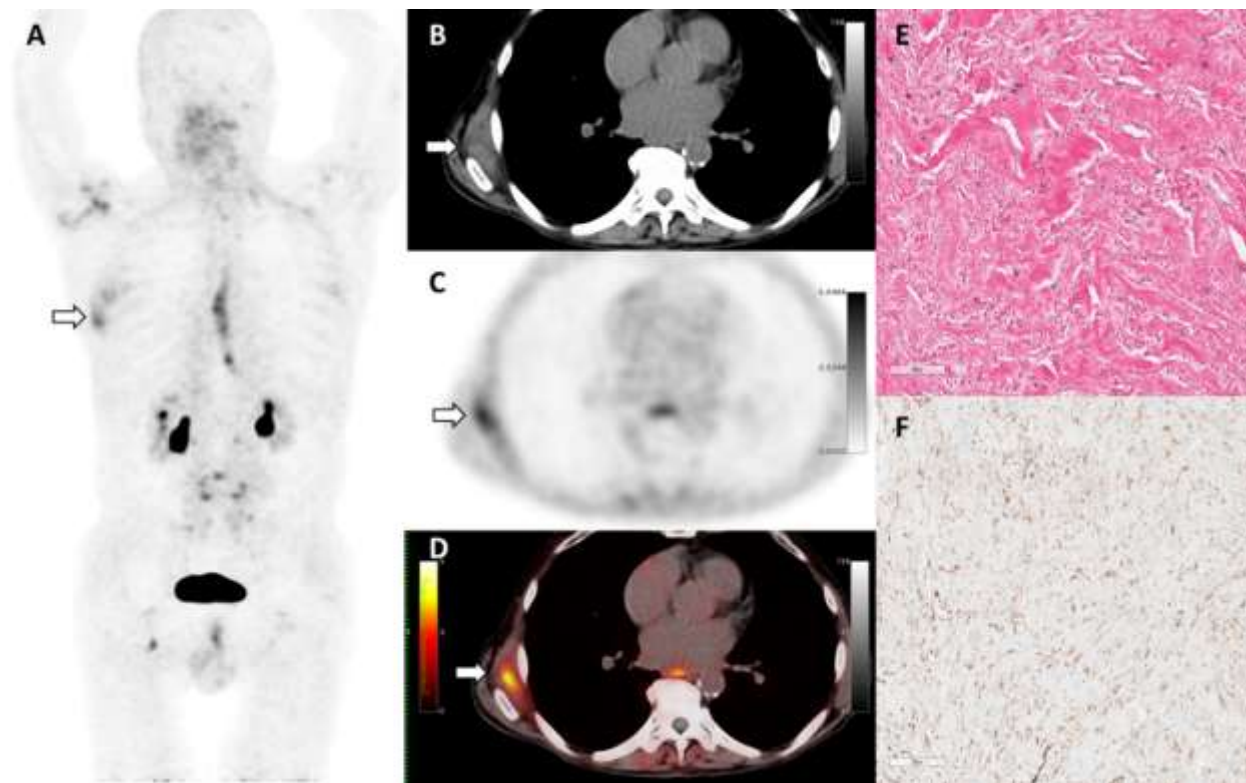
51-year-old female patient with right breast invasive ductal adenocarcinoma who underwent right mastectomy and lymphadenectomy (ypT0 N0 M0). In correspondence of the resected lesion as shown by the white arrows, ^{68}Ga -FAPi-46 PET/CT showed no increased uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 1.7 and SUVmean 1.4, respectively). H&E (**E**) and FAP IHC staining (**F**) demonstrated moderate FAP expression in the area of the lesion that on histologic sections revealed a complete response to neoadjuvant therapy with no residual viable tumor.

Supplemental Figure 15: Patient #015 matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



56-year-old female patient with left colon adenocarcinoma with liver metastasis who underwent left hemicolectomy (ypT3 N1b M1a). In correspondence of the resected lesion as shown by the yellow arrows, ^{68}Ga -FAPi-46 PET/CT showed moderate uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 2.5 and SUVmean 2.0, respectively). FAP IHC on representative histologic sections of the muscularis propria of the bowel wall demonstrated absent to weak FAP expression in vessel endothelium for normal tissue (**E**) and moderate expression for tumor tissue (**F**). White arrows depict normal region resected.

Supplemental Figure 16: Patient #002 Elastofibroma Dorsi matched ^{68}Ga -FAPi-46 PET/CT and immunohistochemistry



A 71-year-old male patient with a right sub-scapula elastofibroma dorsi underwent ^{68}Ga -FAPi-46 PET/CT. In correspondence of the resected lesion as shown by the white arrows, ^{68}Ga -FAPi-46 PET/CT showed moderate diffuse increased uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 5.4 and SUVmean 4.3, respectively). H&E and FAP IHC of histologic sections of the benign elastofibroma (**E** and **F**) revealed weak FAP expression.

Full case report available PMID: 32701818 DOI: 10.1097/RLU.0000000000003218.

Second Topic: Randomized Trials of PSMA PET imaging trials powered for clinical outcome.

Papers Provided:

- 1- ***Impact of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography on Prostate Cancer Salvage Radiotherapy Management: Results from a Prospective Multicenter Randomized Phase 3 Trial (PSMA-SRT NCT03582774).***

Armstrong WR, Kishan AU, Booker KM, Grogan TR, Elashoff D, Lam EC, Clark KJ, Steinberg ML, Fendler WP, Hope TA, Nickols NG, Czernin J, **Calais J.**

Eur Urol. 2024 Jul;86(1):52-60. doi: 10.1016/j.eururo.2024.01.012. PMID: 38290964

- 2- ***Randomized Trial of Prostate-Specific Membrane Antigen PET/CT Before Definitive Radiotherapy for Unfavorable Intermediate- and High-Risk Prostate Cancer (PSMA-dRT Trial).***

Nikitas J, Lam E, Booker KA, Fendler WP, Eiber M, Hadaschik B, Herrmann K, Hirmas N, Lanzafame H, Stuschke M, Czernin J, Steinberg ML, Nickols NG, Kishan AU, **Calais J.**

J Nucl Med. 2024 Jul 1;65(7):1076-1079. doi: 10.2967/jnumed.123.267004. PMID: 38664019.

Second Topic: Randomized Trials of PSMA PET imaging trials powered for clinical outcome.

Article 4:

Title: *Impact of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography on Prostate Cancer Salvage Radiotherapy Management: Results from a Prospective Multicenter Randomized Phase 3 Trial (PSMA-SRT NCT03582774).*

Authors: Armstrong WR, Kishan AU, Booker KM, Grogan TR, Elashoff D, Lam EC, Clark KJ, Steinberg ML, Fendler WP, Hope TA, Nickols NG, Czernin J, **Calais J.**

Reference: *Eur Urol.* 2024 Jul;86(1):52-60. doi: 10.1016/j.eururo.2024.01.012. PMID: 38290964

Brief Outline:

The PSMA-SRT NCT03582774 trial randomized 193 patients to proceed with SRT without PSMA-PET (control arm) or to undergo a PSMA-PET scan prior to SRT planning (investigational arm). Unlike most of the published studies on the impact of PSMA-PET on RT management, which are retrospective single-arm studies, this randomized trial included a control arm that allowed other contemporary diagnostic imaging. This is a secondary endpoint analysis: impact of PSMA-PET on SRT planning.

The junior first author was Wesley R Armstrong, who was working as clinical research coordinator before entering in an MD/PhD program at UCLA. This work was presented at the ASCO and ASTRO in 2022.

The paper was published in *European Urology* which has an impact factor of 25 and highlighted in AuntMinnie:

<https://www.auntminnie.com/clinical-news/molecular-imaging/article/15663117/psmapet-helps-plan-treatment-in-men-with-relapsed-prostate-cancer>

Prostate Cancer

Impact of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography on Prostate Cancer Salvage Radiotherapy Management: Results from a Prospective Multicenter Randomized Phase 3 Trial (PSMA-SRT NCT03582774)

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Abstract

Background and objective: Both imaging and several prognostic factors inform the planning of salvage radiotherapy (SRT). Prostate-specific membrane antigen positron emission tomography (PSMA-PET) can localize disease unseen by other imaging modalities. The main objective of the study was to evaluate the impact of PSMA-PET on biochemical recurrence-free survival rate after SRT.

Methods: This prospective randomized, controlled, phase 3 clinical trial randomized 193 patients with biochemical recurrence of prostate cancer after radical prostatectomy to proceed with SRT (control arm, n = 90) or undergo a PSMA-PET/computed tomography (CT) scan prior to SRT planning (investigational arm, n = 103) from June 2018 to August 2020. Any other approved imaging modalities were allowed in both arms (including fluciclovine-PET). This is a secondary endpoint analysis: impact of PSMA-PET on SRT planning. Case-report forms were sent to referring radiation oncologists to collect the management plans before randomization and after completion of SRT. The relative frequency (%) of management changes within each arm were compared using chi-square and Fisher's exact tests.

Key findings and limitations: The delivered SRT plan was available in 178/193 patients (92.2%; 76/90 control [84.4%] and 102/103 PSMA-PET [99%]). Median prostate-specific antigen levels at enrollment was 0.30 ng/ml (interquartile range [IQR] 0.19–0.91) in the control arm and 0.23 ng/ml (IQR 0.15–0.54) in the PSMA-PET arm. Fluciclovine-

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PET was used in 33/76 (43%) in the control arm. PSMA-PET localized recurrence(s) in 38/102 (37%): nine of 102 (9%) outside of the pelvis (M1), 16/102 (16%) in the pelvic LNs (N1, with or without local recurrence), and 13/102 (13%) in the prostate fossa only. There was a 23% difference (95% confidence interval [CI] 9–35%, $p = 0.002$) of frequency of major changes between the control arm (22% [17/76]) and the PSMA-PET intervention arm (45% [46/102]). Of the major changes in the intervention group, 33/46 (72%) were deemed related to PSMA-PET. There was a 17.6% difference (95% CI 5.4–28.5%, $p = 0.005$) of treatment escalation frequency between the control arm (nine of 76 [12%]) and the intervention arm (30/102 [29%]). Treatment de-escalation occurred in the control and intervention arms in eight of 76 (10.5%) and 12/102 (11.8%) patients, and mixed changes in zero of 76 (0%) and four of 102 (3.9%) patients, respectively.

Conclusions and clinical implications: In this prospective randomized phase 3 study, PSMA-PET findings provided information that initiated major management changes to SRT planning in 33/102 (33%) patients. The final readout of the primary endpoint planned in 2025 may provide evidence on whether these changes result in improved outcomes.

Patient summary: Prostate-specific membrane antigen positron emission tomography leads to management changes in one-third of patients receiving salvage radiotherapy for post-radical prostatectomy biochemical recurrence of prostate cancer.

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ADVANCING PRACTICE

What does this study add?

The PSMA-SRT NCT03582774 trial randomized 193 patients to proceed with SRT without PSMA-PET (control arm) or to undergo a PSMA-PET scan prior to SRT planning (investigational arm). Unlike most of the published studies on the impact of PSMA-PET on RT management, which are retrospective single-arm studies, this randomized trial included a control arm that allowed other contemporary diagnostic imaging. Based on these non-PSMA-PET imaging studies (which included fluciclovine-PET/CT in 43% of the control group patients), 22% of patients had a change in their SRT management. This defines the “floor” of expected changes in management based on existing diagnostic tools and emphasizes how noncontrolled retrospective assessment of management changes can overestimate the impact of the novel imaging technology.

Clinical Relevance

Biochemical recurrence following radical prostatectomy is most often managed with salvage radiotherapy directed at the prostate fossa. While this approach can be curative, its effect is limited by our ability to localize and treat recurrent disease. PSMA PET/CT offers improved accuracy in disease localization compared to conventional imaging. However, it is not clear how PSMA PET/CT affects patients' care and outcomes. In this randomized clinical trial, the investigators report that nearly one-third of patients with biochemical recurrence after radical prostatectomy in the PSMA-PET arm experienced a management change because of their PET/CT findings. While we await robust oncological outcomes from this trial, these results lay the foundation for quantifying the patient population that may ultimately benefit from PSMA PET/CT in the salvage setting after surgery.

Patient summary

In more than one-third of patients who have recurrence of PCa after SRT, PSMA-PET molecular imaging can optimize patient selection for SRT, can trigger changes in RT volumes and doses, and the use of systemic therapy. It remains speculative whether these treatment management changes result in improved outcomes.

1. Introduction

Salvage radiotherapy (SRT) is a potentially curative therapeutic intervention for men with prostate cancer biochemical recurrence (BCR) after radical prostatectomy (RP). Post-SRT outcomes are influenced heavily by a host of prognostic factors (adverse pathology), predictive factors (prostate-specific antigen [PSA] levels and PSA doubling time (PSADT) at the time of treatment), as well as treatment parameters (use of androgen deprivation therapy [ADT] and radiotherapy [RT] field size) [1–4]. Overall survival at 12 yr after

SRT ranges between 70% and 85% [5,6]. Metastasis-free survival ranges between 70% and 75% at 12 yr and between 90% and 95% at 5 yr [3,5,6]. BCR-free survival (BCRFS) ranges between 45% and 65% at 12 yr and 60% and 85% at 5 yr [3–6]. Intuitively, SRT can be curative when recurrent disease is isolated within the pelvis, fully encompassed by treatment volumes, and irradiated to sufficient dose [7]. Conventional imaging (computed tomography [CT], magnetic resonance imaging [MRI], and bone scan) rarely localizes disease recurrences at serum PSA values of <1.0 ng/ml, while growing evidence suggests that early salvage therapy, typically

with pre-SRT PSA levels of <0.3 – 0.5 , is optimal [8–12]. In the absence of radiographically visible disease, the Radiation Therapy Oncology Group (RTOG) and other groups have developed consensus contouring guidelines for both prostate bed and pelvic lymph node (LN) RT volumes based on expert consensus and ultrasound/MRI studies [13–17].

Prostate-specific membrane antigen positron emission tomography (PSMA-PET) is now the standard of care imaging modality for initial staging and restaging of prostate cancer [18,19]. PSMA-PET is more sensitive than conventional imaging, choline-PET, and fluciclovine-PET for detecting recurrent prostate cancer at low PSA levels [20,21]. Accordingly, SRT guided by PSMA-PET may achieve greater disease control through individualization of treatment volumes to include recurrences detected outside of consensus treatment volumes, dose escalation to gross disease otherwise missed on conventional imaging, and selection of intensified systemic therapy particularly when distant metastases are identified [22–25]. However, the actual impact of incorporating PSMA-PET into SRT planning on clinical outcome has yet to be evaluated prospectively.

The randomized phase 3 trial *PSMA-SRT NCT03582774* was designed to evaluate the impact on the BCRFS rate at 5 yr after SRT of using PSMA-PET for patient selection and RT volume definition as opposed to the standard of care imaging. The final readout of the primary endpoint is planned for 2025. We report here a secondary endpoint of the trial: the impact of PSMA-PET/CT on SRT management.

2. Patients and methods

2.1. Study design and participants

The PSMA-SRT NCT03582774 trial is a prospective, multicenter, randomized, controlled, open-label, phase 3 clinical trial conducted at University of California, Los Angeles (UCLA; coordinating central leading site) and University of California, San Francisco (UCSF; ancillary imaging site). This institutionally funded investigator-initiated trial was done under an investigational new drug approval protocol (IND#130649), approved by the local institutional review board (IRB#18-000484), registered on clinicaltrials.gov (NCT03582774) and published previously [26].

Patients planning to undergo SRT for prostate cancer BCR after RP and PSA ≥ 0.1 ng/ml were eligible. Patients with evidence of extrapelvic metastasis (M1) on any imaging or biopsy, exposure to ADT within 3 mo of intervention, or with contraindications to pelvic RT were excluded. Informed written consent was obtained from all patients.

Patients were randomized to proceed with SRT without PSMA-PET (control arm) or to undergo a PSMA-PET scan prior to SRT planning (investigational arm). Any other imaging, aside from PSMA-PET, was allowed in both arms. Notably, fluciclovine-PET was the US Food and Drug Administration (FDA) approved and standard of care imaging for BCR localization at the time of enrollment and was therefore allowed in the control arm. The primary endpoint is to evaluate the success rate of SRT at 5 yr (defined as BCRFS) in the group of patients who were selected by PSMA-PET to undergo SRT in comparison with the control group. Power analysis, Sample size determination, and randomization ratio rationale (1:1.3) were described previously and are provided in the study protocol and [Supplementary material](#) [26]. In brief, our hypothesis was that the incorporation of PSMA-PET into SRT planning can improve 5-yr progression-free survival by 20% (13% by detection of extrapelvic metastasis and 7% by modification of the target volumes). We estimated 5-yr progression-free survival to be 60% in the control arm and 80% in the intervention arm. Patients who do not undergo SRT will

not be included in the primary endpoint analysis (success rate of SRT) but will still be followed. Based on these estimates, 193 individuals were required to be randomized in a 1:1.13 ratio (90 in the control group and 103 in the PSMA group) to obtain an eligible sample size of $n = 90$ in each group (hypothesis of 13% with extrapelvic lesions detected by PSMA-PET in the intervention arm).

We report here the results of a secondary endpoint of the trial: to compare the rate of change of treatment plan (pre-randomization RT plan and delivered RT plan) between the two arms.

2.2. Procedures

2.2.1. PSMA-PET imaging

Patients allocated to the PSMA intervention arm underwent one 68Ga-PSMA-11 PET/CT scan at UCLA ($n = 99$, 97%) or UCSF ($n = 3$, 3%) before SRT planning (imaging protocols provided in the [Supplementary material](#)). PSMA-PET/CT images were interpreted in consensus by a board-certified nuclear medicine physician and a board-certified radiologist with access to all patient medical information during clinical readouts. Clinical imaging reports and CD/DVD containing the PSMA-PET/CT DICOM images were delivered to the treating radiation oncologist.

2.2.2. SRT management

SRT was performed at the treating radiation oncologist's local facility (list of treating facilities are provided in [Supplementary Table 1](#)) with doses, treatment volumes, and any systemic therapy as per the discretion of the treating radiation oncologist. Case-report forms (provided in the [Supplementary material](#)) were sent by the UCLA central investigators to referring radiation oncologists to collect the management plans before randomization (intended SRT plan) and 3 mo after the completion of RT (delivered SRT plan). The following treatment information was collected: targeted radiation volumes (prostate fossa and pelvic LN), total prescribed dose, dose per fraction, RT duration, ADT use, ADT duration, whether the PSMA-PET influenced clinical target volumes, or other (free text). When available, electronic medical records, and e-mail and telephone communications were also used to collect follow-up management information.

Changes between the intended SRT plan before randomization and the delivered treatment management were classified as major, minor, or no change. Major changes were defined as follows: addition or removal of ADT for a duration of ≥ 3 mo, addition or removal of the standard RT target volumes (prostate fossa and/or pelvic LN), modification of target volume delineation beyond the standard volumes, addition of simultaneous-integrated boost (SIB) beyond the standard RT fields, and initiation of advanced systemic therapy (novel AR axis targeted agents and/or chemotherapy). Minor changes consisted of SIB volumes being added within the standard RT fields.

Changes in treatment plans were further described as escalation, de-escalation, or mixed. Treatment escalation was defined as one or more of the following: addition of a new treatment volume not intended initially (eg, addition of whole-pelvis LNs and extension of the contours of the standard RT field), increase in prescribed dose, addition of ADT, or addition of advanced systemic therapy if ADT was already planned. Treatment de-escalation was defined as one or more of the following: removal of an intended treatment volume, removal of ADT, or omission of SRT entirely. Treatment plans that included one or more of both were defined as mixed.

In the intervention arm, an assessment of the causal relationship of the management change classification to the PSMA-PET scan was performed by the investigators. Changes were categorized as PSMA-PET related versus non-PSMA-PET related (patient/physician choice, questionnaire bias, anatomic limitation on RT planning, or concurrent medical episode).

2.3. Statistical analysis

Patient baseline characteristics and scan findings are provided with summary statistics. Comparison of populations were used to evaluate relative frequency (%) of management changes within each arm. Baseline characteristics and management data were compared using the Pearson's chi-square test or Fisher's exact test (five or fewer observations) for categorical variables, and the nonparametric Wilcoxon test for continuous variables. Differences in groups and binomial confidence intervals were performed using the Wilson procedure without a correction for continuity. Multivariable logistic regression models were used to assess the relationship between clinical variables and management changes. A *p* value of <0.05 was considered significant. Statistical calculations were performed using R software version 4.2.1 (www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

A total of 193 patients were enrolled from September 6, 2018 to August 17, 2020: 90 were randomized to the control arm and 103 to the PSMA-PET arm (Fig. 1). Patient characteristics are presented in Table 1. The median time from RP to enrollment, median PSA, and PSADT at enrollment were 21.6 mo (IQR 7.3–73.0), 0.30 ng/ml (IQR 0.19–0.91), and 5.5 mo (IQR 2.7–8.9) in the control arm, and 28.5 mo (IQR 8.9–62.4), 0.23 ng/ml (IQR 0.15–0.54), and 6.6 mo (IQR 3.4–10.1) in the PSMA-PET arm, respectively. There were nine of 76 (11.8%) patients with positive LN by pathology (pN1) at the time of RP in the control arm and four of 102 (3.9%) in the investigational arm (*p* = 0.07). Fourteen of 90 (15.6%) patients dropped out from the control arm: nine (10%) underwent PSMA-PET outside of the trial and five (6%) withdrew from follow-up. One of 103 (1%) patients in the investigational arm dropped out because RT was completed prior to receiving PSMA-PET due to COVID-19-related scheduling complications.

3.2. Imaging

In the control arm, patients were staged with fluciclovine-PET (33/76, 43%), CT (28/76, 37%), bone scan (15/76, 20%), or MRI (21/76, 28%), while 22/76 had no dedicated diagnostic imaging prior to SRT planning (29%; Supplementary Table 2).

In the investigational arm, 102/103 (99%) patients underwent PSMA-PET at UCLA (*n* = 99, 96.1%) and UCSF (*n* = 3, 2.9%). Additional imaging performed within the PSMA-PET arm consisted of fluciclovine-PET (16/102, 16%), CT (19/102, 19%), bone scan (15/102, 15%), and MRI (24/102, 24%), while 45/102 had no additional diagnostic imaging prior to SRT planning (45%; Supplementary Table 2).

PSMA-PET localized recurrence(s) in 38/102 (37.3%) patients: nine (9%) outside of the pelvis, 16 (16%) in the pelvic LNs (with or without local recurrence), and 13 (13%) in the prostate fossa only (detailed findings are available in Supplementary Table 3). One patient had a rectal cancer detected by the PSMA-PET scan and no other lesion suspicious of prostate cancer.

3.3. SRT management

Pre-randomization SRT intended management plans were collected at the time of enrollment for all 193 patients (100%). The delivered SRT plan was available in 178/193 patients (92.2%; 76/90 control [84.4%] and 102/103 PSMA-PET [99%]). SRT was performed at 33 sites (list provided in Supplementary Table 1). The median time from randomization to SRT was 2.3 mo (range 0.2–13.3 mo) in the control arm and 1.9 mo (range 0.2–8.9 mo) in the PSMA-PET arm. Overall, 21 patients did not receive SRT; hence, these patients were excluded from the primary endpoint analysis (success rate of SRT at 5 yr): eight of 76 (10.5%) in the control group and 13/102 (13%) in the intervention group (four of 10 [40%] with extrapelvic disease by PSMA-PET, three of 28 [10.7%] with intrapelvic disease only by PSMA-PET, and six of 64 [9.3%] with negative PSMA-PET; Fig. 1).

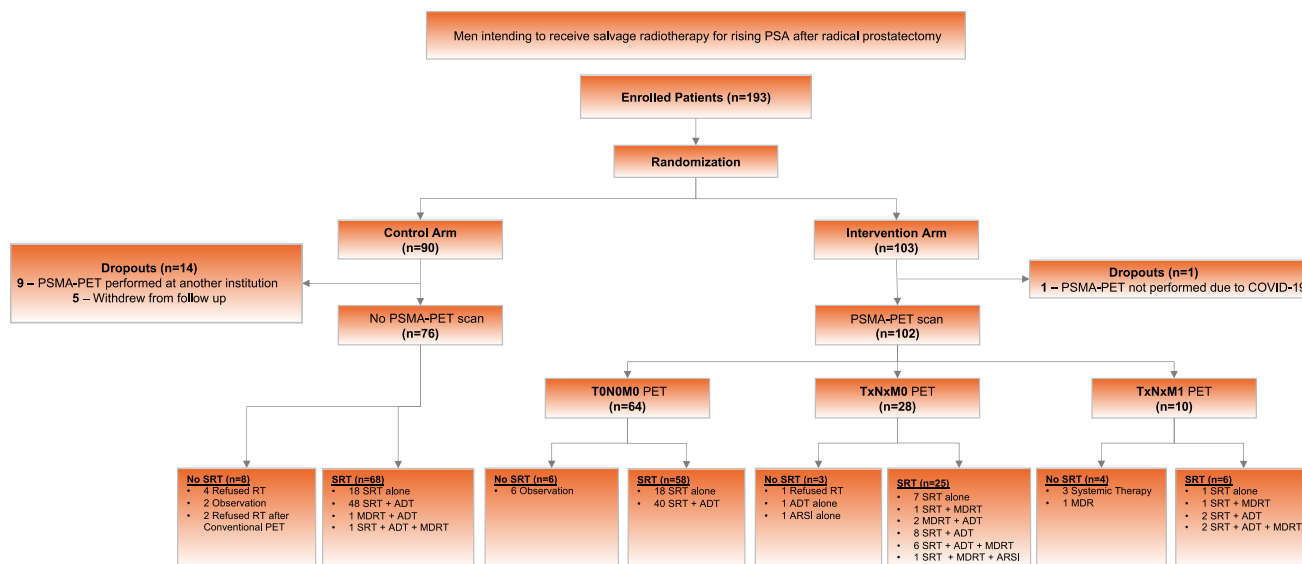


Fig. 1 – Flowchart. ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitor; COVID-19 = coronavirus disease 2019; MDRT = metastasis-directed radiotherapy; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RT = radiotherapy; SRT = salvage radiotherapy.

Table 1 – Baseline patient characteristics

Characteristics	Intervention (n = 102)	Control (n = 76)
Age at enrollment (yr), median (range)	69 (48–89)	68 (42–82)
Gleason score, n (%)		
≤6	6 (5.9)	2 (2.6)
7	68 (66.7)	51 (67.1)
≥8	28 (27.5)	22 (28.9)
Unknown	0 (0)	1 (1.3)
Pathologic primary tumor stage, n (%)		
pT2	56 (54.9)	35 (46.1)
pT3a	31 (30.4)	24 (31.6)
pT3b	15 (14.7)	16 (21.1)
pT4	0 (0)	0 (0)
Unknown	0 (0)	1 (1.3)
Pathologic regional lymph node stage, n (%)		
pN0	83 (81.4)	53 (69.7)
pN1	4 (3.9)	9 (11.8)
pNx	14 (13.7)	14 (18.4)
Positive margin, n (%)		
R0	58 (56.9)	44 (57.9)
R1	41 (40.2)	30 (39.5)
Unknown	3 (2.9)	2 (2.6)
Initial National Comprehensive Cancer Network risk group, ^a n (%)		
Low	4 (3.9)	1 (1.3)
Intermediate	40 (39.2)	30 (39.5)
High	40 (39.2)	22 (28.9)
Very high	14 (13.7)	13 (17.1)
N1	4 (3.9)	9 (11.8)
Unknown	0 (0)	1 (1.3)
Prior androgen deprivation therapy, n (%)		
Within 3–6 mo prior enrollment	2 (2)	0 (0)
Since more than 6 mo prior enrollment	6 (6)	6 (8)
Time between surgery and enrollment (mo), median (IQR)	28.5 (8.9–62.4)	21.6 (7.3–73.0)
Last PSA value before enrollment (ng/ml), median (IQR)	0.23 (0.15–0.54)	0.3 (0.19–0.91)
PSA doubling time (mo), ^b median (IQR)	5.65 (3.0–9.3)	6.0 (3.10–9.3)
European Association of Urology Biochemical Recurrence Risk Group, ^b n (%)		
Low	12 (14.6)	9 (16.3)
High	70 (85.3)	46 (83.6)

IQR = interquartile range; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

^a Biopsy core percentage information not available for NCCN.

^b Data available for 136 patients: 82 in the PSMA arm and 55 in the control arm.

Management changes are provided in aggregated form in [Table 2](#) and in detail [Supplementary Table 5](#) (intervention group) and [Supplementary Table 6](#) (control group). Major changes occurred in 17/76 (22.4%) and 46/102 (45.1%) (difference of 23% [95% confidence interval [CI] 9–35%, $p = 0.002$), minor changes in zero of 76 (0%) and seven of 102 (7%), and no change in 59/76 (77.6%) and 56/102 (54.9%) of the control and intervention arms, respectively.

In the PSMA-PET arm, the causality of the major changes was deemed not related to PSMA-PET in 13/46 (28%): seven of 46 (15%) patient/physician choice, four of 46 (9%) questionnaire bias, and two of 46 (4%) concurrent medical episode ([Supplementary Table 4](#)).

Among major treatment changes, treatment escalation occurred in nine of 76 (12%) and 30/102 (29%; difference of 17.6%, 95% CI 5.4–28.5%, $p = 0.005$), de-escalation in eight of 76 (10.5%) and 12/102 (11.8%; difference of 1.2%, 95% CI –

8.9% to 10.5%, $p = 0.796$), and mixed changes in zero of 76 (0%) and four of 102 (3.9%; difference of 3.9%, 95% CI –1.5% to 9.7%, $p = 0.137$) in the control and intervention arms, respectively. Management changes for each PSMA-PET miTNM pattern in the intervention group are provided in [Figure 2](#) and [Supplementary Table 7](#) (major escalation, major de-escalation, minor escalation, minor de-escalation, major alternative, and no change), [Supplementary Figure 1](#) and [Supplementary Table 8](#) (major, minor, and no change), [Supplementary Figure 2](#) and [Supplementary Table 9](#) (escalation, de-escalation, alternative, and no change), and [Supplementary Figure 3](#) and [Supplementary Table 10](#) (ADT management).

Nine of 102 (9%) patients of the intervention arm received advanced systemic therapy in relation to PSMA-PET findings, whereas only one of 76 (1.3%) patients in the control arm received advanced therapy. Of note, 13 patients had ADT added to their therapy plan ([Table 2](#), and [Supplementary Tables 5 and 10](#)). In seven of these patients, the change was attributed to PSMA-PET: five were due to N1 or M1 disease depicted by PSMA-PET. One patient decided to not undergo pelvic LN RT and added ADT instead due to negative PSMA-PET (TONOMO). One patient decided to treat indeterminate pelvic LNs on PSMA-PET as positive. In six of 13 of these cases, the addition of ADT was deemed to be non-PSMA related ([Supplementary Table 4](#)): three cases were patient/physician choice, two cases were classified as a questionnaire bias (physician reported mistakes in initial RT plan), and one case was due to a bladder sling procedure that caused the patient to delay RT and start ADT during the interim.

Multivariable logistic regression models were used to evaluate clinical characteristics that impacted treatment decisions independent of PSMA-PET imaging ([Table 3](#)). Clinical variables included enrollment PSA levels, Gleason grade (6–9), National Comprehensive Cancer Network (NCCN) risk group (low, intermediate, high, very high, and N1), PSADT, European Association of Urology (EAU) risk group (low vs high), and randomization arm (control vs PSMA-PET). Patients with missing values ($n = 41$ missing PSA DT, $n = 24$ missing EAU risk group) were excluded from the multivariable model to perform a complete case analysis ($n = 136$). This model testing the variables PSA, grade group (GG), PSADT, NCCN, EAU, and randomization arm demonstrated an odds ratio of 2.83 (95% CI 1.3–6.4) for the randomization arm (PSMA-PET). A sensitivity analysis was performed to include all patients ($n = 176$) without the variables with missing values. This model testing only the variables PSA, GG, NCCN, a randomization arm resulted in an odds ratio of 3.6 (95% CI 1.8–7.0, $p < 0.001$) for the randomization arm (PSMA-PET).

4. Discussion

In this prospective randomized controlled phase 3 trial, there were 23% more major changes between intended SRT management before randomization and delivered SRT, and 18% more treatment escalation, in the PSMA-PET intervention arm than in the control arm.

Unlike most of the published studies on the impact of PSMA-PET on RT management, which are retrospective single-arm studies, this study included a control arm that allowed other contemporary diagnostic imaging. Based on these non-PSMA-PET imaging studies (which included fluciclovine-PET/CT in 43% of the control group patients),

Table 2 – Frequency of management changes in both arms and causal relationship to PSMA-PET in the intervention arm^a

	Control arm (N = 76)	Intervention arm (N = 102)	% Change related to PSMA-PET (only for intervention arm)
No change	59 (77.6)	56 (54.9)	–
Major change	17 (22.4)	46 (45.1)	33/46 (72)
Escalation	9 (12)	30 (29)	18/30 (60)
Addition of RT fields	0	17 (16.6)	12/17 (71)
Alone	3 (3.9)	10 (9.8)	7/10 (70)
With additional ADT	1 (1.3)	6 (5.9)	4/6 (67)
With addition of ARSi	0	1 (0.9)	1 (100)
Addition of ADT	4 (5.2)	9 (9)	3/9 (33)
Alone	0	7 (6.8)	2/7 (29)
With reduction of RT fields	0	1 (0.9)	0 (0)
With change of RT fields	0	1 (0.9)	1 (100)
Switch to ADT only	0	3 (2.9)	2/3 (67)
Alone	0	2 (2)	2 (100)
With addition of ARSi	0	1 (0.9)	0 (0)
Addition of ARSi	1 (1.3)	0	–
With reduction of RT fields	1 (1.3)	0	–
Chemotherapy	0	1 (0.9)	1 (100)
De-escalation	8 (10.5)	12 (11.8)	11/12 (92)
Switch to observation	4 (5.2)	7 (6.9)	6/7 (86)
Switch to ADT only	0	1 (0.9)	1 (100)
Removal of ADT	1 (1.3)	1 (0.9)	1 (100)
Alone	1 (1.3)	0	–
With addition of RT fields	0	1 (0.9)	1 (100)
Reduction of RT fields	1 (1.3)	2 (2)	2 (100)
Alone	0	2 (2)	2 (100)
Removal of ADT	1 (1.3)	0	–
Change of RT fields	0	1 (0.9)	1 (100)
No RT	2 (2.6)	0	–
Alternative	0	4 (3.9)	4 (100)
Change of RT Fields	0	2 (2)	2 (100)
With additional ADT	0	1 (0.9)	1 (100)
With removal of ADT	0	1 (0.9)	1 (100)
Minor change	0	7 (7)	7(100)
Escalation	0	6 (5.8)	6 (100)
In-field dose increase	0	6 (5.8)	6 (100)
De-escalation	0	1 (0.9)	1 (100)
In-field dose decrease	0	1 (0.9)	1 (100)

ADT = androgen deprivation therapy; ARSi = androgen receptor signaling inhibitor; PET = positron emission tomography; PSMA= prostate- specific membrane antigen; RT = radiation therapy.

^a Quantitative results are expressed as n (%).

22% of patients had a change in their SRT management. This defines the “floor” of expected changes in management based on existing diagnostic tools and emphasizes how noncontrolled retrospective assessment of management changes can overestimate the impact of the novel imaging technology.

The investigators also assessed the causal relationship of the management changes with the PSMA-PET scan. The causality of the major changes in the PSMA-PET arm was deemed not related to PSMA-PET in 28% (13/46) of changes (patient/physician choice, questionnaire bias, anatomic limitation for RT planning, and concurrent medical episode). Changes to patient management are often influenced by personal patient decisions owing to quality of life and desired treatment aggression, examples of which include the decision to undergo ADT.

Using multivariate testing, there were no clinical variables other than PSMA-PET (among GG, PSA, PSADT, NCCN risk group, EAU risk group, and PSMA-PET) that impacted significantly the frequency of management change (odds ratio 2.83).

The information that PSMA-PET provides can potentially impact the outcome of the therapy in several ways. PSMA-PET can identify extraprostatic disease. Evidence of distant metastatic disease indicates that local therapy alone would not offer cure; hence, SRT may be considered futile and abandoned in favor of intensified systemic therapy and/or metastasis-directed therapy in select cases. In addition,

PSMA-PET can be used directly in the SRT planning workflow as an imaging tool to guide and optimize contouring, coverage, and dose prescription of RT.

In this trial, the main management change observed in the PSMA-PET arm was treatment escalation (addition of RT field region, ADT, advanced systemic therapy, or change to systemic therapy only), which occurred in 36% (37/102) versus 12% (nine of 76) in the control arm. About 10% of the PSMA-PET patients received advanced systemic therapy and/or stereotactic body radiation due to extraprostatic disease detection (vs 1% in the control arm). The significance of extraprostatic disease seen only on PSMA-PET remains unclear, and there is a potential for a lead-time bias. The RTOG-9601 trial showed a benefit to adding ADT in patients with PSA >0.7, and 50–85% of these patients can have N1 and/or M1 visible on PSMA-PET [5,27]. Results from RTOG-0534 were released in part during the enrollment period of this trial, which may present one of the multiple factors for the proportion of patients who received ADT (64/178 [36%]). Of note, our trial population was balanced with respect to factors (PSA, PSADT, and EAU BCR risk groups) that would impact the use of ADT and whole-pelvis RT (WPRT). Moreover, the ORIOLE trial post-hoc analysis showed improved distant metastasis-free survival when all PSMA-PET–defined lesions were targeted [28,29]. At this time, whether the treatment escalation triggered by the improved extraprostatic disease detection from

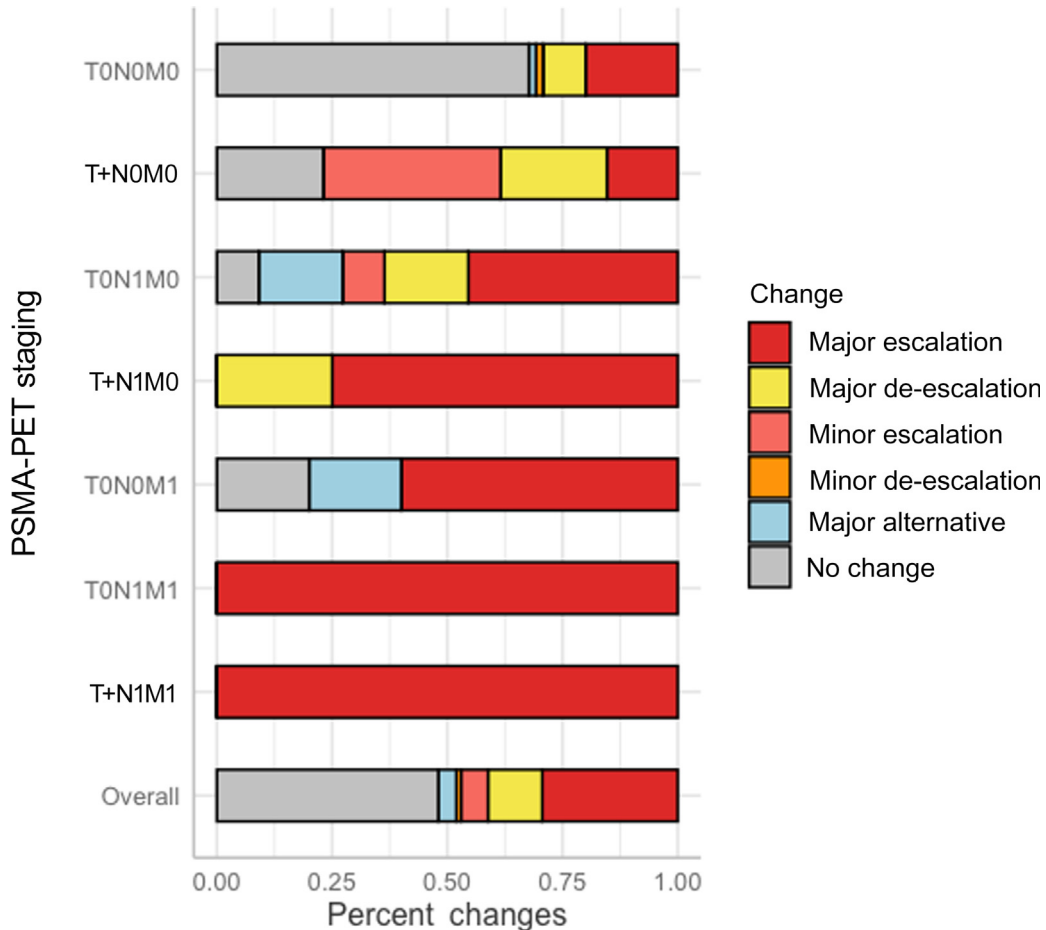


Fig. 2 – Management changes (major escalation, major de-escalation, minor escalation, minor de-escalation, major alternative, and no change) for each PSMA-PET miTNM pattern (TONOMO [n = 64], T+NOMO [n = 13], TON1M0 [n = 11], T+N1M0 [n = 4], TON0M1 [n = 5], TON1M1 [n = 3], T+N1M1 [n = 1], and overall [n = 102]; see numbers in Supplementary Table 7). PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Table 3 – Multivariable logistic regression model to predict clinical factors impacting management change frequency^a

	Management change Odds ratio (95% CI)
Randomization arm	2.8* (1.3–6.4)
Observations	136 ^b

CI = confidence interval; EAU = European Association of Urology; PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Network; PSMA = prostate-specific membrane antigen.

^a Covariates in model include PSA at enrollment, PSA doubling time, Gleason grade, NCCN risk group, and EAU risk group.

^b N = 136 in complete case analysis. Patients with missing values (n = 41 missing PSA doubling time; n = 24 missing EAU risk group) were excluded from the multivariable model.

* p < 0.01.

PSMA-PET is beneficial to patient outcomes remains speculative.

Treatment de-escalation was also tempting for patients and referring physicians: 9% of patients in the intervention arm who had negative PSMA-PET decided to omit SRT. Given the known limits of sensitivity of PSMA-PET and the long-standing literature supporting SRT as more effective when delivered early, this practice is not currently supported by high-level evidence [29]. A study reported that initiating SRT when PSMA-PET is negative provides the greatest BCRFS at 3 yr, while failure to initiate SRT in PSMA-PET negative

patients lead to significantly higher rates of BCR [29]. Similarly, RTOG-0534 supports a role for intensification with ADT and WPRT in selected patients, and omitting this due to lack of nodal lesions visible on PSMA-PET may constitute potentially harmful undertreatment [3,30].

The other imaging modalities in the control arm were not predefined and left to the discretion of the patient/referring physician. Of note, >40% of the control arm and 16% of the intervention arm were able to receive a fluciclovine-PET scan, the FDA-approved standard of care imaging for BCR localization at the time of enrollment. It is important to point out that this may not be representative of clinical practice elsewhere.

PSMA-PET is more sensitive than fluciclovine-PET in this patient population candidate for SRT. Previous results from the randomized EMPIRE-1 trial demonstrated a 25% benefit in BCRFS at 4 yr among patients receiving SRT selected by fluciclovine-PET compared with conventional imaging alone [31]. In EMPIRE-1, a less sensitive PET imaging modality was used with strictly prespecified management changes. In the PSMA-SRT trial, a more sensitive PET imaging modality was used, but freedom was provided to guide how these results were used. Given the widespread availability of PSMA-PET imaging, these results are likely to be more generalizable to general practice, where the ultimate choice of SRT plan is based on physician and patient discretion. Thus,

this trial may show if improved sensitivity in disease staging leads to treatment planning changes associated with a higher treatment success rate [20].

The rapid development and increased usage of PSMA-PET have outpaced the ability to perform prospective randomized trials to define how to best use PSMA-PET for clinically meaningful outcome endpoints. This current trial is one of the rare randomized controlled imaging trials powered for patient outcome with few others (NCT04794777, NCT04557501, NCT03525288, NCT01666808, and NCT03762759). These trials may prove that PSMA-PET findings must be considered and implemented in clinical trial designs given their increasing availability and benefit.

4.1. Limitations

There are limitations to this study.

First, this is an early analysis of a secondary endpoint, and we cannot draw any conclusion on the impact of PSMA-PET on the outcome of patients with recurrent prostate cancer. A primary endpoint analysis and final readout of the trial are planned for 2025.

Second, study protocol guidelines did not predefine rigid guidelines for the choice of the other imaging modalities and the implementation of PSMA-PET findings into the therapy plan, leaving management to the patient and treating oncologist's decision. This may have an impact on the statistical power for the trial's primary endpoint. There is no consensus on the standard for the initial treatment plan, in the absence of PSMA-PET results. The choice of initial treatment plan may or may not be representative of clinical practice elsewhere. Practice patterns change over time, informed by FDA approvals (fluciclovine-PET) and results from trials such as RTOG-0534 and others (eg, GETUG-AFU-16). The benefit of this approach may be the generalizability of the trial results to the broader setting, where prespecified instructions on how to use PSMA-PET results will not be available.

Finally, no toxicity assessment was built into the trial. More studies are needed to assess the toxicity rates associated with PSMA-PET-guided SRT.

5. Conclusions

In this secondary endpoint analysis of the prospective randomized controlled PSMA-SRT trial, the information from PSMA-PET imaging influenced major management decisions in more than one-third of patients (33/102) who were planning to undergo SRT.

PSMA-PET molecular imaging optimizes patient selection for SRT, triggers changes in RT volumes and doses, and the selection for systemic therapy. There was 18% more treatment escalation in the PSMA-PET group than in the control group.

It remains speculative whether these treatment management changes result in improved outcomes.

Author contributions: Wesley R. Armstrong and Jeremie Calais had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Calais, Nickols, Elashoff, Fendler, Czernin.

Acquisition of data: Armstrong, Booker, Nickols, Kishan, Calais, Hope.

Analysis and interpretation of data: Armstrong, Grogan, Calais.

Drafting of the manuscript: Armstrong, Calais.

Critical revision of the manuscript for important intellectual content: Armstrong, Kishan, Booker, Lam, Clark, Grogan, Elashoff, Steinberg, Fendler, Hope, Nickols, Czernin, Calais.

Statistical analysis: Armstrong, Grogan, Calais.

Obtained funding: Calais, Czernin.

Administrative, technical, or material support: Armstrong, Booker, Kishan, Nickols, Hope, Steinberg, Czernin, Calais.

Supervision: Calais, Kishan, Nickols, Czernin.

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Peer Review Summary

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Supplementary material

PSMA PET imaging protocol

The ⁶⁸Ga-PSMA-11 was synthesized based on harmonized release criteria, and imaging was performed following European Association of Nuclear Medicine Practice Guideline/ Society of Nuclear Medicine and Molecular Imaging guidelines¹. Target injected activity was 185 MBq (5 mCi) (allowed range, 111-259 MBq [3-7 mCi]), and patients received a mean (SD) of 5.1 [0.4] mCi. Target uptake period was 60 minutes (allowed range, 50-100 minutes), and image acquisition began a mean (SD) of 66 (12) minutes after injection. A diagnostic CT scan (200-240 mAs, 120 kV) with 5-mm slice thickness was performed. Intravenous contrast media (iodinated or gadolinium) was administered in 98 of 102 patients (96%). Whole-body PET images were acquired from pelvis to vertex. Depending on patient weight and bed position, emission time was 2 to 5 minutes per bed position. All PET images were corrected for attenuation, dead time, random events, and scatter. PET images were reconstructed with an iterative algorithm (ordered-subset expectation maximization).

Power analysis and sample size calculation (1)

In our previous study (2), 52/270 patients (19%) had at least one lesion detected by PSMA PET/CT which was not covered by the standard radiation field that covered both the prostate bed and pelvic lymph nodes (RTOG consensus delineations). Standard SRT would not have resulted in durable disease control because gross disease would have been missed. Therefore, we hypothesized that the incorporation of PSMA PET/CT to SRT planning will improve 5-year PFS survival by 20%. Based on available published literature we estimated the 5 y PFS at 60% with standard SRT. Therefore, we assume 5-year PFS to be 60% in Arm 1 (standard SRT) and 80% in Arm 2 (PSMA PET/CT based SRT). We also assume that approximately 13% of subjects randomized to Arm 2 will have extra-pelvic metastasis detected by PSMA PET/CT, and therefore are not curable by SRT directed to the pelvis. Based on these estimates, 193 subjects are required to be randomized in a 1:1.13 ratio (90 in control group and 103 in the PSMA group). Randomized, eligible, sample size in each group is therefore $n = 90$. When the randomized, eligible, sample size in each group is 90, with an estimated total number of events required of 46, an exponential maximum likelihood test of equality of survival curves with a 0.050 two-sided significance level will have 80% power to detect the difference between a PSMA group exponential parameter of 0.0446 (assuming a 5-year failure rate of 20%) and a

control group exponential parameter of 0.1022 (assuming a 5-year failure rate of 40%), which equals a constant hazard ratio of 0.436; this assumes a maximum follow-up time of 5 years and a common exponential dropout rate of 0.0211 (assuming 10% 5-year drop-out rate in each group). The planned log-rank test should have similar power to the exponential MLE survival test.

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SUPPLEMENTARY TABLES

Supplementary Table 1: List of treating facilities

Institution	State	Country	n=	%
UCLA Health	CA	USA	51	26%
City of Hope	CA	USA	28	15%
West Los Angeles VA	CA	USA	20	10%
Coastal Radiation Oncology	CA	USA	11	6%
Kaiser Permanente	CA	USA	11	6%
USC Norris	CA	USA	9	5%
Oregon Health and Science University	OR	USA	7	4%
BC Cancer Agency	BC	Canada	5	3%
Hoag	CA	USA	5	3%
Los Alamitos Medical Center	CA	USA	5	3%
Scripps MD Anderson Cancer Center	CA	USA	5	3%
Sutter Sacramento	CA	USA	4	2%
UCSF Health	CA	USA	4	2%
cCARE	CA	USA	3	2%
Mission Hope Center	CA	USA	3	2%
Alaska Cancer Treatment Center	AK	USA	2	1%
Mayo Clinic	MN	USA	2	1%
Precision Radiation Oncology	CA	USA	2	1%
Ridley Tree Cancer Center	CA	USA	2	1%
Anderson Cancer Centetr	TX	USA	1	1%
Brecon Medical Group	CA	USA	1	1%
Cedars-Sinai Medical Center	CA	USA	1	1%
Dana Farber Cancer Institute	MA	USA	1	1%
Hawaii Pacific Onc Center	HI	USA	1	1%
North Puget Cancer Center	WA	USA	1	1%
St Johns Health Center	CA	USA	1	1%
Sunny Brook Health Sciences Center	NY	USA	1	1%
Texas Oncology	TX	USA	1	1%
The Center of Radiation Therapy of Beverly Hills	CA	USA	1	1%
UCSD Health	CA	USA	1	1%
University of Colorado	CO	USA	1	1%
University of Miami	MI	USA	1	1%
Vincere Cancer Center	AZ	USA	1	1%

Supplementary Table 2: Additional imaging modalities used for SRT planning in both arms

Detailed Imaging Modalities	Control (n=76)	PSMA (n=102)
Fluciclovine-PET Only	19 (25%)	11 (10.8%)
Fluciclovine-PET+BS	1 (1.3%)	2 (2%)
Fluciclovine-PET+CT	1 (1.3%)	1 (1%)
Fluciclovine-PET+MRI	2 (2.6%)	2 (2%)
Fluciclovine-PET+MRI+BS	2 (2.6%)	0 (0%)
Fluciclovine-PET+MRI+CT	6 (7.9%)	0 (0%)
Fluciclovine-PET+BS+CT	1 (1.3%)	0 (0%)
Fluciclovine-PET+MRI+CT+BS	1 (1.3%)	0 (0%)
BS Only	1 (1.3%)	5 (4.9%)
BS+MRI	1 (1.3%)	3 (2.9%)
BS+MRI+CT	5 (6.6%)	0 (0%)
CT Only	7 (9.2%)	8 (7.8%)
CT+BS	3 (3.9%)	5 (4.9%)
CT+MRI	4 (5.3%)	6 (5.9%)
MRI Only	0 (0%)	14 (13.7%)
None	22 (28.9%)	45 (44.1%)
Overall Imaging Modalities**		
Fluciclovine-PET +/-others	33 (43.4%)	16 (16%)
BS +/-others	15 (19.7%)	15 (15%)
MRI +/-others	21 (27.6%)	24 (24%)
CT +/-others	28 (36.8%)	19 (19%)
None	22 (28.9%)	45 (44.1%)

* Sum of numbers and percentages not equal to original sum

Supplementary Table 3

Table 2: PSMA-PET/CT scan findings in the intervention group

<i>Intervention (n=102)</i>	
<i>PSMA-PET/CT scan findings</i>	N=102
PSMA T0N0M0	64 (62.7%)
PSMA PET +	38 (37%)
PSMA T+	18 (17.6%)
PSMA N1	20 (19.6%)
PSMA Any M1	9 (8.8%)
PSMA M1a	3 (2.9%)
PSMA M1b	8 (7.8%)
PSMA M1c	0 (0%)
PSMA other cancer	1 (1%)
<i>PSMA-PET miTNM</i>	
PSMA T+N0M0	13 (12.7%)
PSMA T+N1M0	4 (3.9%)
PSMA T0N1M0	12 (11.8%)
PSMA T+N1M1	1 (1%)
PSMA T0N1M1	3 (2.9%)
PSMA T0N0M1	4 (3.9%)
<i>Number of lesions</i>	
N target 1-3	31 (30.3%)
N target 4-5	3 (2.9%)
N target >5	3 (2.9%)

Supplementary Table 4. Assessment of Causal Relationship of the Management change and the PSMA-PET scan

	Control n=76	Intervention n=102
Major Change*	17 (22.4%)	46 (45.1%)
Non-PSMA-PET related	17 (22.4%)	13 (12.7%)
Patient/Physician Choice	15 (19.7%)	7 (6.9%)
Questionnaire Bias	1 (1.3%)	4 (3.9%)
Anatomic Limitation RT planning	1 (1.3%)	0 (0%)
Concurrent Medical Episode	0 (0%)	2 (2%)
PSMA-PET related	0 (0%)	33 (32.4%)
Minor Change**	0 (0%)	7 (6.9%)
Non-PSMA-PET related	0 (0%)	(0%)
PSMA-PET Related	0 (0%)	7 (6.9%)

*Boost to out-field disease, CTV delineation, change to ADT administration

**Change to In-Field Dose

Supplementary Table 5. Change in Treatment Plan - Intervention Group

Change	Management	Change Details	Change Details										% PSMA Related
			n	TNDMM	TNDMM	TNDMM	TNDMM	TNDMM	TNDMM	TNDMM	TNDMM	TNDMM	
Minor Change			7	1	5	1	0	0	0	0	0	0	100%
prostate bed -> Prostate bed + In-Field Prostate bed SB		Escalation	7	1	5	1	0	0	0	0	0	0	100%
Prostate bed -> Prostate bed + In-Field Bladder wall SB		Escalation	1	1	1	1	0	0	0	0	0	0	100%
prostate bed + pelvic LN + prostate bed + pelvic LN + PLN Dose Decrease		De-escalation	1	1	0	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN + In-Field pelvic LN SB + 6 months Lupron		Escalation	1	1	0	0	0	0	0	0	0	0	100%
Prostate bed + 4 months Lupron -> Prostate bed + In-Field Prostate bed SB + 5 months Lupron		Escalation	1	1	0	0	0	0	0	0	0	0	100%
Major Change			14	9	1	2	0	2	0	0	0	0	87%
Intended treatment = Prostate Bed			14	9	1	2	0	2	0	0	0	0	87%
prostate bed -> Active Surveillance	Switch to Active Surveillance	De-escalation	3	2	1	0	0	0	0	0	0	0	100%
prostate bed -> prostate bed + 6 months Degarelix prostate bed + 6 months Lupron	Addition of ADT	Escalation	1	1	0	0	0	0	0	0	0	0	0%
prostate bed -> prostate bed + 6 months Lupron	Addition of ADT	Escalation	2	1	0	0	0	1	0	0	0	0	50%
prostate bed -> prostate bed + 12 months Lupron	Addition of ADT	Escalation	1	1	0	0	0	0	0	0	0	0	0%
prostate bed -> prostate bed + SBRT 9th Rib	Addition of RT fields	Escalation	1	1	0	0	0	1	0	0	0	0	100%
prostate bed -> prostate bed + pelvic LN	Addition of RT fields	Escalation	2	1	0	1	0	0	0	0	0	0	50%
prostate bed -> prostate bed + pelvic LN + 6 months Lupron	Addition of ADT, Addition of RT fields	Escalation	2	2	0	0	0	0	0	0	0	0	50%
prostate bed -> prostate bed + pelvic LN + 18 months Lupron	Addition of ADT, Addition of RT fields	Escalation	1	1	0	0	0	0	0	0	0	0	0%
prostate bed -> pelvic LN + PLN CTV Delineation + PLN In-Field SB + 6 months Lupron	Change of RT fields, Addition of ADT	Alternative	1	1	0	0	0	0	0	0	0	0	100%
Intended treatment = Prostate Bed + ADT			9	5	0	1	2	1	0	0	0	0	87%
prostate bed + 6 months Lupron -> Active Surveillance	Switch to Active Surveillance	De-escalation	1	1	0	0	0	0	0	0	0	0	100%
prostate bed + 6 months Lupron -> 6 months Lupron	Switch to ADT only	De-escalation	1	0	0	0	1	0	0	0	0	0	100%
prostate bed + 6 months Lupron -> 6 months Lupron and Zytiga	Switch to ARS and ADT only	Escalation	1	0	0	0	1	0	0	0	0	0	0%
prostate bed + 6 months Lupron -> SBRT L4 Lesion	Change of RT fields, Removal of ADT	Alternative	1	0	0	0	0	1	0	0	0	0	100%
prostate bed + 6 months Lupron -> SBRT RB + 4 months Lupron	Change of RT fields	Alternative	1	0	0	1	0	0	0	0	0	0	100%
prostate bed + 9 months Lupron -> prostate bed + pelvic LN + 9 months Degarelix prostate bed + 6 months Lupron -> prostate bed + pelvic LN + 4 months Bicalutamide	Addition of RT fields	Escalation	1	1	0	0	0	0	0	0	0	0	0%
prostate bed + 6 months Lupron -> prostate bed + pelvic LN + 18 months Lupron	Addition of RT fields	Escalation	1	1	0	0	0	0	0	0	0	0	0%
prostate bed + 6 months Lupron -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB + 6 months Lupron	Addition of RT fields	Escalation	2	2	0	0	0	0	0	0	0	0	100%
Intended treatment = Prostate Bed + Pelvic Lymph Nodes			8	3	1	1	1	0	2	0	0	0	75%
prostate bed + pelvic LN -> 6 months Lupron	Switch to ADT only	Escalation	1	0	0	0	0	0	1	0	0	0	100%
prostate bed + pelvic LN -> prostate bed + PB CTV Delineation	Change of RT fields	De-escalation	1	0	1	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN -> prostate bed + PB CTV Delineation + PB In-Field SB + 6 months Lupron	Change of RT fields, Addition of ADT	Alternative	1	1	0	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN -> prostate bed + pelvic LN + 6 months Lupron	Addition of ADT	Escalation	2	2	0	0	0	0	0	0	0	0	0%
prostate bed + pelvic LN -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB	Addition of RT fields	Escalation	1	0	0	1	0	0	0	0	0	0	100%
prostate bed + pelvic LN -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB + 6 months Lupron	Addition of ADT, Addition of RT fields	Escalation	1	0	0	0	1	0	0	0	0	0	100%
prostate bed + pelvic LN -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB + SBRT M1a Retro-P + 24 months Lupron	Addition of ADT, Addition of RT fields	Escalation	1	0	0	0	0	1	0	0	0	0	100%
Intended treatment = Prostate Bed + Pelvic Lymph Nodes + ADT			15	3	3	5	1	1	1	1	1	1	87%
prostate bed + pelvic LN -> 6 months Lupron -> Active Surveillance	Switch to Active Surveillance	De-escalation	2	2	0	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 24 months Lupron -> Active Surveillance	Switch to Active Surveillance	De-escalation	1	1	0	0	0	0	0	0	0	0	0%
prostate bed + pelvic LN -> 6 months Lupron	Switch to ADT only	Escalation	1	0	0	0	0	0	1	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN + Lupron 24 months	Addition of ADT	Escalation	1	1	0	0	0	0	1	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB	Removal of ADT, Addition of RT fields	De-escalation	-1	1	0	1	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN + PB CTV Delineation + 12 months Lupron	Addition of ADT, Change of RT fields	Escalation	-1	1	0	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB + 6 months Lupron	Addition of RT fields	Escalation	-1	1	0	1	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB + Lupron 24 months	Addition of ADT, Addition of RT fields	Escalation	-1	1	0	1	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + 12 months Lupron	Addition of ADT, Reduction of RT fields	Escalation	-1	0	0	0	0	0	0	0	0	0	0%
prostate bed + pelvic LN + 6 months ADT -> prostate bed + ADT (Unknown NIS006)	Reduction of RT fields	De-escalation	1	0	0	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + SBRT pelvic LN + 6 months Lupron	Reduction of RT fields	De-escalation	1	0	0	0	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 6 months ADT -> prostate bed + PB In-Field SB + pelvic LN + PLN CTV Delineation + PLN In-Field SB + 24 months Lupron and Abiraterone prostate bed + pelvic LN + 2 year Lupron + Bicalutamide -> 2 year Lupron + Bicalutamide + 6 Cycles Taxotere	Addition of ADT, Addition of ARS, Addition of RT fields Switch to Chemotherapy	Escalation	1	0	0	1	0	0	0	0	0	0	100%
prostate bed + pelvic LN + 12 months Lupron -> prostate bed + pelvic LN + PLN CTV Delineation + PLN In-Field SB + 12 months Lupron	Addition of RT fields	Escalation	1	0	0	0	0	0	0	0	1	0	100%
	Addition of RT fields	Escalation	1	0	0	1	0	0	0	0	0	0	100%

Supplementary Table 6. Change in Treatment Plan - Control Group

Change	Management	Change Details	Change Details			n
			n	TNDMM	TNDMM	
Major Change (Prostate Bed)			7	1	5	7
prostate bed -> Active Surveillance	Switch to Active Surveillance	De-escalation	1	1	0	1
prostate bed -> No RT	No RT	De-escalation	1	0	0	1
prostate bed -> prostate bed + 6 months Lupron	Addition of ADT	Escalation	1	0	0	1
prostate bed -> prostate bed + 18 months Lupron	Addition of ADT	Escalation	1	0	0	1
prostate bed -> prostate bed + pelvic LN	Addition of RT fields	Escalation	2	0	0	2
prostate bed -> prostate bed + pelvic LN + 6 months Lupron	Addition of ADT, Addition of RT fields	Escalation	1	0	0	1
Major Change (Prostate Bed + ADT)			5	3	2	5
prostate bed + 6 months Lupron -> Active Surveillance	Switch to Active Surveillance	De-escalation	3	3	0	3
prostate bed + 6 months Lupron -> No RT	No RT	De-escalation	1	0	0	1
prostate bed + 6 months Lupron -> prostate bed + pelvic LN + 6 months Lupron	Addition of RT fields	Escalation	1	0	0	1
Major Change (Prostate Bed + Pelvic Lymph Nodes)			1	1	0	1
Prostate Bed + pelvic LN -> Prostate Bed Alone	Reduction of RT fields	De-escalation	1	0	0	1
Major Change (Prostate Bed + Pelvic Lymph Nodes + ADT)			4	1	3	4
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + pelvic LN	Removal of ADT	De-escalation	1	0	0	1
prostate bed + pelvic LN + 6 months Lupron -> prostate bed	Reduction of RT fields, Removal of ADT	De-escalation	1	0	0	1
prostate bed + pelvic LN + 6 months Lupron -> prostate bed + 6 months Bicalutamide	Reduction of RT fields	De-escalation	1	0	0	1
prostate bed + pelvic LN + 18 months Lupron -> prostate bed + PB Dose Decrease + pelvic LN + PLN Dose Decrease + 18 months Abiraterone and Lupron	Addition of ARS, Reduction of RT fields	Escalation	1	0	0	1

Supplementary Table 7. Management changes (Major Escalation, Major De-escalation, Minor Escalation, Minor De-escalation, Major Alternative, No Change) for each PSMA-PET miTNM pattern:

PSMA-PET miTNM	Major Escalation	Major De-escalation	Minor Escalation	Minor De-escalation	Major Alternative	No Change
T0N0M0 (n=64)	13 (20%)	6 (9.2%)	0 (0%)	1 (1.5%)	1 (1.5%)	44 (67.7%)
T+N0M0 (n=13)	2 (15.4%)	3 (23.1%)	5 (38.5%)	0 (0%)	0 (0%)	3 (23.1%)
T0N1M0 (n=11)	5 (45.5%)	2 (18.2%)	1 (9.1%)	0 (0%)	2 (18.2%)	1 (9.1%)
T+N1M0 (n=4)	3 (75%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
T0N0M1 (n=5)	3 (60%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	1 (20%)
T0N1M1 (n=3)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
T+N1M1 (n=1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Overall (n=102)	30 (29.4%)	12 (11.8%)	6 (5.9%)	1 (1%)	4 (3.9%)	49 (48%)

Supplementary Table 8. Management changes (Major, Minor, No Change) for each PSMA-PET miTNM pattern:

PSMA-PET miTNM	Major	Minor	No Change
T0N0M0 (n=64)	20 (30.8%)	1 (1.5%)	44 (67.7%)
T+N0M0 (n=13)	5 (38.5%)	5 (38.5%)	3 (23.1%)
T0N1M0 (n=11)	9 (81.8%)	1 (9.1%)	1 (9.1%)
T+N1M0 (n=4)	4 (100%)	0 (0%)	0 (0%)
T0N0M1 (n=5)	4 (80%)	0 (0%)	1 (20%)
T0N1M1 (n=3)	3 (100%)	0 (0%)	0 (0%)
T+N1M1 (n=1)	1 (100%)	0 (0%)	0 (0%)
Overall (n=102)	46 (45.1%)	7 (6.9%)	49 (48%)

Supplementary Table 9. Management changes (Escalation/De-Escalation, Alternative, No Change) for each PSMA-PET miTNM pattern:

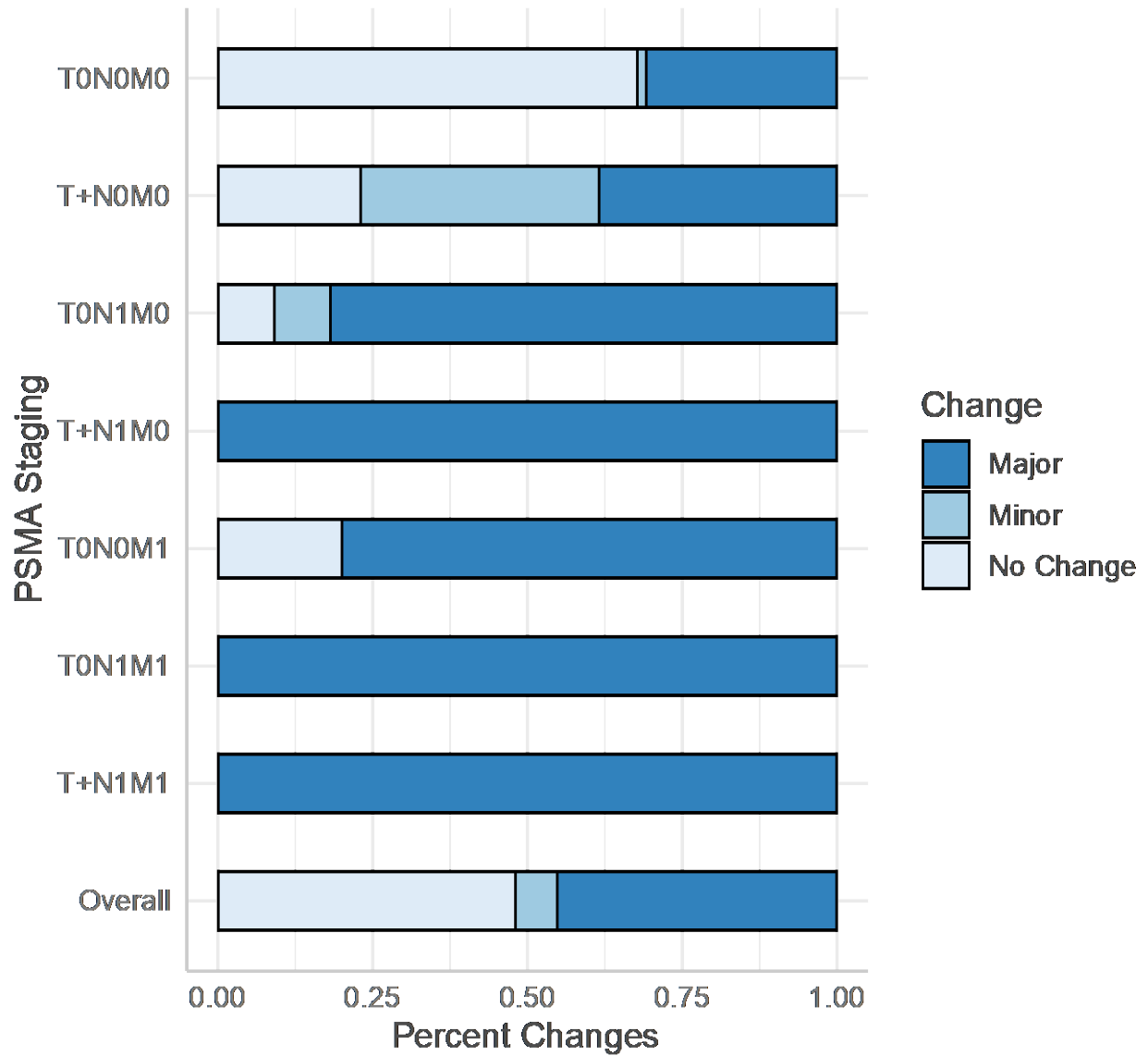
PSMA-PET miTNM	Escalation	De-Escalation	Alternative	No Change
T0N0M0 (n=64)	13 (20%)	7 (10.8%)	1 (1.5%)	44 (67.7%)
T+N0M0 (n=13)	7 (53.8%)	3 (23.1%)	0 (0%)	3 (23.1%)
T0N1M0 (n=11)	6 (54.5%)	2 (18.2%)	2 (18.2%)	1 (9.1%)
T+N1M0 (n=4)	3 (75%)	1 (25%)	0 (0%)	0 (0%)
T0N0M1 (n=5)	3 (60%)	0 (0%)	1 (20%)	1 (20%)
T0N1M1 (n=3)	3 (100%)	0 (0%)	0 (0%)	0 (0%)
T+N1M1 (n=1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Overall (n=102)	36 (35.3%)	13 (12.7%)	4 (3.9%)	49 (48%)

Supplementary Table 10. Management changes (ADT management) for each PSMA-PET miTNM pattern:

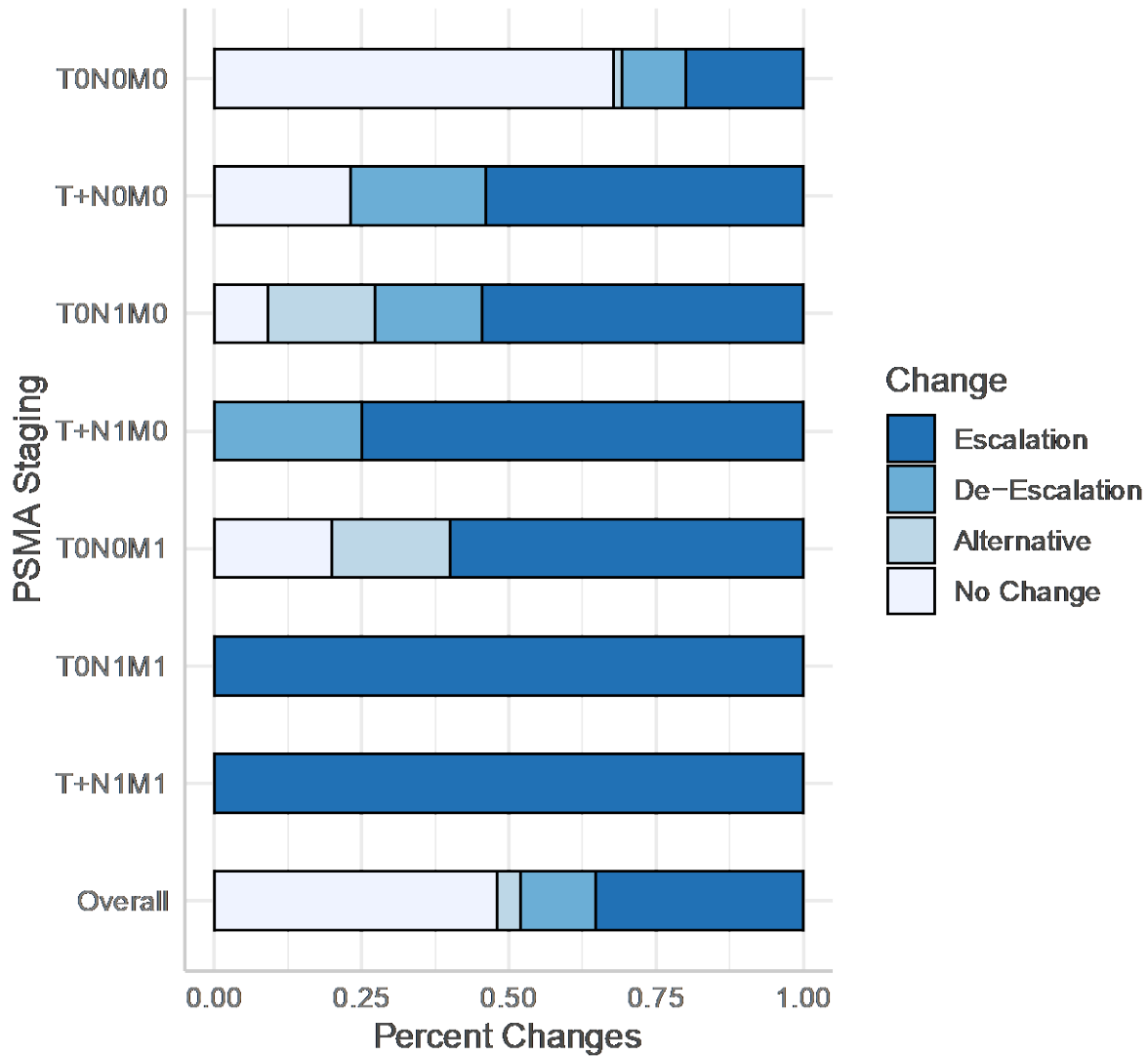
PSMA-PET miTNM	Addition ADT	Remove ADT	Maintain ADT	Maintain No ADT
T0N0M0 (n=64)	8 (12.5%)	4 (6.3%)	32 (50%)	20 (31.3%)
T+N0M0 (n=13)	0 (0%)	1 (7.7%)	8 (61.5%)	4 (30.8%)
T0N1M0 (n=11)	1 (9.1%)	1 (9.1%)	6 (54.5%)	3 (27.3%)
T+N1M0 (n=4)	1 (25%)	0 (0%)	3 (75%)	0 (0%)
T0N0M1 (n=5)	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (50%)
T0N1M1 (n=3)	2 (66.7%)	1 (33.3%)	0 (0%)	0 (0%)
T+N1M1 (n=1)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Overall (n=102)	13 (13%)	8 (8%)	51 (51%)	28 (28%)

SUPPLEMENTARY FIGURES

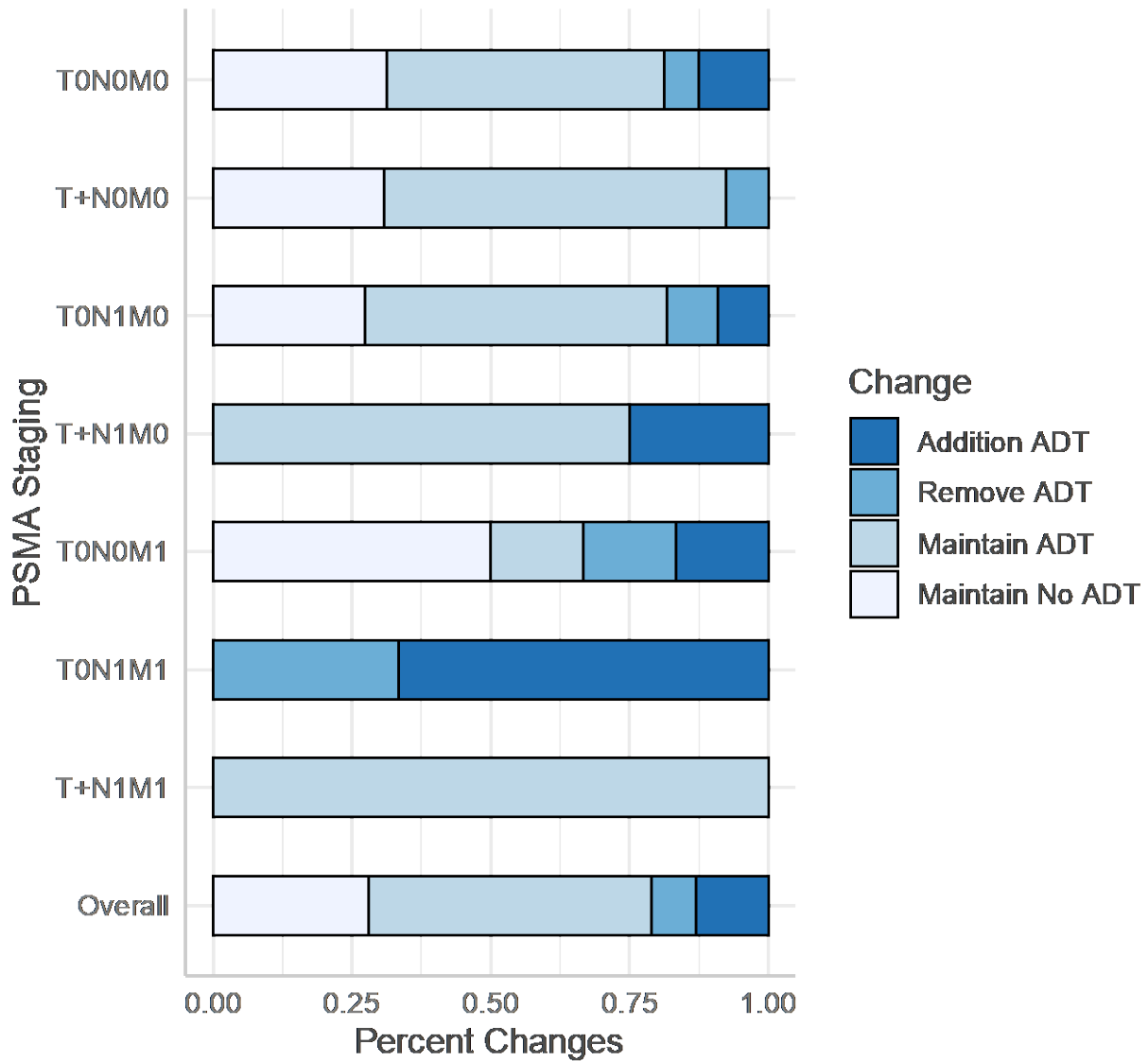
Supplementary Figure 1 Management changes (Major, Minor, No Change) for each PSMA-PET miTNM pattern (T0N0M0 (n=64), T+N0M0 (n=13), T0N1M0 (n=11), T+N1M0 (n=4), T0N0M1 (n=5), T0N1M1 (n=3), T+N1M1 (n=1), Overall (n=102)) (see numbers in Supplementary Table 8):



Supplementary Figure 2 Management changes (Escalation/De-Escalation, Alternative, No Change) for each PSMA-PET miTNM pattern (T0N0M0 (n=64), T+N0M0 (n=13), T0N1M0 (n=11), T+N1M0 (n=4), T0N0M1 (n=5), T0N1M1 (n=3), T+N1M1 (n=1), Overall (n=102)) (see numbers in Supplementary Table 9):



Supplementary Figure 3 Management changes (ADT management) for each PSMA-PET miTNM pattern (T0N0M0 (n=64), T+N0M0 (n=13), T0N1M0 (n=11), T+N1M0 (n=4), T0N0M1 (n=5), T0N1M1 (n=3), T+N1M1 (n=1), Overall (n=102)) (see numbers in Supplementary Table 10):



Pre-randomization RT Plan

Study ID _____

Radiation Treatment

Target volume: Prostate Bed Alone
 Prostate Bed and Pelvic Lymph Nodes

Prostate Bed: Total Dose _____

(gy)

Prostate Bed: Dose per fraction _____

(gy)

Pelvic Lymph Nodes: Total Dose _____

(gy)

Pelvic Lymph Nodes: Dose per fraction _____

(gy)

Concurrent ADT/anti-androgen

Concurrent use of ADT or anti-androgen Yes
 No

Which drug _____

Planned duration _____

(months)

Additional notes _____

Delivered RT Plan

Study ID _____

Radiation Treatment

Treatment performed:

- Prostate Bed Alone
- Prostate Bed and Pelvic Lymph Nodes
- Prostate Bed and metastasis-directed RT
- Prostate Bed and Pelvic Lymph Nodes and metastasis-directed RT
- Other
- No RT

Prostate Bed: Total Dose _____

(gy)

Prostate Bed: Dose per fraction _____

(gy)

Pelvic Lymph Nodes: Total Dose _____

(gy)

Pelvic Lymph Nodes: Dose per fraction _____

(gy)

Metastasis directed-RT: Total Dose _____

(gy)

Metastasis directed-RT: Dose per fraction _____

(gy)

RT start date _____

RT end date _____

Concurrent ADT/anti-androgen

Concurrent use of ADT or anti-androgen

- Yes
- No

Which drug _____

Planned duration

_____ (months)

PSMA Influence (Treatment group only)

PSMA PET/CT influence recorded? Yes
 No

PSMA PET/CT influence on CTV delineation or dose? Delineation
 Dose (Boost)

Prostate bed CTV delineation _____

Pelvic node CTV delineation _____

Metastasis CTV delineation _____

PSMA PET/CT influenced dose prescribed (to any CTV) _____

Additional notes _____

Second Topic: Randomized Trials of PSMA PET imaging trials powered for clinical outcome.

Article :

Title: *Randomized Trial of Prostate-Specific Membrane Antigen PET/CT Before Definitive Radiotherapy for Unfavorable Intermediate- and High-Risk Prostate Cancer (PSMA-dRT Trial).*

Authors: Nikitas J, Lam E, Booker KA, Fendler WP, Eiber M, Hadaschik B, Herrmann K, Hirmas N, Lanzafame H, Stuschke M, Czernin J, Steinberg ML, Nickols NG, Kishan AU, **Calais J.**

Reference: *J Nucl Med.* 2024 Jul 1;65(7):1076-1079. doi: 10.2967/jnumed.123.267004. PMID: 38664019.

Brief Outline:

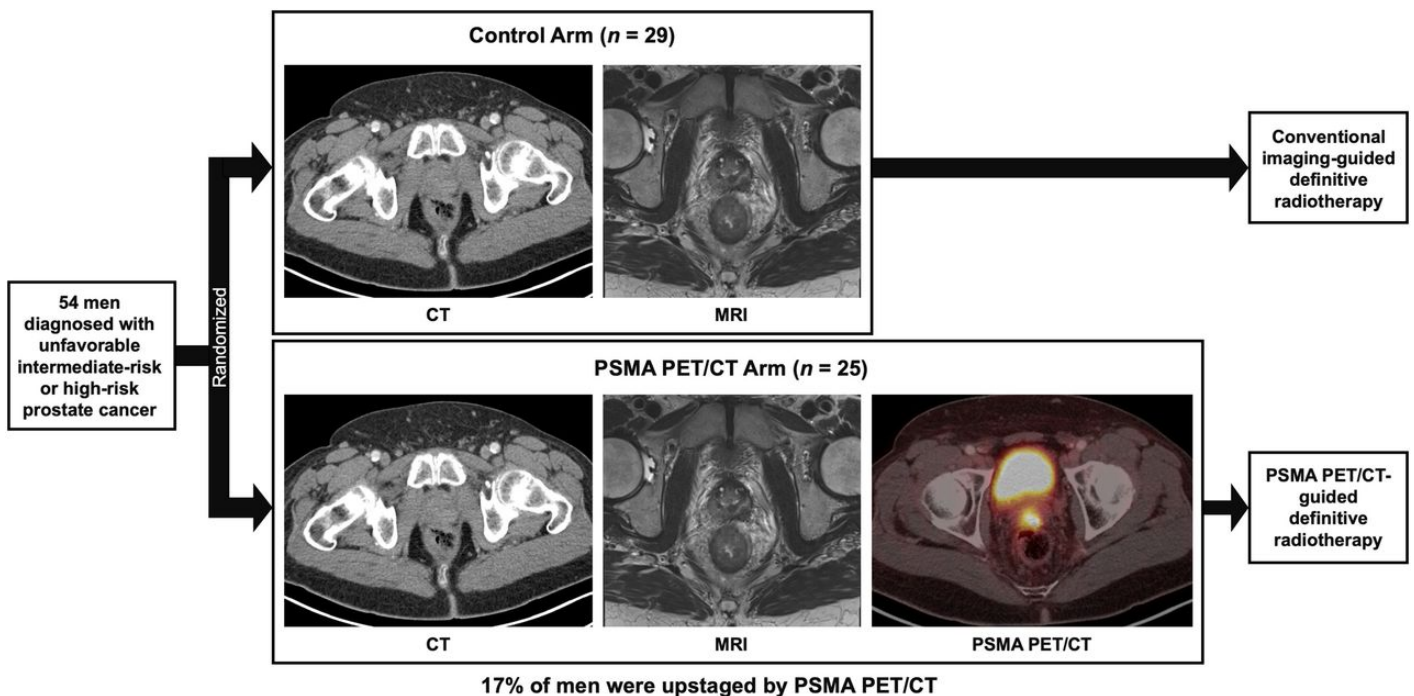
The PSMA-dRT trial was a multicenter phase III randomized controlled trial (ClinicalTrials.gov identifier NCT04457245). This was an investigator-initiated trial supported by Progenics Pharmaceuticals Inc. This study was designed to randomize 312 men with unfavorable intermediate- or high-risk prostate cancer 1.08:1 between receiving and not receiving a PSMA PET/CT scan.

After U.S. Food and Drug Administration approval of PSMA PET/CT radiotracers in 2021, patients gained access to PSMA PET/CT as a standard, medically reimbursed procedure. Consequently, the trial closed prematurely in February 2022 after the recruitment rate significantly decreased.

The junior first author was John Nikitas, who was a radiation oncology resident PG 4 UCLA. This work was presented at the ASCO GU and the SNMMI in 2024.

The work was published in the JNM in 2024 and highlighted in Urotoday:

<https://www.urotoday.com/conference-highlights/snmmi-2024/152694-snmmi-2024-update-from-the-psma-drt-trial-a-randomized-phase-iii-trial-of-psma-pet-ct-prior-to-definitive-radiation-therapy-for-unfavorable-intermediate-risk-or-high-risk-prostate-cancer.html>



Randomized Trial of Prostate-Specific Membrane Antigen PET/CT Before Definitive Radiotherapy for Unfavorable Intermediate- and High-Risk Prostate Cancer (PSMA-dRT Trial)

John Nikitas¹, Ethan Lam², Kiara Adame Booker², Wolfgang P. Fendler³, Matthias Eiber², Boris Hadaschik⁴, Ken Herrmann³, Nader Hirmas³, Helena Lanzafame³, Martin Stuschke⁵, Johannes Czernin², Michael L. Steinberg¹, Nicholas G. Nickols^{1,6}, Amar U. Kishan¹, and Jeremie Calais²

¹Department of Radiation Oncology, UCLA, Los Angeles, California; ²Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, UCLA, Los Angeles, California; ³Department of Nuclear Medicine, University of Duisburg–Essen and German Cancer Consortium–University Hospital Essen, Essen, Germany; ⁴Department of Urology, University of Duisburg–Essen and German Cancer Consortium–University Hospital Essen, Essen, Germany; ⁵Department of Radiotherapy, University Hospital Essen, University of Duisburg–Essen, Essen, Germany; and ⁶Radiation Oncology Service, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California

This multicenter randomized phase III trial (NCT04457245) evaluated the effect of performing prostate-specific membrane antigen (PSMA) PET/CT before definitive radiotherapy. **Methods:** Men with unfavorable intermediate- or high-risk prostate cancer were randomized 1.08:1 between receiving and not receiving a PSMA PET/CT scan before definitive radiotherapy. All other imaging modalities were allowed in the control arm. The primary endpoint was 5-y progression-free survival. **Results:** Fifty-four men were randomized between November 2020 and December 2021 (PSMA PET/CT, $n = 25$; control, $n = 29$). The trial closed early after approval and insurance coverage of PSMA PET/CT. In the PSMA PET/CT arm, 14 patients had localized disease (miT2b-cN0M0), 6 had locally advanced disease (miT3a-bN0M0), 3 had regional metastasis (miN1M0), and 1 had distant metastasis (miM1b). Four patients were upstaged. **Conclusion:** PSMA PET/CT upstaged 17% of patients, which allowed for more accurate radiotherapy planning. Unfortunately, this trial closed early before completion of target enrollment (54/316, 17%) and was underpowered to assess the effect of PSMA PET/CT on progression-free survival.

Key Words: PET; prostate cancer; prostate-specific membrane antigen; radiation therapy; randomized clinical trial

J Nucl Med 2024; 00:1–4

DOI: 10.2967/jnumed.123.267004

Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancer cells, making it an excellent target for PET radiotracers used to detect prostate cancer. PSMA PET/CT offers superior diagnostic accuracy for nodal and distant metastasis compared with both conventional imaging (CT, bone scanning, and MRI) (1,2) and non-PSMA radiotracer PET scans (3–5).

Nonrandomized studies that used PSMA PET/CT for staging before definitive radiotherapy (dRT) reported distant metastasis in 6%–9% of patients and findings that led to either radiation dose escalation or pelvic lymph node irradiation in 13%–20% of patients (6–9). However, the effect of PSMA PET/CT staging before dRT on clinical outcomes has not been well studied in a randomized controlled trial. Here, we discuss the results of the PSMA-dRT phase III randomized controlled trial.

MATERIALS AND METHODS

Study Population

The PSMA-dRT trial was a multicenter phase III randomized controlled trial (ClinicalTrials.gov identifier NCT04457245). This was an investigator-initiated trial supported by Progenics Pharmaceuticals Inc., conducted under investigational new drug application 147591. The UCLA institutional review board approved this study (approval 20-000378) and all subjects gave written informed consent. The study protocol (supplemental material, available at <http://jnm.snmjournals.org>) was previously published (10).

This study was designed to randomize 312 men with unfavorable intermediate- or high-risk prostate cancer 1.08:1 between receiving and not receiving a PSMA PET/CT scan. This randomization was chosen to account for an estimated detection rate of 8% for extrapelvic metastasis on PSMA PET/CT. Patients in the intervention arm who were found to have extrapelvic metastasis were no longer eligible for dRT and were not included in the primary endpoint analysis. In the intervention arm, reports and DICOM images of the PSMA PET/CT were transferred to the treating radiation oncologist before radiotherapy planning. In the control arm, patients were staged per physician discretion (CT, MRI, bone scanning, or PET/CT with a non-PSMA radiotracer).

Radiotherapy Delivery

Radiotherapy was delivered at the treating radiation oncologist's facility. The treating radiation oncologist decided on the radiation modality (external-beam radiotherapy, low-dose-rate brachytherapy, high-dose-rate brachytherapy, or external-beam radiotherapy with a brachytherapy boost), radiation dose, fractionation (conventionally fractionated, moderately hypofractionated, or stereotactic body radiotherapy),

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inclusion of elective pelvic lymph nodes, and inclusion of androgen deprivation therapy.

Patient Follow-up

Patients had follow-up visits with the treating radiation oncologist every 3–4 mo for the first year and every 6 mo thereafter. Patients underwent prostate-specific antigen testing around the time of each follow-up visit. Imaging follow-up was ordered per physician discretion if disease progression was suspected on the basis of a rising prostate-specific antigen level.

Study Endpoints

The primary endpoint was progression-free survival (PFS) at 5 y. Progression was defined as whichever of the following occurred first: prostate-specific antigen level more than 2 ng/mL above the post-radiotherapy nadir, recurrence on imaging or biopsy, initiation of salvage therapy, or death. Progression was calculated starting from the time of randomization.

Statistical Analysis

Differences in patient and treatment characteristics between the 2 cohorts were compared using the Pearson χ^2 test for categorical variables and 2-tailed *t* tests for continuous variables. PFS was calculated using Kaplan–Meier survival analysis. Comparisons were made using log rank testing. All statistical analyses were performed using SPSS Statistics, version 28 (IBM Corp.).

RESULTS

Between November 2020 and December 2021, 54 patients were randomized (PSMA PET/CT, *n* = 25; control, *n* = 29). Two patients withdrew after randomization and were excluded (Fig. 1). Table 1 describes patient and treatment characteristics. There were no significant differences between the 2 groups.

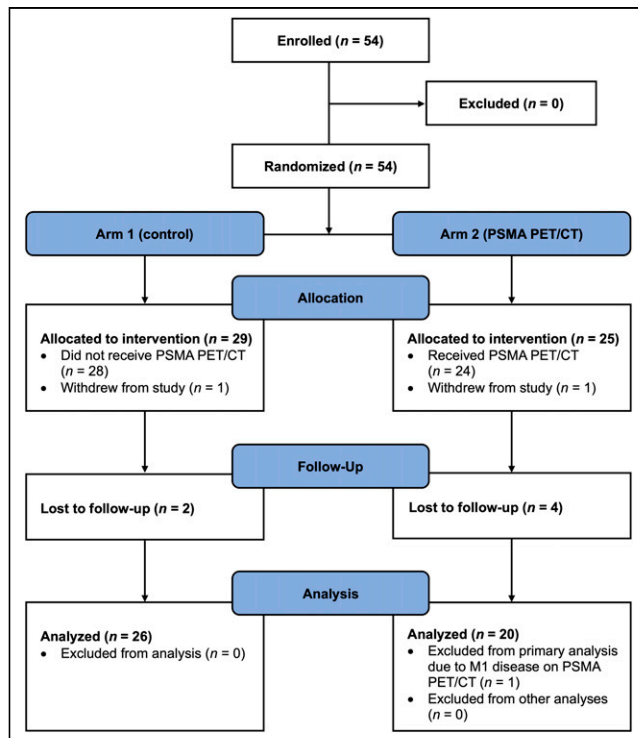


FIGURE 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Among patients staged using PSMA PET/CT in the intervention arm (*n* = 24), 14 had localized disease (miT2b-cN0M0), 6 had locally advanced disease (miT3a-bN0M0), 3 had regional metastasis (miN1M0), and 1 had regional and distant metastasis (miN1M1b). Four were upstaged relative to baseline: 1 with locally advanced disease, 2 with regional metastasis, and 1 with distant metastasis.

All 3 patients with miN1M0 disease received pelvic lymph node irradiation. The patient with miN1M1b disease received upfront androgen deprivation therapy with abiraterone acetate and prednisone followed by consolidative radiotherapy to the prostate and pelvic lymph nodes.

After U.S. Food and Drug Administration approval of PSMA PET/CT radiotracers in 2021, patients gained access to PSMA PET/CT as a standard, medically reimbursed procedure. Consequently, the trial closed prematurely in February 2022 after the recruitment rate significantly decreased.

At the time of this analysis (August 2023), median follow-up was 21 mo (interquartile range, 17.6–26.3 mo). There were no cases of biochemical recurrence, disease recurrence, or prostate cancer–specific death in either arm. There were 2 nonprostate cancer deaths in the PSMA PET/CT arm. Two-year PFS was 93.8% for the PSMA PET/CT arm and 100% for the control arm. There were no significant differences between the 2 groups (Fig. 2, *P* = 0.13).

DISCUSSION

In this study of men with unfavorable intermediate- or high-risk prostate cancer, PSMA PET/CT upstaged 1 in 6 patients relative to baseline staging. This information guided target volume delineation, radiation dose, and hormone therapy intensification. This suggests that the adoption of PSMA PET/CT for primary staging in this patient population impacts management choices.

Unfortunately, this study was terminated prematurely after Food and Drug Administration approval of PSMA PET/CT radiotracers. Before Food and Drug Administration approval, there was significant interest in this trial among patients and enrolling physicians because of the otherwise significant hurdles to obtaining PSMA PET/CT. After Food and Drug Administration approval, most medical insurance companies in the United States covered PSMA PET/CT scans for primary staging of men with high-risk or unfavorable intermediate-risk prostate cancer, significantly reducing enrollment and the feasibility of the control arm.

As a result, this trial was closed after randomizing only 54 men, thus significantly reducing the statistical power of this study to detect a PFS difference. A second limitation is the low frequency of biochemical recurrence and disease progression in the first 2 y after dRT. Even in cohorts that include men with high-risk prostate cancer, reported 2-y rates are less than 5% (11). Thus, the only observed PFS events were 2 nonprostate cancer deaths in the PSMA PET/CT arm.

When examining upstaging rates of PSMA PET/CT compared with other imaging modalities, we found consistency with previously reported, prospective trials. The proPSMA study reported that PSMA PET/CT led to more frequent management changes than did conventional imaging (28% vs. 15%, *P* = 0.008) (1). A prospective, multicenter study in Australia by Roach et al. found that PSMA PET/CT changed management in 21% of cases (9). These are both similar to the 16.7% reported in our study.

Across multiple prospective studies, PSMA PET/CT has been shown to have superior accuracy and sensitivity for staging patients compared with conventional imaging. This information

TABLE 1
Patient and Treatment Characteristics

Characteristic	Control arm	PSMA PET/CT arm
All patients*		
Median age (y)	73.6	70.7
Race		
White	17 (58.6%)	16 (64.0%)
African American	2 (6.9%)	2 (8.0%)
Other	10 (34.5%)	7 (28.0%)
NCCN risk group		
Unfavorable intermediate risk	14 (48.3%)	11 (44.0%)
High risk	15 (51.7%)	14 (56.0%)
Median initial PSA (ng/mL)	8.4 (IQR, 4.9–20.5)	10.7 (IQR, 6.4–12.9)
Gleason score		
≤7	18 (62.1%)	13 (52.0%)
8	5 (17.2%)	4 (16.0%)
9–10	6 (20.7%)	8 (32.0%)
T stage by conventional imaging		
T1–2	25 (86.2%)	20 (80.0%)
T3–4	4 (13.8%)	5 (20.0%)
N stage by conventional imaging		
N0/Nx	27 (93.1%)	23 (92.0%)
N1	2 (6.9%)	2 (8.0%)
Conventional imaging performed		
CT	1 (3.4%)	1 (4.0%)
MRI	8 (27.6%)	7 (28.0%)
CT and MRI	3 (10.3%)	2 (8.0%)
Bone scan and CT	1 (3.4%)	1 (4.0%)
Bone scan and MRI	0 (0%)	3 (12.0%)
Bone scan, CT, and MRI	11 (37.9%)	10 (40.0%)
¹⁸ F-fluciclovine PET and MRI	4 (13.8%)	0 (0%)
¹⁸ F-fluciclovine PET, MRI, bone scan, and CT	1 (3.4%)	0 (0%)
¹⁸ F-fluciclovine PET, bone scan, and CT	0 (0%)	1 (4.0%)
Patients included in primary endpoint analysis[†]		
Concurrent ADT	21 (75.0%)	18 (75%)
Pelvic lymph node irradiation	7 (25.0%)	8 (33.3%)
PSMA PET/CT miTNM stage		
miT2bN0M0	—	10 (41.7%)
miT2cN0M0	—	4 (16.7%)
miT3aN0M0	—	4 (16.7%)
miT3bN0M0	—	2 (8.3%)
miT3aN1M0	—	3 (12.5%)
miT3bN1M1b	—	1 (4.2%)

*All patients in the study ($n = 29$ patients in the control arm and 25 patients in the PSMA PET/CT arm).

[†]Patients included in primary endpoint analysis ($n = 28$ patients in the control arm and 24 patients in the PSMA PET/CT arm).

NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; IQR = interquartile range; ADT = androgen deprivation therapy.

Data are number and percentage unless otherwise indicated.

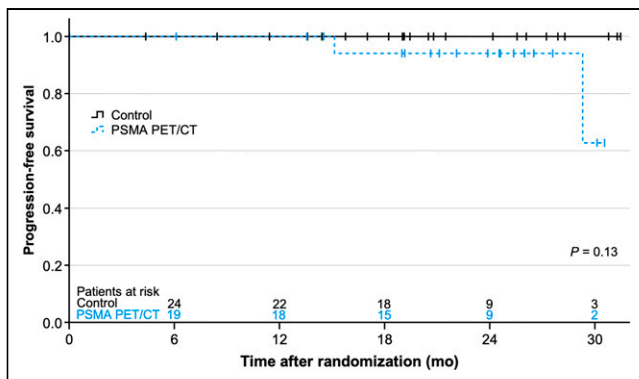


FIGURE 2. PFS: control and PSMA PET/CT cohorts were compared using log rank testing. Ticks represent censored cases. Patients with extrapelvic metastasis on PSMA PET/CT who were not eligible for dRT were excluded (1 patient).

can guide radiation volume delineation, radiation dose escalation, and hormone therapy intensification. The rapid adoption and availability of PSMA PET/CT staging has already changed prostate cancer treatment across the world. As a result of its success, the window to conduct prospective randomized controlled trials and show long-term clinical outcome benefits is closing. This raises questions about the expectations of the medical community to first demonstrate improved oncologic outcomes before widespread adoption. Including PSMA PET/CT staging in the design of future clinical trials is now warranted, and strong consideration must be given to how and whether PSMA PET/CT-based endpoints should be included as primary or secondary endpoints in clinical trials.

CONCLUSION

PSMA PET/CT upstaged 17% of patients, which allowed for more accurate radiotherapy planning. Unfortunately, this trial was underpowered to assess the effect of PSMA PET/CT on progression-free survival.

DISCLOSURE

This is an investigator-initiated trial with institutional funding (UCLA Ahmanson Translational Theranostics Division). This study is supported by Progenics Pharmaceuticals Inc., which supplies the study drug (^{18}F -DCFPyL) and financial support for the PET/CT technical costs associated with the study under the PyL Research Access Program (Progenics Pharmaceuticals, Inc.). John Nikitas received funding from the Christiaan W. Schiepers Theranostics Fellowship award. Jeremie Calais reported consulting fees from AAA, Astellas, Blue Earth Diagnostics, Curium Pharma, DS Pharma, EXINI, GE Healthcare, Isoray, IBA RadioPharma, Janssen, Lightpoint Medical, Lantheus, Monrol, Novartis, Progenics, POINT Biopharma, Radiomedix, Sanofi, and Telix Pharmaceuticals. Amar Kishan reported personal fees from ViewRay, Varian Medical Systems, and Janssen Pharmaceuticals and research funding from ViewRay. Boris Hadaschik reported serving on advisory boards for Janssen, Bayer, ABX, Lightpoint, Amgen, MSD, Pfizer,

and Novartis; serving as an invited speaker for Accord, Astellas, and Janssen R&D; receiving honoraria from Uromed; receiving research support from AAA/Novartis, Bristol Myers Squibb, and the German Research Foundation; and having a leadership role with DKG, AUO, and DGU. Nicholas Nickols reported research grants from Janssen, Lantheus, and Bayer and personal fees from OncoLinea. Michael Steinberg reported receiving consulting fees from ViewRay. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the effect of performing PSMA PET/CT before dRT for prostate cancer?

PERTINENT FINDINGS: One in 6 patients was upstaged by PSMA PET/CT. This study closed early before completion of target enrollment (54/316, 17%) and was underpowered to assess the effect on PFS.

IMPLICATIONS FOR PATIENT CARE: Information from PSMA PET/CT can guide radiation volume delineation, radiation dose escalation, and hormone therapy intensification.

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Third Topic: Beyond the approved use of PSMA theranostics.

Papers Provided:

- 1- Impact of 68Ga-PSMA-11 PET/CT on Staging and Management of Prostate Cancer Patients in Various Clinical Settings: A Prospective Single Center Study.**
Sonni I, Eiber M, Fendler WP, Alano RM, Vangala SS, Kishan AU, Nickols N, Rettig MB, Reiter R, Czernin J, **Calais J.**
J Nucl Med. 2020 Aug;61(8):1153-1160. PMID: 31924715

- 2- Prognostic Value of End-of-Treatment PSMA PET/CT in Patients Treated with 177Lu-PSMA Radioligand Therapy: A Retrospective, Single-Center Analysis.**
Murthy V, Gafita A, Thin P, Nguyen K, Grogan T, Shen J, Drakaki A, Rettig M, Czernin J, **Calais J.**
J Nucl Med. 2023 Sep 7:jnumed.122.265155. PMID: 37678927

- 3- The impact of monosodium glutamate on 68Ga-PSMA-11 biodistribution in men with prostate cancer: a prospective randomized, controlled, imaging study.**
Armstrong WR, Gafita A, Zhu S, Thin P, Nguyen K, Alano RM, Lira S, Booker K, Gardner L, Grogan T, Elashoff D, Allen-Auerbach MS, Dahlbom MS, Czernin J, **Calais J.**
J Nucl Med. 2021 Sep 1;62(9):1244-1251. doi: 10.2967/jnumed.120.257931. PMID: 33509974

Third Topic: Beyond the approved use of PSMA theranostics.

Article 6:

Title: *Impact of 68Ga-PSMA-11 PET/CT on Staging and Management of Prostate Cancer Patients in Various Clinical Settings: A Prospective Single Center Study.*

Authors: Sonni I, Eiber M, Fendler WP, Alano RM, Vangala SS, Kishan AU, Nickols N, Rettig MB, Reiter R, Czernin J, **Calais J.**

Reference: *J Nucl Med.* 2020 Aug;61(8):1153-1160. PMID: 31924715

Brief Outline:

The goal of this study was to determine the impact of 68Ga-PSMA-11 PET/CT on initial and subsequent management decisions in a cohort of PCa patients referred for various indications (i.e., a basket trial) excluding the 2 main classic indications: biochemical recurrence and presurgical staging.

The junior first author was Ida Sonni, who was a research project scientist at UCLA. This work was presented at ASCO GU in 2020 in 2022. The paper was highly cited (117 citations by Google Scholar, 86 citations by Web of Science as of Sept 1st 2024).

Impact of ⁶⁸Ga-PSMA-11 PET/CT on Staging and Management of Prostate Cancer Patients in Various Clinical Settings: A Prospective Single-Center Study

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The impact of prostate-specific membrane antigen (PSMA) PET/CT on management of prostate cancer (PCa) patients with biochemical recurrence (BCR) is well established. However, whether and how PSMA PET/CT affects the management of patients undergoing scans for other clinical indications remains unknown. The goal of this study was to determine the impact of ⁶⁸Ga-PSMA-11 PET/CT on initial and subsequent management decisions in a cohort of PCa patients referred for various indications (i.e., a basket trial) excluding the 2 main classic indications: BCR and presurgical staging. **Methods:** This was a prospective study of 197 patients that aimed to determine the impact of ⁶⁸Ga-PSMA-11 PET/CT on PCa stage and management. The indications for PSMA PET/CT were initial staging of nonsurgical candidates (30 patients) and restaging after definitive treatment (167 patients). The restaging cohort comprised patients restaged with known advanced metastatic disease ($n = 103$), after androgen deprivation therapy only ($n = 16$), after surgery and with serum prostate-specific antigen levels lower than 0.2 ng/mL ($n = 13$), after radiation therapy and not meeting the Phoenix criteria ($n = 22$), and after other primary local treatments (i.e., high-intensity focused ultrasound, focal laser ablation, cryoablation, hyperthermia, or irreversible electroporation) ($n = 13$). Patients with BCR and candidates for curative surgery were excluded. Impact on management was assessed using pre- and post-PET questionnaires completed by referring physicians, electronic chart review, or patient telephone calls. **Results:** PSMA PET/CT changed the disease stage in 135 of 197 (69%) patients (upstaging in 38%, downstaging in 30%, and no change in stage in 32%). Management was affected in 104 of 182 (57%) patients. Specifically, PSMA PET/CT impacted the management of patients who were restaged after radiation therapy without meeting the Phoenix criteria for BCR, after other definitive local treatments, and with advanced metastatic disease in 13 of 18 (72%), 8 of 12 (67%), and 59 of 96 (61%), respectively. **Conclusion:** PSMA PET/CT has a profound impact on stage and management of PCa patients outside the 2 main classic indications (BCR and presurgical staging) across all examined clinical scenarios.

Key Words: PSMA PET; prostate cancer; impact on management; staging; restaging

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DOI: 10.2967/jnumed.119.237602

Prostate-specific membrane antigen (PSMA) PET/CT stages and restages prostate cancer (PCa) with high accuracy (1–3), even at low serum prostate-specific antigen (PSA) levels (3,4). The impact of PSMA PET on the clinical management of PCa patients has been investigated in intermediate- and high-risk disease at initial staging (5–8) and after biochemical recurrence (BCR) (9–15) but not in patients who undergo imaging for other indications. Specifically, the impact on management of patients whose PSA has not risen to or beyond the threshold to define BCR (16,17), those with known metastatic or advanced castration-resistant disease, and those with primary treatments other than surgery or radiation therapy (RT) (i.e., high-intensity focused ultrasound, focal laser ablation, cryoablation, hyperthermia, or irreversible electroporation) is unknown. PSMA PET/CT can also be used to select patients for PSMA-targeted radioligand therapies, as well as for subsequent therapy response evaluations (18).

Here, we report the results of an institutional trial that prospectively evaluated the impact of PSMA PET/CT on the clinical management of PCa patients referred for various indications but ineligible for inclusion in simultaneously accruing trials for patients with BCR (NCT02940262) or patients with intermediate- or high-risk disease before surgery (NCT03368547). On the basis of other studies (10,14), we hypothesized that the proportion of patients whose management is changed as a result of PSMA PET would exceed 40%.

MATERIALS AND METHODS

Study Design and Data Collection

This prospective single-center, open-label, single-arm phase 2 imaging study was approved by the local institutional review board, was registered at clinicaltrials.gov (NCT04050215), and relied on an investigational-new-drug application (130649) for ⁶⁸Ga-PSMA-11.

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The primary objective of the study was to determine the rate of implemented management changes after PSMA PET/CT in a cohort of PCa patients referred for various indications (i.e., a basket trial).

The study design is shown in Figure 1. All referring physicians were asked to complete 3 questionnaires (Supplemental Fig. 1; supplemental materials are available at <http://jnm.snmjournals.org>). A pre-PET questionnaire and a post-PET questionnaire inquired about the disease stage and intended treatment strategy before and after PSMA PET/CT, respectively. The post-PET questionnaire asked the referring physicians whether any imaging test or diagnostic procedure was avoided or requested after PSMA PET/CT. A follow-up questionnaire determined whether and how the intended management change was altered by PSMA PET/CT and inquired about any other imaging or diagnostic procedures performed within the same time frame. A complete pre-PET questionnaire was required to enroll the patient in the final analysis. The post-PET questionnaire was required within 4 wk, and the follow-up questionnaire was required between 3 and 6 mo after PSMA PET/CT. If the referring physician did not return the post-PET and follow-up questionnaires, the information was derived from a combination of patient chart review and follow-up patient telephone calls.

Changes from intended (pre-PET) to implemented (post-PET) management were categorized on the basis of the kind of change or the lack of change in management and stratified by subgroups, as well as changes in staging before and after PSMA PET/CT. Intramodality changes in management were not specifically analyzed. The addition of other imaging or diagnostic procedures within 3–6 mo after PSMA PET/CT was also investigated.

We conducted a post hoc subgroup analysis after stratifying the full cohort by clinical indication, type of initial treatment, and serum PSA level. Changes in stage and detection rate stratified by clinical indication and serum PSA level were assessed. Management change rates across the clinical indication subgroups were compared.

Patients

Patients with histologically proven or strongly suspected PCa (serum PSA level > 50 ng/mL) who required an initial management decision, and patients already treated for PCa (16) and requiring a subsequent treatment decision, were eligible for the study. The latter group included PCa patients with new-onset symptoms or with known metastatic disease, rising PSA level, and negative or inconclusive conventional imaging results; BCR patients who were candidates for salvage therapy; and patients treated medically or with radioligand therapy in whom response to treatment needed to be assessed. Patients eligible for the prospective trials NCT02940262 (post-radical prostatectomy BCR with PSA > 0.2 ng/mL or post-RT BCR with PSA > 2 ng/mL + nadir) and NCT03368547 (initial staging of intermediate- or high-risk disease before intended surgery) were not enrolled in the study. Informed written consent was obtained from all subjects.

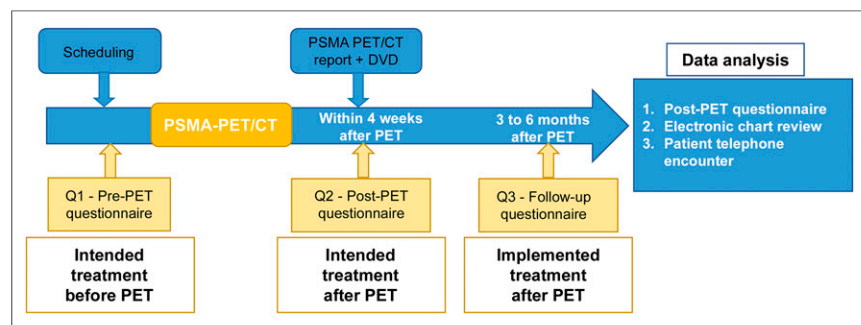


FIGURE 1. Study design flowchart.

The study population included in the final analysis ($n = 197$) was divided into 6 cohorts for a post hoc subgroup analysis. The first cohort was for initial staging in treatment-naïve patients (castration-sensitive PCa) who were not surgical candidates ($n = 30$). The second cohort was for restaging after androgen deprivation as primary therapy ($n = 16$). The third cohort was for restaging after surgery (PSA < 0.2 ng/mL) in castration-sensitive PCa ($n = 13$). The fourth cohort was for restaging after RT (PSA \leq 2 ng/mL + nadir) in castration-sensitive PCa ($n = 22$). The fifth cohort was for restaging after nonconventional primary definitive therapy (i.e., high-intensity focused ultrasound, focal laser ablation, cryoablation, hyperthermia, or irreversible electroporation) in castration-sensitive PCa ($n = 13$). The sixth cohort was patients with advanced disease (castration-resistant PCa [CRPC]) ($n = 103$), including patients with known metastatic disease and patients who underwent multiple salvage or second-line therapies.

PSMA PET/CT Image Acquisition and Analysis

^{68}Ga -PSMA-11 PET/CT imaging was performed according to current guidelines, as previously described (18–20). Briefly, ^{68}Ga -PSMA-11 (Glu-NH-CONH-Lys-(Ahx)-[^{68}Ga (HBED-CC)]) was injected 65.5 ± 9.8 min (range, 44–100 min) before image acquisition at a mean activity of $197.95 \text{ MBq} \pm 14.8$ (range, 236.8–74 MBq). We acquired images using a 64-detector PET/CT scanner (2007 Biograph 64 TruePoint or 2010 Biograph mCT 64; Siemens). A diagnostic CT scan (200–240 mAs, 120 kV) was performed after administration of oral contrast medium (600 mL of barium sulfate, 2.1% [Readi-Cat 2; Bracco] and intravenous contrast (115 mL of iohexol [Omnipaque; GE Healthcare], 350 mg iodine/mL, injection speed of 2 mL/s, portal venous phase + 80 s after injection) unless contraindicated. The PET image acquisition included a whole-body scan (pelvis to vertex, 2–4 min/bed position depending on the patient weight (21)) and, if deemed necessary by the responsible nuclear medicine physician, a dedicated pelvic scan after voiding (same acquisition time per bed position as used for the whole body). All PET images were reconstructed using correction for attenuation, dead time, random events, and scatter. PET images were reconstructed with an iterative algorithm (ordered-subset expectation maximization) in an axial 168×168 matrix on the Biograph 64 TruePoint (2-dimensional, 2 iterations, 8 subsets, 5.0-mm gaussian filter) and in a 200×200 matrix on the Biograph mCT 64 (3-dimensional, 2 iterations, 24 subsets, 5.0-mm gaussian filter).

Images were interpreted during clinical rounds by a consensus reading by a board-certified nuclear medicine physician and a board-certified radiologist as routinely done in our clinic.

PSMA PET/CT findings were reported as follows: any focal uptake of ^{68}Ga -PSMA-11 above background level, not associated with physiologic uptake or known pitfalls (19,22), was considered PSMA-positive. Additionally, a PSMA PET-based TNM staging system (Prostate Cancer Molecular Imaging Standardized Evaluation) was used, as done routinely in our clinic (20).

Statistical Analysis

Sample Size Calculation. This study was designed to provide more than 90% power to determine whether the proportion of patients whose management is changed as a result of PSMA PET/CT exceeds 40%, assuming an exact binomial test and a 1-sided α of 0.025. Further, a sample size of 200 patients is expected to produce a margin of error of 6.9% for the proportion of patients with implemented management change, assuming a 2-sided 95% confidence level.

TABLE 1
Patient Characteristics

Characteristic	Initial staging: treatment-naïve	Restaging				Advanced disease	Full cohort
		After ADT	After surgery, PSA < 0.2	After RT, PSA < nadir + 2	Other primary treatment		
Number of patients	30 (15%)	16(8%)	13(7%)	22(11%)	13(6%)	103(62%)	197
Mean age (y)	69.70 ± 7.02 (51–85)	64.38 ± 9.53 (49–82)	68.85 ± 8.73 (47–76)	69.82 ± 8.06 (56–86)	63.85 ± 8.86 (49–77)	69.72 ± 8.61 (46–95)	68.52 ± 8.64 (46–95)
Mean PSA at time of PET (ng/mL)	19.43 ± 27.58 (2.4–135.50)	62.48 ± 100.36 (0.17–322)	0.13 ± 0.05 (0.04–0.2)	1.79 ± 1.31 (0.3–5.6)	11.53 ± 19.65 (1.10–74.30)	40.66 ± 186.04 (0.02–1,789)	30.03 ± 139.95 (0.02 –1,789)
PSA (ng/mL) at time of PSMA PET*	12 to ≤5: 6	0 to ≤0.2: 1	0 to ≤0.2: 13	0 to ≤0.2: 0	0 to ≤0.2: 0	0 to ≤0.2: 10	0 to ≤0.2: 24
	5 to ≤10: 11	0.2 to ≤0.5: 2	0.2 to ≤0.5: 0	0.2 to ≤0.5: 3	0.2 to ≤0.5: 0	0.2 to ≤0.5: 16	0.2 to ≤0.5: 21
	10 to ≤20: 5	0.5 to ≤2: 2	0.5 to ≤2: 0	0.5 to ≤2: 10	0.5 to ≤2: 1	0.5 to ≤2: 25	0.5 to ≤2: 38
	>20: 8	>2: 11	>2: 0	>2: 9	>2: 12	>2: 52	>2: 114
Currently under ADT	0	16 (100%)	4 (13%)	5 (20%)	0	37 (43%)	59 (30%)
Gleason score	≤: 19	≤7: 4	≤7: 8	≤7: 12	≤7: 7	≤7: 41	≤7: 91
	≥8: 11	≥8: 10	≥8: 4	≥8: 6	≥8: 3	≥8: 45	≥8: 79
	Unknown: 0	Unknown: 2	Unknown: 1	Unknown: 4	Unknown: 3	Unknown: 17	Unknown: 27

*Serum PSA ranges used for treatment-naïve group are different from other groups.
ADT = androgen deprivation therapy; known M1 = known metastatic disease.
Qualitative data are expressed as number followed by percentage in parentheses; continuous data are expressed as mean ± SD followed by range in parentheses.

TABLE 2
Study Result Summary

Result	Initial staging: treatment-naïve	Restaging					Full cohort
		After ADT	After surgery, PSA < 0.2	After RT, PSA < nadir + 2	Other primary treatment	Advanced disease	
Detection rate	30/30 (100%)	16/16 (100%)	1/13 (8%)	19/22 (86%)	13/13 (100%)	86/103 (84%)	166/197 (84%)
Number of miT1 (% by subgroup)	29 (97%)	15 (94%)	0 (0%)	13 (59%)	10 (77%)	27 (26%)	95 (48%)
Number of miN1 (% by subgroup)	11 (38%)	8 (47%)	0 (0%)	4 (18%)	3 (23%)	48 (47%)	71 36%
Number of miM1 (% by subgroup)	M1a: 5 (17%)	M1a: 3 (18%)	M1a: 0 (0%)	M1a: 4 (18%)	M1a: 1 (8%)	M1a: 40 (39%)	M1a: 51 (26%)
	M1b: 4 (14%)	M1b:6 (35%)	M1b: 1 (8%)	M1b: 4 (18%)	M1b: 3 (23%)	M1b: 57 (55%)	M1b: 75 (38%)
	M1c: 0	M1c: 1 (6%)	M1c: 0 (0%)	M1c: 0	M1c: 1 (8%)	M1c: 11 (11%)	M1c: 13 (7%)
Change in stage	Change: 67%	Change: 81%	Change: 38%	Change: 86%	Change: 69%	Change: 67%	Change: 69%
	No change: 33%	No change: 19%	No change: 62%	No change: 14%	No change: 31%	No change: 33%	No change: 31%
Change in management* (%)	12/28 (43%)	6/15 (40%)	6/13 (46%)	13/18 (72%)	8/12 (67%)	59/96 (61%)	104/182 (57%)

*Change-in-management analysis was conducted on 182 patients.

Molecular imaging TNM classification: T = PSMA uptake in prostate gland or prostate bed or prostatic fossa; N = PSMA uptake in pelvic lymph nodes; M = PSMA uptake in distant lymph nodes (M1a), bone (M1b), or other visceral organs (M1c).

Post Hoc Subgroup Analysis. The planned sample of 200 patients provides 80% power to detect effect sizes between pairs of study arms ranging from 0.59 to 1.12 SD, assuming a 2-sample *t* test and a 0.05 2-sided significance level.

Descriptive statistics were used to characterize the population and the rates of changes in stage and management for the full cohort and among the subgroups. Quantitative variables were described using means, SDs, and ranges. Categorical variables were summarized using frequencies and percentages. Comparisons between subgroups were performed using 1-way ANOVAs for the quantitative variables and Fisher exact tests for the categorical variables. *P* values of less than 0.05 were considered statistically significant. Analyses were performed using R, version 3.5.0 (<http://www.r-project.org/>).

RESULTS

Patient Population and Questionnaires

In total, 234 patients were enrolled between April 2018 and January 2019. Of these, 197 (84%) were included in the final analysis. Thirty-seven patients were excluded because of an incomplete pre-PET questionnaire (*n* = 14) or because they were lost to follow-up (*n* = 23).

Patient and subgroup characteristics and are summarized in Table 1. The post-PET questionnaire was available for only 53 of the 197 patients (27%), and the follow-up questionnaire was available for 65 (33%). Because of the low rate of returned post-PET questionnaires and difficulty in recovering the interim information derived from it, data on intended management from the post-PET questionnaire were excluded from the final analysis. Follow-up information was collected from electronic chart review or direct patient contact for 132 of the 197 patients (77%).

Detection Rate and Location of Disease

PSMA PET/CT detection rates varied significantly among subgroups (*P* < 0.001). The detection rate was 166 of 197 (84%) for the whole cohort. It was lowest in patients restaged after radical prostatectomy with a PSA level of 0.2 ng/dL or less 1/13 (8%), and it ranged from 84% to 100% in the other subgroups (Table 2; Supplemental Fig. 2). Disease location stratified by subgroups is shown in Supplemental Figure 3.

Changes in Stage

The pre-PET stage as determined by the referring physicians changed after PSMA PET/CT in 135 of the 197 patients (69%) (Table 2; Figs. 2 and 3). PSMA PET/CT upstaged 75 of the 197 patients (38%), downstaged 59 (30%), and had no effect on stage in 63 (32%).

Rates of stage changes did not differ significantly among subgroups (*P* = 0.081). The post-RT restaging cohort had the highest rates of stage change (19/22 [86%]) and upstaging (13/22 [69%]). However, PSMA PET/CT also changed the stage frequently in the other subgroups (ranging from 67% to 81%). As expected, the lowest impact on stage occurred in the postsurgery subgroup with serum PSA levels of 0.2 ng/mL or less (5/13 patients, 38%, all downstaged) (Fig. 3).

Changes in Management

Change-in-management data were available in 182 of the 197 patients (92% of the full cohort) (Table 2). Management was changed by the PSMA PET/CT findings in 104 of 182 patients (57%) but was not affected in 78 (43%) (Fig. 4; Supplemental Table 1).

Rates of management changes did not differ significantly among subgroups (*P* = 0.183). The subgroups for restaging after RT (13/18 [72%]) and restaging after other definitive treatment

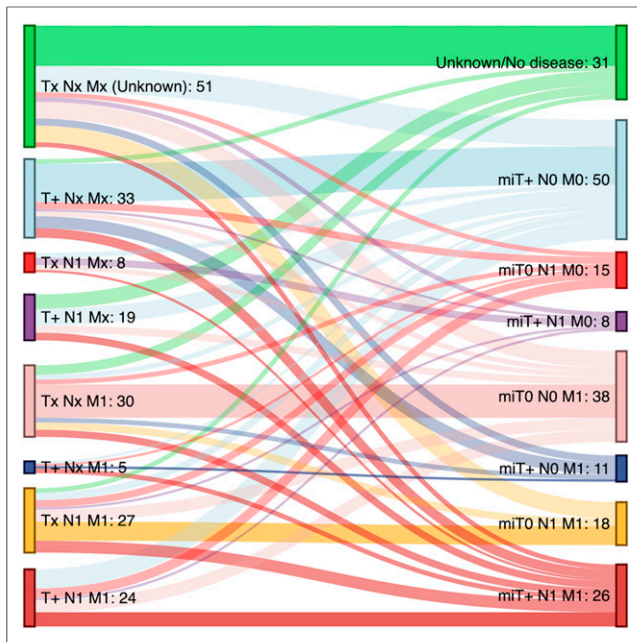


FIGURE 2. Impact of PSMA PET/CT imaging on staging of PCa. Sankey diagram showing per-patient differences in staging of disease before (left) and after (right) PSMA PET/CT. Staging of disease before PSMA PET/CT was indicated by referring physician on pre-PET questionnaire, staging after PSMA was based on PSMA PET/CT results (T+ = presence of disease in prostate/prostate bed on PSMA PET/CT; 1 = presence of disease in location on PSMA PET/CT). Sixty-two (31%) patients had no change in staging, and 135 (69%) patients had change in staging. On Sankey diagram, each color of vertical bars indicates same TNM or molecular imaging TNM staging, color of flow reflects color of destination, and darker color in each flow indicates no changes in stage.

(8/12 [67%]) experienced the most frequent management changes. The subgroups for restaging after androgen deprivation therapy, restaging after surgery, and restaging with advanced disease had management changes in 6 of 15 (40%), 6 of 13 (46%), and 59 of 96 (61%) patients, respectively. Management changes occurred in 12 of 28 (43%) treatment-naïve patients (Supplemental Table 1).

The most common changes in management in the full cohort were conversion from systemic to focal treatment (29/182 patients [16%]) and changes in focal treatments (19/182 patients [10%]). A detailed analysis of management changes stratified by stage change is shown in Supplemental Figure 4. An example of the impact on management is shown in Supplemental Figure 5.

Imaging and Other Diagnostic Procedures

No additional imaging or diagnostic procedure was performed within 3–6 mo after PSMA PET/CT in 128 of the 197 patients (64%), whereas MRI was performed in 36 (18%), PET with PSMA or different radiotracer in 16 (8%), CT in 12 (6%), biopsy in 13 (6%), and bone scanning in 9 (4%).

DISCUSSION

The impact of PSMA PET/CT on therapeutic decisions has been reported comprehensively for PCa patients with BCR (9–15) and those who underwent presurgical staging (5–8). Here, we prospectively studied the impact of ⁶⁸Ga-PSMA-11 PET/CT on the stage

and management of PCa patients with other clinical indications. We stratified the analysis on the basis of clinical indications to evaluate how PSMA PET/CT impacts the management of PCa patients in different clinical scenarios. The primary endpoint of the study was met, with a 57% (>40%) rate of management change in the entire cohort (14). This finding confirms the impact of PSMA PET/CT on clinical decisions beyond the 2 main classic indications: BCR and presurgical staging.

Patients restaged after RT who did not meet the Phoenix criteria for BCR (PSA ≤ 2 ng/mL + nadir) (16) seem to be those who benefit most from PSMA PET/CT. PSMA PET/CT detected PCa recurrence in 86% of these patients who were not supposed to have BCR per definition. In this cohort, we found the highest rates of change in stage and management (86% and 72%, respectively). Our findings suggest that recurrence after RT may need to be redefined and that this cohort may benefit from PSMA PET imaging.

In patients restaged after other nonconventional definitive treatments, the PSMA PET/CT detection rate was 100% and impacted management in 67% of patients. Excepting one who underwent active surveillance, all received focal lesion treatment identified by PSMA PET/CT.

In patients restaged with advanced or metastatic disease, PSMA PET/CT had a high detection rate (84%) and impacted management in 61%. Because of the heterogeneity of the cohort, a wide range of management changes was induced by PSMA PET/CT. Consistent with other reports, management changed most frequently from intended systemic to implemented focal treatment (10,13,14). This finding highlights that high lesion detection rates can lead to focal (metastasis-targeted) treatment. Whether this approach will affect patient outcomes needs to be determined in future prospective studies.

Detection rates were lowest (1/13 patients [8%]) in patients restaged after definitive surgery who had serum PSA levels of 0.2 ng/mL or less. The impact on patient stage was also lowest in this group (38%), but changes in management still occurred in 6 of 13 (46%) of these patients. Despite the small size of the subgroup (only 13 subjects), these findings suggest that this population with an early stage of disease and a very low tumor burden may not benefit from the current imaging techniques.

In the 2 subgroups of patients who did not undergo definitive treatment, that is, treatment-naïve patients at initial staging who were not surgical candidates and those who underwent androgen deprivation therapy as first-line monotherapy after PCa diagnosis, PSMA PET/CT had a detection rate of 100% and induced changes in stage in 67% and 81% of patients, respectively. However, changes in management occurred less frequently in these 2 subgroups than in all others (43% and 40%, respectively). This finding may be explained by the limited treatment options in these cohorts. The primary tumor had not been treated, and most patients were scheduled to undergo a definitive focal treatment after the scan. After PSMA PET/CT, the treatment plan either remained the same (no changes in focal therapy in most cases) or there was a change in focal treatment (Fig. 4).

Müller et al. (13) found that metastasis-targeted treatments in patients with BCR with PSMA PET/CT–positive lesions resulted in a complete biochemical response in 45% of patients within 6 mo after PSMA PET/CT. Since a large proportion of the patients involved in our study were not treated in our hospital, we could not assess the clinical impact of PSMA PET/CT on patient outcome. Also, whether the PSMA PET/CT–induced management

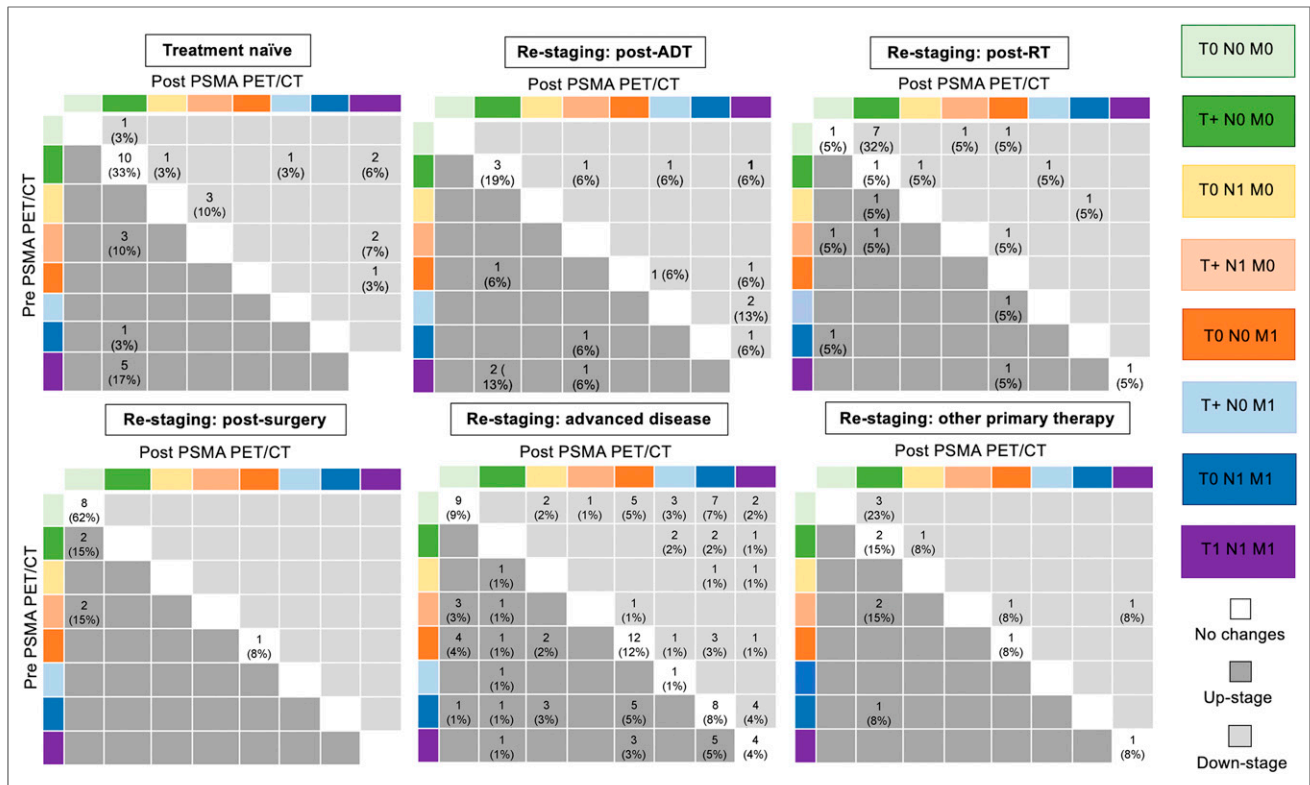


FIGURE 3. Changes in stage of disease before and after PSMA PET/CT stratified by subgroup.

changes translate into survival benefits remains unknown. Prospective studies with long-term follow-up are required to answer this question.

The low rate of returned postscan questionnaires is a major limitation of this study. Patients were referred from multiple outside institutions, and physicians' interest in sending back paperwork decreased dramatically after the scan. With only 27% of

post-PET questionnaires available, we were not able to include in the analysis the postscan intended management (intended management can be obtained only prospectively). Late follow-up questionnaires were returned for only 33% of patients. We were able to overcome this limitation by determining the final implemented management through electronic chart review or patient telephone calls for 132 of the 197 (77%) patients. The critical information that must be obtained prospectively is the prescan intended management, which was systematically obtained for all included patients. However, we acknowledge that telephone calls with patients are not a reliable source of medical information and do not allow a detailed analysis of intramodality changes, (i.e., changes in the radiation field, surgical approach, or androgen deprivation therapy regimen). Therefore, these cases were considered as "no change in focal or systemic therapy," but they still indicate changes attributable to information derived from PSMA PET/CT. The lack of information on how PSMA PET/CT altered specific intramodality treatment represents a limitation of our study because it underestimates the reported changes in management. This issue needs to be further addressed by dedicated prospective studies of each treatment modality.

Another limitation of the study is the lack of histopathologic validation of the

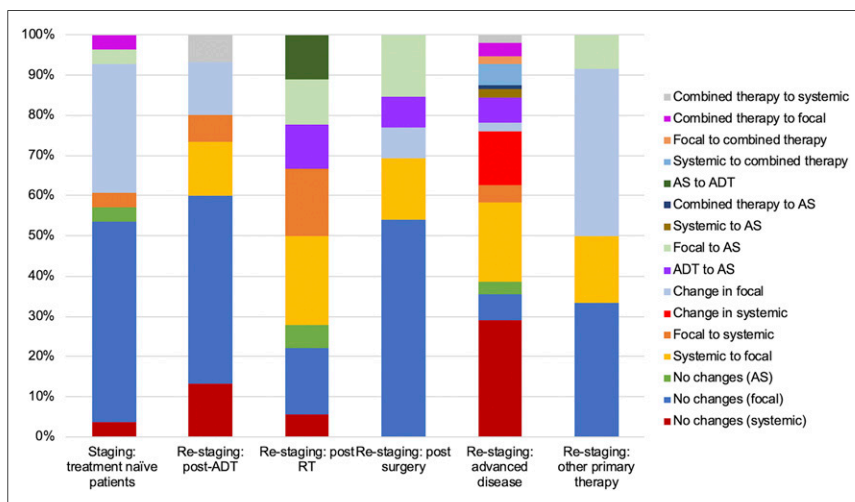


FIGURE 4. Impact of PSMA PET/CT imaging on management stratified by clinical indication. Both focal and systemic treatments are intended with or without androgen deprivation therapy (ADT). ADT as monotherapy was considered systemic treatment. AS = active surveillance.

PSMA-positive lesions. Obtaining a firm reference standard in recurrent PCa is a well-known challenge, even in prospective studies. Thus, false-positive findings cannot be ruled out. However assessing PSMA PET/CT diagnostic performance was not the aim of this study. Of note, high positive predictive values for PSMA PET (>85%) were reported in a metaanalysis that included only patients with BCR with histopathologic verification (23) and in a prospective multicenter phase 3 trial (3).

Despite the differences in stage and management changes that were observed among subgroups, they did not reach statistical significance. Although the heterogeneity of the population is a strength of our basket study, dividing the full cohort into 6 subgroups reduced the size of the subcohorts. The initial sample size calculation was not powered to evaluate differences in rates of change between indications. Because some subgroups were small, changes in management should be interpreted with caution. Therefore, the results need to be further explored in larger prospective trials for each of the subpopulations and clinical indications.

One final limitation of the study is that some of our patients had varying conventional imaging and diagnostic procedures performed before—and in 36% of cases after—the protocol PSMA PET/CT; the postprotocol procedures may have affected patient management.

CONCLUSION

PSMA PET/CT significantly impacted the stage and management of PCa patients across all relevant clinical scenarios, beyond the 2 main classic applications in BCR and presurgical staging. Further prospective studies need to determine whether these changes in management ultimately result in improved patient outcomes.

DISCLOSURE

This was an investigator-initiated trial with institutional academic funding (Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, UCLA). Jeremie Calais was the recipient of a grant from the Philippe Foundation Inc. and from the Fondation ARC pour la recherche sur le cancer (grant SAE20160604150), received personal fees from Progenics Pharmaceuticals and RadioMedix, and is a consultant for Blue Earth Diagnostics outside the submitted work. Johannes Czernin was the recipient of a grant from the U.S. Department of Energy (DE SC0012353), from the Prostate Cancer Foundation (2019 and 2017 Challenge Award, 17CHAL02), and from the Johnson Comprehensive Cancer Center National Institutes of Health–National Cancer Institute Cancer Center (support grant P30 CA016042). He is a founder and board member and holds equity in Sofie Biosciences and Trethera Therapeutics and serves on the medical advisory board of Actinium outside the submitted work. Wolfgang P. Fendler was the recipient of a scholarship from the German Research Foundation (Deutsche Forschungsgemeinschaft grant) and is a consultant for Endocyte and Ipsen. He received personal fees from RadioMedix outside the submitted work. Mattias Eiber was supported by the SFB 824 (DFG Sonderforschungsbereich 824, project B11) from the Deutsche Forschungsgemeinschaft and received grants from ABX Advanced Biochemical Compounds and Blue Earth Diagnostics. He is a consultant for Janssen, received personal fees from Progenics Pharmaceuticals, and has a patent rhPSMA issued outside the

submitted work. Matthew B. Rettig received research grants from Novartis, Johnson and Johnson, Merck, Astellas, Medivation, and Progenics. He is a consultant for Constellation Pharmaceuticals and a member of the speakers bureau for Johnson and Johnson and Bayer. Amar U. Kishan received personal fees from ViewRay, Inc., Varian Medical Systems, Inc., and Janssen Pharmaceuticals outside the submitted work. Nicholas Nickols received research support from Janssen, Varian, and Progenics. No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: Does PSMA PET/CT have an impact on the clinical management of PCa patients referred for indications other than BCR or presurgical staging?

PERTINENT FINDINGS: This prospective single-center, open-label, single-arm phase 2 imaging trial showed that PSMA PET/CT significantly impacts the stage and management of PCa patients across all relevant clinical scenarios.

IMPLICATIONS FOR PATIENT CARE: The results of this study demonstrate that PSMA PET/CT can be used in PCa patients in a wide variety of clinical settings other than BCR and presurgical staging, significantly impacting clinical staging and management.

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PATIENT INFORMATION	
Last name: _____	First Name: _____
Date of Birth: _____	Medical Record Number: _____

1. Indicate where do you know/think that prostate cancer disease is located before ⁶⁸Ga-PSMA PET (select all that apply):

- Prostate fossa
- intrapelvic lymph nodes
- extrapelvic lymph nodes
- bone
- extrapelvic soft-tissue (non-bone)

2. If ⁶⁸Ga-PSMA PET was not available, which other imaging test would you order?

- | | |
|---|---|
| <ul style="list-style-type: none"> <input type="checkbox"/> MRI <input type="checkbox"/> CT <input type="checkbox"/> FDG PET <input type="checkbox"/> Acetate PET <input type="checkbox"/> Choline PET | <ul style="list-style-type: none"> <input type="checkbox"/> Fluciclovine PET <input type="checkbox"/> ProstaScint <input type="checkbox"/> Bone scan <input type="checkbox"/> Fluoride PET <input type="checkbox"/> Other: _____ |
|---|---|

3. If ⁶⁸Ga-PSMA PET was not available, which treatment would you recommend/perform?

- | | |
|--|--|
| <ul style="list-style-type: none"> <input type="checkbox"/> Surgery – Prostatectomy <input type="checkbox"/> Surgery – Pelvic lymph node dissection <input type="checkbox"/> Surgery – Elective lymphadenectomy <input type="checkbox"/> XRT - Prostate fossa <input type="checkbox"/> XRT - Whole pelvic lymph nodes <input type="checkbox"/> XRT - Single pelvic lymph node <input type="checkbox"/> XRT - Extra-pelvic metastasis <input type="checkbox"/> Other focal therapy (please describe below): | <ul style="list-style-type: none"> <input type="checkbox"/> Androgen deprivation therapy <input type="checkbox"/> Chemotherapy <input type="checkbox"/> PSMA Radionuclide therapy <input type="checkbox"/> Bone targeted Radionuclide therapy <input type="checkbox"/> Immunotherapy <input type="checkbox"/> Active surveillance <input type="checkbox"/> Other (please describe below): |
|--|--|

Referring Physician Name: _____

Signature: _____ Date: _____

PATIENT INFORMATION

Last name: _____ First Name: _____

Date of Birth: _____ Medical Record Number: _____

1. Indicate where do you know/think that prostate cancer disease is located after ⁶⁸Ga-PSMA PET (select all that apply):

- Unknown
- Prostate fossa
- intrapelvic lymph nodes
- extrapelvic lymph nodes
- bone
- extrapelvic soft-tissue (non-bone)

2. Did the ⁶⁸Ga-PSMA PET enable you to avoid any diagnostic procedure?

- Yes
- No

If yes, which one? _____

3. Did the ⁶⁸Ga-PSMA PET result in any diagnostic procedure?

- Yes
- No

If yes, which one? _____

4. Based on ⁶⁸Ga-PSMA PET findings what is your treatment plan?

- | | |
|---|---|
| <input type="checkbox"/> Surgery – Prostatectomy | <input type="checkbox"/> Androgen deprivation therapy |
| <input type="checkbox"/> Surgery – Pelvic lymph node dissection | <input type="checkbox"/> Chemotherapy |
| <input type="checkbox"/> Surgery – Elective lymphadenectomy | <input type="checkbox"/> PSMA Radionuclide therapy |
| <input type="checkbox"/> XRT - Prostate fossa | <input type="checkbox"/> Bone targeted Radionuclide therapy |
| <input type="checkbox"/> XRT - Whole pelvic lymph nodes | <input type="checkbox"/> Immunotherapy |
| <input type="checkbox"/> XRT - Single pelvic lymph node | <input type="checkbox"/> Active surveillance |
| <input type="checkbox"/> XRT - Extra-pelvic metastasis | <input type="checkbox"/> Other (please describe below): |
| <input type="checkbox"/> Other focal therapy (please describe below): | |

Referring Physician Name: _____

Date: _____ Signature: _____

PATIENT INFORMATION	
Last name: _____	First Name: _____

Date of Birth: _____	Medical Record Number: _____

1. Were any of the following diagnostic procedure performed after the ⁶⁸Ga-PSMA PET/CT?

- | | |
|---|----------------------------------|
| <input type="checkbox"/> Biopsy/Surgery | <input type="checkbox"/> CT |
| <input type="checkbox"/> MRI | <input type="checkbox"/> PET/CT |
| <input type="checkbox"/> Bone scan | <input type="checkbox"/> Other : |

If Yes, please indicate the date and the findings :

2. On the post scan questionnaire (questionnaire #2) you indicated an intended treatment management of:

- | | |
|---|---|
| <input type="checkbox"/> Surgery – Prostatectomy | <input type="checkbox"/> Androgen deprivation therapy |
| <input type="checkbox"/> Surgery – Pelvic lymph node dissection | <input type="checkbox"/> Chemotherapy |
| <input type="checkbox"/> Surgery – Elective lymphadenectomy | <input type="checkbox"/> PSMA Radionuclide therapy |
| <input type="checkbox"/> XRT - Prostate fossa | <input type="checkbox"/> Bone targeted Radionuclide therapy |
| <input type="checkbox"/> XRT - Whole pelvic lymph nodes | <input type="checkbox"/> Immunotherapy |
| <input type="checkbox"/> XRT - Single pelvic lymph node | <input type="checkbox"/> Active surveillance |
| <input type="checkbox"/> XRT - Extra-pelvic metastasis | <input type="checkbox"/> Other (please describe below): |
| <input type="checkbox"/> Other focal therapy (please describe below): | |

3. Please indicate whether the intended management noted on the post scan questionnaire (questionnaire #2) was implemented:

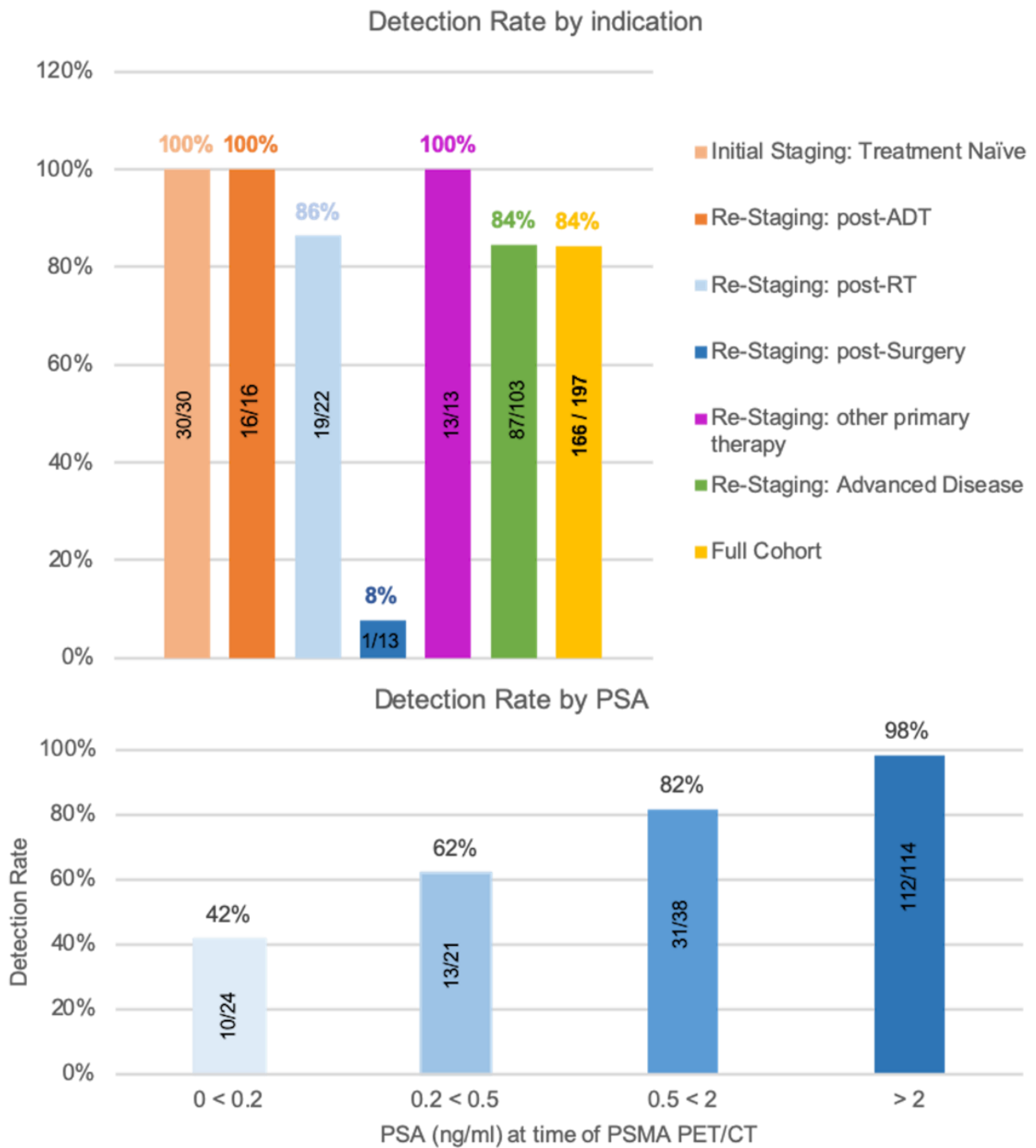
- Yes
- No

If No, please indicate why: _____

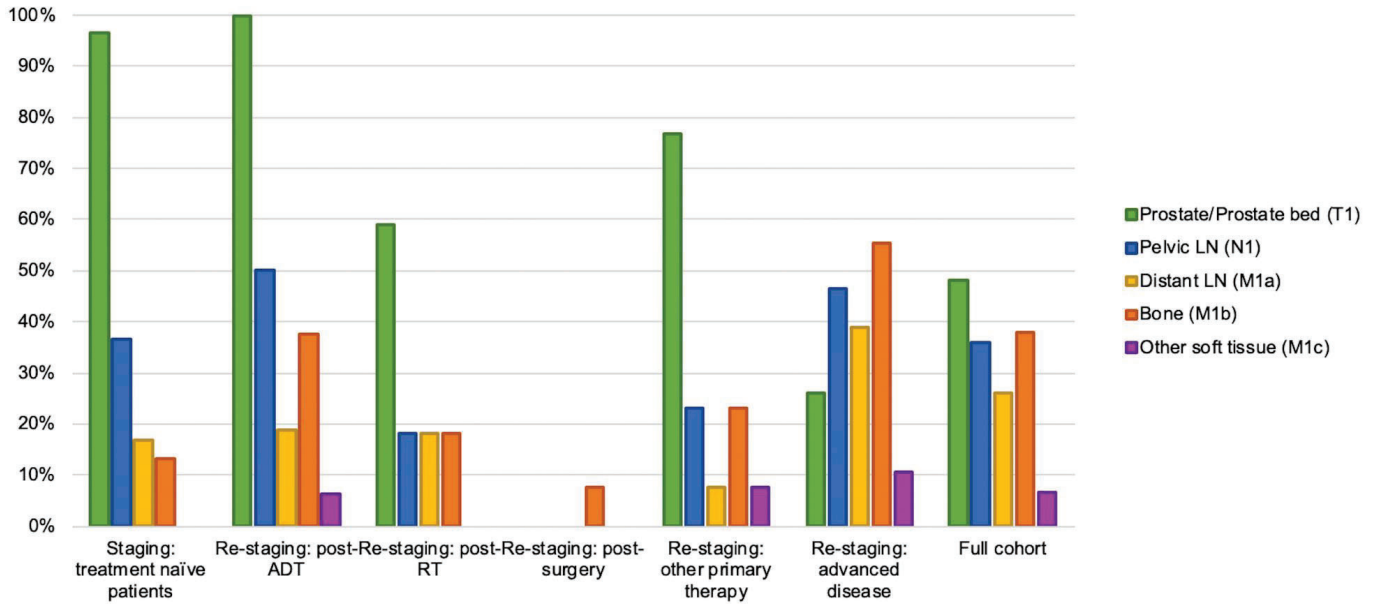
Referring Physician Name: _____

Date: _____ Signature: _____

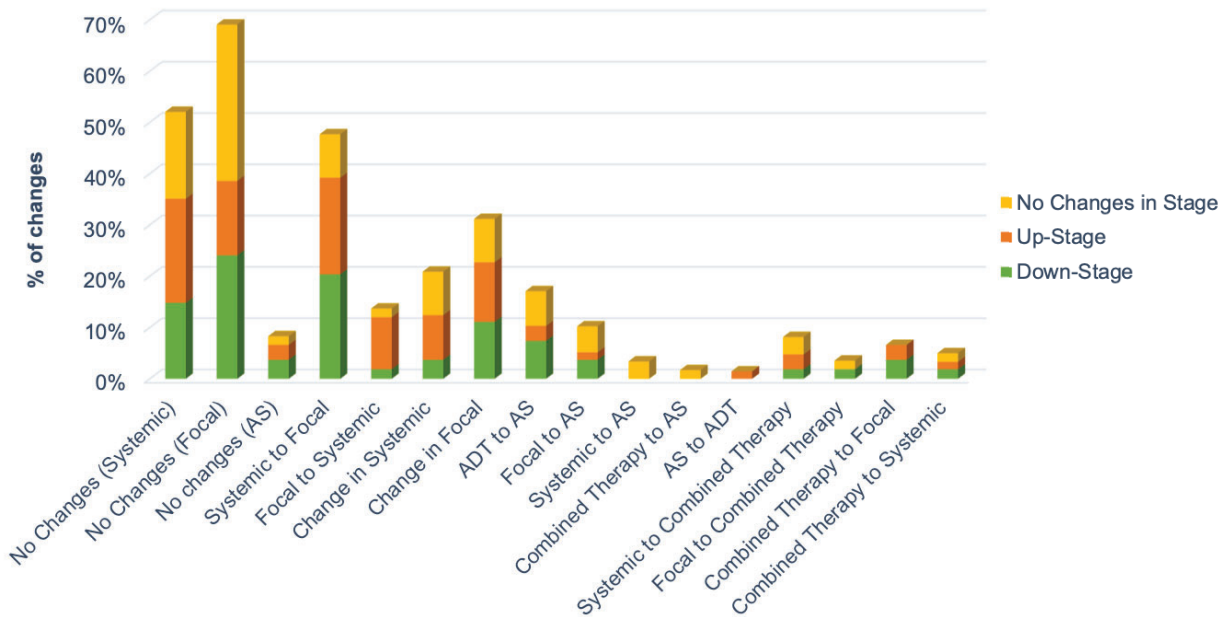
Supplemental Figure 1: Questionnaires.



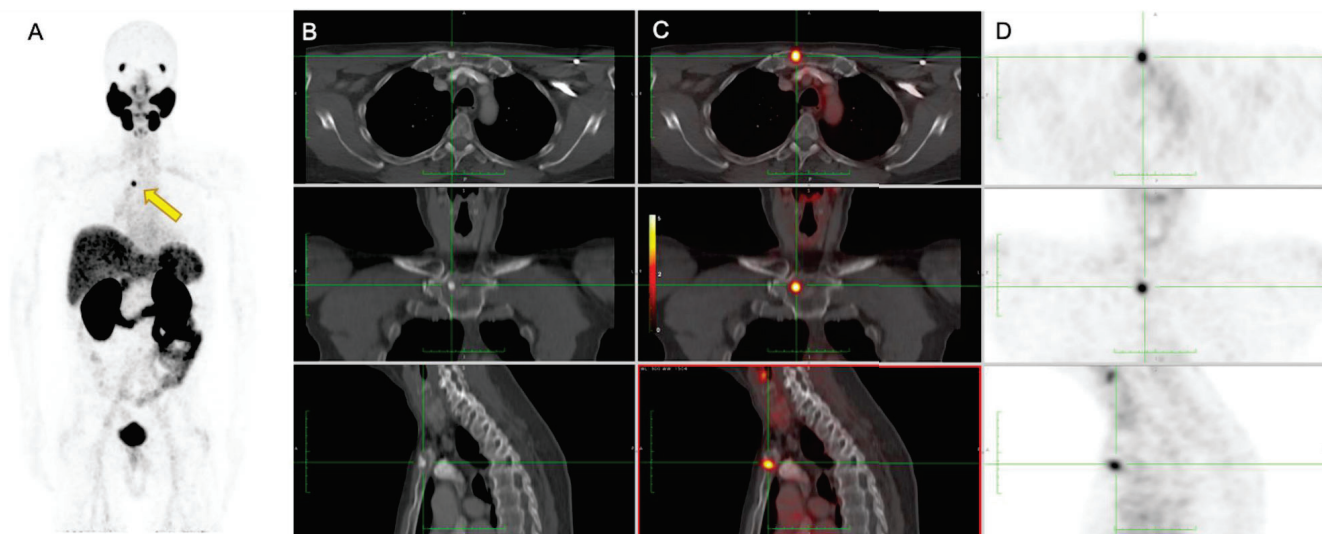
Supplemental Figure 2. Detection rate stratified by sub-groups (upper image) and PSA levels (lower image).



Supplemental Figure 3: Location of disease based on PSMA PET/CT results. ADT: androgen deprivation therapy; RT: radiation therapy; LN: lymph nodes



Supplemental Figure 4. Impact of PSMA PET/CT imaging on management stratified by changes in stage.



Supplemental Figure 5. Example of a change in management: 54-year-old patient with increasing serum PSA levels post multiple treatments (advanced disease sub-group). PSA at time of PSMA PET/CT was 0.29 ng/ml. Radical prostatectomy on 3/2006 (Gleason Score 3+4=7 with extracapsular extension) and adjuvant radiation therapy on the prostatic fossa on 9/2007. In 2010, due to increasing PSA values, the patient started first-line hormonal therapy and developed castration-resistant prostate cancer in 2013. The patient was treated with two different immunotherapies with temporary reduction of PSA levels, but in 4/2017 serum PSA levels started to increase. The intended treatment before PSMA PET/CT was continuation of ADT. PSMA PET/CT on 4/2018 detected a single focus of increased uptake in the sternum. The lesion was treated with stereotactic RT on 5/2018. PSA started decreasing in 10/2018, became undetectable on 4/2019 and remained so until the day this manuscript was finalized. 68Ga-PSMA-11 PET/CT MIP (A), CT (row B), fusion PSMA PET/CT (row C) and PET (row D).

	Staging: treatment naïve patients	Re-Staging: Post-ADT	Re-staging: Post-RT	Re-staging: Post-surgery	Re-staging: Advanced Disease	Re-staging: other primary therapy	TOT	Down-stage	Up-stage	No Change in stage
No Changes (Systemic)	1 (4%)	2 (13%)	1 (6%)	0	28 (29%)	0	32 (18%)	8 (15%)	14 (20%)	10 (17%)
No Changes (Focal)	14 (50%)	7 (47%)	3 (17%)	7 (54%)	6 (6%)	4 (33%)	41 (23%)	13 (24%)	10 (14%)	18 (31%)
No changes (AS)	1 (4%)	0	1 (6%)	0	3 (3%)	0	5 (3%)	2 (4%)	2 (3%)	1 (2%)
Systemic to Focal	0	2 (13%)	4 (22%)	2 (15%)	19 (20%)	2 (17%)	29 (16%)	11 (20%)	13 (19%)	5 (8%)
Focal to Systemic	1 (4%)	1 (7%)	3 (17%)	0	4 (4%)	0	9 (5%)	1 (2%)	7 (10%)	1 (2%)
Change in Systemic	0	0	0	0	13 (14%)	0	13 (7%)	2 (4%)	6 (9%)	5 (8%)
Change in Focal	9 (32%)	2 (13%)	0	1 (8%)	2 (2%)	5 (42%)	19 (10%)	6 (11%)	8 (12%)	5 (8%)
ADT to AS	0	0	2 (11%)	2 (11%)	6 (6%)	0	10 (5%)	4 (7%)	2 (3%)	4 (7%)
Focal to AS	1 (4%)	0	2 (11%)	2 (15%)	0	1 (8%)	6 (3%)	2 (4%)	1 (1%)	3 (5%)
Systemic to AS	0	0	0	0	2 (2%)	0	2 (1%)	0	0	2 (3%)
Combined Therapy to AS	0	0	0	0	1(1%)	0	1 (1%)	0	0	1 (2%)
AS to ADT	0	0	1 (6%)	0	0	0	1 (1%)	0	1 (1%)	0
Systemic to Combined Therapy	0	0	0	0	5 (5%)	0	5 (3%)	1 (2%)	2 (3%)	2 (3%)
Focal to Combined Therapy	0	0	0	0	2 (2%)	0	2 (1%)	1 (2%)	0	1 (2%)
Combined Therapy to Focal	1 (4%)	0	0	0	3 (3%)	0	4 (2%)	2 (4%)	2 (3%)	0
Combined Therapy to Systemic	0	1 (7%)	0	0	2 (3%)	0	3 (2%)	1 (2%)	1 (1%)	1 (2%)
TOT	28 (100%)	15 (100%)	18 (100%)	13 (100%)	96 (100%)	12 (100%)	182 (100%)	54 (100%)	69 (100%)	59 (100%)
Tot No Change	16 (57%)	9 (60%)	5 (28%)	7 (54%)	37 (39%)	4 (33%)	78 (43%)			
Tot CHANGE	12 (43%)	6 (40%)	13 (72%)	6 (46%)	59 (61%)	8 (67%)	104 (57%)			

Supplemental Table 1. Detailed analysis of changes in management stratified by clinical indication and by changes in stage. In parenthesis are percentages by column.

Third Topic: Beyond the approved use of PSMA theranostics.

Article 7:

Title: Prognostic Value of End-of-Treatment PSMA PET/CT in Patients Treated with ¹⁷⁷Lu-PSMA Radioligand Therapy: A Retrospective, Single-Center Analysis.

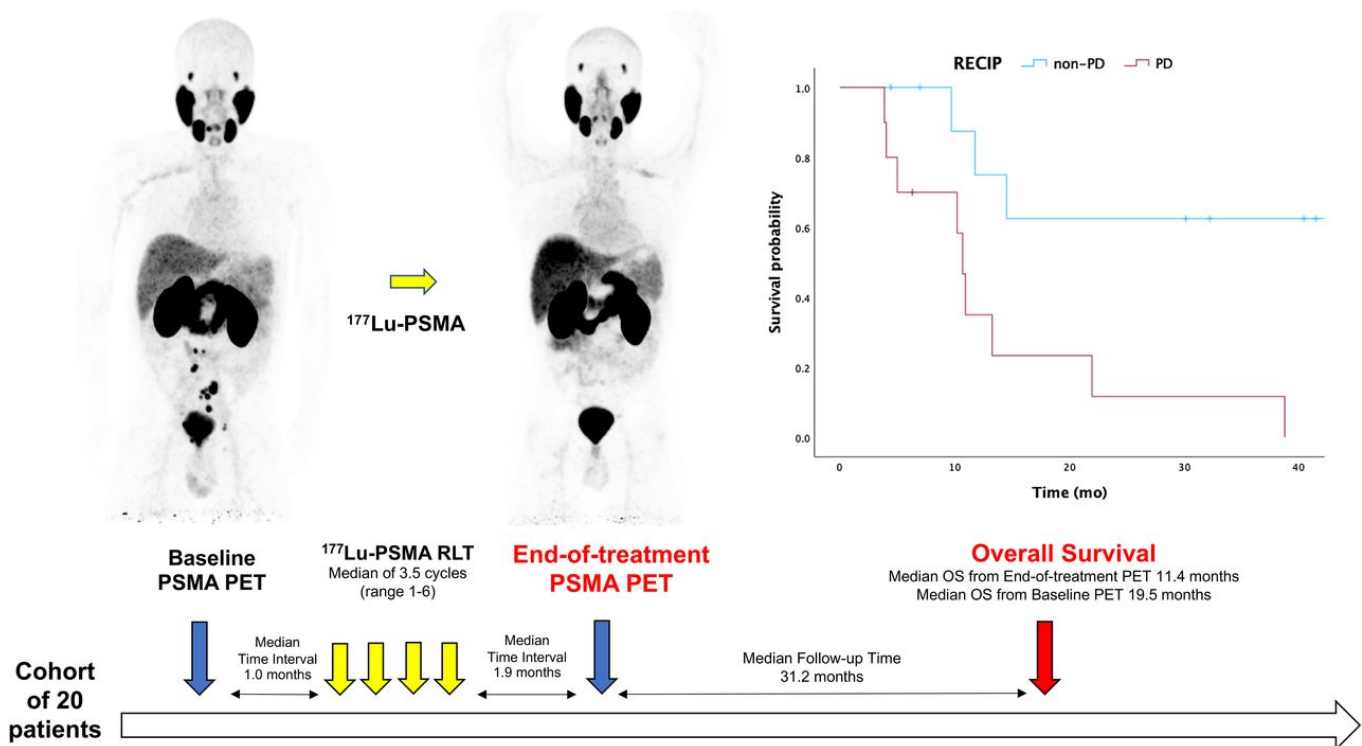
Authors: Murthy V, Gafita A, Thin P, Nguyen K, Grogan T, Shen J, Drakaki A, Rettig M, Czernin J, Calais J.

Reference: *J Nucl Med.* 2023 Sep 7; jnumed.122.265155. PMID: 37678927

Brief Outline:

In this retrospective study, we investigated the prognostic value of progression on end-of-treatment PSMA PET (ePET) in patients with metastatic castration resistant prostate cancer treated with PSMA-RLT. In these 20 mCRPC patients treated with PSMA-RLT, progression on ePET by the appearance of new lesions, changes in PSMA-VOL, was prognostic for Overall Survival.

The junior first author was Vishnu Murthy, who was a 3rd year medical student at UCLA. This work was presented at the SNMMI in 2022. The work was published in the JNM in 2023.



Prognostic Value of End-of-Treatment PSMA PET/CT in Patients Treated with ¹⁷⁷Lu-PSMA Radioligand Therapy: A Retrospective, Single-Center Analysis

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Our objective was to evaluate the prognostic value of end-of-treatment prostate-specific membrane antigen (PSMA) PET/CT (PSMA-PET) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with ¹⁷⁷Lu-PSMA radioligand therapy (PSMA-RLT). **Methods:** This was a single-center retrospective study. mCRPC patients who underwent PSMA-RLT with available baseline PSMA-PET (bPET) and end-of-treatment PSMA-PET (ePET) within 6 mo of the last PSMA-RLT cycle were eligible. Overall survival (OS) and prostate-specific antigen (PSA) progression status at the time of ePET (by Prostate Cancer Clinical Trials Working Group 3 criteria) were collected. PSMA-PET tumor segmentation was performed to obtain whole-body PSMA tumor volume (PSMA-VOL) and define progressive ($\geq 20\%$ increase) versus nonprogressive disease. Pairs of bPET and ePET were interpreted for appearance of new lesions. Response Evaluation Criteria in PSMA-PET/CT (RECIP) 1.0 were also applied to define progressive versus nonprogressive disease. The associations between changes in PSMA-VOL, new lesions, RECIP 1.0, and PSA progression status at the time of ePET with OS were evaluated by Kaplan–Meier analysis. **Results:** Twenty mCRPC patients were included. The median number of treatment cycles was 3.5 (interquartile range [IQR], 2–4). The median time between bPET and cycle 1 of PSMA-RLT was 1.0 mo (IQR, 0.7–1.8 mo). The median time between the last cycle of PSMA-RLT and ePET was 1.9 mo (IQR, 1.2–3.5 mo). Twelve of 20 patients (60%) had died at the last follow-up. The median follow-up time from ePET for survivors was 31.2 mo (IQR, 6.8–40.7 mo). The median OS from ePET was 11.4 mo (IQR, 6.8–30.7 mo). Patients with new lesions on ePET had shorter OS than those without new lesions (median OS, 10.7 mo [95% CI, 9.2–12.2] vs. not reached; $P = 0.002$). Patients with progressive PSMA-VOL had shorter OS than those with nonprogressive PSMA-VOL (median OS, 10.7 mo [95% CI: 9.7–11.7 mo] vs. not reached; $P = 0.007$). Patients with progressive RECIP had shorter OS than those with nonprogressive RECIP (median OS, 10.7 mo [95% CI, 9.7–11.7 mo] vs. not reached; $P = 0.007$). PSA progression at the time of ePET was associated with shorter OS (median, 10.9 mo [95% CI, 9.4–12.4 mo] vs. not reached; $P = 0.028$). **Conclusion:** In this retrospective study of 20 mCRPC patients treated with PSMA-RLT, progression on ePET by the appearance of new lesions, changes in PSMA-VOL, and RECIP

1.0 was prognostic for OS. Validation in larger, prospective multicentric clinical trials is warranted.

Key Words: metastatic castration-resistant prostate cancer; radioligand therapy; PSMA-PET; end-of-treatment PET; ¹⁷⁷Lu-PSMA

J Nucl Med 2023; 64:1737–1743

DOI: 10.2967/jnumed.122.265155

The small-molecule inhibitor ¹⁷⁷Lu-PSMA binds with high affinity to prostate-specific membrane antigen (PSMA) and delivers β -radiation. In the phase III VISION trial, which led to approval by the Food and Drug Administration, ¹⁷⁷Lu-PSMA-617 prolonged overall survival (OS) and image-based progression-free survival when added to the standard of care for patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior taxane-based chemotherapy (1).

In metastatic prostate cancer, treatment response is typically evaluated using conventional imaging (CT and bone scanning) according to the Prostate Cancer Clinical Trials Working Group 3 criteria (2). The Food and Drug Administration approved PSMA PET/CT (PSMA-PET) for different clinical settings in men with prostate cancer (3). However, further research is necessary to evaluate the prognostic value of PSMA-PET for OS in mCRPC patients undergoing treatment with ¹⁷⁷Lu-PSMA radioligand therapy (PSMA-RLT) (4).

Progression on end-of-treatment PSMA-PET (ePET) by modified PSMA-PET progression criteria was reported to be prognostic for OS in mCRPC patients undergoing treatment with PSMA-RLT (5,6). Increased whole-body PSMA tumor volume (PSMA-VOL) on ePET was also reported to be prognostic for OS, independent of ¹⁸F-FDG PET/CT parameters (7). Recently, Response Evaluation Criteria in PSMA-PET/CT (RECIP) 1.0 were introduced. Patients were classified as having progressive disease (PD) if they had at least a 20% increase in PSMA-VOL and the appearance of new lesions on interim PSMA-PET after the first 2 cycles of PSMA-RLT (4). Progression on interim PSMA-PET by RECIP 1.0 was also found to be prognostic for OS in mCRPC patients treated with PSMA-RLT. However, the prognostic value of progression on ePET by RECIP 1.0 has not, to our knowledge, been previously investigated.

In this retrospective study, we aimed to evaluate the prognostic value of progression on ePET by RECIP 1.0 in mCRPC patients treated with PSMA-RLT.

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TABLE 1
RECIP 1.0

Criteria	Definition
New lesions	Any new focus of PSMA uptake higher than surrounding background, with tumor SUV _{max} > blood-pool SUV _{max} , not present on bPET (tumor SUV _{max} < blood-pool SUV _{max}), and with tumor uptake not attributable to physiologic uptake or pitfalls; alternatively, any new malignant lesion detected on follow-up CT imaging independent of PSMA-ligand uptake
RECIP 1.0	
Complete response	Absence of any PSMA uptake on follow-up PET scan
Partial response	≥30% decrease in PSMA-VOL without appearance of new lesions
PD	≥20% increase in PSMA-VOL with appearance of new lesions
Stable disease	<30% decrease in PSMA-VOL with or without appearance of new lesions, ≥30% decrease in PSMA-VOL with appearance of new lesions, <20% increase in PSMA-VOL with or without appearance of new lesions, or ≥20% increase in PSMA-VOL without appearance of new lesions

MATERIALS AND METHODS

Patients and Study Design

In this single-center retrospective study, mCRPC patients who underwent PSMA-PET or PSMA-RLT between October 2016 and April 2022 at UCLA were retrospectively screened for inclusion. Eligible patients underwent PSMA-RLT, had available baseline PET (bPET) and ePET performed within 6 mo of the last PSMA-RLT cycle, and had available survival data. The cutoff date for follow-up was November 5, 2022. Patients who did not have a confirmed date of death and had a follow-up time of less than 3 mo were excluded. This retrospective analysis was approved by the Ethics Committee (UCLA institutional review board approval 20-000954), which waived the study-specific consent requirement. The primary outcome of the study was to evaluate the prognostic value of ePET for OS. The secondary outcome was to evaluate the correlation of prostate-specific antigen (PSA) changes with ePET.

PSMA-PET Image Acquisition

Twenty pairs of PET scans (40 PET scans total) were used for this analysis. ⁶⁸Ga-PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[⁶⁸Ga(H-BEDCC)]) was used as the PSMA ligand. PSMA-PET/CT images were acquired after intravenous injection of a median of 191 MBq of ⁶⁸Ga-PSMA-11 (interquartile range [IQR], 183–204 MBq) and a median uptake time of 63 min (IQR, 59–68 min). Thirty-six of 40 (90%) PET scans were done at UCLA, whereas 4 of 40 (10%) were done at outside institutions. Twenty-one of 40 (53%) PET scans were acquired on a Siemens Biograph 64 Truepoint scanner (image reconstruction parameters: no time of flight, ordered-subsets expectation maximization 2-dimensional [2 iterations, 8 subsets], 5-mm gaussian postreconstruction filter), 18 of 40 (45%) on a Siemens Biograph 64 mCT scanner (image reconstruction parameters: no time of flight, ordered-subsets expectation maximization 3-dimensional [2 iterations, 24 subsets], 5-mm gaussian postreconstruction filter), and 1 of 40 (2%) on a GE Healthcare Discovery VCT scanner (image reconstruction parameters: 3-dimensional, no time of flight).

Image Analysis

Changes in Tumor Burden. The PSMA-positive tumor lesions on bPET and ePET were segmented by 1 nuclear medicine physician, who was masked to outcome data, using qPSMA software as described previously (8). PSMA-VOL was extracted, and percentage changes on ePET relative to bPET were calculated. Patients were classified as having PD (progressive PSMA-VOL, ≥20% increase) versus non-PD.

New Lesions. Pairs of bPET and ePET were interpreted by 1 nuclear medicine physician. The appearance of at least 1 new lesion on ePET was recorded.

RECIP. RECIP 1.0 were applied as previously described (4). Patients were classified as having PD if they had at least a 20% increase in PSMA-VOL with the appearance of new lesions on ePET versus non-PD. Table 1 summarizes RECIP 1.0 classifications (4).

Statistical Analysis

OS was calculated in a landmark analysis from time of bPET (to permit comparisons with the VISION trial) and from time of ePET (for Kaplan–Meier analyses) to death or date of last follow-up alive. PSA progression status at the time of ePET was recorded and categorized according to Prostate Cancer Clinical Trials Working Group 3 criteria (2).

Patient characteristics and study variables were summarized overall and by group (progressive RECIP vs. nonprogressive RECIP) using frequencies (percentages) or medians (quarters 1–3) unless otherwise noted. To assess the association between OS and clinical parameters such as changes in PSMA-VOL, appearance of new lesions, RECIP 1.0, and PSA progression status at the time of ePET, we used the Kaplan–Meier method. The 95% CIs for the median OS (if it existed) were computed and the corresponding *P* values from the log-rank test were used to formally assess the associations of interest. The correlations between percentage changes in serum PSA and percentage changes in PSMA-VOL from bPET to ePET were assessed using Spearman rank correlation coefficients. The associations between PSMA-PET–derived parameters and PSA progression status at the time of ePET were evaluated using the Fisher exact test. Analyses were performed using Jamovi, and *P* values of less than 0.05 were considered statistically significant.

RESULTS

Patients

Retrospective data from 425 men with prostate cancer who underwent 2 PSMA-PET scans between October 2016 and April 2022 were screened. Of these, 20 mCRPC patients treated with PSMA-RLT with available bPET and ePET met the eligibility criteria and were included (Fig. 1). Patients were treated with PSMA-RLT at UCLA and other international sites. Seven of 20 (35%) patients were treated with PSMA-RLT under compassionate-access programs, 10 of 20 (50%) in a phase II clinical trial (NCT03042312), and 3 of 20 (15%) under an expanded-access protocol (NCT04825652) (9). Baseline characteristics are summarized in Table 2.

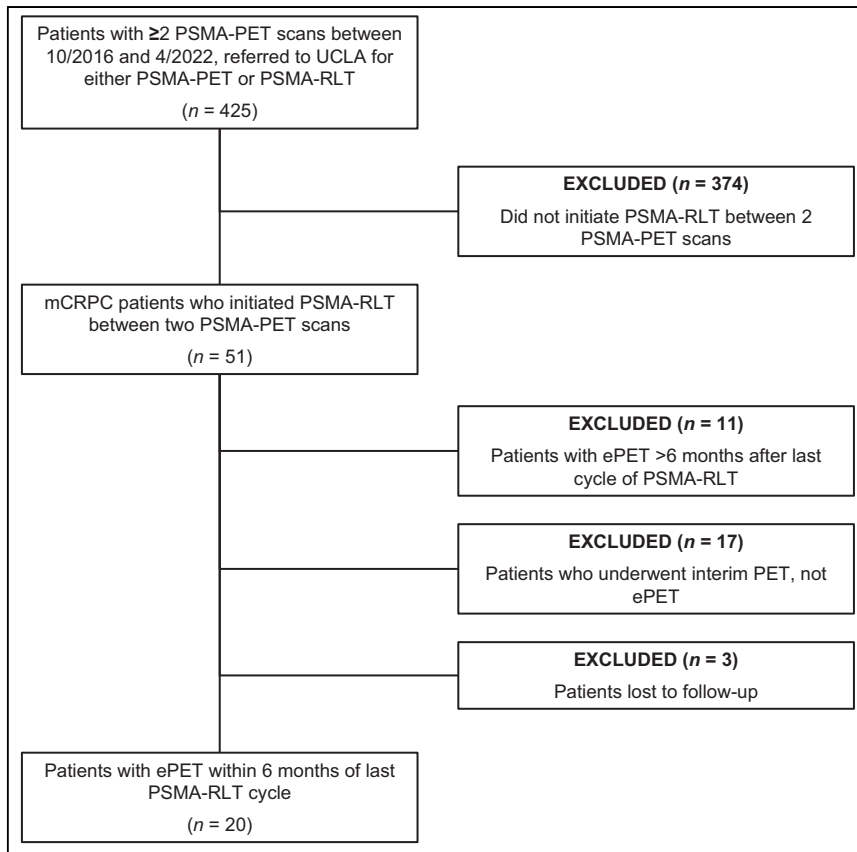


FIGURE 1. Study flowchart.

PSMA-RLT

The median number of treatment cycles was 3.5 (IQR, 2–4). The median activity per cycle was 7.3 GBq (IQR, 6.6–7.4 GBq). Injected activity data were not available in 5 patients for 8 cycles. The median time between bPET and cycle 1 of PSMA-RLT was 1.0 mo (IQR, 0.7–1.8 mo), whereas the median time between the last cycle of PSMA-RLT and ePET was 1.9 mo (IQR, 1.2–3.5 mo).

Clinical Outcomes

Twelve of 20 patients (60%) had died at last follow-up. The median follow-up time from ePET for survivors was 31.2 mo (IQR, 6.8–40.7 mo). The median OS was 19.5 mo from bPET (IQR, 16.3–36.6 mo) and 11.4 mo from ePET (IQR, 6.8–30.7 mo).

Image Analysis

Case summary images for each patient are provided in the supplemental figures (supplemental materials are available at <http://jnm.snmjournals.org>). Four of 20 patients (20%) did not have sufficient PSA data to document changes during PSMA-RLT. Sample cases of PSMA-PET and PSA responders and nonresponders are also shown in Figure 2.

New Lesions. Eleven of 20 patients (55%) had new lesions on ePET and had a shorter OS than patients without new lesions (median OS, 10.7 mo [95% CI, 9.2–12.2] vs. not reached; $P = 0.002$; Fig. 3).

PSMA-VOL Changes. The median change in PSMA-VOL on ePET relative to bPET was +21.5% (IQR, –76.9% to +266.5%). Ten of 20 patients (50%) had progressive PSMA-VOL at the time of ePET and had a shorter OS than patients with nonprogressive

PSMA-VOL (median OS, 10.7 mo [95% CI, 9.7–11.7 mo] vs. not reached; $P = 0.007$; Fig. 3).

RECIP. Ten of 20 patients (50%) had progressive RECIP at the time of ePET and had a shorter OS than patients with nonprogressive RECIP (median OS, 10.7 mo [95% CI, 9.7–11.7] vs. not reached; $P = 0.007$; Fig. 3).

PSA and ePET. Eighteen of 20 patients (90%) had available serum PSA values to assess PSA progression status at the time of ePET. Ten of 18 patients (55.6%) experienced PSA progression at the time of ePET. Two of 18 patients (11.1%) experienced PSA progression at the time of ePET but were classified as non-PD by RECIP 1.0. PSA progression at the time of ePET was associated with shorter OS (median, 10.9 mo [95% CI, 9.4–12.4] vs. not reached; $P = 0.028$; Fig. 3). Associations between progression by PSMA-VOL, new lesions, and RECIP 1.0 with PSA progression status at ePET are summarized in Table 3. Changes in PSA and PSMA-VOL between bPET and ePET were strongly correlated (Spearman $\rho = 0.776$; $P < 0.001$).

DISCUSSION

In this single-center retrospective cohort study of 20 mCRPC patients treated with PSMA-RLT, progression on ePET by

RECIP 1.0 was prognostic for OS. Changes in PSMA-VOL correlated with changes in PSA and were associated with PSA progression status.

These findings are consistent with Michalski et al., who found that progression on ePET using modified PSMA-PET progression criteria was prognostic for OS in mCRPC patients treated with PSMA-RLT (5). Our results are also consistent with Pathmanandavel et al., who demonstrated that changes in total tumor volume on ePET were prognostic for OS, independent of ^{18}F -FDG parameters, in mCRPC patients who underwent PSMA-RLT (7). Although RECIP 1.0 was initially introduced using interim PSMA-PET, our analysis now suggests that response assessment on ePET using RECIP 1.0 can be prognostic for OS (4).

Because the extraction of quantitative, whole-body PSMA-PET parameters is not widely available in clinical practice, lesion-based response criteria still provide easily accessible prognostic information. Similar to prior reports, we found that the appearance of new lesions on ePET is prognostic for OS (4,5). However, it should also be noted that the appearance of new lesions on ePET as a single lesion assessment may not fully capture disease heterogeneity. In our analysis, among 11 of 20 patients who had new lesions on ePET, 1 (9%) patient (case 9, supplemental materials) was classified as non-PD by PSMA-VOL and RECIP 1.0 and had an OS of 9.7 mo after ePET. In the original RECIP 1.0 study, which analyzed 124 patients, 13% of patients had new lesions despite a decrease in tumor volume and were classified as having stable disease, with a different survival outcome from true

TABLE 2
Baseline Characteristics

Characteristic	All patients (n = 20)	Progressive RECIP (n = 10)	Nonprogressive RECIP (n = 10)
Age (y)	71 (66–75)	74 (69–77)	68 (61–72)
Time since diagnosis of prostate cancer (y)	8 (5–13)	9 (7–16)	7 (4–12)
Gleason score at diagnosis*			
<8	6 (31.6)	5 (50)	1 (11.1)
≥8	13 (68.4)	5 (50)	8 (88.9)
M status at diagnosis†			
M0 (%)	11 (61.1)	7 (77.8)	4 (44.4)
M1 (%)	7 (38.9)	2 (22.2)	5 (55.6)
Primary treatment			
Prostatectomy ± lymphadenectomy	9 (45)	6 (60)	3 (30)
Local radiotherapy	1 (5)	1 (10)	0 (0)
Systemic treatment	10 (50)	3 (30)	7 (70)
Previous mCRPC treatments			
Previous chemotherapy			
Docetaxel	11 (55)	7 (70)	4 (40)
Cabazitaxel	6 (30)	3 (30)	3 (30)
Other chemotherapy	4 (20)	1 (10)	3 (30)
Androgen receptor-signaling inhibitor			
Abiraterone	16 (80)	8 (80)	8 (80)
Enzalutamide	14 (70)	8 (80)	6 (60)
²²³ Ra	4 (20)	2 (20)	2 (20)
Other	14 (70)	8 (80)	6 (60)
Prior lines of mCRPC systemic treatment			
0	2 (10)	1 (10)	1 (10)
1	3 (15)	0	3 (30)
≥2	15 (75)	9 (90)	6 (60)
≥3	14 (70)	8 (80)	6 (60)
≥4	12 (60)	7 (70)	5 (50)
Baseline PSA (ng/mL), closest to cycle 1	19.5 (3.4–30.3)	20.0 (10.4–32.2)	5.3 (0.8–27.8)
Time between PSA and cycle 1 (d)	6 (3–11)	7 (4–11)	6 (2–12)
Baseline lactate dehydrogenase (U/L)‡	215 (178–224)	218.5 (206.8–271)	174 (167–200)
Baseline total alkaline phosphatase (U/L)§	94.5 (70–117.5)	113 (85–132)	81 (68–95)
Baseline hemoglobin (g/dL)¶	13.1 (11.6–13.5)	13.1 (11.4–13.4)	13.1 (11.6–13.6)
Baseline ECOG performance status¶			
0	10 (62.5)	5 (55.6)	5 (71.4)
1	5 (31.3)	3 (33.3)	2 (28.6)
2	1 (6.3)	1 (11.1)	0 (0)
Sites of disease on bPET			
Bone	2 (10)	2 (20)	0 (0)
Nodal	1 (5)	0 (0)	1 (10)
Bone + nodal	10 (50)	6 (60)	4 (40)
Visceral + bone	1 (5)	0 (0)	1 (10)
Visceral + nodal	2 (10)	1 (10)	1 (10)
Bone + nodal + visceral	4 (20)	1 (10)	3 (30)

*Data missing 1 for patient overall, 0 for progressive RECIP cohort, and 1 for nonprogressive RECIP cohort.

†Data missing for 2 patients overall, 1 for progressive RECIP cohort, and 1 for nonprogressive RECIP cohort.

‡Data missing for 13 patients overall, 6 for progressive RECIP cohort, and 7 for nonprogressive RECIP cohort.

§Data missing for 2 patients overall, 1 for progressive RECIP cohort, and 1 for nonprogressive RECIP cohort.

¶Data missing for 1 patient overall, 0 for progressive RECIP cohort, and 1 for nonprogressive RECIP cohort.

¶Data missing for 4 patients overall, 1 for progressive RECIP cohort, and 3 for nonprogressive RECIP cohort.

ECOG = Eastern Cooperative Oncology Group.

Qualitative data are number and percentage of available data in cohort; continuous data are median and IQR.

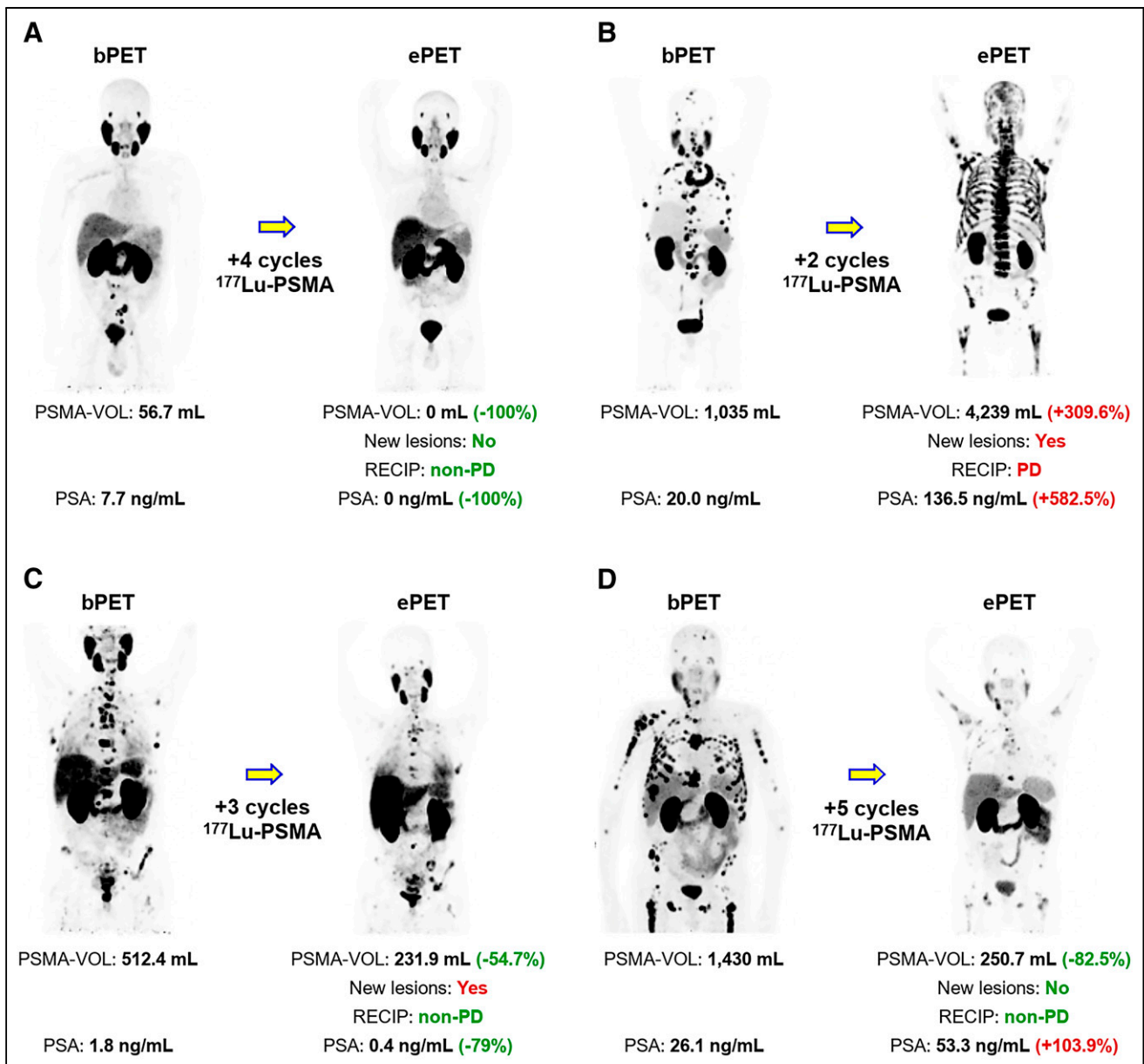


FIGURE 2. Sample cases. (A) 48-y-old man with mCRPC treated with 4 cycles of PSMA-RLT between bPET and ePET. Patient had no new lesions on ePET, was classified as non-PD on basis of PSMA-VOL and RECIP 1.0, and experienced PSA decrease of 100% from bPET to ePET. Patient had follow-up of 41.5 mo from ePET. (B) 77-y-old man with mCRPC treated with 2 cycles of PSMA-RLT between bPET and ePET. Patient had new lesions on ePET, was classified as PD on basis of PSMA-VOL and RECIP 1.0, and experienced PSA increase of 582.5% from bPET to ePET. Patient had OS of 5.0 mo from ePET. (C) 59-y-old man with mCRPC treated with 3 cycles of PSMA-RLT between bPET and ePET. Patient had new lesions on ePET but was classified as non-PD on basis of PSMA-VOL and RECIP 1.0 and experienced PSA decrease of 79% from bPET to ePET. Patient had OS of 9.7 mo from ePET. (D) 65-y-old man with mCRPC treated with 5 cycles of PSMA-RLT between bPET and ePET. Patient had no new lesions on ePET and was classified as non-PD on basis of PSMA-VOL and RECIP 1.0 but experienced PSA increase of 103.9% from bPET to ePET. Patient had OS of 11.8 mo from ePET.

progressors (4). This discrepancy illustrates the importance of incorporating quantitative, whole-body PSMA-PET parameters in response assessment. Furthermore, in a comparative analysis of criteria for therapy response assessment in mCRPC, RECIP 1.0 identified fewer patients with PD, and patients classified as PD had a higher risk of death than non-PD patients by RECIP 1.0 compared with PSMA PET Progression criteria (10). These findings suggest that the incorporation of changes in PSMA-VOL in response evaluation may be more informative than per-lesion analyses (10).

Automatic segmentation software is currently in development to provide fast and reproducible tools to extract whole-body quantitative PSMA-PET metrics and enable their widespread use in clinical practice (8,11). As an alternative to the extraction of whole-body quantitative PSMA-PET parameters, a recent study also demonstrated that RECIP 1.0 determined by visual reads had excellent interreader reliability and agreement with quantitative RECIP 1.0 as determined by semiautomatic segmentation software, and progression by visual RECIP 1.0 was prognostic for OS in mCRPC patients undergoing

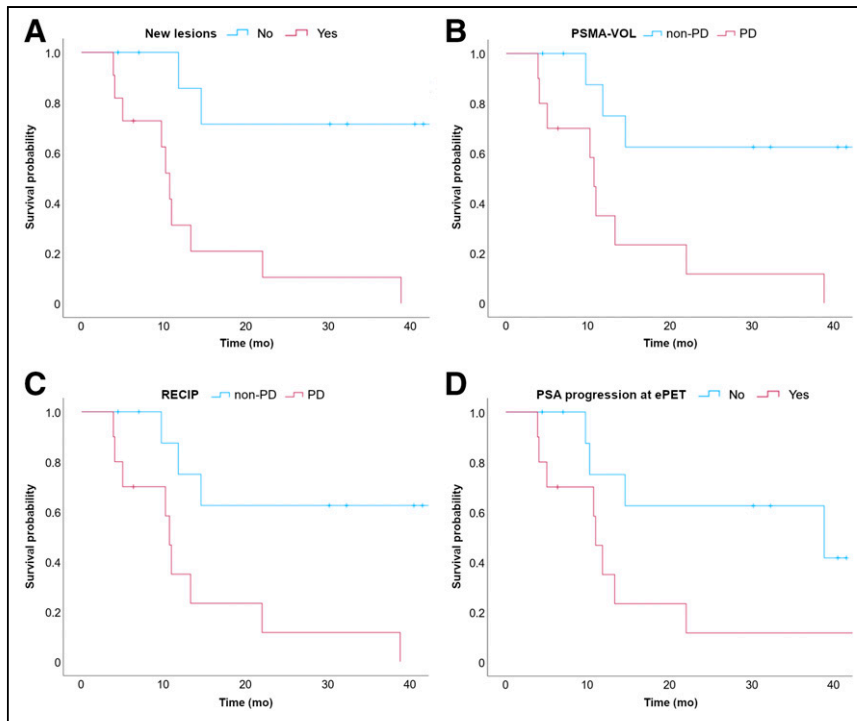


FIGURE 3. Kaplan-Meier curves. (A) Appearance of new lesions on ePET. (B) Progressive PSMA-VOL vs. nonprogressive PSMA-VOL on ePET. (C) Progressive RECIP vs. nonprogressive RECIP on ePET. (D) PSA progression status at time of ePET. PD = progressive disease.

PSMA-RLT (12). Visual RECIP can serve as an effective surrogate for quantitative changes derived from a tumor segmentation software.

The prognostic value of ePET has been extensively explored with ^{18}F -FDG in lymphoma both using visual scores (Deauville/IHC) and using quantitative parameters (changes in SUV_{max} and metabolic tumor volume) (13–16). ^{18}F -FDG PET is a response assessment and surveillance tool routinely incorporated in the management of lymphoma patients. Response monitoring and prognostic assessments based on multiple PSMA-PET parameters including ePET may be considered in the management of mCRPC patients to guide treatment decisions in a more personalized manner. However, the value of ePET for clinical management may be more limited in mCRPC patients undergoing treatment with PSMA-RLT than is end-of-treatment ^{18}F -FDG PET in lymphoma patients, since mCRPC patients rarely have a complete response to PSMA-RLT. Still, changes in PSMA-PET parameters from baseline to end of treatment may be able to predict OS and progression-free survival in mCRPC patients.

If ePET is shown to be an independent predictor of OS and progression-free survival in large, prospective trials, it can serve as an expedited novel endpoint for clinical trials assessing novel drugs.

For other molecular targeted therapeutics, there are only limited series reporting on the prognostic value of end-of-treatment PET/CT with ^{68}Ga -DOTATATE in patients with neuroendocrine tumors undergoing treatment with somatostatin receptor-targeted RLT (17). In a retrospective analysis of 12 patients, decreases in the H-lesion SUV_{max} on end-of-treatment DOTATATE PET indicated a lower risk for PD within 20 mo of therapy (18). In another retrospective analysis of 30 patients, increases in whole-body somatostatin receptor tumor volume on end-of-treatment DOTATATE PET were associated with lower OS (19). Future studies that investigate the prognostic value of whole-body targeted PET imaging metrics in patients undergoing targeted therapy are warranted.

The main limitation of this study is the selection bias inherent in its retrospective design. First, we only included patients who survived long enough to undergo ePET. Therefore, the OS from bPET in

our cohort was 19.5 mo, compared with 15.3 mo from randomization in the treatment arm of the VISION trial. This difference in OS can also be explained by the difference in patient populations: multiple patients in our cohort did not previously undergo taxane-based chemotherapy, which was a prerequisite for enrollment in the VISION trial. Second, patients were more likely to be referred to undergo a restaging PSMA-PET scan after their last PSMA-RLT cycle because of suspicion of disease progression based on PSA. Therefore, there was a general concordance between PSA progression status and characteristics on PSMA-PET. There were only 2 patients (cases 5 and 15, supplemental materials) who experienced PSA progression at ePET but were classified as non-PD on the basis of RECIP 1.0. Given the small size of our cohort, we were not able to directly compare the prognostic value of PSA with PSMA-PET in this analysis. In the original RECIP 1.0 study, among the patients without a PSA response at 12 wk (76/124, 61%), patients classified as RECIP-PR (10/76, 13%) had an OS

TABLE 3
ePET and PSA Progression

Parameter	Total	PSA progression at ePET	No PSA progression at ePET	P
Total	18	10 (55.6)	8 (44.4)	NA
New lesions on ePET	9 (50)	8 (80)*	1 (12.5)	0.015
PSMA-VOL, PD	8 (44.4)	8 (80)*	0 (0)	0.001
RECIP, PD	8 (44.4)	8 (80)*	0 (0)	0.001

*Significant by Fisher exact test.
NA = not applicable.
Data are number and percentage.

superior to that of patients without RECIP-PR (66/76, 87%): 22.7 versus 9.0 mo (4). These results demonstrate the potential added value of PSMA-PET to PSA for therapy response assessment.

Other limitations of this retrospective study include the small sample size, the use of a single PET reader, the heterogeneous number of PSMA-RLT cycles administered for each patient before ePET, and the heterogeneity of prior and concomitant mCRPC therapies. Five patients initiated other treatments in addition to PSMA-RLT between bPET and ePET (supplemental materials). Thus, the impact of PSMA-RLT on PSMA-PET findings could not be teased out in these patients.

Larger prospective trials are necessary to define the prognostic value of progression on ePET by RECIP 1.0 for progression-free survival and OS. These trials could provide data to support the use of PSMA-PET as a novel surrogate endpoint in clinical trials.

CONCLUSION

In this retrospective cohort of 20 mCRPC patients treated with PSMA-RLT, progression on ePET by the appearance of new lesions, changes in PSMA-VOL, and RECIP 1.0 was prognostic for OS. These findings warrant validation in a larger, multicentric patient cohort.

DISCLOSURE

Jeremie Calais reports prior consulting services for Advanced Accelerator Applications, Astellas, Blue Earth Diagnostics, Curium Pharma, DS Pharma, EXINI, GE Healthcare, Isoray, IBA RadioPharma, Janssen Pharmaceuticals, Lightpoint Medical, Lantheus, Monrol, Novartis, Progenics, POINT Biopharma, Radiomedix, Sanofi, and Telix Pharmaceuticals outside the submitted work. Johannes Czernin is the founder of Sofie Biosciences and Trethera Therapeutics and serves as a scientific advisor for Point Biopharma, RayzeBio, Jubilant Radiopharma, and Amgen. Matthew Rettig reports consulting services for Progenics, Amgen, INmune Bio, Bayer, Astra-Zeneca, and Myovant; receives research funding from Novartis, Merck, and Progenics; and is on the speakers' bureau for Bayer and Janssen. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the prognostic value of ePET in mCRPC patients treated with PSMA-RLT?

PERTINENT FINDINGS: In this retrospective study of 20 mCRPC patients treated with PSMA-RLT, progression on ePET by the appearance of new lesions, changes in PSMA-VOL, and RECIP 1.0 was prognostic for OS.

IMPLICATIONS FOR PATIENT CARE: Progression on ePET by RECIP 1.0 is prognostic for OS and may be considered in the management of mCRPC patients to guide treatment decisions in a more personalized manner.

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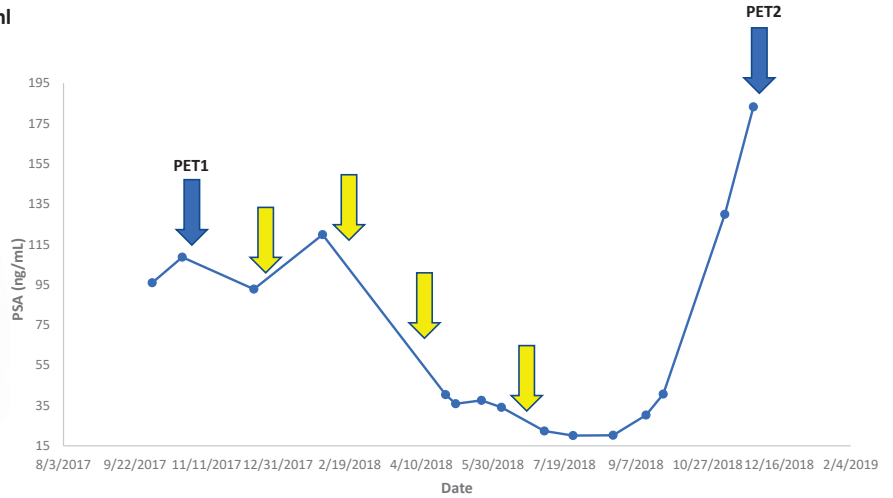
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bPSA = 108.6 ng/ml
bPET

ePSA = 183.2 ng/ml
ePET



+4 Cycles
¹⁷⁷Lu-PSMA



- 76-year-old male with mCRPC treated with 4 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Carboplatin, Taxotere, Jevtana, Zytiga, Xtandi, Xofigo, Olaparib, Provenge, Keytruda, Revlimid, and Cytosane
- Concomitant treatments (initiated before bPET): Lupron
- Subsequent treatments (initiated after ePET): ²²⁵Ac-J591
- Time from bPET to ePET: 13.3 months
- Time from last cycle to ePET: 5.5 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+531.9%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +68.7%
- OS from ePET: 4.0 months

Patient #01

CONCORDANT CASE

PD by RECIP / PSA Progression at ePET

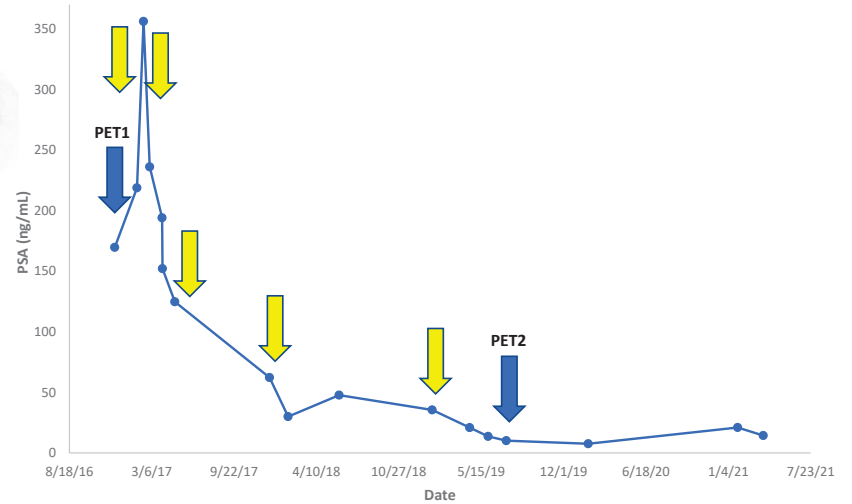
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bPSA = 218.7 ng/ml
bPET

ePSA = 13.6 ng/ml
ePET



+5 Cycles
¹⁷⁷Lu-PSMA



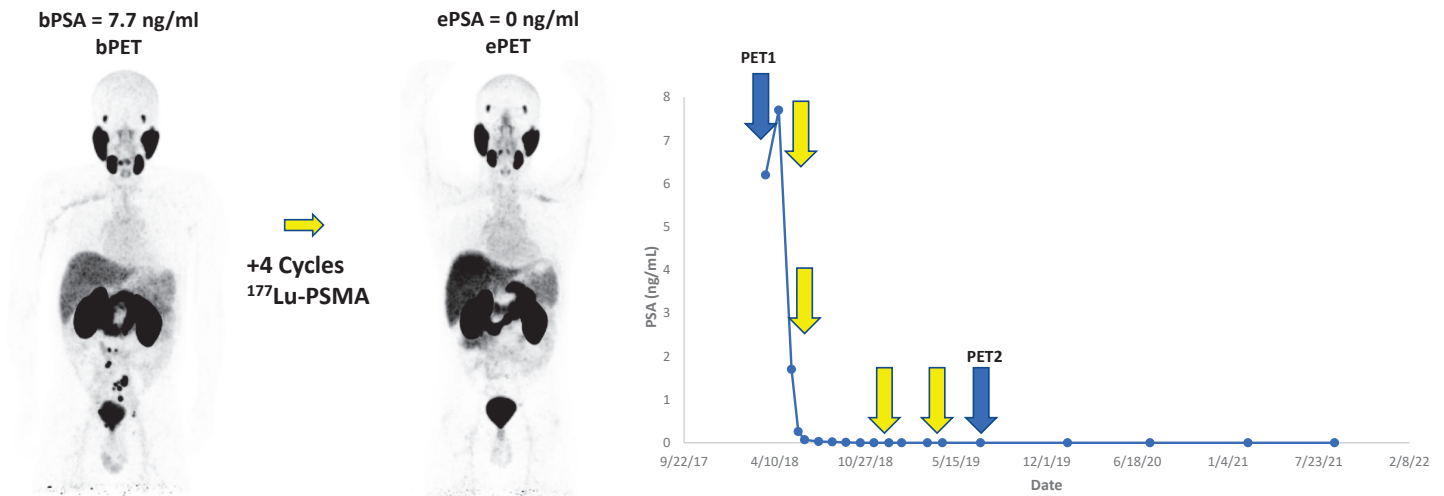
- 66-year-old male with mCRPC treated with 5 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: NK cell immunotherapy
- Concomitant treatments (initiated between bPET and ePET): Proton beam therapy after cycle 5
- Subsequent treatments (initiated after ePET): ¹⁷⁷Lu-PSMA RLT (separate treatment course)
- Time from bPET to ePET: 29.6 months
- Time from last cycle to ePET: 6.0 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-75.8%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: -93.8%
- Follow-up from ePET: 32.2 months

Patient #02

CONCORDANT CASE

non-PD by RECIP / No PSA Progression at ePET

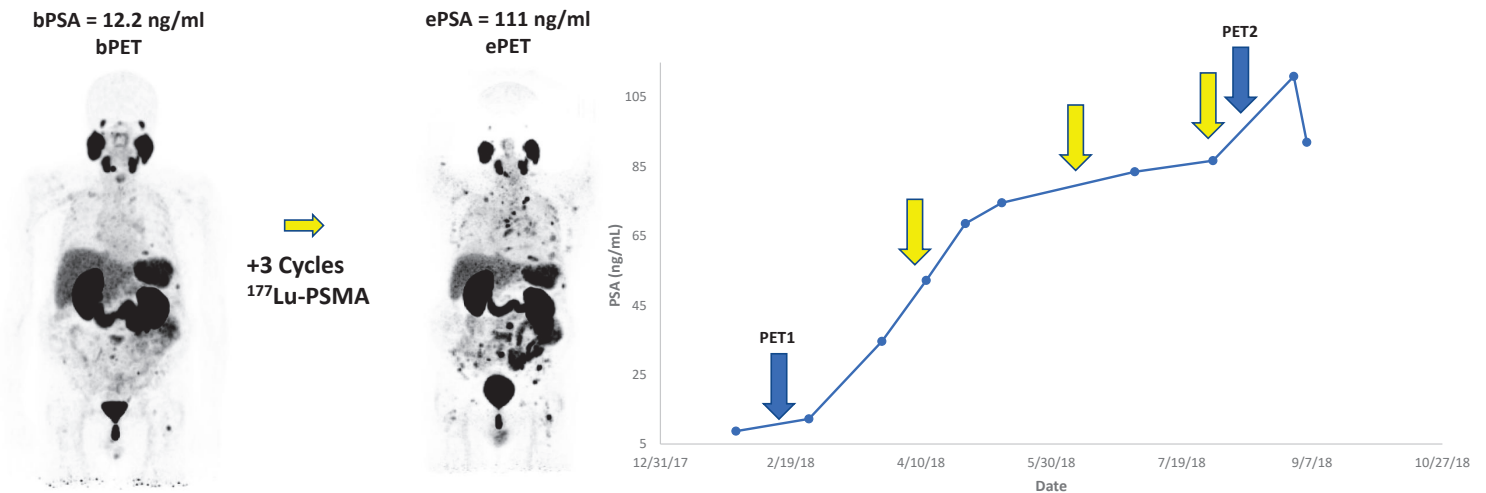
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- 48-year-old male with mCRPC treated with 4 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Zytiga
- Concomitant treatments (initiated between bPET and ePET): Lupron, Zytiga, Prednisone before cycle 1
- Subsequent treatments (initiated after ePET): Stereotactic body radiation therapy
- Time from bPET to ePET: 13.9 months
- Time from last cycle to ePET: 1.9 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-100.0%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: -100.0%
- Follow-up from ePET: 41.5 months

Patient #03
CONCORDANT CASE
non-PD by RECIP / No PSA Progression at ePET

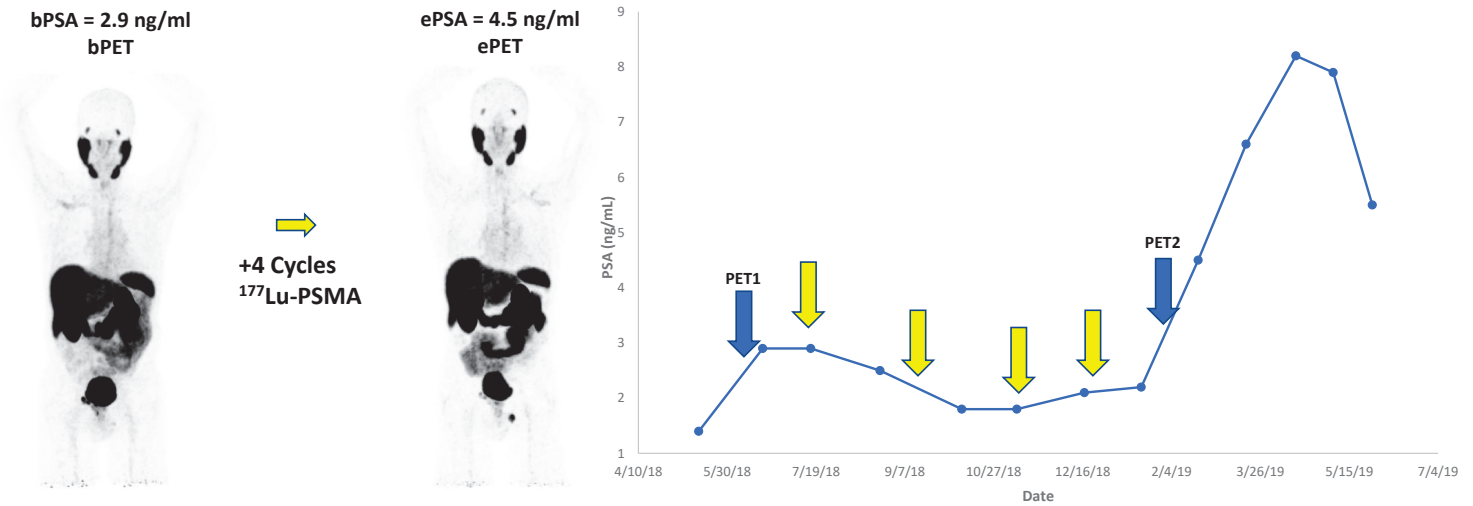
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- 77-year-old male with mCRPC treated with 3 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Taxotere, Jevtana, Zytiga, Xtandi, Provenge, Keytruda
- Subsequent treatments (after ePET): Xtandi, Xofigo
- Time from bPET to ePET: 6.2 months
- Time from last cycle to ePET: 0.5 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+252.2%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +807.6%
- OS from ePET: 13.3 months

Patient #04
CONCORDANT CASE
PD by RECIP / PSA Progression at ePET

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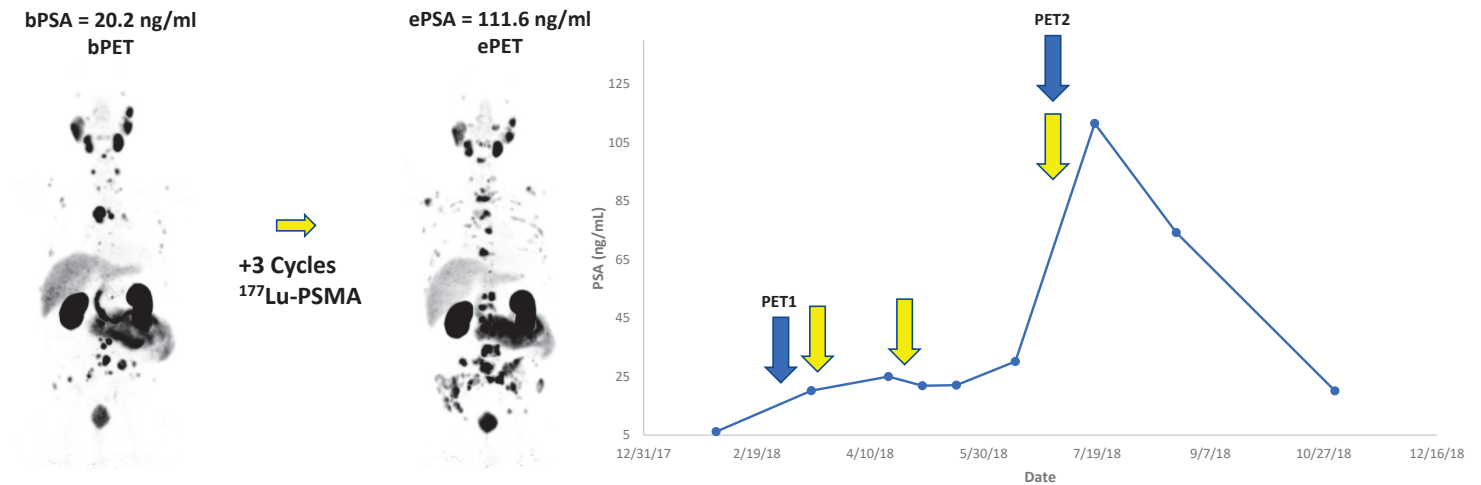


- 68-year-old male with mCRPC treated with 4 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Lupron, Casodex, Zytiga
- Concomitant treatments (initiated before bPET): Zytiga
- Subsequent treatments (initiated after ePET): Jevtana, Carboplatin, Stereotactic body radiation therapy, Etrumadenant, Zimberelimab, Cyclophosphamide
- Time from bPET to ePET: 8.4 months
- Time from last cycle to ePET: 2.4 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-23.8%), no new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +55.2%
- Follow-up from ePET: 44.9 months

Patient #05
DISCORDANT CASE

non-PD by RECIP / PSA Progression at ePET

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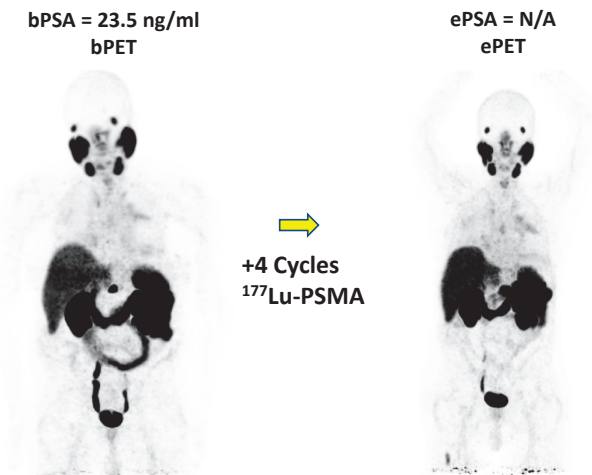


- 73-year-old male with mCRPC treated with 3 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Taxotere, Jevtana, Xtandi, Provenge, Sipuleucel-T
- Concomitant treatments (initiated before bPET): Lupron
- Subsequent treatments (initiated after ePET): Zytiga, Xofigo, Keytruda, Taxotere, Carboplatin, Olaparib, Nubeqa
- Time from bPET to ePET: 4.3 months
- Time from last cycle to ePET: 0.0 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+239.4%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +451.9%
- OS from ePET: 22.0 months

Patient #06
CONCORDANT CASE

PD by RECIP / PSA Progression at ePET

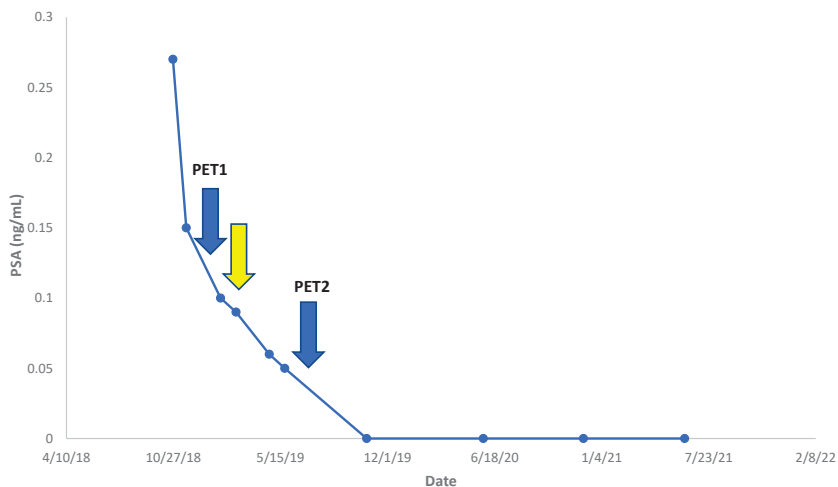
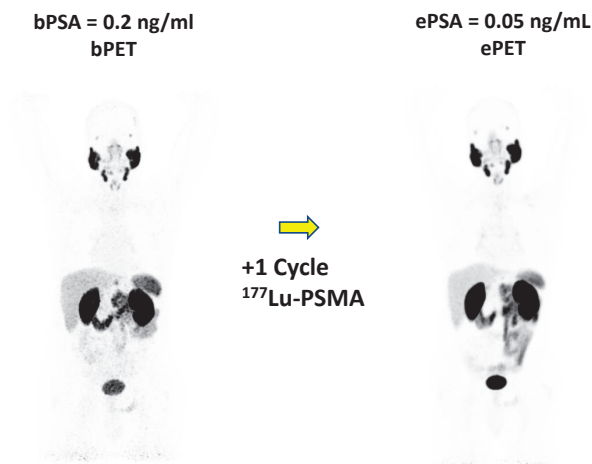
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- 80-year-old male with mCRPC treated with 4 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Lupron, Casodex, Carboplatin, Taxotere, Jevtana, Zytiga, Xtandi, Provenge, Keytruda
- Concomitant treatment (initiated before bPET): Lupron, Zytiga, Xtandi
- Time from bPET to ePET: 9.0 months
- Time from last cycle to ePET: 2.0 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-83.6%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: N/A
- OS from ePET: 14.5 months

Patient #07
CONCORDANT CASE
non-PD by RECIP / PSA Progression at ePET

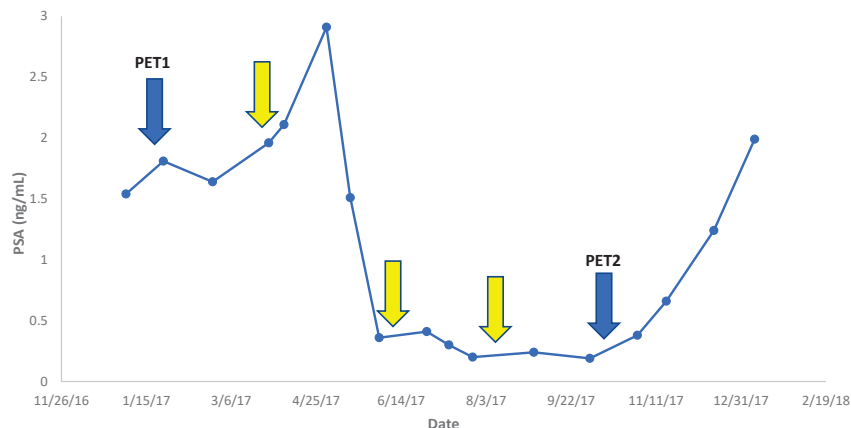
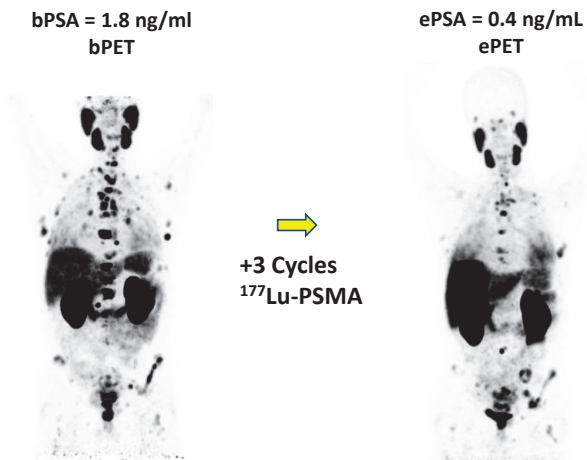
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- 70-year-old male with mCRPC treated with 1 cycle of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radiation therapy, Lupron, Zytiga
- Concomitant treatments (initiated before bPET): Lupron, Zytiga, Prednisone
- Time from bPET to ePET: 6.1 months
- Time from last cycle to ePET: 6.0 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-80.1%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: -66.7%
- Follow-up from ePET: 40.4 months

Patient #08
CONCORDANT CASE
non-PD by RECIP / No PSA Progression at ePET

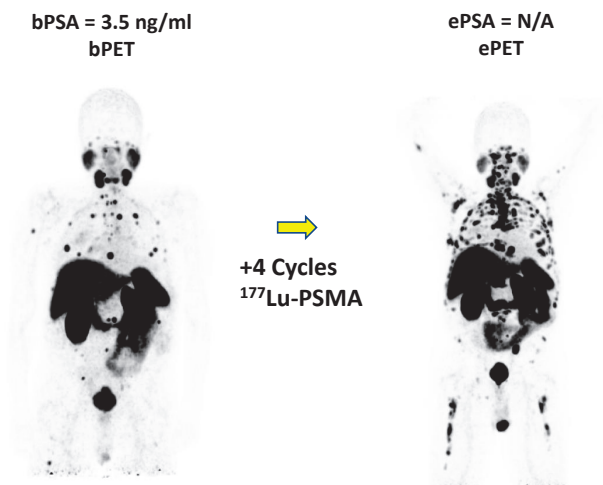
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- 59-year-old male with mCRPC treated with 3 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Lupron, Carboplatin, Taxotere, Jevtana, Zytiga, Xtandi, Xofigo, Cabozantinib, Everolimus
- Concomitant treatments (initiated before bPET): Lupron, Xtandi
- Concomitant treatments (initiated between bPET and ePET): Increased dose of Xtandi before cycle 1, subsequently held and restarted at original dose after cycle 1
- Subsequent treatments (initiated after ePET): Stereotactic body radiation therapy, Olaparib, Zytiga
- Time from bPET to ePET: 9.3 months
- Time from last cycle to ePET: 2.5 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-54.7%), new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: -79.0%
- OS from ePET: 9.7 months

Patient #09
CONCORDANT CASE
non-PD by RECIP / No PSA Progression at ePET

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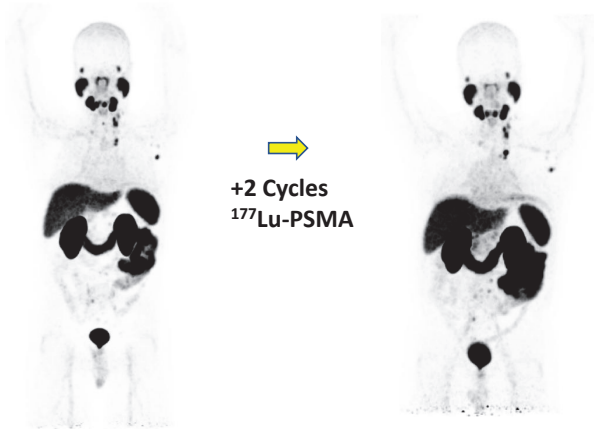
- 59-year-old male with mCRPC treated with 4 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Taxotere, Zytiga, Xtandi, Sipuleucel-T, Opdivo, Yervoy
- Concomitant treatments (initiated before bPET): Zytiga
- Time from bPET to ePET: 6.3 months
- Time from last cycle to ePET: 0.0 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+1396.0%), new lesions on ePET)
- PSA progression at the time of ePET: N/A
- PSA change at the time of ePET: N/A
- OS from ePET: 10.2 months

Patient #10
CONCORDANT CASE
PD by RECIP / Could not assess PSA Progression

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bPSA = 0.4 ng/ml
bPET

ePSA = N/A
ePET



- 57-year-old male with mCRPC treated with 2 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Zytiga, Xtandi, Provenge, Leukine, Vivelle
- Concomitant treatments (initiated before bPET): Xtandi, Lupron, Leukine
- Subsequent treatments (initiated after ePET): Nubeqa, Stereotactic body radiation therapy, Taxotere
- Time from bPET to ePET: 4.3 months
- Time from last cycle to ePET: 1.1 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (+12.3%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: N/A
- Follow-up from ePET: 30.1 months

Patient #11

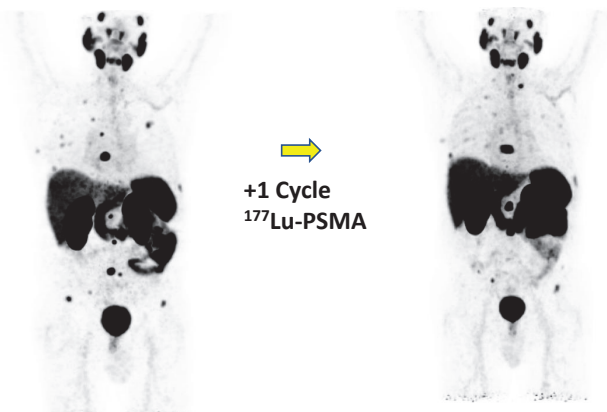
CONCORDANT CASE

non-PD by RECIP / No PSA Progression at ePET

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bPSA = 7.2 ng/ml
bPET

ePSA = 11.0 ng/mL
ePET



- 71-year-old male with mCRPC treated with 1 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Zytiga, Xtandi, Provenge, Opdivo, Yervoy
- Concomitant treatments (initiated before bPET): Zytiga, Xtandi
- Subsequent treatments (initiated after ePET): ²²⁵Ac-PSMA RLT, Taxotere, Carboplatin, Jevtana, Olaparib, Xofigo, Nubeqa
- Time from bPET to ePET: 4.1 months
- Time from last cycle to ePET: 1.9 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+132.8%), new lesions on ePET)
- PSA progression at the time of ePET: N/A
- PSA change at the time of ePET: +52.0%
- OS from ePET: 38.8 months

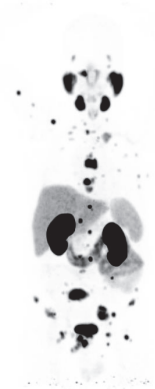
Patient #12

CONCORDANT CASE

PD by RECIP / Could not assess PSA Progression

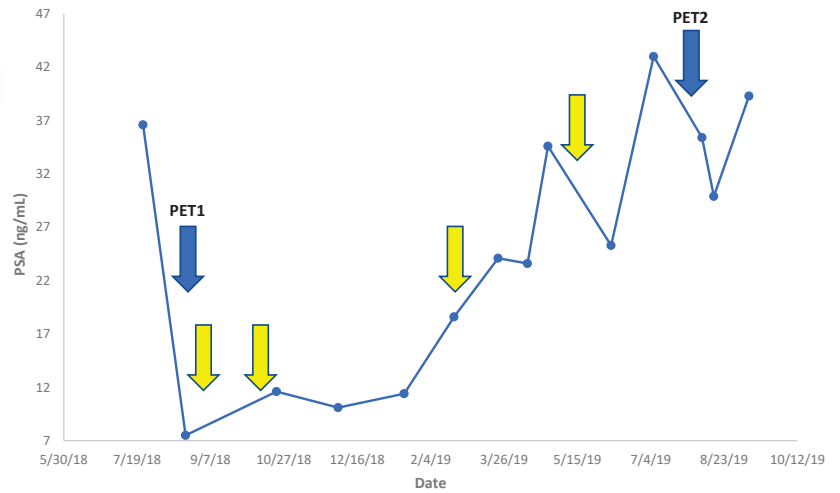
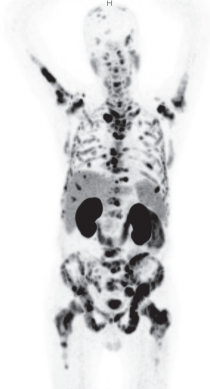
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bPSA = 7.5 ng/ml
bPET



+3 Cycles
¹⁷⁷Lu-PSMA

ePSA = 35.4 ng/ml
ePET



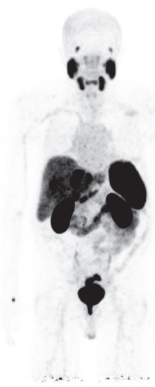
- 67-year-old male with mCRPC treated with 3 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radiation therapy, Lupron, Casodex
- Concomitant treatments (initiated before bPET): Lupron, Xgeva
- Concomitant treatments (initiated between bPET and ePET): Stereotactic body radiation therapy before cycle 1 and after cycle 3, ²²⁵Ac/¹⁷⁷Lu RLT on cycle 4, Taxotere
- Subsequent treatments (initiated after ePET): Xtandi
- Time from bPET to ePET: 11.9 months
- Time from last cycle to ePET: 5.1 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+478.1%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +372.0%
- OS from ePET: 3.9 months

Patient #13
CONCORDANT CASE

PD by RECIP / PSA Progression at ePET

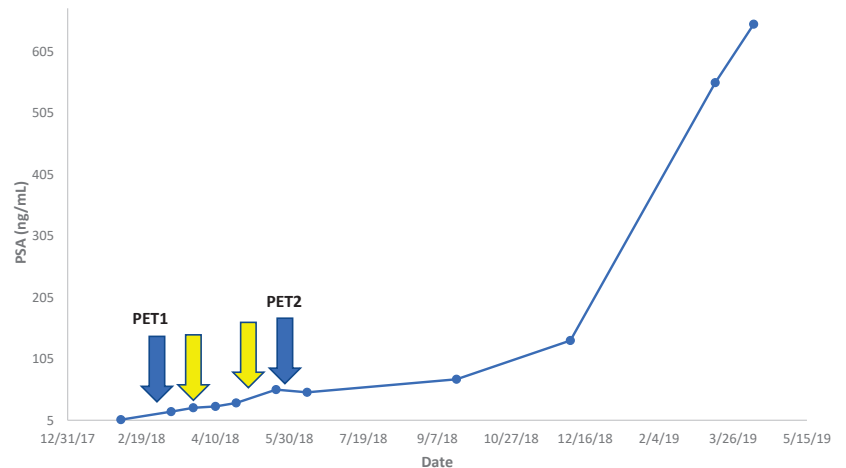
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bPSA = 19.1 ng/ml
bPET



+2 Cycles
¹⁷⁷Lu-PSMA

ePSA = 54.9 ng/ml
ePET

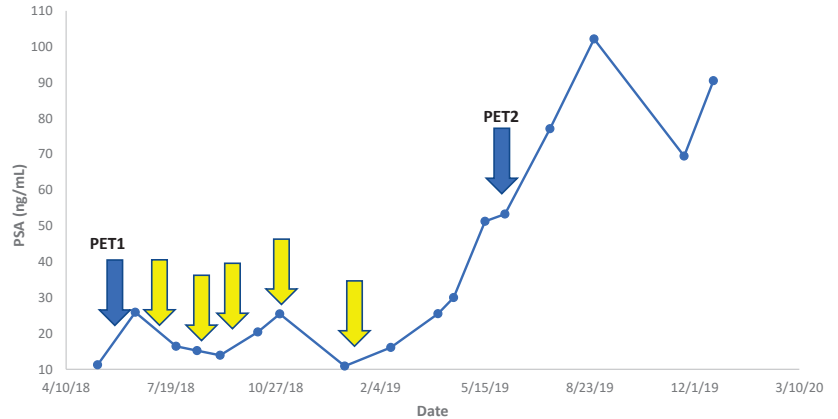
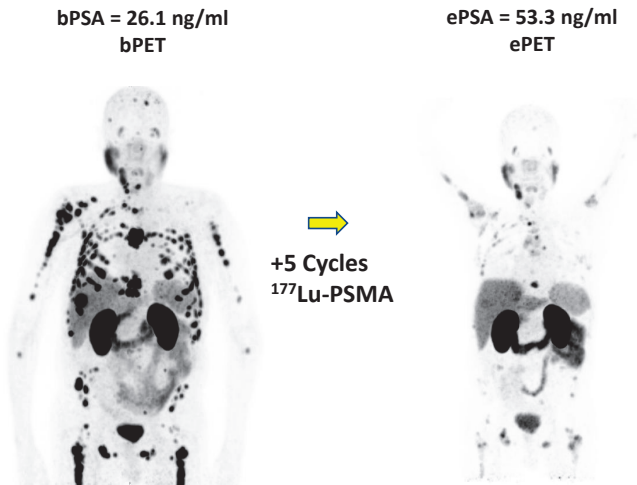


- 74-year-old male with mCRPC treated with 2 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Taxotere, Zytiga, Xtandi, Provenge, Keytruda
- Concomitant treatments (initiated before bPET): Lupron, Zytiga
- Subsequent treatments (initiated after ePET): Jevtana, Cisplatin, Gentamicin, ⁹⁰Y, Rituximab, Mitoxantrone
- Time from bPET to ePET: 3.2 months
- Time from last cycle to ePET: 0.7 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+111.3%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +187.3%
- OS from ePET: 10.9 months

Patient #14
CONCORDANT CASE

PD by RECIP / PSA Progression at ePET

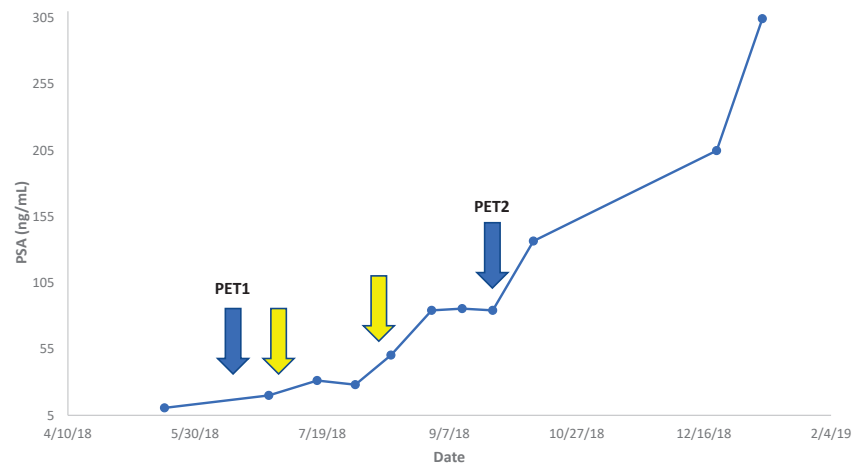
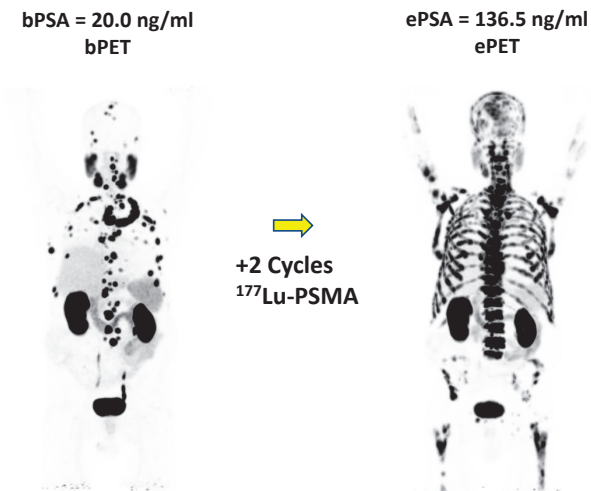
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- 65-year-old male with mCRPC treated with 5 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Taxotere, Jevtana, Zytiga, Xtandi, Xofigo, ¹⁵³Sm, Provenge, Keytruda, Revlimid
- Concomitant treatments (initiated before bPET): Xtandi, Zytiga, Keytruda
- Concomitant treatments (initiated between bPET and ePET): Stereotactic body radiation therapy after cycle 3, Lupron after cycle 4
- Subsequent treatments (initiated after ePET): Taxotere, Carboplatin
- Time from bPET to ePET: 12.4 months
- Time from last cycle to ePET: 4.0 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-82.5%), no new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +103.9%
- OS from ePET: 11.8 months

Patient #15
DISCORDANT CASE
non-PD by RECIP / PSA Progression at ePET

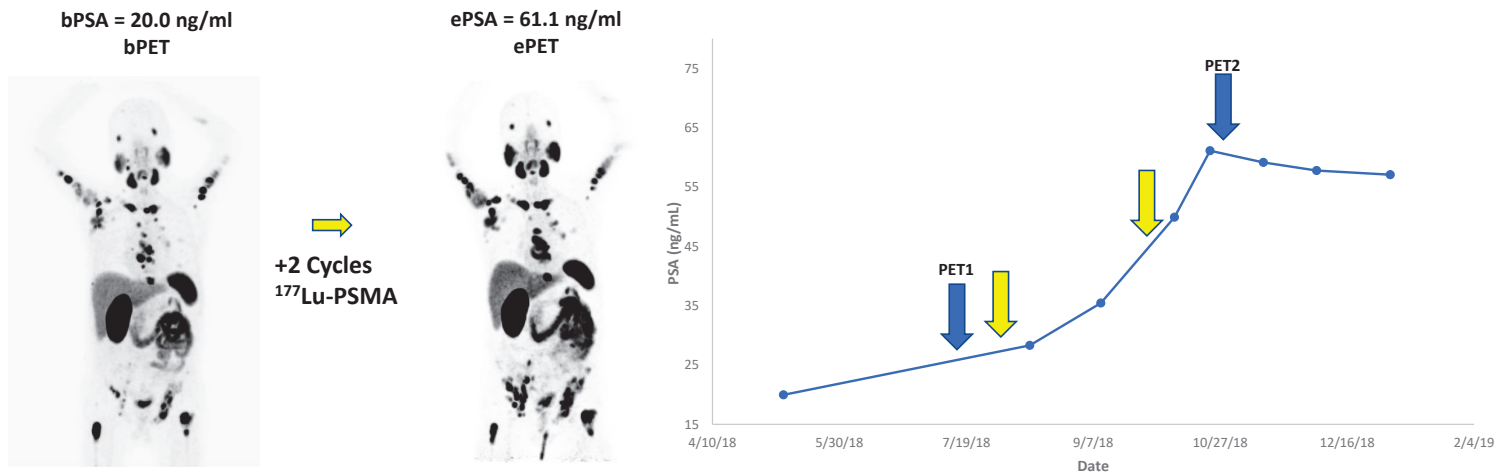
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- 77-year-old male with mCRPC treated with 2 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Lupron, Radiation therapy, Zytiga, Olaparib
- Subsequent treatments (initiated after ePET): Taxotere, Carboplatin, Xtandi
- Time from bPET to ePET: 4.0 months
- Time from last cycle to ePET: 1.7 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+309.6%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +582.5%
- OS from ePET: 5.0 months

Patient #16
CONCORDANT CASE
PD by RECIP / PSA Progression at ePET

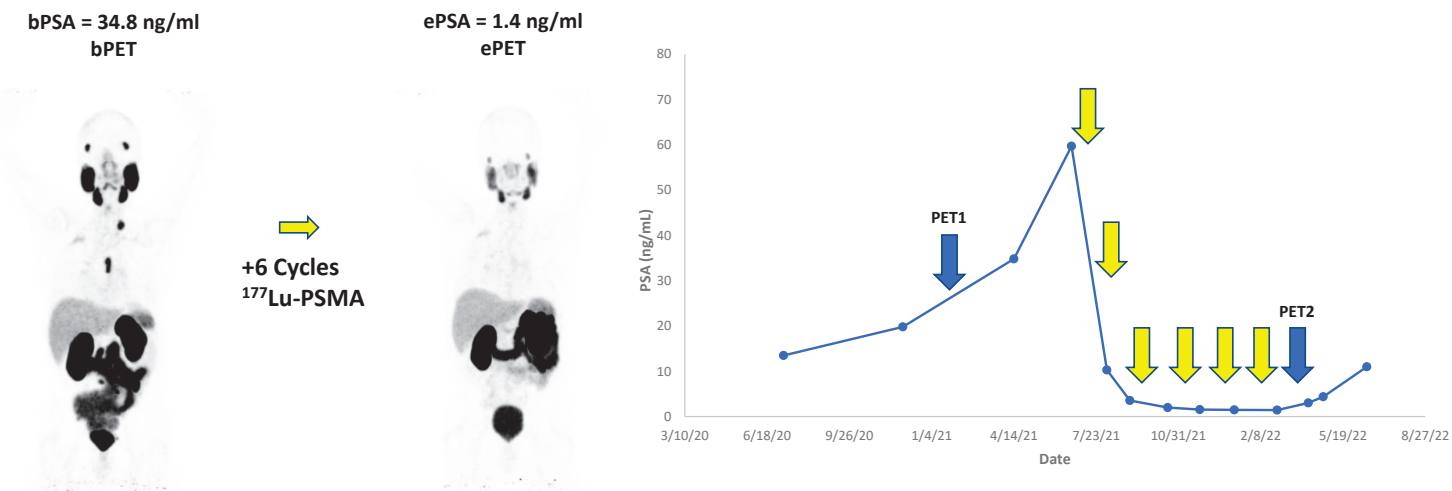
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- 68-year-old male with mCRPC treated with 2 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radiation therapy, Taxotere, Zytiga, Xtandi, Xofigo, Provenge
- Concomitant treatments (initiated before bPET): Lupron
- Subsequent treatments (initiated after ePET): Jevtana, Zytiga, Carboplatin
- Time from bPET to ePET: 3.4 months
- Time from last cycle to ePET: 1.2 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+30.6%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +206.2%
- OS from ePET: 10.7 months

Patient #17
CONCORDANT CASE
PD by RECIP / PSA Progression at ePET

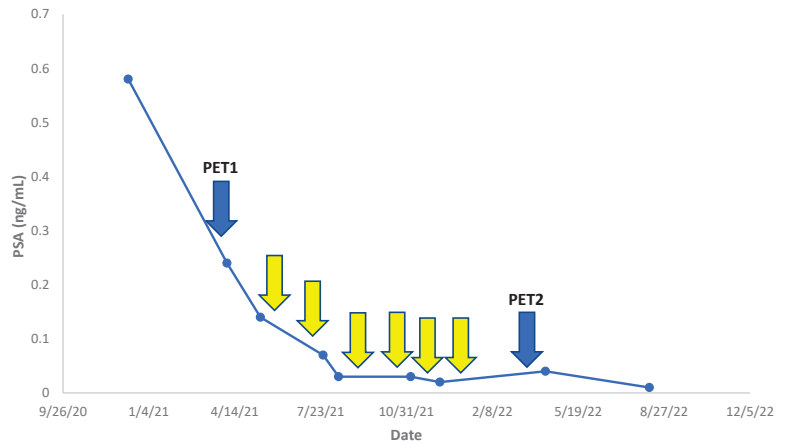
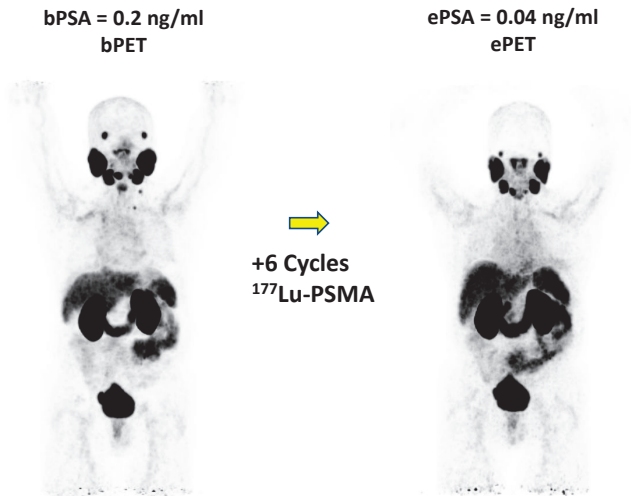
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- 73-year-old male with mCRPC treated with 6 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radical prostatectomy, Zytiga, Xtandi, Nubeqa, Revlimid, Olaparib
- Subsequent treatments (initiated after ePET): Zytiga, Prednisone, Provenge
- Time from bPET to ePET: 12.6 months
- Time from last cycle to ePET: 1.4 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-100.0%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: -95.9%
- Follow-up from ePET: 7.0 months

Patient #18
CONCORDANT CASE
non-PD by RECIP / No PSA Progression at ePET

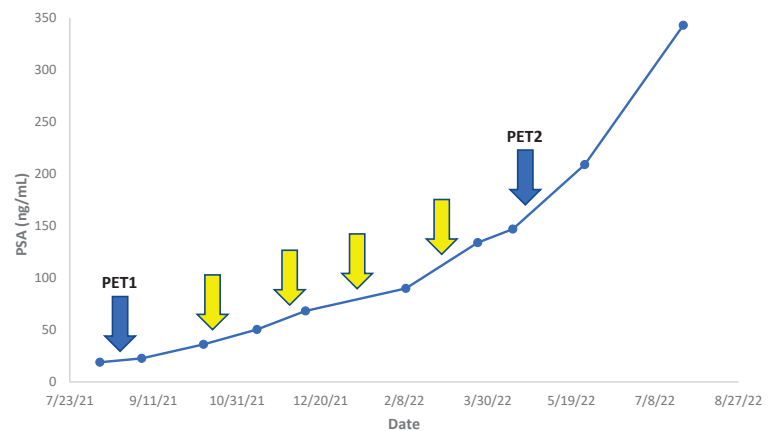
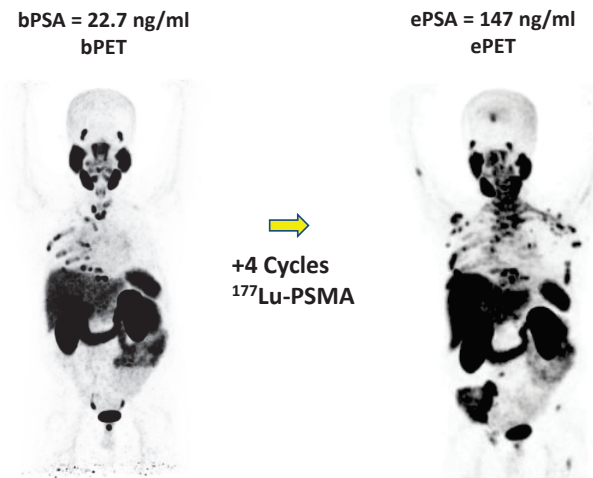
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- 75-year-old male with mCRPC treated with 6 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Lupron, Taxotere, Xtandi, RLT
- Concomitant treatments (initiated before bPET): Lupron, Xtandi
- Time from bPET to ePET: 12.4 months
- Time from last cycle to ePET: 3.3 months
- PSMA PET RECIP classification: **non-PD** (non-PD by PSMA-VOL (-2.0%), no new lesions on ePET)
- PSA progression at the time of ePET: No
- PSA change at the time of ePET: -83.3%
- Follow-up from ePET: 4.4 months

Patient #19
CONCORDANT CASE
non-PD by RECIP / No PSA Progression at ePET

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- 67-year-old male with mCRPC treated with 4 cycles of ¹⁷⁷Lu-PSMA RLT
- Primary and previous mCRPC systemic treatments: Radiation therapy, Casodex, Firmagon, Taxotere, Zytiga, Xtandi
- Subsequent treatments (initiated after ePET): Xofigo, Radiation therapy
- Time from bPET to ePET: 7.9 months
- Time from last cycle to ePET: 1.8 months
- PSMA PET RECIP classification: **PD** (PD by PSMA-VOL (+745.2%), new lesions on ePET)
- PSA progression at the time of ePET: Yes
- PSA change at the time of ePET: +547.6%
- Follow-up from ePET: 6.3 months

Patient #20
CONCORDANT CASE
PD by RECIP / PSA Progression at ePET

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Third Topic : Beyond the approved use of PSMA theranostics.

Article 8:

Title: The impact of monosodium glutamate on ^{68}Ga -PSMA-11 biodistribution in men with prostate cancer: a prospective randomized, controlled, imaging study.

Authors: Armstrong WR, Gafita A, Zhu S, Thin P, Nguyen K, Alano RM, Lira S, Booker K, Gardner L, Grogan T, Elashoff D, Allen-Auerbach MS, Dahlbom MS, Czernin J, **Calais J.**

Reference: *J Nucl Med.* 2021 Sep 1;62(9):1244-1251. doi: 10.2967/jnumed.120.257931. PMID: 33509974

Brief Outline:

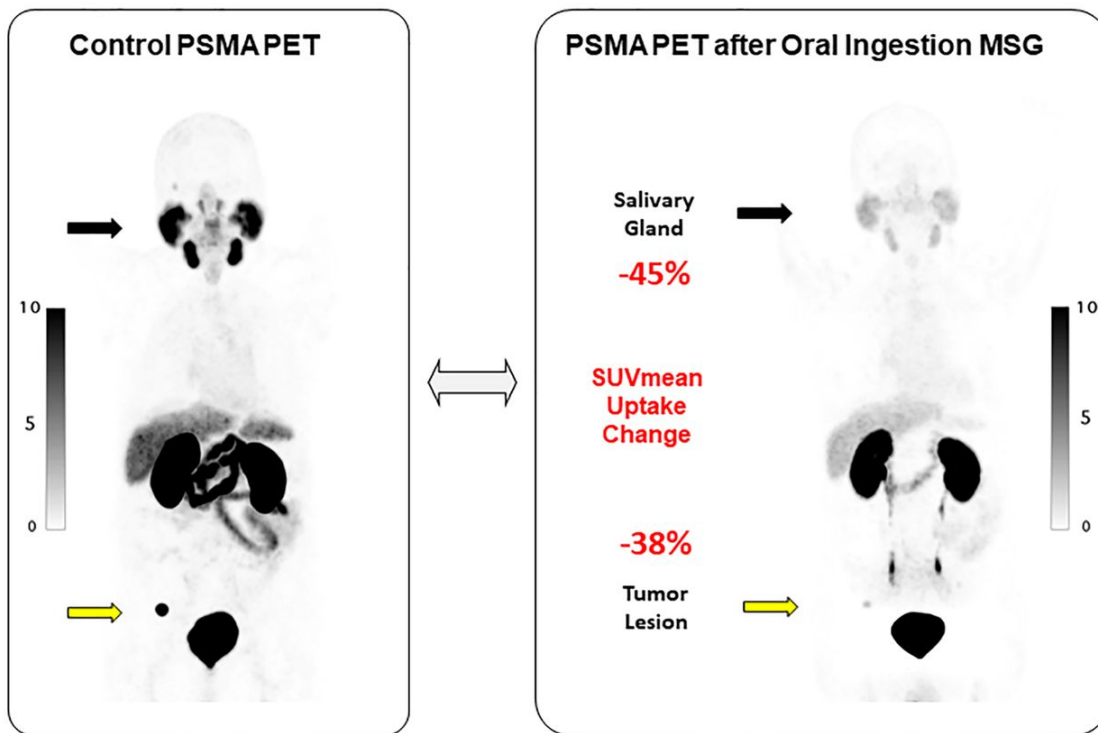
Xerostomia is a common side effect of RLT because of the high salivary gland uptake of PSMA radioligands. Here, we aimed to determine the impact of monosodium glutamate (MSG) administration on PSMA-radioligand biodistribution within healthy organs and tumor lesions by using ^{68}Ga -PSMA-11 PET imaging.

The junior first author was Wesley R Armstrong, who was working as clinical research coordinator before entering in an MD/PhD program at UCLA.

The paper published in JNM in 2021 received the SNMMI Alavi–Mandell Award in 2022.

The impact of monosodium glutamate (MSG) on ^{68}Ga -PSMA-11 biodistribution in men with prostate cancer

A PROSPECTIVE CONTROLLED IMAGING TRIAL
Paired PSMA PET scans in 16 patients with Prostate Cancer



Significant effect of oral ingestion of MSG on ^{68}Ga -PSMA-11 distribution

The Impact of Monosodium Glutamate on ⁶⁸Ga-PSMA-11 Biodistribution in Men with Prostate Cancer: A Prospective Randomized, Controlled Imaging Study

Wesley R. Armstrong*¹, Andrei Gafita*¹, Shaojun Zhu¹, Pan Thin¹, Kathleen Nguyen¹, Rejah Alano¹, Stephanie Lira¹, Kiara Booker¹, Linda Gardner¹, Tristan Grogan², David Elashoff², Martin Allen-Auerbach^{1,3,4}, Magnus Dahlbom^{1,5}, Johannes Czernin^{1,3-5}, and Jeremie Calais^{1,3-5}

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The prostate-specific membrane antigen (PSMA) has been targeted for PET imaging and radioligand therapy (RLT) in patients with prostate cancer. Xerostomia is a common side effect of RLT because of the high salivary gland uptake of PSMA radioligands. Here, we aimed to determine the impact of monosodium glutamate (MSG) administration on PSMA-radioligand biodistribution within healthy organs and tumor lesions by using ⁶⁸Ga-PSMA-11 PET imaging. **Methods:** Sixteen men with prostate cancer were randomized (1:1) into oral ingestion and oral topical application (“swishing”) arms. Each subject underwent 2 ⁶⁸Ga-PSMA-11 PET/CT scans within 14 d under baseline and MSG conditions. The salivary glands and whole-body tumor lesions were segmented using qPSMA software. We quantified tracer uptake via SUV_{mean} and SUV_{max} and compared parameters within each patient. **Results:** For the oral ingestion arm, salivary gland SUV_{mean} and SUV_{max} decreased on average from the control scan to the MSG scan by 45% ± 15% (*P* = 0.004) and 53% ± 11% (*P* < 0.001), respectively. Tumor lesion SUV_{mean} and SUV_{max} also decreased by 38% (interquartile range, −67% to −33%) and −52% (interquartile range, −70% to −49%), respectively (*P* = 0.018). Swishing had no significant effect on ⁶⁸Ga-PSMA-11 accumulation in normal organs or tumor lesions. **Conclusion:** Oral ingestion but not topical application of MSG reduced ⁶⁸Ga-PSMA-11 uptake in salivary glands. Tumor uptake also declined; therefore, the clinical application of MSG is unlikely to be useful in the framework of RLT.

Key Words: monosodium glutamate; PSMA; PET/CT; xerostomia; salivary glands;

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DOI: 10.2967/jnumed.120.257931

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein highly overexpressed by prostate cancer (PCa) cells (1). In recent years, PSMA has become an attractive target for both diagnosis and treatment of PCa (2). After their

introduction for whole-body imaging with PET/CT, small-molecule PSMA ligands with a DOTA chelator, such as PSMA I&T or PSMA-617, were labeled with β-emitting (¹⁷⁷Lu) or α-emitting (²²⁵Ac) isotopes for therapeutic purposes. PSMA-targeted radioligand therapy (RLT) with ¹⁷⁷Lu demonstrated significant reductions in serum prostate-specific antigen (PSA) levels in phase 2 trials of metastatic castration-resistant PCa (3) and is currently being investigated in a phase 3 trial (VISION: NCT03511664). PSMA RLT with ²²⁵Ac, an α-emitter with a high energy deposition, may have enhanced therapeutic efficacy but has a less favorable toxicity profile (4, 5). The most concerning side effects include xerostomia, long-term nephrotoxicity, and myelosuppression (6–8). In particular, ²²⁵Ac-PSMA is associated with grade 2 or higher xerostomia, which often led to treatment cessation despite an initially favorable PSA response (4, 5, 9, 10). After the preliminary effects of ²²⁵Ac-PSMA on serum PSA levels, multiple efforts have failed to apply protective measures against salivary gland and kidney toxicity (11–14).

The salivary gland binding and uptake mechanism of PSMA radioligands remain unclear. There appears to be limited target expression by the salivary glands (low or intermediate immunohistochemistry PSMA staining intensity; patchy and focal expression, limited in extent [5% of salivary gland tissue]), whereas radioligand uptake is very high (15). In contrast, PSMA-targeted radioantibodies, such as ¹¹¹In-J591 and ¹⁷⁷Lu-J591, do not accumulate in the salivary glands or accumulate only at low levels (16). The high accumulation of the PSMA radioligands in the salivary glands may thus represent an off-target effect (i.e., related not to the PSMA target expression but to the radioligand molecules).

PSMA (also known as glutamate carboxypeptidase II) is targeted by small molecules via interaction of the glutamate moiety of the radioligands (among other features) with its enzymatic region, which has high glutamate affinity (17–19). Therefore, it was hypothesized that the administration of monosodium glutamate (MSG), a well-known food additive, could act as a competitor by blocking the binding of the PSMA-targeting radioligands. In a pre-clinical model, MSG reduced ⁶⁸Ga-PSMA-11 salivary gland and renal uptake, whereas tumor accumulation was unaffected, in LNCap-bearing mice (20). Moreover, MSG stimulates salivary flow as shown in a controlled study, with up to a 1 mL/min mean salivary flow compared with 0.25 mL/min at baseline (21). We

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Guest Editor: Todd E. Peterson, Vanderbilt University.
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also hypothesized that MSG could be used as an oral salivary flow stimulant to remove accumulated radioligands from the salivary glands.

^{68}Ga -PSMA-11 PET imaging is a rapid, noninvasive, and safe technique that provides reliable estimates of the biodistribution of therapeutic PSMA ligands.

In this imaging-controlled study on men with PCa, we determined the impact of MSG administration on PSMA-radioligand biodistribution in normal organs and tumors by using ^{68}Ga -PSMA-11 PET/CT with and without MSG administration. We tested 2 administration methods: “swishing” (i.e., oral topical, to increase the salivary flow) and oral ingestion (for competitive binding).

MATERIALS AND METHODS

Study Design and Patient Population

This was a prospective single-center, open-label, randomized, controlled imaging study conducted at UCLA using 16 paired PSMA PET/CT studies with (MSG scan) and without (control scan) MSG administration, with less than 14 d between the 2 scans. The study was investigator-initiated, self-funded, conducted under an investigational new drug application (application 130649), approved by the local institutional review board (approval 18-001776), and registered on clinicaltrials.gov (NCT04282824).

Patients with histopathologically proven PCa who volunteered to undergo 2 PSMA PET/CT scans within 14 d and without any treatment change between the 2 scans were eligible. Patients with prior salivary gland surgery or radiation therapy, a history of salivary gland disease, severe uncontrolled hypertension, or a known allergic responses to MSG or who were unable to comply with the study procedures were excluded (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>). We obtained oral and written informed consent from all patients.

To preclude the potential confounding factor of stimulus effect, patients were initially randomized into 2 arms based on the type of MSG administration: oral ingestion ($n = 8$) and swishing ($n = 8$). A second

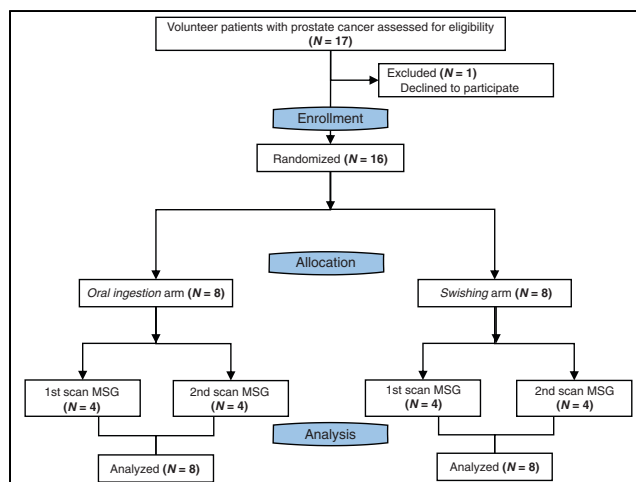


FIGURE 1. Study flowchart.

randomization process subdivided the patients into receiving the control or MSG scan first. Figure 1 depicts the study flowchart.

Procedures

MSG Administration. We obtained food-grade MSG as a sealed salt powder (Ajinomoto). The U.S. Food and Drug Administration has designated MSG to be generally recognized as safe. Patients randomized to oral ingestion received a 150 mg/kg dose of food-grade MSG dissolved in 300 mL of drinking-grade water 30 min before ^{68}Ga -PSMA-11 injection. Patients randomized to swishing received 0.5 M MSG, which they swished within the mouth for 30 s before removing the solution without swallowing. The swishing procedure was repeated at 0, 30, and 45 min after ^{68}Ga -PSMA-11 injection.

Image Acquisition. ^{68}Ga -PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga (HBED-CC)]) was used as the PSMA ligand and was obtained from the Biomedical Cyclotron Facility at UCLA. ^{68}Ga -PSMA-11 PET/CT imaging was performed according to international guidelines (22). The target injected activity dose was 185 MBq (allowed range, 111–259

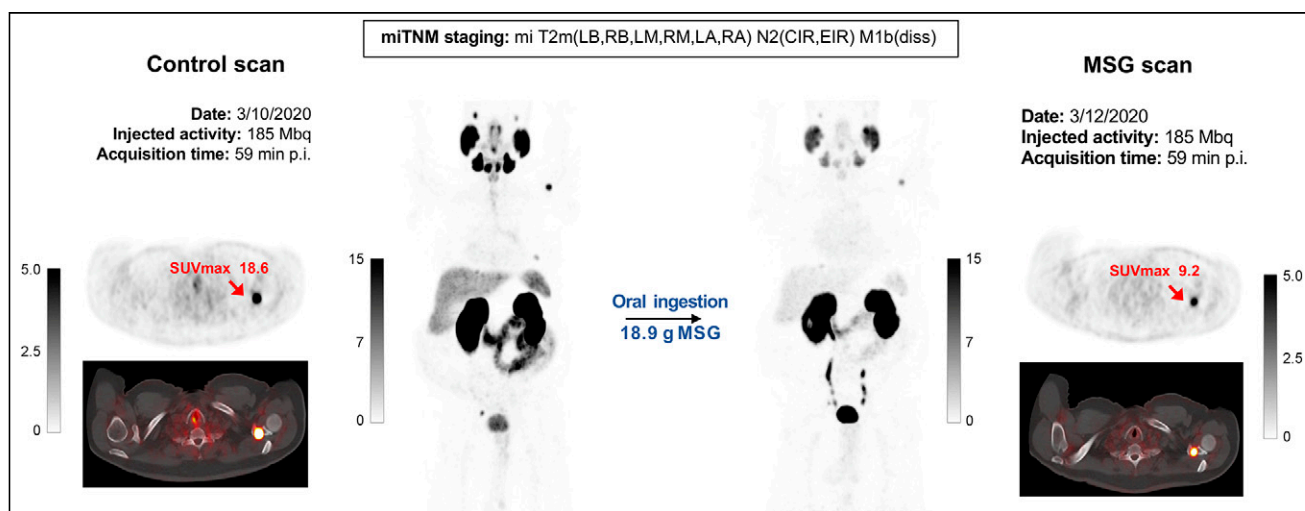


FIGURE 2. Set of images of 73-year-old patient after radiation therapy (initial PSA, 16 ng/mL; biopsy Gleason score, 8; pT2c) and concurrent androgen hormone treatment, currently presenting for rising PSA value (6.27 ng/mL). After enrollment, patient was randomized to oral ingestion arm and received 18.9 g of MSG before second ^{68}Ga -PSMA-11 injection. PSMA PET/CT images revealed multifocal prostate involvement, common iliac right and external iliac right pelvic lymph nodes, and multiple bone lesions. Maximum-intensity-projection images show overall decline in ^{68}Ga -PSMA-11 accumulation within normal organs as well as tumor lesions on MSG scan relative to control scan. Axial view images display relevant case example of bone lesion with significant PSMA decrease after MSG administration (SUV_{max} from 18.6 to 9.2). p.i. = after injection.

TABLE 1
Patient Characteristics

Characteristic	Data
Age (y)	72 (56–81)
Time since diagnosis of PCa (y)	7 (0.6–21)
PSA at diagnosis (ng/mL)	36 (2.5–308)
Gleason score at diagnosis*	
<8	7 (44%)
≥8	8 (50%)
T stage at diagnosis*	
T1	1 (6%)
T2	11 (66%)
T3	3 (18%)
M status at diagnosis [†]	
M0	15 (94%)
M1	1 (6%)
Primary treatment [‡]	
Prostatectomy ± lymphadenectomy	7 (49%)
Local radiotherapy	6 (42%)
Systemic treatment	1 (7%)
Salvage treatment	
None	9 (56%)
Radiotherapy	3 (19%)
Systemic treatment	4 (25%)
Indication for scan	
Primary staging	2 (12%)
Biochemical recurrence	7 (42%)
Metastatic restaging	7 (42%)
PSA at time of PSMA (ng/mL)	6.2 (0.2–53.7)

*Data missing for 1 patient.

[†]M1 was defined as metastatic disease (distant metastases).

[‡]Data missing for 2 patients.

Qualitative data are number and percentage (total $n = 16$); continuous data are median and range.

MBq). The target uptake period was 60 min (allowed range, 50–100 min). We applied oral but no intravenous CT contrast medium for the control and MSG scans. We acquired images using a 64-detector PET/CT scanner (2007 Biograph 64 Truepoint or 2010 Biograph mCT 64; Siemens). The same scanner was used for both visits. A diagnostic CT scan (200–240 mAs, 120 kV) with a 5-mm slice thickness was obtained. PET images were acquired in 3-dimensional mode from mid thigh to vertex (whole-body scan) with a time of 2–4 min per bed position using a weight-based protocol (22). All PET images were reconstructed using corrections for attenuation, dead time, random events, and scatter. PET images were reconstructed with an iterative algorithm (ordered-subset expectation maximization) in an axial 168 × 168 matrix on the Biograph 64 Truepoint (2-dimensional, 2 iterations, 8 subsets, 5.0-mm gaussian filter) and in a 200 × 200 matrix on the Biograph mCT 64 (3-dimensional, 2 iterations, 24 subsets, 5.0-mm gaussian filter).

Image Analyses. Board-certified nuclear medicine physicians and radiologists used a PSMA PET/CT–based TNM staging system (PROMISE) to generate clinical reports of the control scans by consensus (23).

Two nuclear medicine physicians, who did not know the study condition (control vs. MSG administration and type of MSG application), used qPSMA software to interpret the research MSG and control PSMA PET/CT scans by consensus (24). They segmented all detected tumor lesions and normal organs manually. Normal organs included the lacrimal glands, parotid glands, submandibular glands, liver, spleen, kidneys, and urinary bladder. Output parameters included SUV_{mean} and SUV_{max} for both tumor lesions and normal organs.

Measurements of Salivary Radioactivity. To assess the effect of MSG on radioligand excretion, we collected saliva from all patients at 5 time points after ^{68}Ga -PSMA-11 injection at 0 min (range, 0–7 min), 10 min (range, 9–17 min), 30 min (range, 28–39 min), 45 min (range, 44–54 min), and 100 min (range, 88–126 min). We transferred saliva collected in disposable medication cups to disposable borosilicate test tubes. Samples were weighed and radioactivity was measured in a γ -well counter (Capintec CAPRAC-t; Mirion Technologies). Background was measured before each patient injection. We assayed ^{68}Ga decay within a range of 10–1,200 keV and recorded the time of radioactivity collection and measurement to adjust for tracer decay. We corrected tracer uptake in saliva for background and radioactive decay.

Safety. We monitored safety before/after injection of the radiotracer, before/after the MSG administration, and before/after the scan procedure. We recorded blood pressure and heart rate before injection of ^{68}Ga -PSMA-11 and directly after completion of the scan. We communicated with all patients within 72 h after the scan and asked whether they had any untoward side effects or symptoms. Adverse events were documented and evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0.

Outcomes

The primary objective of this trial was to compare the degree of ^{68}Ga -PSMA-11 uptake in the salivary glands with and without MSG administration. A 2-fold reduction after MSG administration was a priori defined as a successful reduction in salivary gland PSMA uptake (25). The secondary objectives were to determine the impact of MSG administration on ^{68}Ga -PSMA-11 uptake in normal organs and tumor lesions, to measure whether MSG stimulates ^{68}Ga -PSMA-11 excretion in the saliva, and to assess the safety of oral MSG ingestion and salivary flow stimulation at the proposed doses.

Statistical Analyses

Radiation doses to the salivary glands from 1 cycle of ^{225}Ac -PSMA or ^{177}Lu -PSMA were estimated at 17 and 10 Gy, respectively (9, 10, 26, 27). The commonly applied safe upper limit for external-beam salivary gland radiation therapy is 32 Gy, which can be reached after 2 cycles of ^{225}Ac -PSMA (28). On the basis of these numbers, we aimed to achieve a 2-fold reduction in the ^{68}Ga -PSMA-11 accumulation in the salivary glands after MSG administration. The primary endpoint measure was the mean difference in SUV_{max} and SUV_{mean} in all assessable salivary glands with and without the administration of MSG interventions. Patients were randomized (1:1) using a computer-generated randomization list. The randomization plan used a permuted block design with 2 blocks of $n = 8$ (arms A and B, Supplemental Table 2).

We report descriptive values as mean ± SD or median and interquartile range (if data were not normally distributed according to the Shapiro–Wilk test). Because individual patients served as their own control, paired t tests were performed. Differences between paired data that were not normally distributed were determined using the Wilcoxon signed-rank test. The independent t test was used to compare the means between unrelated groups. In each analysis, a P value of less than 0.05 was considered statistically significant. We conducted

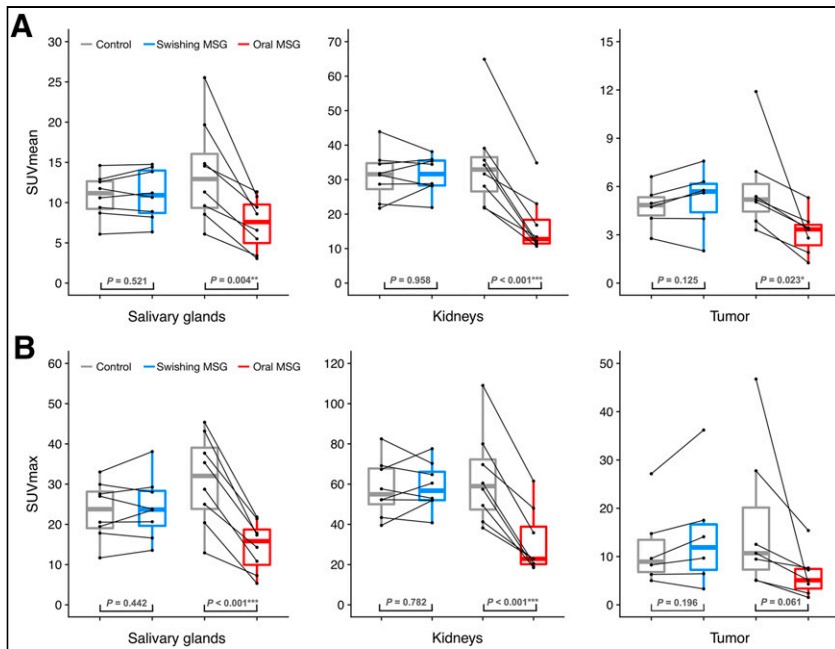


FIGURE 3. SUV_{mean} (A) and SUV_{max} (B) of salivary glands, kidneys, and tumor lesions in control and MSG studies in oral ingestion and swishing arms.

all analyses using SPSS Statistics, version 26.0 (IBM Corp.), and R Studio, version 3.6.1 (R Foundation for Statistical Computing).

RESULTS

A summary image of each of the 16 patients, with all measurements, is provided in the supplemental materials (Supplemental Fig. 1). One patient example (patient 012) is displayed in Figure 2.

Patient Population

Between December 20, 2019, and April 4, 2020, 17 patients were screened to identify 16 patients who met the eligibility criteria (Fig. 1). One patient declined to participate. The demographics and clinical characteristics of the study population are presented in Table 1. Two of 16 (16%) patients underwent the PSMA PET/CT scan for initial staging of PCa, 7 of 16 (42%) for localization of biochemical recurrence, and 7 of 16 (42%) for restaging of metastatic disease.

PSMA PET/CT Images

In the oral ingestion arm, the mean injected activity was 184 ± 1 and 183 ± 2 MBq for the MSG and control scans, respectively ($P = 0.18$). Image acquisition commenced at 61 ± 8 and 61 ± 7 min, respectively, after tracer injection ($P = 0.87$).

In the swishing arm, the mean injected activity was 184 ± 1 and 184 ± 1 MBq for the MSG and control scans, respectively ($P = 0.40$). Image acquisition commenced at 67 ± 15 and 66 ± 14 min, respectively, after tracer injection ($P = 0.87$).

Table 2 summarizes the scan findings and PSMA PET-based staging. Three patients had no visible PCa lesions (1 in the oral ingestion arm and 2 in the swishing arm). There was no change in stage between the control and MSG scans.

^{68}Ga -PSMA-11 Uptake in Normal Organs

In the oral ingestion arm, MSG administration was associated with a significant decrease in ^{68}Ga -PSMA-11 accumulation in all

TABLE 2
PSMA PET Findings

Study arm	Swishing		Oral ingestion	
	Control	MSG	Control	MSG
^{68}Ga-PSMA-11 PET/CT+				
Prostate/prostate bed (T+)	4 (50%)	4 (50%)	5 (63%)	5 (63%)
Pelvic LN (N1)	1 (13%)	1 (13%)	2 (25%)	2 (25%)
Extrapelvic LN (M1a)	1 (13%)	1 (13%)	1 (13%)	1 (13%)
Bone (M1b)	2 (25%)	1 (13%)	3 (38%)	3 (38%)
Visceral (M1c)	0	0	0	0
^{68}Ga-PSMA-11 TNM pattern				
PSMA T0 N0 M0	2 (25%)	2 (25%)	1 (13%)	1 (13%)
PSMA T+ N0 M0	3 (38%)	3 (38%)	2 (25%)	2 (25%)
PSMA T0 N1 M0	0	0	0	0
PSMA T+ N1 M0	1 (13%)	1 (13%)	1 (13%)	1 (13%)
PSMA T+ N0 M1	0	0	1 (13%)	1 (13%)
PSMA T0 N0 M1	2 (25%)	2 (25%)	2 (25%)	2 (25%)
PSMA T0 N1 M1	0	0	0	0
PSMA T+ N1 M1	0	0	1 (13%)	1 (13%)

Data are number and percentage.

TABLE 3
Comparison of ⁶⁸Ga-PSMA11 Uptake in Normal Organs in Control and MSG Scans

Site	SUV _{mean}				SUV _{max}			
	Control	MSG	Change	P	Control	MSG	Change	P
Oral ingestion (n = 8)								
Lacrimal glands	5.5 ± 2.3	2.6 ± 0.9	-50.9% ± 6.5%	0.001	9.9 ± 4.7	4.3 ± 1.6	-55.5% ± 6.1%	0.002
Parotid glands	10.9 ± 4.1	6.9 ± 3.3	-32.9% ± 22.6%	0.002	19.0 ± 6.6	13.2 ± 6.2	-34.1% ± 21.7%	0.020
Submandibular glands	15.9 ± 5.7	6.6 ± 2.5	-58.9% ± 8.9%	<0.001	29.0 ± 10.5	10.4 ± 3.7	-63.2% ± 9.9%	<0.001
Salivary glands	12.1 ± 4.6	6.8 ± 3.1	-45.5% ± 14.6%	0.004	29.0 ± 10.5	13.5 ± 5.9	-53.4% ± 11.1%	<0.001
Liver	4.6 ± 0.5	2.1 ± 0.3	-54.2% ± 5.3%	<0.001	10.7 ± 1.3	5.5 ± 0.4	-50.1% ± 8.3%	<0.001
Spleen	8.1 ± 2.0	3.0 ± 0.9	-62.8% ± 6.9%	<0.001	13.7 ± 3.5	5.3 ± 1.5	-61.5% ± 8.6%	<0.001
Kidney	34.5 ± 14.8	17.4 ± 8.8	-51.5% ± 13.7%	<0.001	63.6 ± 25.0	32.7 ± 16.6	-51.3% ± 13.3%	<0.001
Urinary bladder	16.0 ± 8.7	69.1 ± 34.3	+371.6% ± 300.2%	0.004	33.7 ± 23.9	184.2 ± 97.5	+593.2% ± 659.5%	0.003
Total tumor lesions	6.6 ± 3.5	3.5 ± 2.1	-45.0% ± 19.0%	0.023	21.5 ± 19.8	8.2 ± 8.7	-55.7% ± 22.0%	0.061
Swishing (n = 8)								
Lacrimal glands	6.5 ± 1.6	6.0 ± 2.5	+4.9% ± 22.0%	0.625	12.3 ± 3.2	11.1 ± 4.6	-5.2% ± 25.0%	0.556
Parotid glands	11.7 ± 2.2	12.0 ± 2.7	+0.1% ± 8.4%	0.917	22.2 ± 6.1	22.5 ± 6.0	+1.9% ± 10.4%	0.792
Submandibular glands	12.8 ± 3.5	13.4 ± 3.6	+5.6% ± 6.8%	0.061	21.3 ± 7.0	22.6 ± 7.3	+7.7% ± 11.6%	0.188
Salivary glands	11.5 ± 2.3	11.9 ± 2.9	+1.6% ± 7.8%	0.521	25.8 ± 6.0	26.6 ± 7.2	+4.3% ± 12.3%	0.442
Liver	4.1 ± 0.8	4.3 ± 0.9	+5.7% ± 17.3%	0.317	9.8 ± 1.3	10.4 ± 3.0	+5.3% ± 15.7%	0.321
Spleen	6.1 ± 2.0	6.3 ± 1.7	+6.2% ± 18.6%	0.458	10.8 ± 3.9	10.1 ± 2.6	-0.3% ± 15.2%	0.622
Kidney	30.1 ± 8.0	30.1 ± 5.8	+ 1.9% ± 13.9%	0.958	57.1 ± 15.9	57.6 ± 13.6	+3.4% ± 15.8%	0.782
Urinary bladder	20.2 ± 13.5	24.2 ± 8.3	+36.5% ± 41.4%	0.357	50.6 ± 42.4	56.4 ± 20.2	+52.0% ± 70.0%	0.651
Total tumor lesions	4.9 ± 1.1	5.4 ± 1.6	7.8% ± 13.8%	0.125	12.5 ± 7.7	15.0 ± 11.3	12.6% ± 27.8%	0.196

Data are average ± SD.

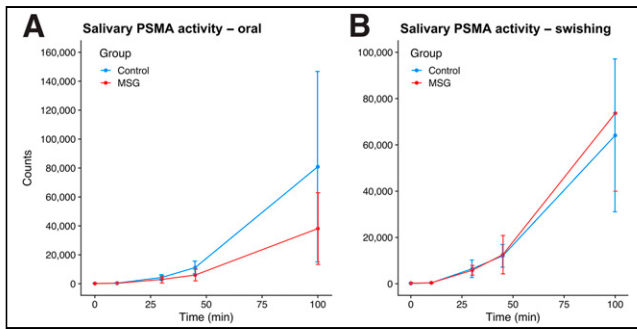


FIGURE 4. Median changes in ^{68}Ga -PSMA11 activity in saliva between control and MSG groups at 0, 10, 30, 45, and 100 min after tracer injection for oral ingestion arm (A) and swishing arm (B).

normal organs ($P < 0.05$) and a large increase in bladder activity (mean difference, $+372\%$ SUV_{mean} and $+593\%$ SUV_{max} ; Table 3). ^{68}Ga -PSMA-11 uptake decreased by more than 50% in the salivary glands (mean difference, -46% SUV_{mean} and -53% SUV_{max}), with a more prominent effect on the submandibular glands (mean difference, -59% SUV_{mean} and -63% SUV_{max}) than on the parotid glands (mean difference, -33% SUV_{mean} and -34% SUV_{max}).

In the swishing arm, no statistically significant difference in ^{68}Ga -PSMA-11 accumulation measured by either SUV_{mean} and SUV_{max} was observed in normal organs after MSG administration ($P > 0.05$) (Table 3).

^{68}Ga -PSMA-11 Uptake in Tumor Lesions

In the oral ingestion arm, MSG administration was associated with a significant decline in ^{68}Ga -PSMA-11 accumulation in tumor lesions (median difference, -38% SUV_{mean} and -52% SUV_{max} ; Table 4). One pelvic bone lesion showed a dramatic decrease in SUV_{max} (from 46.8 to 4.3) after MSG administration (case MSG05 in the supplemental materials).

In the swishing arm, no significant difference in tumor accumulation of ^{68}Ga -PSMA-11 as measured by SUV_{mean} and SUV_{max} was observed between the 2 PET scans ($P = 0.11$ and $P = 0.17$, respectively) (Table 4).

A comparison of pooled SUV_{mean} and SUV_{max} between the control and MSG studies for each arm is depicted in Figure 3.

Saliva Radioactivity Measurements

Salivary radioactivity increased over time, demonstrating ^{68}Ga -PSMA-11 salivary excretion. The median activity counts after

tracer injection for both arms are provided in Supplemental Table 3. Figure 4 shows the median saliva counts over time.

In the oral ingestion arm, a significant decrease in salivary activity counts was observed at 45 and 100 min, with median reductions of -42% and -53% , respectively. In the swishing arm, no significant difference in salivary activity was observed at any time point ($P > 0.05$).

Adverse Events

Grade 1 nausea after administration was recorded in 1 (6%) of 16 patients after oral ingestion of MSG. Five non-study-related events were recorded (diarrhea [$n = 2$ in each arm] and abdominal discomfort [$n = 1$ in the swishing arm]; Supplemental Table 4).

DISCUSSION

This prospective randomized imaging study revealed that oral ingestion of MSG, a food additive, is associated with a significant decrease in ^{68}Ga -PSMA-11 accumulation within normal organs and tumor lesions, whereas topical oral application of MSG has no impact on ^{68}Ga -PSMA-11 biodistribution. The primary endpoint of at least a 50% decrease in ^{68}Ga -PSMA-11 accumulation in the salivary glands was met when expressed as change in SUV_{max} (53%). However, oral administration of MSG also significantly diminished ^{68}Ga -PSMA-11 uptake in tumor lesions (52% and 39% decline in SUV_{max} and SUV_{mean} , respectively) and all other organs. A 3-fold increase in ^{68}Ga -PSMA-11 signal in the urinary bladder highlighted rapidly increased urinary excretion after oral MSG administration. Previous work found a repeatability coefficient of 33%–38% for SUV measurements in PSMA PET/CT, indicating that the reduction in tumor uptake in our patients ($>45\%$) is related to MSG administration (29). The application of MSG to reduce salivary gland toxicity (xerostomia) induced by PSMA RLT is therefore unlikely to be a successful clinical strategy.

Various direct attempts to reduce the salivary gland toxicity of ^{225}Ac -PSMA have been reported: salivary gland duct dilation and clearance via sialendoscopy (30), vasoconstriction of parotid gland blood vessels through external cooling with ice packs (11, 13), and local injection of botulinum toxin A to suppress saliva formation metabolically (31). Indirect attempts to alter the biochemical mechanism of off-target binding by competition included PSMA inhibitors such as 2-(phosphonomethyl) pentanedioic acid or serum glutamate-elevating approaches (20, 32–35). Dosimetry data showed that coadministration of oral polyglutamate administration

TABLE 4
Comparison of SUV_{mean} and SUV_{max} Derived from Control and MSG Scans

Parameter	Control	MSG	Change (%)	<i>P</i>
Oral ingestion ($n = 7$)				
SUV_{mean}	5.4 (3.9, 11.4)	3.3 (1.9, 3.8)	-37.8 (-67.3 , -32.5)	0.018
SUV_{max}	10.7 (6.5, 46.8)	5.1 (2.6, 9.7)	-52.3 (-70.0 , -48.5)	0.018
Swishing ($n = 6$)				
SUV_{mean}	4.9 (4.2, 5.5)	5.7 (4.1, 6.3)	13.8 (-4.0 , 15.4)	0.116
SUV_{max}	9.0 (7.8, 14.8)	11.9 (6.7, 17.5)	17.9 (-14.0 , 33.3)	0.173

Data are median and interquartile range for total tumor lesions.

may reduce salivary gland ligand uptake. However, the impact on tumor uptake has not yet been determined (36).

Application of MSG in murine models reduced salivary PSMA radioligand uptake in a dose-dependent manner without affecting tumor uptake (20). In contrast, oral MSG administration in humans led to significant decreases in tumor uptake. Consistent with our findings, a significant decrease in ¹⁸F-DCFPyL accumulation in normal organs and tumor lesions after oral administration of MSG was also observed by others (32). Harsini et al. (32) applied a fix dose of 12.7 g, whereas our patients received a 150 mg/kg dose of MSG, which led to higher average dose of 15.1 g. This difference might explain the higher impact of MSG on tracer biodistribution observed in our study, a finding that suggests a dose-dependent effect of MSG. Although the MSG dosages were 10-fold higher than the MSG concentration in a normal meal (37), intake of food containing glutamate (e.g., MSG, umami, tomatoes, cheese, and mushrooms) may impact the biodistribution of PSMA radioligands, and a potential impact on diagnostic or therapy efficacy cannot be formally excluded. Further studies investigating the impact of food containing glutamate on imaging-and-therapy PSMA radioligands may be warranted.

⁶⁸Ga-PSMA-11 is excreted in the saliva, as shown by our measurements. Oral ingestion of MSG led to diminished salivary excretion of ⁶⁸Ga-PSMA-11. This finding suggests that its off-target accumulation in the salivary glands interacts with saliva formation, potentially impacting ductal cell transporters within the glands (15, 38). Alternatively, the macromolecular composition of saliva itself may be interacting with PSMA and glutamate, trapping or binding to the molecules and causing an accumulation in the salivary glands within saliva.

Our study had limitations. First, both the dosing and the timing of MSG administration were chosen empirically on the basis of studies largely concerned with safe dosing of MSG rather than application as a blood glutamate-modulating tool (39). Second, although not evaluated in this study, tumor burden may play a role in the efficacy of MSG's impact on radioligand distribution. Although PSMA RLT is currently offered in heavily metastasized patients with late-stage metastatic castration-resistant PCa, our patients were mainly in earlier disease stages that have a low tumor burden. Nevertheless, considering the tumor sink effect, we expect a higher impact of MSG administration on tumor uptake in patients with a high tumor burden (40).

CONCLUSION

Oral administration of MSG successfully decreased ⁶⁸Ga-PSMA-11 uptake in normal organs, including the salivary glands and kidneys, in human subjects but also reduced tumor uptake significantly. This result suggests that MSG strategies reducing the salivary gland toxicity of PSMA RLT will negatively impact tumor PSMA uptake. Thus, clinical applicability is unlikely. Future investigations evaluating different doses and timings of MSG administration are warranted, considering the possibility that a lower dose may show differential preference for tumor or normal tissue.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the impact of MSG administration on ⁶⁸Ga-PSMA11 biodistribution?

PERTINENT FINDINGS: This prospective single-center, randomized imaging study, which included 16 men with PCa, met its primary endpoint, defined as a 50% reduction in ⁶⁸Ga-PSMA11 accumulation in the salivary glands when MSG was administered orally (−53.4% SUV_{max}, *P* < 0.001). However, the radiotracer reduction in normal organs was accompanied by a significant reduction within tumor lesions (−55.7% SUV_{max}, *P* = 0.061).

IMPLICATIONS FOR PATIENT CARE: MSG is capable of modulating ⁶⁸Ga-PSMA-11 biodistribution, including tumor uptake, which limits its clinical application in the setting of PSMA RLT.

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Supplemental Table 1. Eligibility criteria for enrollment in trial**Eligibility criteria to enroll**

Inclusion criteria:

- Patient volunteer to undergo 2 PSMA PET/CT scans within 14 days
- Histopathologically proven PCa.
- PSMA PET/CT indicated for:
 - Initial staging before definitive therapy
 - Biochemical recurrence localization
 - Metastatic disease re-staging
- Any prior treatment
- Age > 18 years.
- Ability to understand a written informed consent document and the willingness to sign it

Exclusion criteria:

- Prior salivary gland surgery or radiation therapy.
 - Prior history or current salivary gland disease.
 - Unable to lie flat, still or tolerate a PET scan.
 - Unable to follow the salivary flow stimuli administration regimen
 - Severe uncontrolled hypertension (systolic blood pressure above 140 mm Hg and diastolic blood pressure above 90 mm Hg, or systolic blood pressure above 180 mm Hg, or diastolic blood pressure above 110 mm Hg). Patients with controlled hypertension under medication are eligible.
 - Sodium/salt restricted diet due to other medical conditions
 - History of severe asthma that has led to hospitalizations or emergency room visits
 - History of severe contraindications to MSG consumption including severe headaches, migraines or other intolerance.
 - Change to treatment administered between time of baseline scan and MSG scan.
-

Supplemental Table 2. The randomization plan using a permuted blocks design with 2 blocks of size eight (2 arms, A and B each with or without MSG first) will be as follows:

Block	Patient	Arm	MSG First (+)
1	1	B	-
1	2	A	-
1	3	A	-
1	4	B	-
1	5	A	+
1	6	A	+
1	7	B	+
1	8	B	+

Block	Patient	Arm	MSG First (+)
2	9	A	+
2	10	B	-
2	11	B	+
2	12	A	-
2	13	B	+
2	14	A	-
2	15	A	+
2	16	B	-

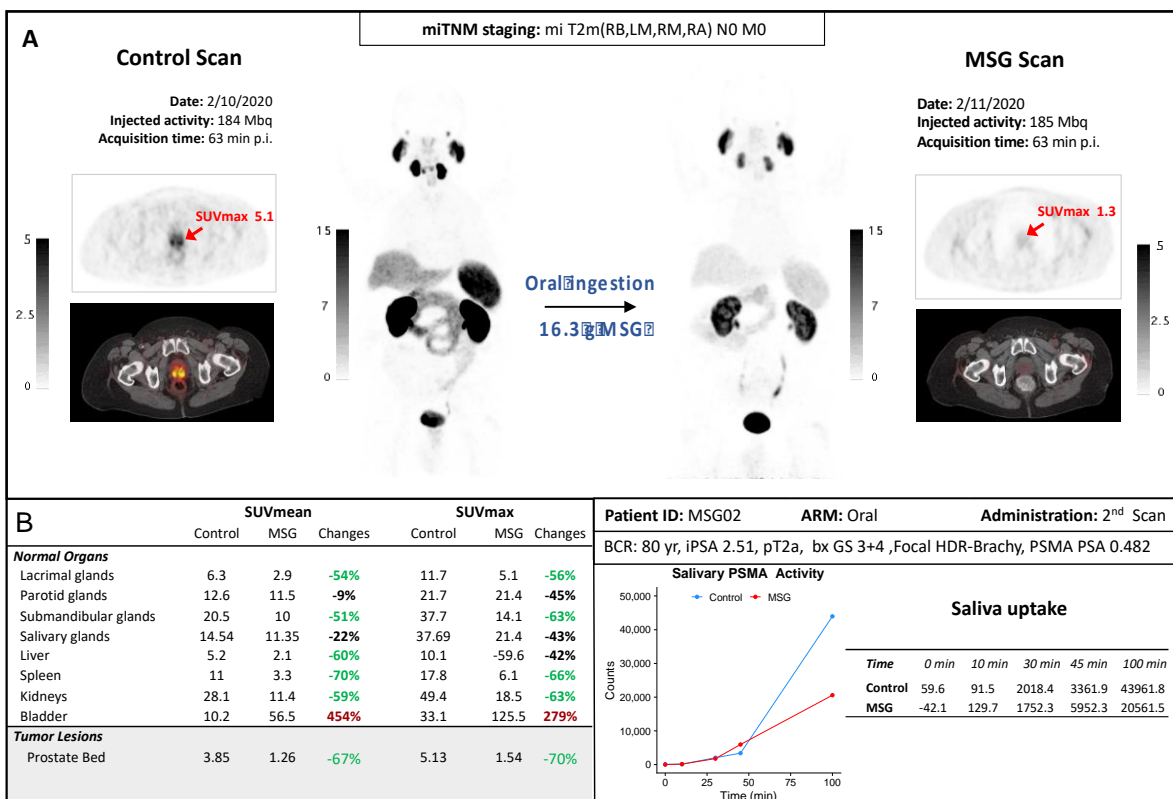
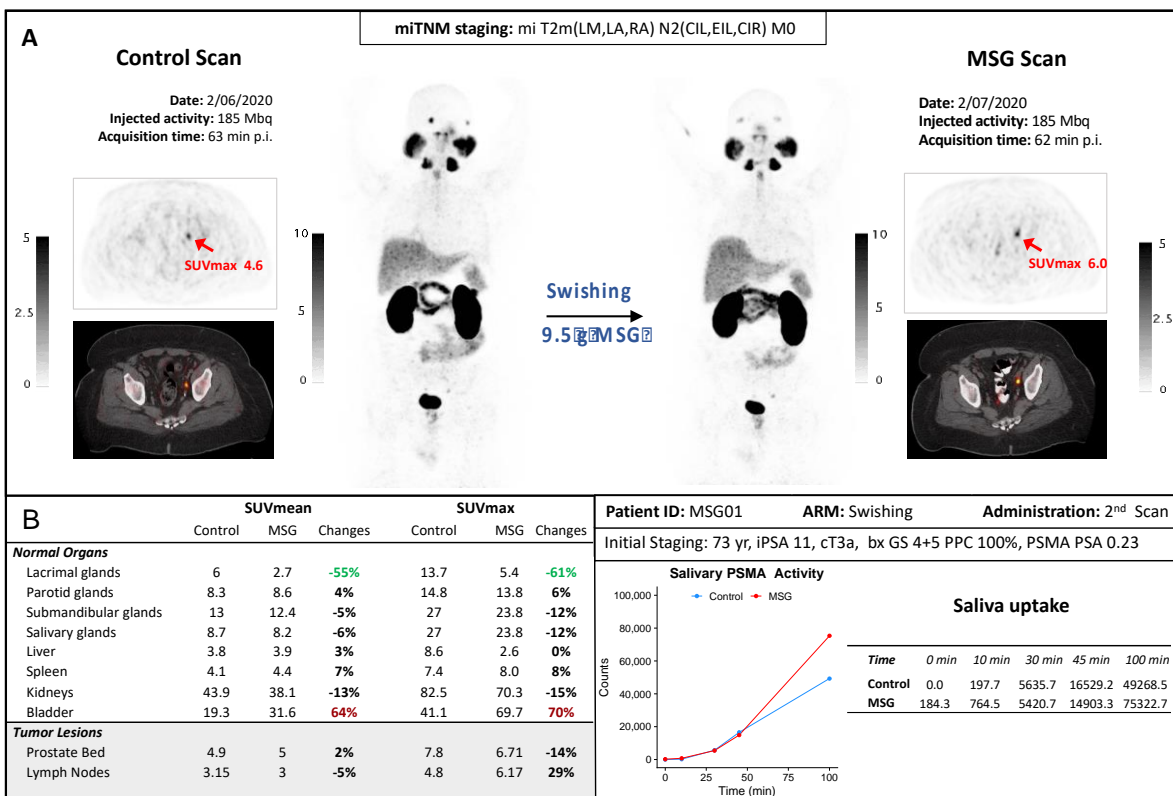
Supplemental Table 3. ⁶⁸Ga-PSMA11 activity in saliva following tracer injection.

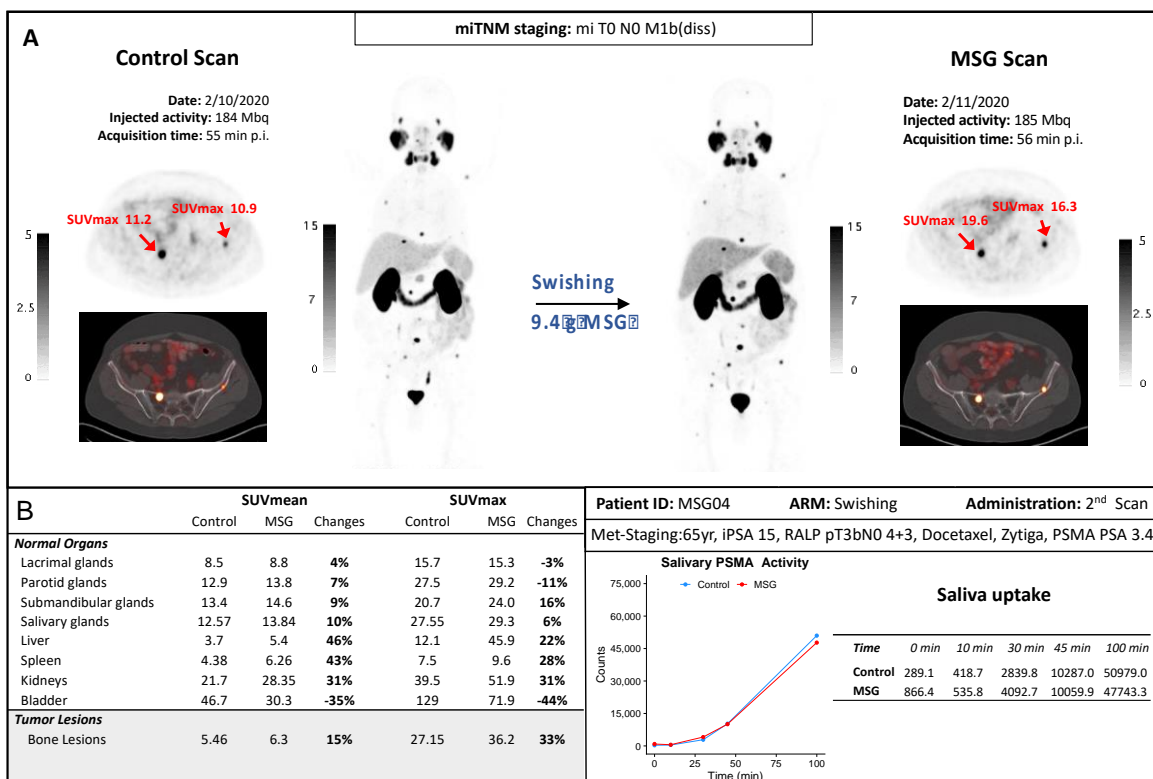
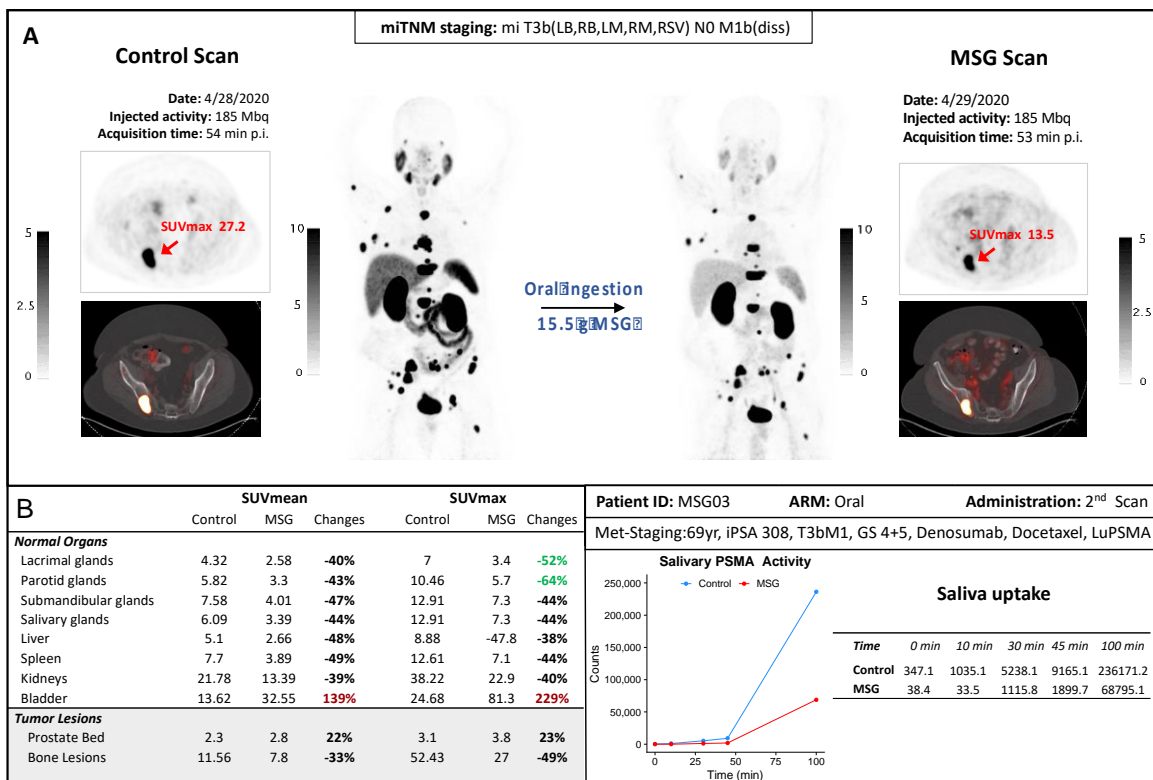
Median (IQR) of ⁶⁸ Ga-PSMA11 Activity in Saliva					
	Time p.i. (min)	Control	MSG	Changes (%)	p value
Oral Ingestion Arm	0	124 (16, 399)	30 (3, 334)	-81.0 (-100.0, 95.3)	0.401
	10	420 (97, 682)	181 (131, 325)	-12.2 (-52.0, 93.0)	0.484
	30	4520 (242, 6261)	2075 (1157, 5323)	-53.1 (-72.6, 7.5)	0.123
	45	10737 (9370, 12776)	5575 (2497, 8785)	-41.9 (-73.7, -29.5)	0.017
	100	70653 (29714, 97148)	38493 (16735, 62492)	-52.9 (-68.6, -28.4)	0.012
Swishing Arm	0	64 (-2, 262)	146 (31, 256)	-77.1 (-456.9, 153.4)	0.327
	10	315 (199, 613)	432 (150, 567)	15.9 (-26.5, 82.1)	0.779
	30	5631 (3203, 9641)	5371 (4323, 7277)	-7.3 (-40.0, 109.0)	0.575
	45	11842 (7346, 15929)	10024 (6835, 14482)	-6.0 (-227.2, 59.8)	0.999
	100	55375 (35457, 96142)	72933 (46173, 105631)	24.3 (-1.5, 51.7)	0.161

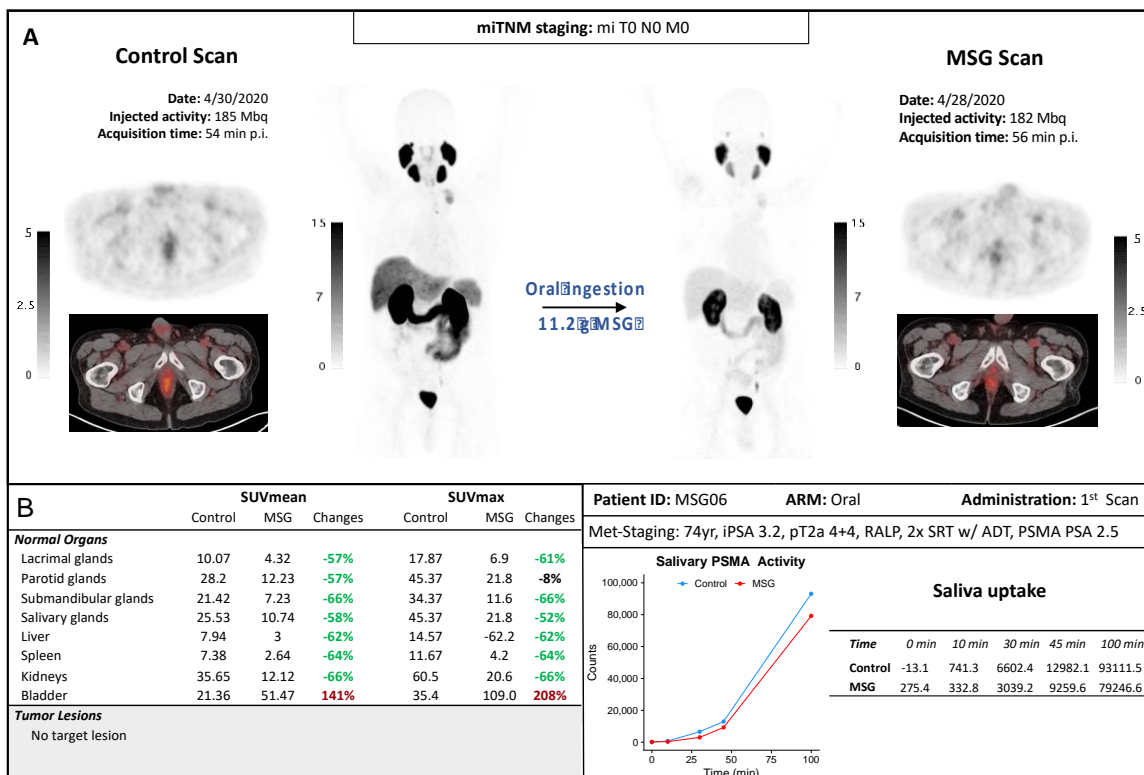
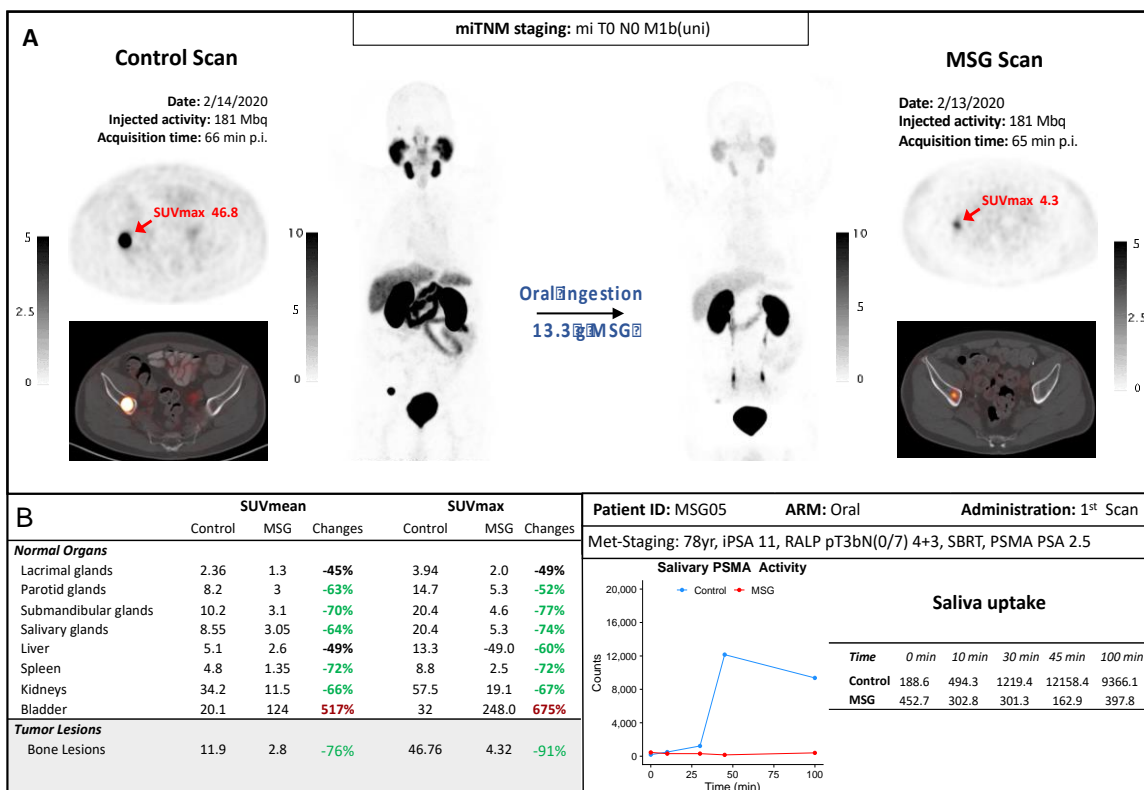
Supplemental Table 4. Adverse event graded according to Common Terminology Criteria for Adverse Events version 5.0.

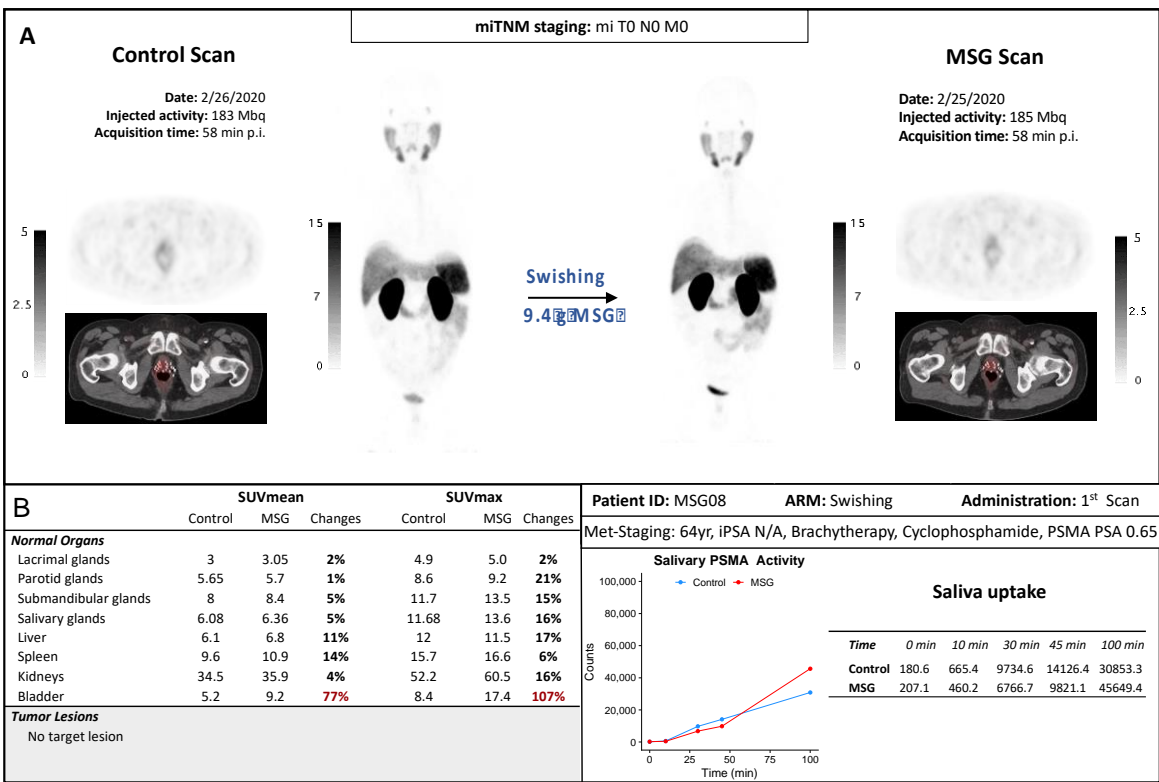
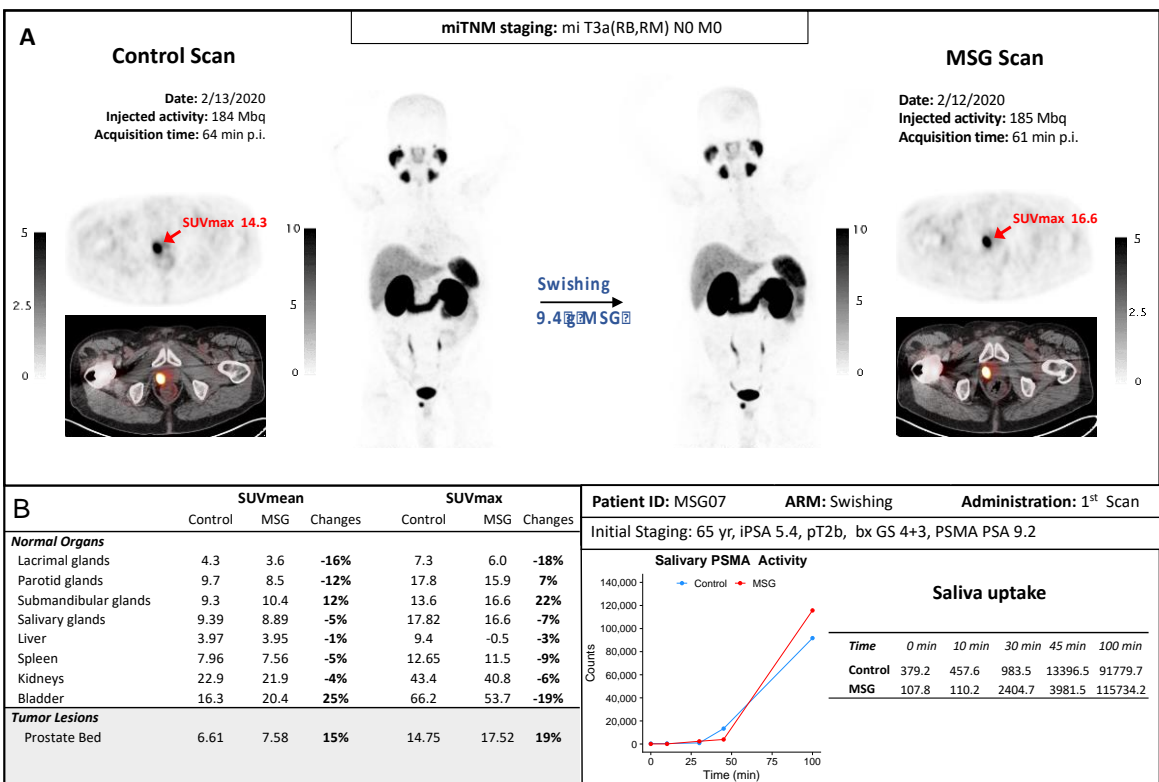
Study arm	“Oral Administration”		“Swishing”	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
MSG administration related				
Nausea	1/16 (6%)	0	0	0
Non MSG administration related				
Bloating	0	0	1/16 (6%)	0
Diarrhea	2/16 (13%)	0	2/16 (13%)	0

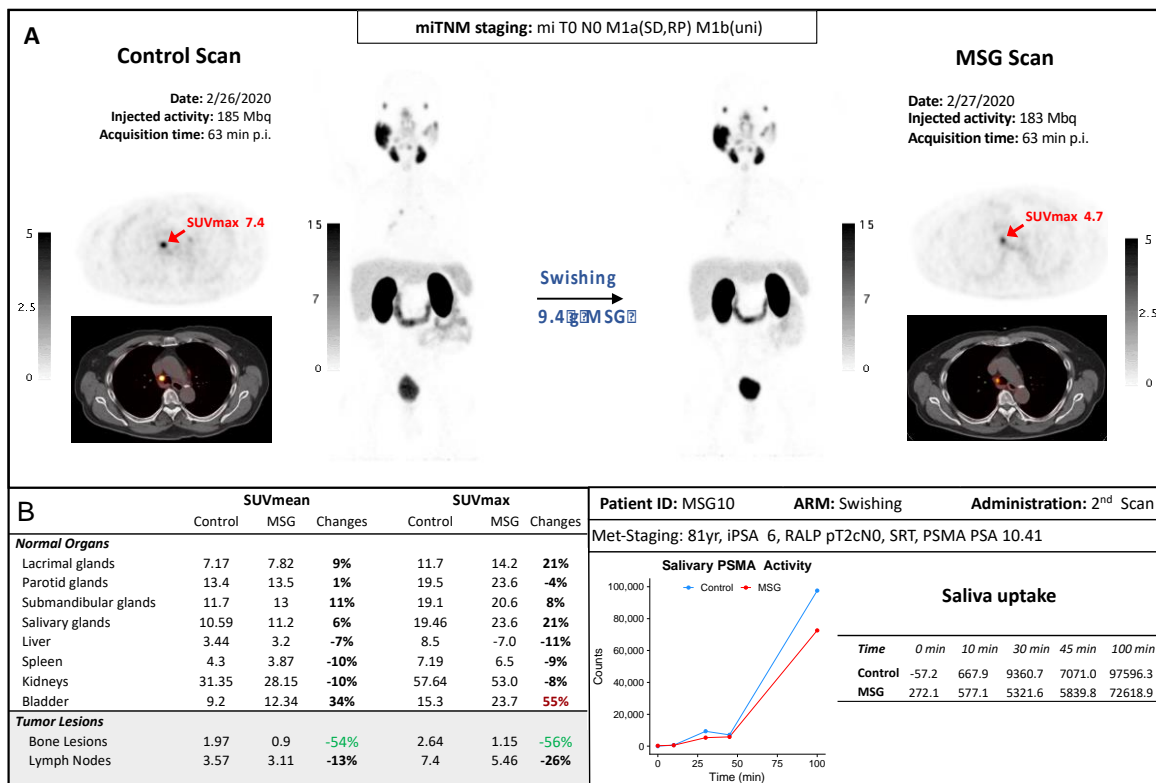
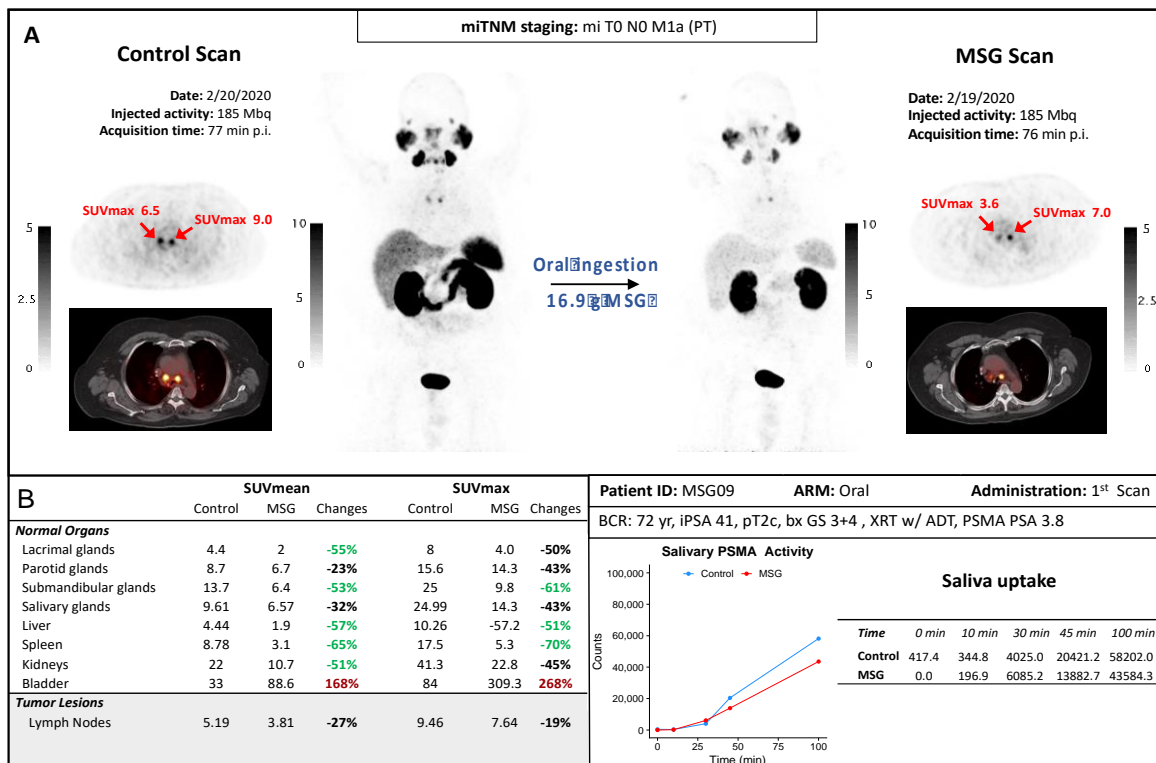
Supplemental Patient Summary Images Brochure (8 pages, whole cohort of 16 patients).

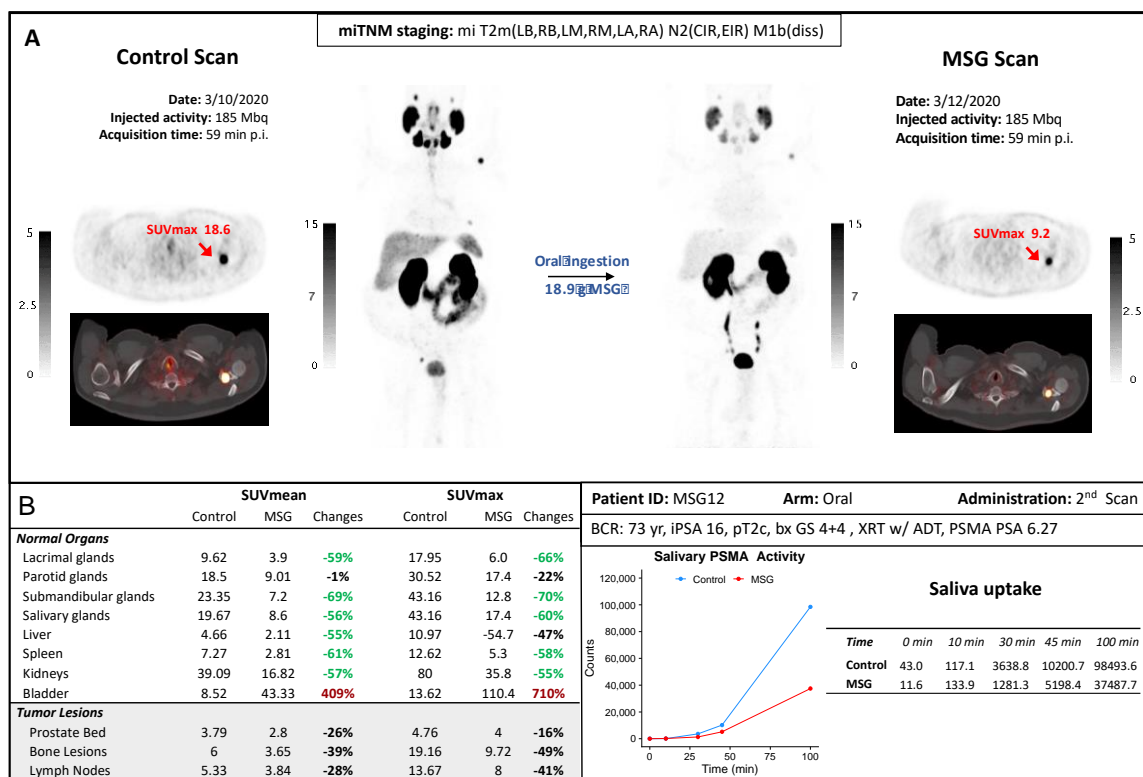
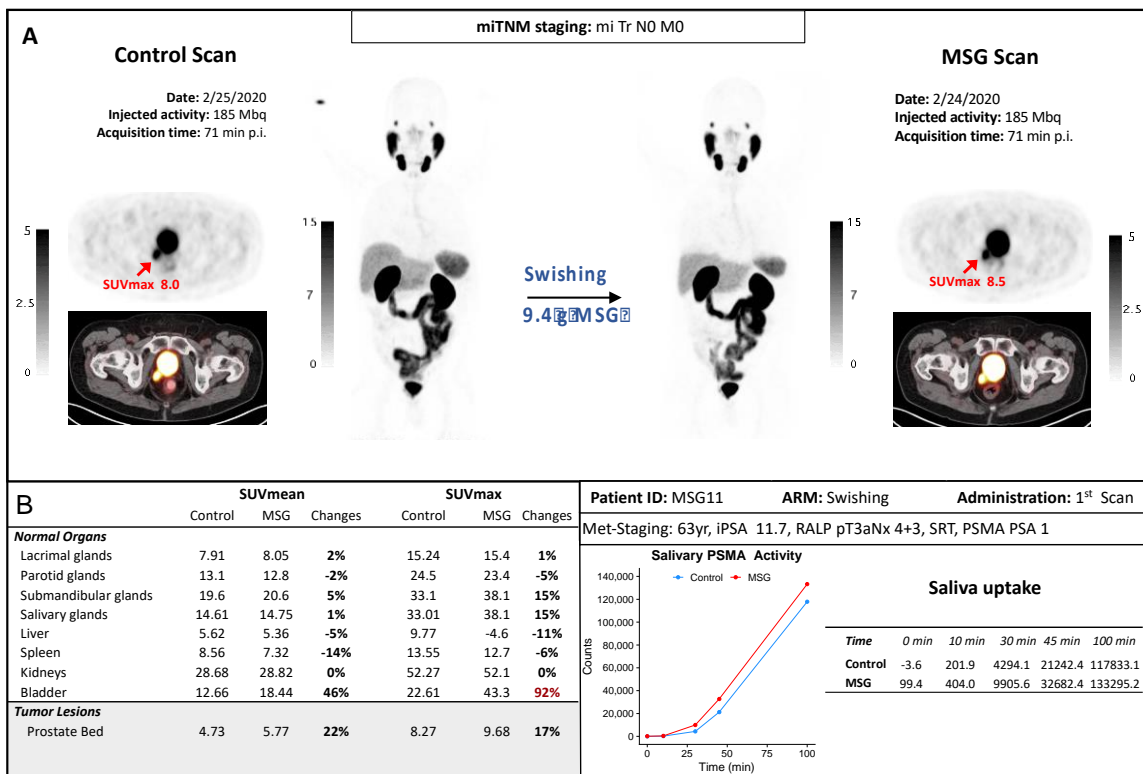


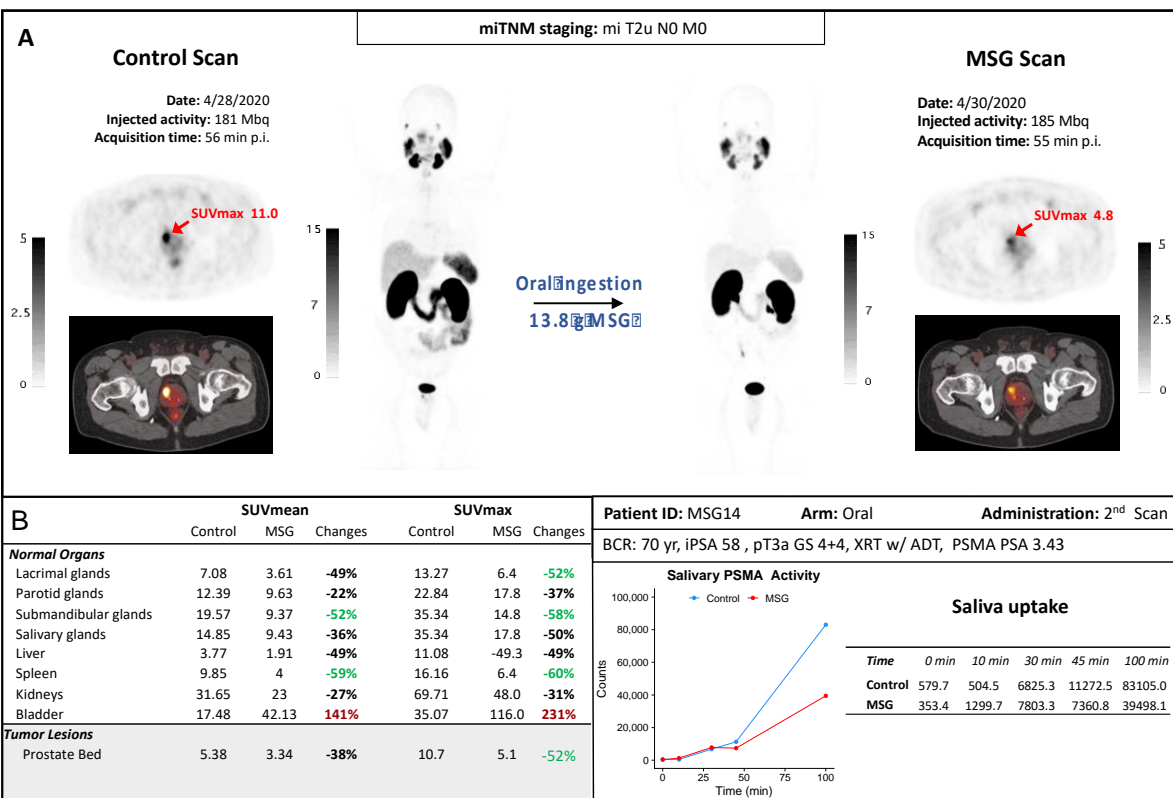
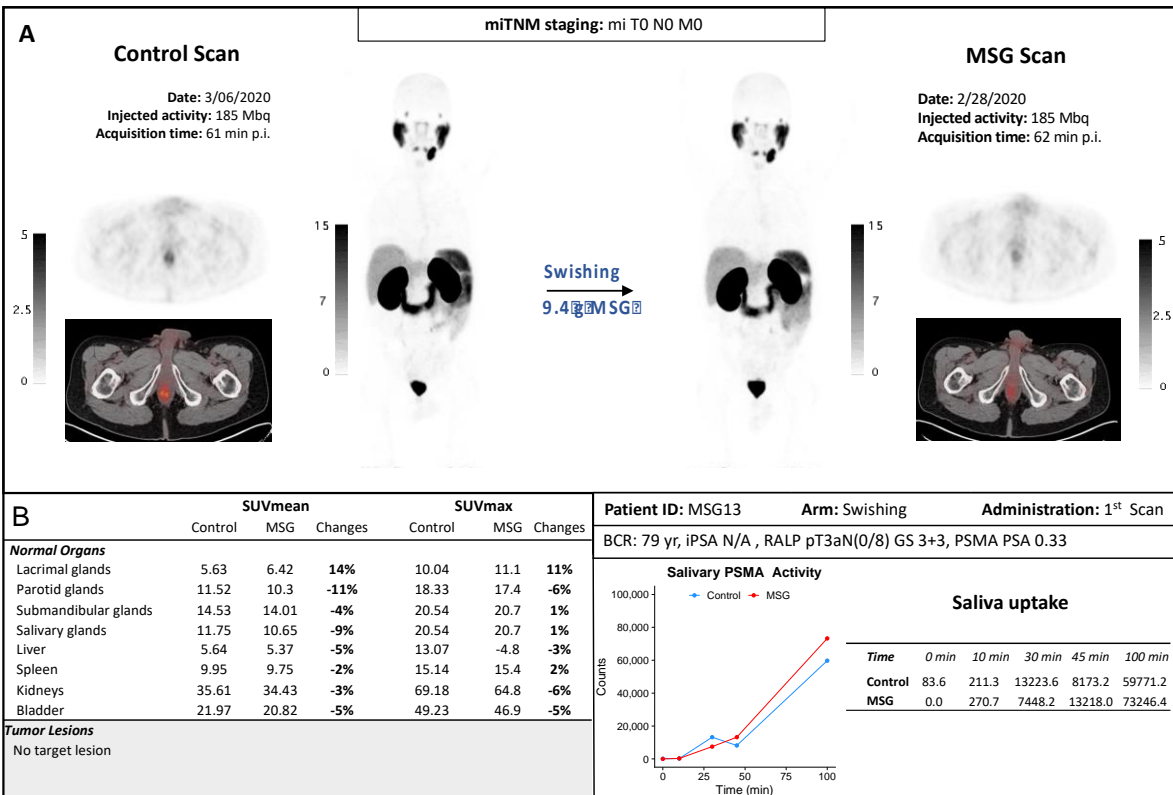


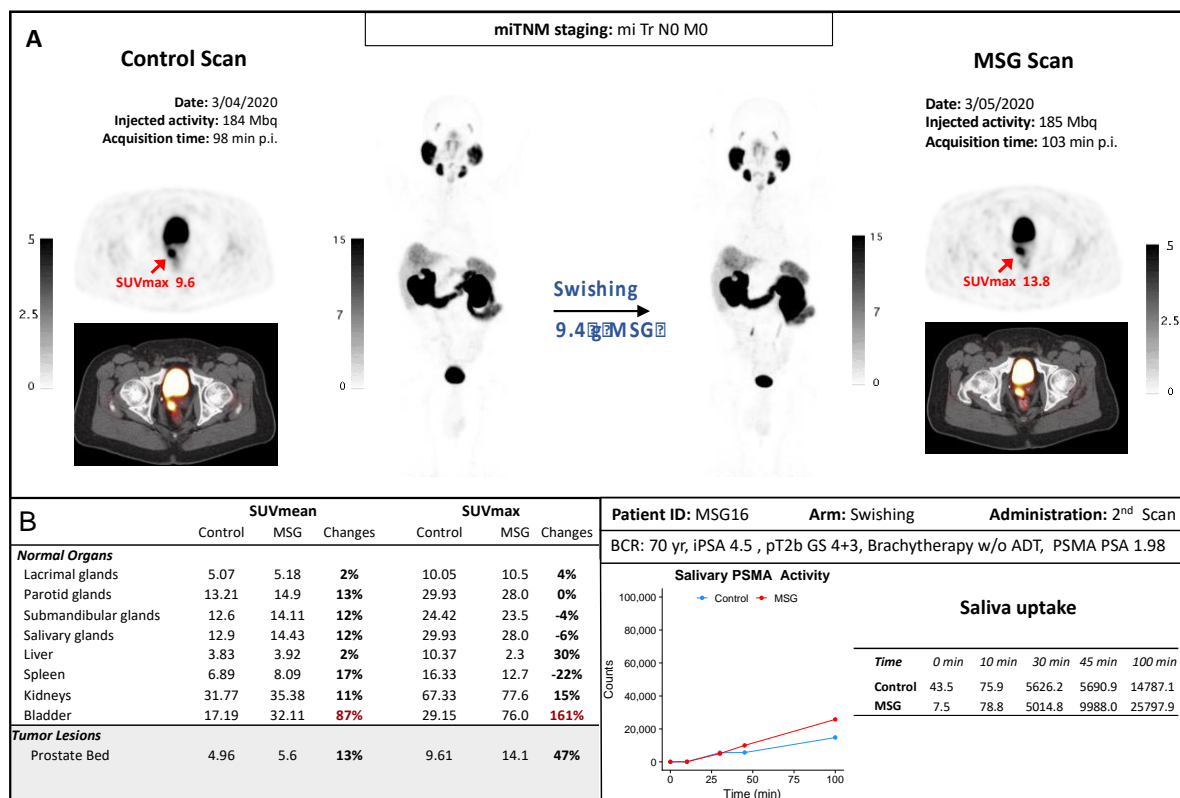












RESEARCH PERSPECTIVES IN FAP-TARGETED AND PSMA-TARGETED RADIOTHERANOSTICS

Perspectives in FAP-targeted PET imaging

FAP-targeted PET imaging has emerged 5 years ago with impressive tumor-to-background ratio images (1). More than 1000 publications have been generated (2). Yet, there is no approved clinical indication for FAP-PET imaging.

Reasons are multiple.

The FAP expression is highly heterogeneous at all levels: tumor type, lesion type, environment type, cell type (2–6). The pan-cancer “basket” approach used in most of the studies lead to highly heterogeneous datasets with diluted statistical signals (2,4,5). Further work is required to identify the cancer sub-types that consistently express FAP at high levels, across patients and across lesions.

FAP expression in non-oncological lesions (scar, inflammation, fibrosis) can be high and impair the FAP-PET signal in the regions of interest (example: pancreatitis and pancreas cancer) (7–10).

Most of the studies focused on reporting the findings of FAP-PET imaging in comparison to FDG-PET imaging (5,11). But in many of the indications, FDG-PET is not the imaging modality of reference. Instead, studies should focus on clinically meaningful endpoint with a clearly defined impact on management (2,12).

Of note, some industry sponsored phase 2 trials that can potentially lead to pivotal registration trials have been initiated in pancreas cancer and gastro-intestinal cancers with the compounds FAPI-46 and FAPI-74 (NCT05262855, NCT05641896). More industry trials are underway from multiple other biopharma companies with different proprietary compounds and other indications (12). These are awaited with provide to the regulators the prospective data showing clinical diagnostic efficacy.

Perspectives in FAP-targeted radiopharmaceutical therapy

The first FAP-targeted PET images with high tumor to background ratio images created an enormous hope for FAP to be the new successful cancer target for radiopharmaceutical therapy (1,2). Yet, 5 years later, there is no approved clinical indication for FAP-targeted radiopharmaceutical therapy.

The high inter-patient and inter-lesion heterogeneity mentioned above lead to an insufficient radiation dose delivery to the tumor lesions from FAP-targeted radiopharmaceutical therapy agents (2–5).

In addition, the first generation of FAP-targeting ligands, FAPI, from the University of Heidelberg have a rapid and high uptake but also a rapid washout for the tumor lesions (13). Although great for imaging at 15 to 120 minutes after injection, the biological half-life does not match the physical half-life of the therapy radionuclides like Lu177 (6.6 days) or Ac225 (10 days): most of radiation energy is delivered after the radiopharmaceutical wash-out from the tumor lesions.

Numerous research teams attempted to generate FAP-targeted radio-ligands with improved chemistry binding properties for radiopharmaceuticals therapy including double binding site, albumin binder, covalent engineering or RGD heterodimers (13–22).

FAP can be used as a direct target of the cancer cells in only a limited number of tumor sub-types (sarcoma, mesothelioma) (23,24). In the majority of cancers, FAP represents an indirect target for cancer cells. It is unclear what is the effect of the killing of the cancer associated fibroblasts on the cancer cells, as a standalone monotherapy strategy. Trials of combination therapy with non FAP-targeted approaches (immunotherapy, chemotherapy) are warranted (25–27,27–33).

The choice of the radionuclide emission (alpha vs beta particles) is also crucial as alpha would reach only the CAFs whereas beta can crossfire to the tumor cells.

Perspectives in PSMA-targeted PET imaging

PSMA PET imaging is now an approved and reimbursed technique for prostate cancer patients. The validated indications for PSMA PET are initial staging of high-risk prostate cancers and localization of biochemical the recurrence assessment and the selection of patients for treatment with molecular radiotherapy targeting PSMA. Potential new indications are being studied, such as PSMA-PET guided intra-prostatic biopsy with ultrasound fusion (NCT05160597) (34–39).

Standardized interpretation criteria have been proposed, such as PROMISE (40), PSMA-RADS (41), E-PSMA (42), PRIMARY (for intra-prostatic analysis) (43), PSG-score (for whole-body evaluation of expression level) (44) or RECIP (for whole-body evaluation of therapeutic response) (45). However, these criteria have not been validated in prospective multicenter trials. In addition, there is still a wide variation in the quality of interpretation of PSMA PET scans and the communication of results to uro-oncologists in the community outside of expert centers (false positives in the analysis of lymph node or bone invasion, in particular). Additional standardization efforts are required to be able to homogenize the use of the information obtained by PSMA PET.

PSMA PET imaging creates new disease staging classification. Patients classified as M0 by conventional imaging can be reclassified as M1 ("upstaging") by PSMA PET imaging and vice versa ("downstaging") (46). There is clear evidence that the use of PSMA PET changes patient management (47). However, clinical recommendations and treatment algorithms are based on conventionally defined staging (RECIST, PCWG). To date, there is insufficient data to demonstrate how the new PSMA PET information can be used to improve patient survival and without increasing toxicity ("overtreatment"). The implementation of PSMA PET imaging in multicenter randomized therapeutic trials (for inclusion and follow-up) will generate the necessary data to optimize treatment algorithms and clinical recommendations based on PSMA PET staging.

In addition to qualitative staging information, PSMA PET also provides quantitative whole-body information, such as the total tumor volume expressing PSMA (mL), or the average intensity of PSMA expression within the total tumor volume (SUV). These quantitative parameters, and others, have the potential to be used as biomarkers to refine patient selection for a given treatment or assessment of therapeutic response to systemic treatments (45,48–51). However, manual segmentation of whole-body tumor volume is time-consuming and there is not yet an unanimously validated and accepted method. These factors have so far limited the generation of large-scale reproducible clinical data that would demonstrate the diagnostic, prognostic and predictive value of quantitative whole-body parameters obtained by PSMA PET. Multiple artificial intelligence solutions are being developed to offer automated tools to obtain these parameters without slowing down the clinical workflow (52–60). Their implementation in nuclear medicine centers is limited by the large number of algorithms proposed (reproducibility), their compatibility with existing systems, the patient data access (security) and above all the lack of demonstrated clinical impact (diagnostic efficiency, improvement of patient survival).

Technical improvements in scanners (digital PET, whole-body wide-field PET) may increase the sensitivity of PET imaging to ligands targeting PSMA (61,62).

In addition, multiple PET radiopharmaceuticals aiming at a better signal-to-noise ratio, via higher tumor uptake (e.g., SAR-bis-PSMA ligand, dimerized with 2 PSMA attachment points), or via the possibility of late imaging to reduce healthy organ signal or urinary signal (e.g. using Zirconium-89 or Copper-64) are under clinical development (63–65).

Perspectives in PSMA-targeted radiopharmaceutical therapy

Molecular radiopharmaceutical therapy targeting PSMA is now approved and reimbursed. The approved indication is the treatment of patients with mCRPC progressing after androgen pathway inhibitor(s) and chemotherapy, and positive by PSMA PET imaging. However, many questions remain open.

The place of Lu177-PSMA-617 therapy in the sequence of systemic therapies for mCRPC (multiple options) is not yet defined and clinical studies comparing therapeutic sequences are warranted.

The criteria for selecting patients by PET imaging can be refined. The use of quantitative PET parameters (e.g. total tumor volume expressing PSMA, mean value of tumor expression measured by SUV_{mean}) is a potential avenue of research. The combined use of FDG PET and PSMA PET is a common practice in Australia or Germany. FDG PET can detect more PSMA-negative lesions than CT, especially in the liver or bone marrow. Lesions with discordant phenotype, i.e. FDG-positive and PSMA-negative, represent a factor in poor prognosis (49,66). However, the combined use of FDG PET and PSMA PET at a large scale may be too complex to be required for all comers. Further work is required to refine the combined use of PSMA/FDG PET.

The total/maximum number of cycles of Lu177-PSMA-617 therapy, the interval between cycles, the injected activity per cycle, the safety thresholds for bone marrow and renal function parameters were derived empirically (compassionate use program of Lu177-PSMA-617 in Germany (67–69), clinical experience with commercially approved radiopharmaceuticals such as 177-Lutetium-DOTATATE (70), 223-Radium (71), 131I-Tositumomab (72) or 90-Yttrium-ibritumomab-tiuxetan (73)). Multiple reports of patients treated with more than 6 cycles suggest a favorable safety profile and benefit on tumor disease progression (74,75). Nevertheless, the

toxicity profile of prolonged use of Lu177-PSMA-617 remains to be evaluated in prospective studies, as well as long-term or late toxicity (≥ 12 months), which remains poorly understood.

The decision for treatment continuation and discontinuation should be based on clinical, biochemical, imaging, and other available management options. However there are no standardized criteria for response and discontinuation. Practices are heterogeneous. Proposals for standardized PSMA-targeted nuclear imaging criteria for the evaluation of therapeutic response have been proposed (PPP (76), RECIP (45), RE-SPECT (77)) and should be tested in clinical trials.

Post-therapeutic SPECT (single-photon emission tomography) imaging of Lu177-PSMA-617 offers the possibility to visualize the biodistribution of the radiopharmaceutical specific to each patient and to estimate the amount of radiation dose delivered in healthy lesions and organs. These individualized data offer the potential to modify the administration regimen for each patient (injected activity, inter-cycle interval) to maximize the antitumor effect profile or safety. However, there is not yet a reference method for each of the calculation steps, from the activity detected by the SPECT scanners to the estimation of the dose deposition in Gray (SPECT scanner models, image acquisition parameters, image reconstruction parameters, segmentation methods, software, activity curve fitting methods, modeling algorithms and dose calculation) (78–80). This heterogeneity of practices combined with the lack of systematic collection of toxicity data do not allow to understand the correlation between the calculated dose from radionuclide therapy and clinical symptoms (81,82). The toxicity thresholds currently used are derived from patients who received external beam radiation therapy between the 1950s and 1990s (83). In addition, the relationship of the administration schedule (injected activity, inter-cycle interval) and the estimated dose deposition remains unclear. Implementation of standardized dosimetry protocols in therapeutic trials with systematic clinical monitoring is warranted to generate the clinical data that would demonstrate an impact on patient survival.

Other therapeutic radiopharmaceuticals targeting PSMA are also in development.

The use of alpha-emitting radionuclides allows for up to 100 times greater energy deposition than beta particles over a much shorter distance (nanometers versus millimeters for beta particles). Actinium-225 has been the most widely used to date, but its large-scale production has not yet been established (84). Other alpha emitters are being studied such as Astatine-211, Lead-212 or Terbium-149 (85–87). It should be noted that the development of Lead-212 generators could allow teams to radio-label radiopharmaceuticals on site independently as with Gallium-68. Preliminary results from Ac225-PSMA-617 therapy are promising and show very strong antitumor activity (88). However, toxicity, particularly in the salivary glands, remains an unresolved problem.

The J591 antibody targeting PSMA and which can be radiolabeled with Lutetium-177 or Actinium-225 does not demonstrate uptake in the salivary glands and could represent an alternative to PSMA-617 (89–92). Preclinical work reports higher tumor uptake and longer retention time than with PSMA-617. In contrast, the blood circulation time of Lu177-J591 is long and the bone marrow and blood toxicity is greater than that of Lu177-PSMA-617. Clinical trials testing Lu177-J591 (limited to 2 cycles) are ongoing (PROSTACT NCT04876651).

Multiple therapeutic trials are underway to evaluate Lu177-PSMA-617 therapy at an earlier disease stage: before chemotherapy (e.g. PSMAfore NCT04689828, SPLASH NCT04647526, PSMAAddition NCT04720157), at the hormone-sensitive stage (e.g. PSMAddition, UpFrontPSMA (93)), oligo-metastatic (e.g. LUNAR) (94) or even as a neoadjuvant (e.g. LuTectomy) (95). The lower the volume to be treated, the more accurate the tolerance and toxicity profile must be evaluated (long life expectancy, delivery of Lu177-PSMA-617 to healthy tissues given limited tumor uptake, effects at distance from the targets). Long-term or late toxicity (≥ 12 months) remains poorly understood and the risk of nephropathy or myelodysplasia should be carefully monitored in populations exposed to Lu177-PSMA-617 at an early stage of disease.

It should be noted that molecular radiotherapy treatment targeting PSMA in patients with low tumor and/or microscopic volume would be potentially effective using alpha emitters (energy delivered on nanometers versus millimeters for beta particles). In contrast, the salivary toxicity profile of alpha therapy with the PSMA-617 ligand is not acceptable in this population. The development of ligands targeting PSMA with a better therapeutic index is required to treat this type of patients.

Multiple clinical trials are underway to test the combination of molecular radiotherapy targeting PSMA with potentially synergistic agents such as androgen receptor-targeting therapeutics, radiosensitizers (e.g., immune checkpoint inhibitor targeted therapies, PARP inhibitors, or chemotherapies) or immunotherapy (96–99).

Other biological targets than PSMA are currently being studied for potential theranostic applications in prostate cancer, such as STEAP1 (Six transmembrane epithelial antigen of the prostate 1), CD46, HK2 (Human-kallikrein-2 hK2), PSA (KLK3) and DLL3 (Delta-like ligand 3) for neuroendocrine prostate cancer (97,100).

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FUTURE PROJECT

Radiotheranostics can be defined as the combined use of a radiopharmaceutical imaging agent (radiotracer) and a radiopharmaceutical therapeutic agent having the same molecular target. It is an individualized medicine approach: visualization by PET imaging of the molecular target expression by the tumor lesions to select patients for the targeted radiopharmaceutical therapy ("you see what you treat, you treat what you see"). The targeted approach of radiopharmaceutical therapy leads to a treatment for metastatic cancers with a reduced toxicity profile.

The current level of technology in radionuclides production, radiochemistry, scanners, and software enables to take full advantage of the potential of radiopharmaceuticals. Targeted imaging enables the estimation of the individualized biodistribution of the radiopharmaceutical drug for each patient. This offers many opportunities for personalized precision medicine, and for pharmaceutical development (imagine if we could have visualized the biodistribution of all the drugs we currently use?).

Following the approvals in the United States and in Europe of radiopharmaceutical therapies targeting SSTR (Lu177-DOTATATE) for neuroendocrine tumors and more importantly PSMA (Lu177-PSMA-617) for metastatic prostate cancer, the radiopharmaceutical market is booming (Senior, M. *Nature Biotechnology* 2024. <https://doi.org/10.1038/s41587-024-02295-z> PMID: 38866995).

The world global radiopharmaceuticals market size forecast is expected to reach around USD 17.05 billion in 2034 (**Figure 1**). Multiple other molecular targets than SSTR and PSMA (FAP, CA-IX, SSTR, GRPR, GPC3) and applications (dosimetry, artificial intelligence) are being studied and numerous clinical trials from the phase 0 to phase 3 are currently being conducted (**Figure 2**).

This is evidenced by the multiple financial investments and acquisitions of pharmaceutical groups: Novartis acquired Advanced Accelerator Applications (USD 3.9 billion in 2017), Endocyte (USD 2.1 billion in 2018) and Mariana Oncology (USD 1 billion in 2024), Eli Lilly acquired POINT biopharma (USD 1.4 billion in 2023), Bristol Myers Squibb acquired RayzeBio (USD 3.1 billion in 2023) and AstraZeneca acquired Fusion Pharmaceuticals (USD 2.5 billion in 2024).

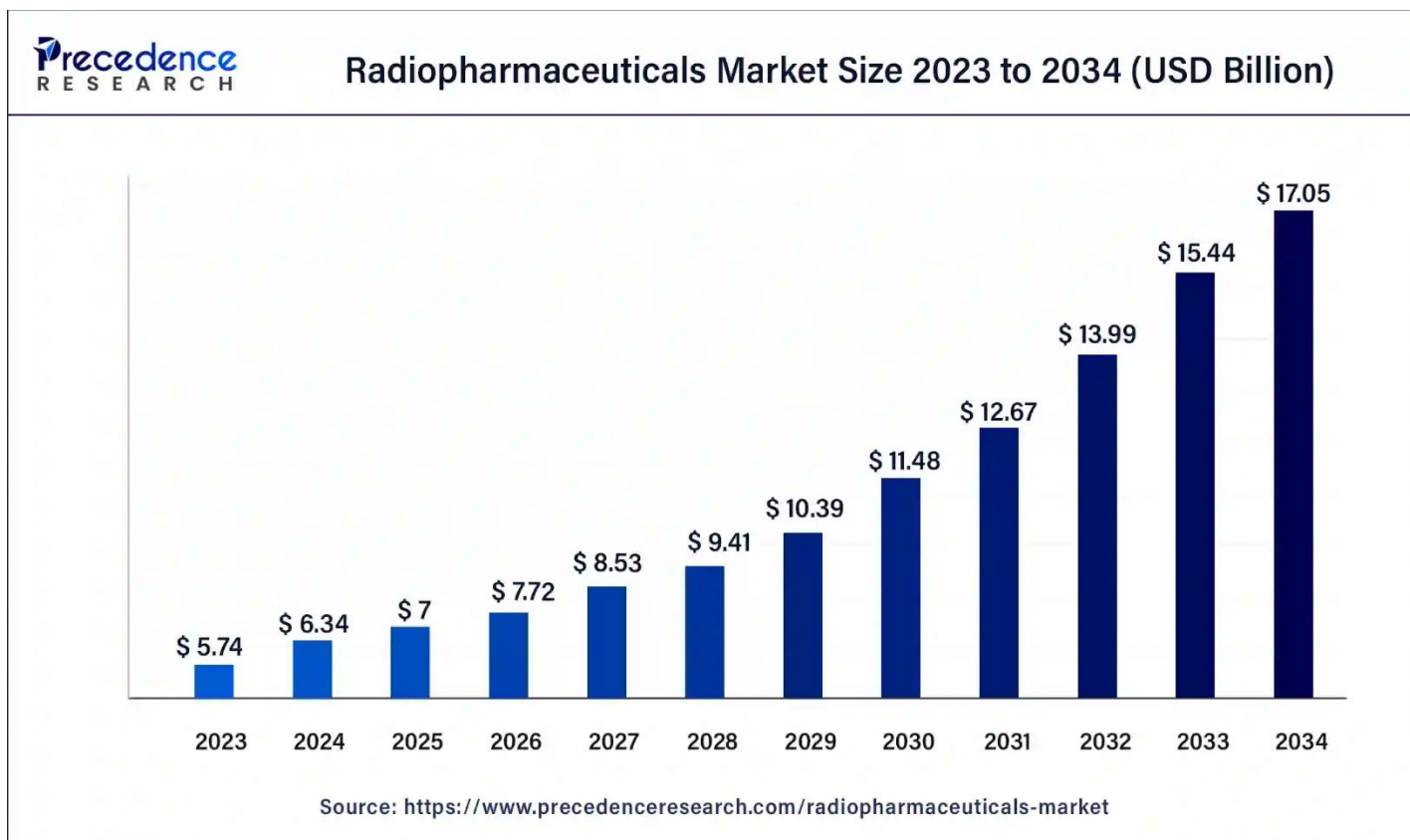


Figure 1: Global (world) radiopharmaceuticals Market Size and Forecast 2024 to 2034.

The global radiopharmaceuticals market size accounted for USD 6.34 billion in 2024 and is expected to reach around USD 17.05 billion by 2034, expanding at a CAGR of 10.4% from 2024 to 2034. The North America radiopharmaceuticals market size reached USD 2.53 billion in 2023.

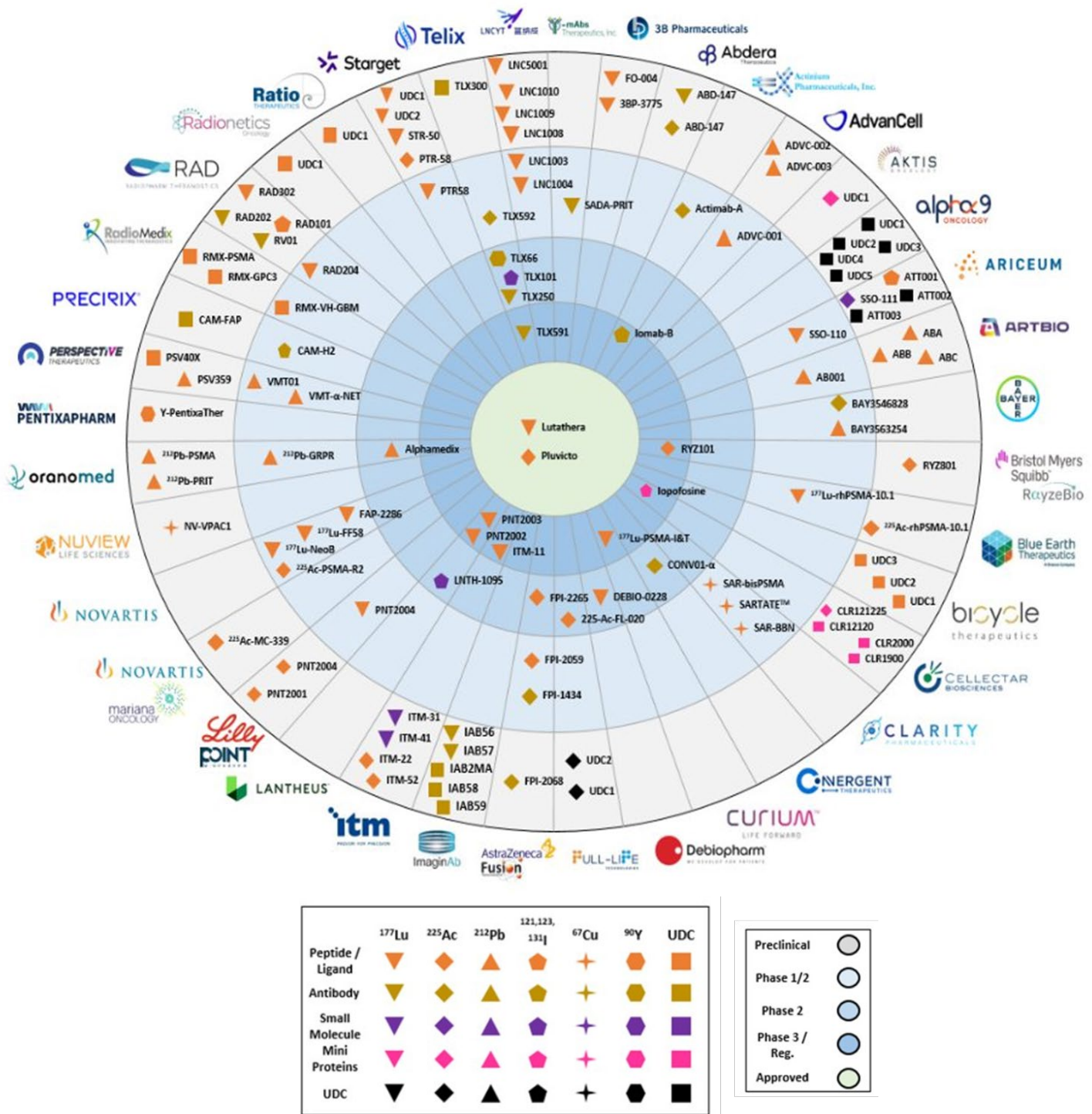


Figure 2: Overview of the current radiopharmaceutical industry clinical programs (from Oppenheimer & Co. 2024): 38 companies and 45 clinical stage programs, including 8 Phase III, 9 Phase II and 28 Phase I/II programs.

Leveraging this industry dynamism and flow of investments can enable the nuclear medicine community to offer cancer patients and their doctors a maximum of innovative radiopharmaceutical techniques.

At UCLA, we started our PSMA imaging research program in 2016 (**Table 1**) and our PSMA therapy research program in 2017 (**Table 2**). Subsequently we initiated other programs for other targets (FAP (**Table 3**), CA-IX (**Table 4**), others (**Table 5**)).

Table 1: PSMA Imaging Clinical Research Program, Ahmanson Translational Theranostics Division at UCLA

IRB #	NCT #	Protocol	enrollment
16-001095	NCT02940262	Biochemical Recurrence	1200 / 1200 - Closed
16-001684	NCT03368547	Primary Staging before Surgery	400 / 400 - Closed
17-001336	NCT04050215	Metastatic Staging / Other indications / "Basket"	1041 / 1200 - Closed
17-001885	NCT03515577	PSMA vs AXUMIN comparison	50 / 50 - Closed
18-000484	NCT03582774	Randomized Trial of PSMA PET based SRT	193 / 193 - Closed
18-001776	NCT04282824	MSG impact on PSMA PET signal	16 / 16 - Closed
19-001868	NCT04348682	PSMA PET Expanded Access protocol	407 / 2500 - Closed
20-000378	NCT04457245	Randomized Trial of PSMA PET based dRT	54 / 316 - Closed
19-002024	NCT04279561	PSMA ADT ARSI in CRPC	09 / 30 - Closed
20-000177	NCT04457232	FAPI PSMA	30 / 30 - Closed
21-000102	NCT04928820	PSMA vs Bone Scan in CRPC	22 / 102 - Closed
20-002256	NCT04857502	99mTc-PSMA-I&S radioguided surgery	19 / 30 - Open
21-001122	NCT05160597	PSMA-guided US prostate biopsy	46 / 50 - Open

Table 2: PSMA Therapy Clinical Research Program, Ahmanson Translational Theranostics Division at UCLA

IRB #	NCT #	Protocol	enrollment
17-000330	NCT03042312	RESIST-PC - Phase 2 Lutetium-177-PSMA-617	43 treated / 51 screened - Closed
18-000693	NCT03511664	VISION - Randomized Phase 3 Lutetium-177-PSMA-617	17 treated / 28 screened - Closed
21-005010	NCT04825652	MAP Expanded Access Program Lutetium-177-PSMA-617	65 treated / 69 screened - Closed
20-000369	NCT03939689	ARROW - Randomized Phase 2/3 Iodine-131-PSMA-MIP-1095	2 treated / 4 screened - Closed
21-000101	NCT04647526	SPLASH - Randomized Phase 3 Lutetium-177-PSMA-I&T	8 treated / 10 screened - Closed
22-000195	NCT04720157	PSMAddition - Randomized Phase 3 Lutetium-177-PSMA-617	2 treated / 4 screened - Closed
22-000750	NCT05496959	LUNAR - Randomized Phase 2 Lutetium-177-PSMA-I&T + SBRT	45 treated - 100 screened - Closed
23-000931	NCT06216249	FLEX-MRT - Randomized Phase 2 Lutetium-177-PSMA-617	4 enrolled / 90 - Open
23-001509	NCT06288113	RE-LuPSMA - Single-arm Phase 2 Lutetium-177-PSMA-617	2 enrolled / 40 - Open

Table 3: FAP imaging Clinical Research Program, Ahmanson Translational Theranostics Division at UCLA

IRB #	NCT #	Protocol	Acronym	Enrollment
19-000756	NCT04147494	FAPI + FDG (+/- PSMA) before surgery in multiple cancers	FAPI PET RDRC 1	29 / 30 - Open
20-000177	NCT04457232	FAPI + PSMA for Prostate Cancer before surgery or biopsy	FAPI PET Prostate	30 / 30 - Closed
20-000623	NCT04457258	FAPI + FDG for Sarcoma before surgery or biopsy	FAPI PET Sarcoma	16 / 30 - Open
20-003628	NCT04459273	FAPI + FDG for multiple cancers before surgery or biopsy	FAPI PET RDRC 2	25 / 30 - Open
21-000678	NCT05365802	FAPI for Lung Interstitial Disease	FAPI Lung ILD	14 / 30 - Open
22-000631	NCT05262855	FAPI PET for PDAC before surgery or neo adjuvant therapy	FAPI-46 PDAC	10 /60 - Open
23-005253	NCT05641896	FAPI-74 PET in Patients With Gastrointestinal Cancers	FAPI-74 GI	1 /80 - Open

Table 4: CA-IX imaging Clinical Research Program, Ahmanson Translational Theranostics Division at UCLA

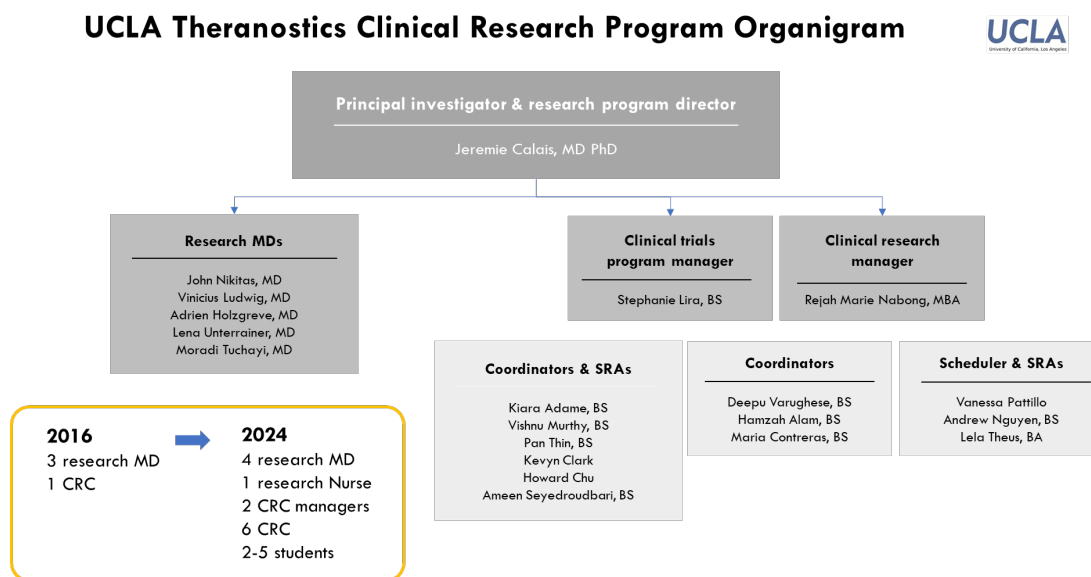
IRB #	NCT #	Protocol	Acronym	Enrollment
20-000992	NCT03849118	89-Zirconium-girentuximab for indeterminate renal mass	ZIRCON	34 - Closed
20-000177	NCT06090331	Expanded Access Program of Zr89-TLX250-CDx	ZIRCAIX EAP	15 - Open
23-001576	NCT06447103	TLX250 PET vs CT for Detection of Recurrent ccRC After Surgery	CA-NINE	2 - Open
24-005072	NCT05563272	CA-IX PET for multiple cancers before surgery or biopsy	STARBURST	0 - Opening soon

Table 5: Radiopharmaceutical clinical trials in activation phase at UCLA (Q3 2024)

NCT #	Acronym	Sponsor	PET/Therapy	Radiopharmaceutical(s)	Target	Patients
NCT05477576	RYZ101-301 ACTION-1	RayzeBio	Therapy	Actinium-225-DOTATATE	SSTR	GEP NET
NCT05595460	RYZ101-101 ES-SCLC	RayzeBio	Therapy	Actinium-225-DOTATATE	SSTR	small cell lung cancer
TBD	RYZ101-201 TRACY-1	RayzeBio	Therapy	Actinium-225-DOTATATE	SSTR	metastatic breast cancer
NA	ITM EAP	ITM	Therapy	Lutetium-177-DOTATOC	SSTR	meningioma
TBD	GaLuCi	Debio Pharm	Therapy	Lutetium-177-DPI-4452	CA-9	Kidney, pancreas PDAC, colon CCR
NCT06402331	AlphaBreak	Fusion / AZ	Therapy	Actinium-225-PSMA I&T	PSMA	mCRPC
NCT06033001	EAP PNT2002	POINT / Lilly	Therapy	Lutetium-177-PSMA I&T	PSMA	mCRPC
NCT06531499	RADIODOSE	Novartis	Therapy	Lutetium-177-PSMA-617	PSMA	mCRPC
NCT06526299	LPS-boost	Novartis	Therapy	Lutetium-177-PSMA-617	PSMA	mCRPC
NCT05849298	PSMA-care	Novartis	Therapy	Lutetium-177-PSMA-617	PSMA	mCRPC
CFXX489A12101	FXX489	Novartis	Therapy	Lutetium-177-FXX489	FAP	breast, pancreas PDAC, lung cancer
NCT04939610	LuMIERE	Novartis	Therapy	Lutetium-177-FAP-2286	FAP	breast, pancreas PDAC, lung cancer
TBD	TBD	Ratio Therapeutics	Therapy	Actinium-225-FAP-RTX	FAP	sarcoma
NCT06247995	CAAA603D12101	Novartis	Therapy	Lutetium-177-NeoB	GRPR	metastatic breast cancer
NCT05739942	CAAA603C12101	Novartis	Therapy	Lutetium-177-NeoB	GRPR	glioblastoma
NCT05870579	NeoB-B1	Novartis	Therapy	Lutetium-177-NeoB	GRPR	metastatic breast cancer
NCT06147037	FPI-2068	Fusion / AZ	Therapy	Actinium-225-FPI-2068	EGFR-cMET	HNSCC, NSCLC, mCRC, PDAC
TBD	ABD-147	Abdera	Therapy	Actinium-225-ABD147-101	DLL3	SCLC LCNEC
TBD	RYZ801-101	RayzeBio	Therapy	Actinium-225-RYZ801	GPC3	Hepatocellular carcinoma
TBD	VMT01-T101	Perspective Therapeutics	Therapy	Lead-212 VMT01-T101	MC1R	melanoma
TBD	NPY1R PET	Radionetics	PET Imaging	Gallium-68-R10602	NPY1R	metastatic breast cancer

To accommodate this growth, we had to expand our staffing. As an illustration, our clinical research team was constituted in 2016 of 3-4 members and now includes 15 people in 2024 (**Figure 3**).

Figure 3: Overview of the clinical research program team of the Ahmanson Translational Theranostics Division

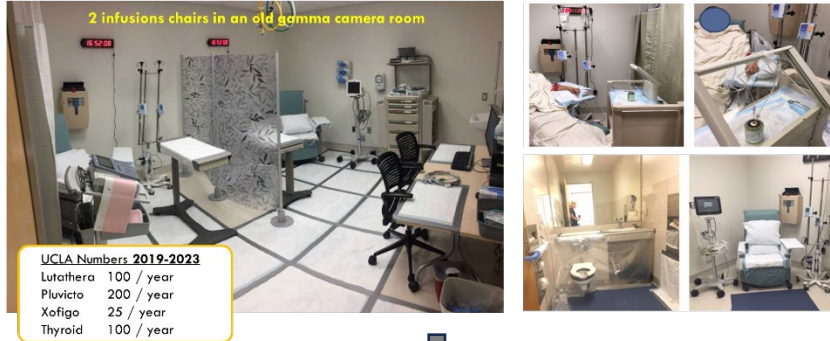


Similarly, we needed to expand our radiopharmaceutical therapy infusion capacity. Between 2017 and 2023 we treated patients in an old gamma camera room with 2 infusion chairs. In 2024, we inaugurated our new theranostics outpatient clinic that has 8 infusion chairs, including 2 beds (**Figure 4**).

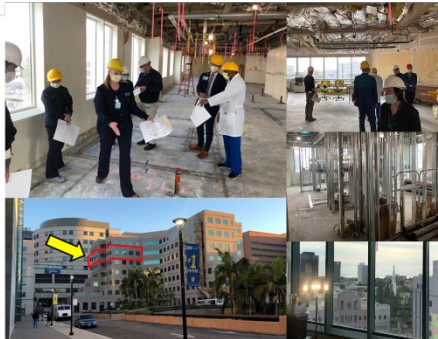
<https://www.uclahealth.org/news/article/theranostics-cancer-center-ucla-health>

Figure 4: Overview of the new UCLA Theranostics Center Opening (2024)

¹⁷⁷Lu-PSMA-617 Therapy UCLA setup in 2017...



Scaling Up = Build a new Theranostics Space 2018 ->2024



May 2024, Opening Ceremony



CAPACITY: Approx. 80 therapy cycles per week possible (> 4000 per year)



- > 8 infusion chairs
 - > 3 nurses – 1 NP
 - > 2 Nuc Med Technologists
 - > 2 radiation safety specialists
 - > 2 physicians
- Thyroid Cancer
 - Neuroendocrine Tumors
 - Pheochromocytoma/Paraganglioma
 - Prostate Cancer



From this experience, the main challenges and lessons learned are:

1. Obtaining the buy-in from the hospital administration to obtain space and budget.
2. A strong alliance with radiation safety officers, specifically during the development and planning of the new space.
3. The importance of partnership with medical oncologists and other referring specialties to ensure patients referrals and overcome the competition (competing centers, competing treatments, competing habits, competing interest). The presence and communication at tumor boards are key.
4. The integration in the existing electronic medical records system was and continues to be a big challenge for us.
5. Nursing and patient navigation: we have recruited dedicated nurses (n=4-5).

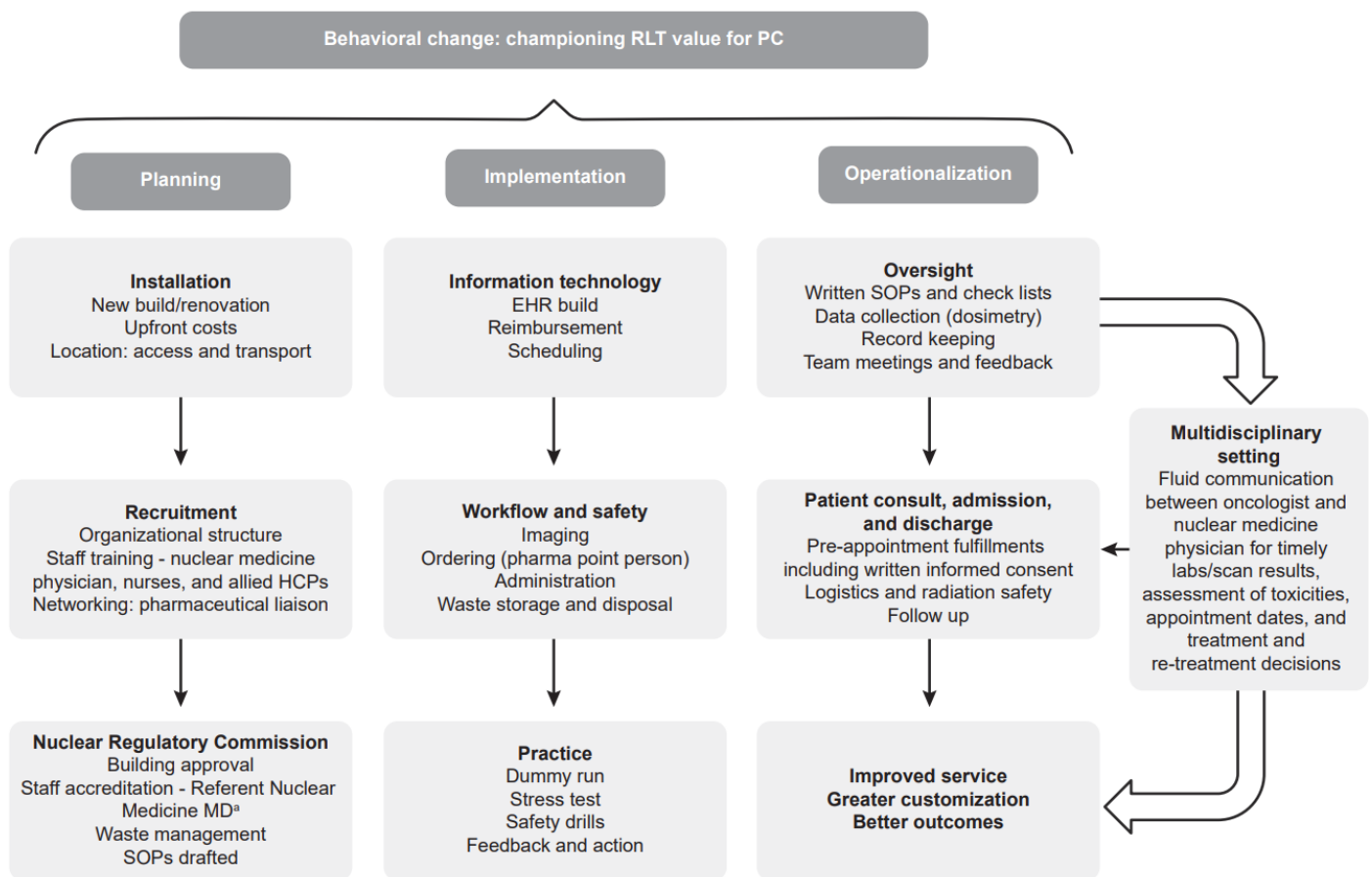
An overview of the key elements to consider when establishing a safe, efficient, and high-quality radiopharmaceutical therapy center is provided in the following article:

Incorporating radioligand therapy in clinical practice in the United States for patients with prostate cancer.

J Calais et al. *Cancer Treatment Reviews* 2023 Apr;115:102524. <https://doi.org/10.1016/j.ctrv.2023.102524> PMID: 36933329.

Figure 5 summarizes the multiple steps and processes related to a successful implementation of a new radiopharmaceutical therapy program.

Figure 5: Development and deployment of a new radiopharmaceutical therapy program.



EHR, electronic health record; HCP, healthcare professional; PC, prostate cancer; RLT, radioligand therapy; SOP, standard operating procedure.

J Calais et al. *Cancer Treatment Reviews* 2023 Apr;115:102524. <https://doi.org/10.1016/j.ctrv.2023.102524> PMID: 36933329.

Table 6 summarizes the duties of the key staff involved in a radiopharmaceutical therapy treatment center

Table 6: Duties of key personnel involved in running a radiopharmaceutical therapy treatment center.

Position	Duties	Training
Medical oncologist/ radiation oncologist ^a	<ul style="list-style-type: none"> Manages entire patient journey by liaising with nuclear medicine/clinical care team regarding eligibility, RLT ordering, concomitant medication entry in EHR, post-treatment scans, and AE monitoring Prioritizes communication with clinical care team, including provision of scans/results to colleagues to ensure continuity of patient care, trust, and communication 	Potentially an NRC Authorized User on completion of CFR part 35 [26] Workflow, eligibility, and safety training
Nuclear medicine physician ^a	<ul style="list-style-type: none"> PSMA PET image analysis Obtains consent from patients and reviews patient radiation safety instructions Confirms RLT dose assay Assesses IV patency and performs time-out procedure before RLT Administers RLT Monitors patient's status during and immediately after RLT Discharges the patient Follows up with the patient Prioritizes communication with medical oncology team and referring provider to ensure continuity of patient care, trust, and communication 	NRC Authorized User The theranostics specialist, defined as a qualified Nuclear Medicine Specialist trained in the practice of theranostics by the appropriate medical regulatory body. Accreditation in theranostics requires deep knowledge and experience in PET and SPECT interpretation, dosimetry, and response assessment for theranostics practice. Advanced training is essential in the RLT services medical subspecialties [64]
Nuclear medicine nurse	<ul style="list-style-type: none"> Checks EHR and orders medication from pharmacy the day before treatment Reviews patient laboratory values Establishes IV catheter^b Administers co-medications Monitors the patient's vital signs, looks for AEs during infusion, and administers anti-emetics Ensures that the patient voids when necessary to avoid radiation accumulation in bladder May perform radiation measurements prior to discharge Provides patients with detailed discharge instructions after treatment, including treatment wallet card and radiation safety instructions Coordinates follow-up phone calls, visits, and laboratory work 	<ul style="list-style-type: none"> Workflow Ordering Radiation safety <ul style="list-style-type: none"> Providing patient care Providing patient education Waste disposal in the treatment room Medication management Infusion pump
Nuclear medicine technologist	<ul style="list-style-type: none"> Orders, receives, and inspects the RLT dose Prepares the dose for administration and the patient for treatment Monitors the restroom floor and path of travel to the treatment area with a Geiger counter (alerts the radiation safety officer if contamination is found and restricts access pending neutralization) Prints a patient dose administration card Measures exposure rate at 1 m (3 ft) from the patient and confirms that the measurement is below the level established by the radiation safety officer once all administrations are complete 	<ul style="list-style-type: none"> Workflow NRC radiation safety credentialed <ul style="list-style-type: none"> Dose preparation Waste disposal Syringe pumps and medication infusion accessories
Radiation safety officer	<ul style="list-style-type: none"> Provides RLT safety training to nuclear medicine staff Prepares treatment room and restroom with contamination control measures Provides radiological survey support May perform radiation measurements prior to patient discharge Collects residual or unused doses and associated contaminated materials and manages inventory of those items for ultimate disposal Reviews each record of therapeutic administration Develops and maintains the basis for release of patients following treatment 	<ul style="list-style-type: none"> NRC radiation safety credentialed Workflow training
Pharmacist Radiopharmacist	<ul style="list-style-type: none"> Provide comedications on treatment day Prepares radiopharmaceuticals requiring manipulation before administration Ensures quality, safety, and efficacy of radiopharmaceuticals 	<ul style="list-style-type: none"> Workflow training Radiopharmacists must be NRC-credentialed Aseptic conditions/techniques Analytical techniques for quality control Workflow training

AE, adverse event; CFR, Code of Federal Regulations; EHR, electronic health record; ft, feet; IV, intravenous; m, meter; NRC, Nuclear Regulatory Commission; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; QC, quality control; RLT, radioligand therapy; SPECT, single-photon emission computerized tomography.

^a Physicians administering RLT may differ among centers: they could be radiation oncologists in some centers and nuclear medicine physicians in others.

^b Can also be performed by the nuclear medicine technologist.

A potential project for me in France would be to leverage my experience at UCLA to create a platform of expertise and logistics attractive to academic and industrial partners who want to conduct clinical trials using radiopharmaceuticals (diagnostic and therapeutic): an integrated center for clinical and translational research in theranostics (CCTRT).

The center would provide the “niche” multidisciplinary expertise of radiotheranostics to conduct radiopharmaceuticals-based trials, including first-in-human phase 1 studies with dedicated specialized staff, technologists, radiopharmacists, physicists, research assistants, radiation safety officers, specialized nurses, nuclear medicine specialists, oncologists, and radiochemists.

The CRCTT would be directly attached to an existing nuclear medicine department and would share its human and material resources. The CRCTT would also collaborate with the pre-clinical research teams (micro PET, artificial intelligence, PhD students). In addition, the CRCTT would have dedicated structures (staff, spaces, scanners). The CRCTT would operate new PET/CT scanners with extended field of view (total-body PET/CT) enabling high patient throughput and dedicated research PET/CT scanner time slots, ideal for clinical trials, especially phase 1. The center would also operate next-generation SPECT/CT systems with CZT digital detectors in a ring-like setup to perform quantitative Lu-177 SPECT imaging in clinical routine.

The CRCTT would provide the opportunity to cancer patients and their doctors to gain access to a maximum of innovative radiopharmaceutical techniques.

This vision concludes this manuscript of Accreditation to Supervise Research (Habilitation à Diriger des Recherches (HDR)).

Appendix: Full CV

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David Geffen School of Medicine at UCLA

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MEDICAL LICENCE and CERTIFICATION :

October 2014 **Regional Medical Board of Paris (France)**
Conseil départemental de la ville de Paris de l'Ordre des médecins
CDOM#75/82203 RPPS#10100673903

July 2020 **Medical Board of California (USA), Section 2113.**
Certificate of registration #F645
NPI# 1053927079

December 2020 **National Medical Board of France, Special Overseas Physicians Section.**
Conseil National de l'Ordre des médecins, Liste spéciale des médecins résidant à l'étranger
CNOM#99/4988 RPPS#10100673903

April 2024 **ACRP Certified Principal Investigator (CPI)**
The Association of Clinical Research Professionals

ACADEMIC DEGREES:

September 2010 **Doctor of Medicine (DCEM) [MD]**
University of Paris-Diderot, X.Bichat Medical School

October 2014 **Nuclear Medicine Specialist (DES) [Board Certification]**
University of Rouen, H.Becquerel Cancer Center

October 2015 **Cancerology Imaging Specialist (DESC)**
University of Rouen, H.Becquerel Cancer Center

October 2017 **Master of Science (M2) [MSc]**
Biomedical Imaging
University of Paris-Sud

December 2023 **Doctor of Science [PhD] by Recognition of Prior Learning (VAE)**
Medical Physics and Imaging
Institut Curie, University Paris-Saclay

ACADEMIC CAREER TRACK:

1995-2002	Middle School + High School Lycée Carnot, Paris
2002-2003	Biology and Sciences Lycée Chaptal, Paris
2003-2010	Medical School Xavier Bichat Hospital and Faculty of Medicine at University of Paris-Diderot
2010-2014	Nuclear Medicine Residency <i>Department of Nuclear Medicine</i> Henri Becquerel Cancer Center at University of Rouen.
2014-2016	University Assistant - Clinical Fellow <i>Department of Nuclear Medicine and Biophysics</i> Xavier Bichat Hospital and Faculty of Medicine at University of Paris-Diderot
2016-2017	Post-doctoral Research Fellow <i>Ahmanson Translational Theranostics Division</i> Department of Molecular and Medical Pharmacology David Geffen School of Medicine at University of California Los Angeles.
2017-2018	Assistant Adjunct Professor <i>Ahmanson Translational Theranostics Division</i> Department of Molecular and Medical Pharmacology David Geffen School of Medicine at University of California Los Angeles.
2018-2021	Assistant Professor <i>Ahmanson Translational Theranostics Division</i> Department of Molecular and Medical Pharmacology David Geffen School of Medicine at University of California Los Angeles.
2021 - Present	Associate Professor <i>Ahmanson Translational Theranostics Division</i> Department of Molecular and Medical Pharmacology David Geffen School of Medicine at University of California Los Angeles.

CLINICAL CAREER TRACK:

➤ **RESIDENCY**

Nov. 2010 - Apr.2011	Resident Year #01 – Semester #01 Medical Oncology University of Rouen, Evreux Hospital
May 2011 - Oct.2011	Resident Year #01 – Semester #02 Radiology University of Rouen, Evreux Hospital
Nov. 2011 - Apr.2012	Resident Year #02 – Semester #03 Nuclear Medicine University of Rouen, H.Becquerel Cancer Center

May 2012 - Oct.2012 Resident Year #02 – Semester #04
Radiology
 University of Rouen, C.Nicolle Hospital

Nov. 2012 - Apr.2013 Resident Year #03 – Semester #05
Nuclear Medicine
 University of Paris-Diderot, St-Louis Hospital

May 2013 - Apr.2014 Resident Years #03#04 – Semesters #06#07
Nuclear Medicine
 University of Rouen, H.Becquerel Cancer Center

May 2014 - Oct.2014 Resident Year #04 – Semester #08
Radiation Oncology
 University of Paris VI, Pitié-Salpêtrière Hospital

➤ **CLINICAL FELLOWSHIP**

Nov.2014 - Oct.2016 University Assistant - Clinical Fellow
Nuclear Medicine - Nuclear Cardiology
 University of Paris-Diderot, X.Bichat Hospital

➤ **PRIVATE PRACTICE – SHORT-TERM CONTRACTS – LOCUM**

2014 **PET/CT + SPECT/CT**
 Regional Hospital of Nevers (58), Dr Ahond-Vionnet

2014 **SPECT**
 ELISE Nuclear Medicine Center - Montargis (45), Dr Bekhechi

2014 **SPECT/CT**
 Claude Galien Private Hospital- Quincy-Sous-Senart (91), Dr Sarandi

2014 **PET/CT**
 Jean Perrin PET Center- Arras (62), Dr Tellier

2014 **SPECT/CT**
 Clinique Bergouignan - Evreux (27), Dr Gendreau

2015 **PET/CT**
 Clinique St Jean - Melun (77), Dr Esnault

2016 **DSPECT + SPECT/CT**
 PARLY II Private Hospital - Le Chesnay (78), Dr Teyton

2016 **PET/CT**
 Nuclear Medicine Center of Soisson (02), Dr Divry

2016 **PET/CT**
 Regional Hospital of Marne-La-Vallee (77), Dr Cuif

2016 **PET/CT**
 Centre Cardiologique Du Nord - European Hospital La Roseraie (93), Dr Banayan

2014-2016 **PET/CT + SPECT/CT**
 Clinique de l'Europe - Amiens (80), Dr Maszelin

2014-2016 **PET/CT**
 Roger Perez Nuclear Medicine Center - Sarcelles (93), Dr Mabilie

CLINICAL RESEARCH TRIAL INVESTIGATOR

Nov 2017-Present	Principal Investigator (PI) of Investigator Initiated Trials (IIT): PET imaging: 14 studies Targeted Molecular Radiotherapy: 2 studies
	Principal Investigator (PI) of Industry Sponsored Research Trials: PET imaging: 1 study Targeted Molecular Radiotherapy: 5 studies
	Co-Principal Investigator (Co-PI) and Co-Investigator (Co-I) of Investigator Initiated Trials (IIT) PET imaging: 5 studies Targeted Molecular Radiotherapy: 2 studies
	Co-Principal Investigator (Co-PI) and Co-Investigator (Co-I) of Industry Sponsored Research Trials PET imaging: 5 studies Targeted Molecular Radiotherapy: 5 studies

PROGRAM DIRECTOR:

Nov.2018 - Present	Director, Clinical Research Program <i>Ahmanson Translational Theranostics Division</i> Department of Molecular and Medical Pharmacology David Geffen School of Medicine at University of California Los Angeles.
July 2021 – Present	Director, Theranostics Program <i>Ahmanson Translational Theranostics Division</i> Department of Molecular and Medical Pharmacology David Geffen School of Medicine at University of California Los Angeles.

TEACHING EXPERIENCE:

2014-2016	Biophysics tutorials - First year of Medical School University of Paris-Diderot, X.Bichat Hospital.
2018-Current	Radiology Oncology lecture series - Radiology Residency Program Department of Radiological Sciences, University of California Los Angeles.
2019-Current	Radiation Oncology Lecture series – Radiation Oncology Residency Program Department of Radiation Oncology, University of California Los Angeles.
2019-Current	Nuclear Medicine lecture series - Radiology Residency Program Department of Radiological Sciences, University of California Los Angeles.
2019-Current	Physics and Biology in Medicine Seminar Series Physics and Biology in Medicine Graduate Program, University of California Los Angeles.

PROFESSIONAL MEMBERSHIPS:

2018 - Present	Faculty Member Jonsson Comprehensive Cancer Center University of California Los Angeles.
2018 - Present	Faculty Member Institute of Urologic Oncology University of California Los Angeles
2019 - Present	Faculty Member Physics and Biology in Medicine Graduate Program David Geffen School of Medicine University of California Los Angeles
2019 - Present	Board Member SNMMI Correlative Imaging Council (CIC) Society of Nuclear Medicine and Molecular Imaging (SNMMI)
2020 - Present	Committee Member Prostate Theranostics and Imaging Centre of Excellence (ProSTIC) Peter MacCallum Cancer Centre, University of Melbourne.
2020 - Present	Associate Editor <i>The Journal of Nuclear Medicine</i>
2021 – Present	Advisory Board Member Oncidium Foundation Ouderghem, Belgium.
2021 - Present	Member SNMMI Prostate Cancer Working Group (PCWG) Society of Nuclear Medicine and Molecular Imaging (SNMMI)
2022 – Present	Editorial Board Member GU Oncology Now Integrated Medical Communications - Mashup Media
2023 – Present	Member SWOG Genitourinary Cancer Committee, ID#84173
2024 -Present	Distinguished Investigator of Theranostics XCancer TheranosticTrials.org

Medical Association Membership

American Society of Clinical Oncology (ASCO)
Society of Nuclear medicine and Molecular Imaging (SNMMI)
Radiological Society of North of America (RSNA)
Association Nationale des Assistants et Internes de Medecine Nucleaire (ANAIMEN)

DOCTORAL COMMITTEE

Doctor of Medicine - Medical Thesis

Name	Date of Thesis Defense	Institution
Anne Chaput	September 30 2016	University of Brest, France

Title: Correlation between fluorodeoxyglucose hotspots on pretreatment positron emission tomography/CT and preferential sites of local relapse after chemoradiotherapy for head and neck squamous cell carcinoma.

<https://hal.archives-ouvertes.fr/hal-01643973>

Supervisor: Ronan Abgral MD PhD

Committee Chair: Pierre Yves Salaun MD PhD

Committee Members: Ronan Abgral MD PhD, Jeremie Calais MD, Ulrike Schick, MD, PhD, Solene Querellou MD

Doctor of Sciences - PhD Thesis

Name	Date of Thesis Defense	Institution
Catherine Meyer	May 18 2022	University of California, Los Angeles

Program Specialty: **Physics and Biology in Medicine**

Title: Advancements in Prostate-Specific Membrane Antigen Targeted Radionuclide Therapy Through Dosimetry

<https://escholarship.org/uc/item/4dn4r0h4>

Supervisor: Magnus Dalhbom PhD

Committee Chair: Magnus Dalhbom PhD

Committee Members: Jeremie Calais MD, Johannes Czernin MD, Keisuke S Iwamoto PhD, Nicholas G Nickols MD PhD, Roger Slavik PhD.

Doctor of Sciences - PhD Thesis

Name	Date of Thesis Defense	Institution
Zachary Ells	2024-2025	University of California, Los Angeles

Program Specialty: **Physics and Biology in Medicine**

Title: Dosimetry for Radionuclide Therapy

Supervisor: Magnus Dalhbom PhD

Committee Chair: Magnus Dalhbom PhD

Committee Members: Jeremie Calais MD, Giuseppe Carlucci PhD, Johannes Czernin MD, Christine Mona PhD,

AWARDS

- 2016 **Achard-Medecine Award, National Academy of Medicine (France)**
Development of a new nuclear imaging probe in oncology: ⁶⁸Ga-Pentixafor
- 2017 **Best Oral Abstract Award, WRSNM annual meeting 2017 (Vancouver, Canada)**
68Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning.
- 2018 **Best Article of the Month (February 2018 Cover Page), The Journal of Nuclear Medicine**
68Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning.
- 2018 **Best Clinical Article of the Month (November 2018), The Journal of Nuclear Medicine**
Potential impact of (68)Ga-PSMA-11 PET/CT on prostate cancer definitive radiation therapy planning.
- 2018 **Top 1 Research Story, PCF Annual Scientific Retreat**
Elucidating mechanisms of effectiveness and resistance to 177Lu-PSMA-617
<https://www.pcf.org/blog/top-5-from-the-pcf-scientific-retreat/>
- 2019 **Best Manuscript of the Year (2018), The Journal of Nuclear Medicine.**
68Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning.
- 2019 **Walter Wolf Young Investigator Award, SNMMI Correlative Imaging Council, SNMMI annual meeting 2019 (Anaheim, CA)**
68Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to 18F-Fluciclovine PET/CT in a prospective head to head comparative phase 3 study
- 2019 **Early Career Abstract Award (Clinical Science), SNMMI Early Career Professionals Committee, SNMMI annual meeting 2019 (Anaheim, CA)**
68Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to 18F-Fluciclovine PET/CT in a prospective head to head comparative phase 3 study
- 2019 **Best Article of the Month (September 2019 Cover Page), The Journal of Nuclear Medicine**
111In-pentetreotide scintigraphy vs. 68Ga-DOTATATE PET: Impact on Krenning Scores and effect of tumor burden.
- 2020 **« Ones to Watch » 2020 Selection , SNMMI early career professionals**
Nominated in the list of 30 early career professionals for the « Ones to Watch » 2020 Campaign Selection
<https://jnm.snmjournals.org/content/jnumed/61/5/14N.full.pdf>
- 2022 **Hal O'Brien Rising Star Award, High Country Nuclear Medicine Conference 2022 (Sun Valley, Idaho)**
for outstanding leadership in Nuclear Medicine Science
<https://cancer.ucla.edu/Home/Components/News/News/1836/>
- 2022 **Best Article of the Month (June 2022 Cover Page), The Journal of Nuclear Medicine** *Head-to-head comparison of 68Ga-PSMA-11 PET/CT and mpMRI with histopathology gold-standard in the detection, intra-prostatic localization and local extension of primary prostate cancer: results from a prospective single-center imaging trial.*
- 2022 **SNMMI Cancer Cooperative Group Junior Faculty Mentorship Award**
SWOG Cancer Research Network – UCLA JCCC

- 2023 **Best Article of the Month (July 2023 Cover Page), The Journal of Nuclear Medicine**
PSMA PET Tumor-to-Salivary Gland Ratio to Predict Response to [177Lu]PSMA Radioligand Therapy: An International Multicenter Retrospective Study.
- 2023 **Best Article of the Month (November 2023 Cover Page), The Journal of Nuclear Medicine**
Do Bone Scans Overstage Disease Compared with PSMA PET at Initial Staging? An International Multicenter Retrospective Study with Masked Independent Readers.
- 2023 **SS. Gambhir Distinguished Scientist Award, WRSNM annual meeting 2023 (Vancouver, Canada)**
for significant contributions to the Clinical Science of Nuclear Medicine or Molecular Imaging.
<https://wrsnm.org/jeremie-calais-md-msc-to-receive-western-region-snm-distinguished-scientist-award/>
- 2024 **Distinguished Investigator of Theranostics, Xcancer TheranosticTrials.org**
<https://www.theranostictrials.org/distinguished-investigators/qt0e9xe7yvdchxi1xsamino4>

GRANTS

PRINCIPAL INVESTIGATOR

2016-2017	ARC Foundation [France] International Mobility Award SAE20160604150 <i>Development and translation of a new nuclear imaging probe for theranostics in cancer patients: 68Ga-Pentixafor</i>	30,000€
2016-2017	Philippe Foundation [NY, USA] Exchange Program Grant <i>Development and translation of a new nuclear imaging probe for theranostics in cancer patients: 68Ga-Pentixafor</i>	\$10,000
2017-2018	Philippe Foundation [NY, USA] Exchange Program Grant <i>Preclinical and clinical exploration of theranostics pairs 68Ga-/177Lu-DOTATATE and 68Ga-/177Lu-PSMA</i>	\$10,000
2019-2021	ERF-SNMMI [USA] Molecular Imaging Research Grant for Junior Academic Faculty <i>Imaging tumor stroma with 68Ga-PSMA-11 and 68Ga-FAPI-46 in patients with non-prostate cancers: an exploratory PET biodistribution study with histopathology validation.</i> https://newsroom.ucla.edu/dept/faculty/grant-expands-new-imaging-techniques-that-target-tumor-environment https://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=35505	\$100,000
2020-2023	Prostate Cancer Foundation [USA] PCF Young Investigator Award 20YOUN05 <i>Validating a PET imaging biomarker for targeting fibroblast activation protein in prostate cancer stroma.</i> https://newsroom.ucla.edu/dept/faculty/jeremie-calais-young-investigator-award-prostate-cancer	\$225,000
2021-2023	Department of Defense (DoD) Health Program Prostate Cancer Research Program (PCRP) FY19 PCRP Clinical Trial Award W81XWH2010351 Subgrant Sponsor: H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida PI: Dr Brian D. Gonzalez Sponsor Award Number: 12-20451-99-01-G3 <i>Measuring Patient-Reported Outcomes Related to Radiopharmaceuticals for Prostate Cancer</i>	\$62,403

INVESTIGATOR INITIATED TRIAL

2020-2022	Lantheus Holdings – Progenics Pharmaceuticals Research Grant Support - PyL Research Access Program <i>Investigator-Initiated Trial NCT04457245: Randomized Trial of PSMA PET Scan Before Definitive Radiation Therapy for Prostate Cancer (PSMA-dRT)</i>	\$	270,000
2022-2023	POINT biopharma Research Grant Support <i>Investigator-Initiated Trial NCT05496959 LUNAR: 177-Lutetium-PSMA Before Stereotactic Body Radiotherapy for the Treatment of Oligorecurrent Prostate Cancer, The LUNAR Study</i>	\$	1,000,000
2024-2025	Novartis Research Grant Support <i>+ Investigator-Initiated Trial IRB#23-000931 IND#168362 Flexible dosing schedule of LuPSMA molecular radiotherapy in mCRPC patients: a randomized phase 2 trial (FLEX-MRT)</i> <i>+ Investigator-Initiated Trial IRB#23-001509 IND#169476 Re-Treatment with 177Lu-PSMA-617 Molecular Radiotherapy for Metastatic Castration Resistant Prostate Cancer: A Prospective Phase 2 Trial (RE-LuPSMA)</i>	\$	4,500,000

FACULTY MENTOR

2020-2021	UCLA JCCC Fellowship Award [USA] Principal Investigator: Andrei Gafita (Post-Doctoral Fellow) <i>Evaluation of novel PSMA PET/CT imaging quantitative tool to improve patient selection and therapeutic outcome of PSMA-targeted radioligand therapy</i>	\$30,000
2021-2023	Prostate Cancer Foundation [USA] PCF Young Investigator Award Principal Investigator: Andrei Gafita (Post-Doctoral Fellow) <i>Development of biomarker-based approaches to optimize PSMA-targeted therapeutics for advanced prostate cancer</i>	\$225,000
2023-2025	Prostate Cancer Foundation [USA] PCF Young Investigator Award Principal Investigator: Adam Weiner Molecular Correlates with Prostate-Specific Membrane Antigen (PSMA) in Prostate Cancer	\$225,000

CO-INVESTIGATOR

2019-2021	Prostate Cancer Foundation [USA] PCF Challenge Award 19CHAL09 - PI: Johannes Czernin (UCLA) <i>Towards Curative RLT in Prostate Cancer Through Dosimetry Optimization, Combination Therapies and Stroma Targeting.</i> https://newsroom.ucla.edu/dept/faculty/grant-will-help-improve-new-imaging-method-for-prostate-cancer	\$1,000,000
2019-2021	Department of Defense (DoD) Health Program - Prostate Cancer Research Program (PCRP) FY19 PCRP Clinical Trial Award W81XWH2010351 - PI: Dr Brian D. Gonzalez (Moffitt Cancer Center, Tampa, Florida) <i>Measuring Patient-Reported Outcomes Related to Radiopharmaceuticals for Prostate Cancer UCLA OCGA Notification of Award Action</i>	
2023-2025	SNMMI Mars Shot Research Award PI: Amir Iravani (University of Washington School of Medicine in Seattle, Washington). <i>Phase II trial of biomarker-modulated PSMA Theranostics</i>	\$1,000,000

COLLABORATOR

2017-2019	Prostate Cancer Foundation PCF Challenge Award 17CHAL02 - PI: Johannes Czernin (UCLA) <i>Elucidating mechanisms of effectiveness and resistance to Prostate Specific Membrane Antigen (PSMA) targeted Radioligand Therapy (RLT) using 177Lu-PSMA-617</i> https://newsroom.ucla.edu/dept/faculty/ucla-cancer-researchers-receive-grants-for-prostate-cancer-research	\$1,000,000
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ACADEMIC RESEARCH:

<https://www.uclahealth.org/medical-services/nuclear-medicine/research/dr-jeremie-calais-lab>

FDA New Drug Application NDA #212642 for PSMA-11 Gallium-68

- *Role: Co-Investigator and clinical study report author*
 - UCLA and UCSF joint application (Principal Investigators: Johannes Czernin and Thomas A Hope)
 - Indication: PSMA-11 Ga 68 Injection for PET Imaging of Detection and Localization of Prostate Cancer
 - <https://newsroom.ucla.edu/releases/fda-approves-imaging-technique-for-prostate-cancer>
 - <https://www.snmim.org/NewsPublications/NewsDetail.aspx?ItemNumber=35254>
 - <https://connect.uclahealth.org/2021/02/17/imaging-technique-investigated-at-ucla-health-a-major-advance-for-patients-with-prostate-cancer/>
 - <https://www.ucsf.edu/news/2020/12/419196/ucsf-ucla-gain-fda-approval-prostate-cancer-imaging-technique>
 - <https://www.uclahealth.org/psma>

FDA New Drug Application NDA #130342 for Fluor-18-Choline

- *Role: Co-Investigator and Blinded Independent Central Reader (BICR)*
 - UCSF and UCLA joint application (Principal Investigator: Thomas A Hope)
 - Indication: Fluor-18 Choline for PET Imaging of Detection and Localization of parathyroid hyperactivity

Principal Investigator (PI) of Investigator Initiated Trials (IIT)

PSMA-targeted PET imaging

- Impact of 68Ga-PSMA-11 PET/CT on initial and subsequent treatment strategies of patients with prostate cancer.
 - ClinicalTrials.gov Identifier: NCT04050215, Start Date: Apr 2018
- Randomized phase 3 Trial of 68Ga-PSMA-11 PET/CT Molecular Imaging for Prostate Cancer Salvage Radiotherapy Planning [PSMA-SRT]
 - ClinicalTrials.gov Identifier: NCT03582774, Start date: July 2018
- Evaluation by 68Ga-PSMA-11 PET imaging of Monosodium Glutamate as a potential agent for Salivary Gland Protection under PSMA-targeted alpha-therapy: a randomized pilot imaging research study
 - ClinicalTrials.gov Identifier: NCT04282824, Start Date: Jan 2020
- Effect of Androgen Receptor Signaling Inhibitors on 68Ga-PSMA-11 PET/CT Imaging in Patients With Metastatic Castration-Resistant Prostate Cancer
 - ClinicalTrials.gov Identifier: NCT04279561, Start Date: Mar 2020
- Expanded Access Protocol of 68Ga-PSMA-11 for Prostate Cancer PET Imaging
 - ClinicalTrials.gov Identifier: NCT04348682, Start Date: Mar 2020
- Randomized Trial of PSMA PET Scan Before Definitive Radiation Therapy for Prostate Cancer (PSMA DRT)
 - ClinicalTrials.gov Identifier: NCT04457245, Start Date: Sept 2020
 - <https://www.oncology-central.com/psma-pet-imaging-an-interview-with-jeremie-calais/>
 - <https://www.urotoday.com/recent-abstracts/urologic-oncology/prostate-cancer/109989-randomized-prospective-phase-iii-trial-of-68ga-psma-11-pet-ct-molecular-imaging-for-prostate-cancer-salvage-radiotherapy-planning-psma-srt-beyond-the-abstract.html>
- 99mTc-PSMA-I&S Biodistribution in Patients With Prostate Cancer
 - ClinicalTrials.gov Identifier: NCT04857502, Start date: June, 2021
 - <https://www.uclahealth.org/news/pioneering-surgical-approach-lifesaver-new-jersey-resident>
- 68Ga-PSMA-11 PET/CT for the Diagnosis of Bone Metastases in Patients With Prostate Cancer and Biochemical Progression During Androgen Deprivation Therapy
 - ClinicalTrials.gov Identifier: NCT04928820, Start date: June, 2021
- Image-Guided (68Ga-PSMA-11 PET/CT) Prostate Biopsy for the Diagnosis of Prostate Cancer in Men With Prior Negative/Inconclusive Biopsy
 - ClinicalTrials.gov Identifier: NCT05160597, Start date: January, 2022

FAP-targeted PET imaging

- PET biodistribution study of 68Ga-FAPI-46 (+/- 68Ga-PSMA-11) in patients with non-prostate cancers: an exploratory study with histopathology validation
 - ClinicalTrials.gov Identifier: NCT04147494, Start Date: Oct 2019
- 68Ga-FAPi-46 PET/CT Scan in Imaging Patients With Sarcoma
 - ClinicalTrials.gov Identifier: NCT04457258, Start Date: Sept 2020
- Prospective Exploratory Study of FAPi PET/CT With Histopathology Validation in Patients With Various Cancers (FAPi PET RDRC)
 - ClinicalTrials.gov Identifier: NCT04459273, Start Date: Sept 2020
- Prospective Exploratory Study of FAPi PET/CT in Prostate Cancer With Histopathology Validation (FAPi PET Prost)
 - ClinicalTrials.gov Identifier: NCT04457232, Start Date: Sept 2020
- PET study of 68Ga-FAPi-46 in patients with interstitial lung disease: an exploratory biodistribution study with histopathology validation
 - ClinicalTrials.gov Identifier: NCT05365802, Start Date: Sept 2021

PSMA-targeted Therapy

- Randomized Phase 2 Trial of Flexible and Extended Dosing of 177Lu-PSMA-617 Molecular Radioligand Therapy (FLEX-MRT)
 - Study Number: NCT06216249 IRB# 23-000931, Start Date: Apr 2024
- Re-Treatment with 177Lu-PSMA-617 Molecular Radiotherapy for Metastatic Castration Resistant Prostate Cancer: A Prospective Phase 2 Trial (RE-LuPSMA)
 - Study Number: NCT06288113 IRB#23-001509, Start Date: Apr 2024

Co-Principal Investigator (Co-PI) and Co-Investigator (Co-I) of Investigator Initiated Trials (IIT)

PSMA-targeted Therapy

- PSMA-directed endoRadiothErapy of Castration-reSISTant Prostate Cancer (RESIST-PC). A Phase II Clinical Trial
 - ClinicalTrials.gov Identifier: NCT03042312, Start Date: July 12, 2017
 - PI: Johannes Czernin (UCLA Nuclear Medicine)
- 177-Lutetium-PSMA Before Stereotactic Body Radiotherapy for the Treatment of Oligorecurrent Prostate Cancer, The LUNAR Study (LUNAR)
 - ClinicalTrials.gov Identifier: NCT05496959, Start date: September 8, 2022
 - PI: Amar Kishan (UCLA Radiation Oncology)

PSMA-targeted PET Imaging

- 68Ga-PSMA PET/CT for Detection of Recurrent Prostate Cancer After Initial Therapy
 - ClinicalTrials.gov Identifier: NCT02940262, Start date: September 5, 2016
 - PI: Johannes Czernin (UCLA Nuclear Medicine)
- 68Ga-PSMA-11 PET/CT for Staging of Intermediate and High-Risk Prostate Cancer Prior to Radical Prostatectomy
 - ClinicalTrials.gov Identifier: NCT03368547, Start Date: December 12, 2016
 - PI: Johannes Czernin (UCLA Nuclear Medicine)
- Prospective Single Center Trial to Compare 68Ga-PSMA-11 and AXUMIN PET/CT (18F-Fluciclovine) for Restaging Prostate Cancer Patients with Biochemical Recurrence After Radical Prostatectomy
 - ClinicalTrials.gov Identifier: NCT03515577, Start date: March 2, 2018
 - PI: Johannes Czernin (UCLA Nuclear Medicine)

KIDNEY imaging

- 99mTc-SestaMIBI SPECT/CT Imaging for the Characterization of Renal Masses: Impact on Clinical Decision Making
 - ClinicalTrials.gov Identifier: NCT03996850, Start Date: Dec 7, 2018
 - PI: Brian Shuch (UCLA Urology)
- 89Zr-TLX250 PET/CT vs Contrast-Enhanced CT for Detection of Recurrent Clear Cell Renal Cell Carcinoma After Surgery
 - Study Number: IRB#23-001576, Start Date: May, 2024
 - PI: Brian Shuch (UCLA Urology)

INDUSTRY SPONSORED RESEARCH:

Principal Investigator (PI) of Industry Sponsored Research Trials

PSMA-targeted Therapy

- ARROW: Study of I-131-1095 Radiotherapy in Combination With Enzalutamide in Patients With Metastatic Castration-resistant Prostate Cancer Who Are Chemotherapy Naive and Have Progressed on Abiraterone
 - ClinicalTrials.gov Identifier: NCT03939689, Start Date: Dec 2020
 - Sponsor: Progenics Pharmaceuticals, Inc.
- SPLASH: Study Evaluating mCRPC Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment
 - ClinicalTrials.gov Identifier: NCT04647526, Start Date: Oct 2021
 - Sponsor: POINT biopharma.
- PSMAddition: An International Prospective Open-label, Randomized, Phase III Study Comparing 177Lu-PSMA-617 in Combination With SoC, Versus SoC Alone, in Adult Male Patients With mHSPC
 - ClinicalTrials.gov Identifier: NCT04720157, Start Date: March 2023
 - Sponsor: Novartis.
- Expanded Access Treatment With [Lu-177]-PNT2002 for Adult Patients With PSMA-Positive mCRPC.
 - ClinicalTrials.gov Identifier: NCT06033001, Start Date: June 2024
 - Sponsor: Lantheus.
- ALphaBreak: A Phase 2/3, Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of FPI-2265 (225Ac-PSMA-I&T) in Patients with PSMA-Positive mCRPC Previously Treated With 177Lu-PSMA Radioligand Therapy (RLT)
 - ClinicalTrials.gov Identifier: IRB#24-005102, FPI-2265-202, Start Date: June 2024
 - Sponsor: FUSION.
- A Phase IV, Post-Authorization Safety Study to Investigate the Long-Term Safety of Lutetium (177Lu) Vipivotide Tetraxetan in Adult Participants With Prostate Cancer
 - ClinicalTrials.gov Identifier: NCT05803941, Start Date: June 2024
 - Sponsor: Novartis.
- CAAA617A12101: A Phase I, open-label, multi-center study of radiation dosimetry, safety, and tolerability of extended lutetium (177Lu) vipivotide tetraxetan treatment in chemo-naïve adults with metastatic castration-resistant prostate cancer.
 - ClinicalTrials.gov Identifier: NA, Start Date: June 2025
 - Sponsor: Novartis.

HK2-targeted Therapy

- HOXTON: A Study of JNJ-69086420, an Actinium-225-Labeled Antibody Targeting Human Kallikrein-2 (hK2) for Advanced Prostate Cancer
 - ClinicalTrials.gov Identifier: NCT04644770, Start Date: March 2024
 - Sponsor: JANSSEN.

SSTR-targeted Therapy

- Single Patient IND for 177Lu-Edotreotide (lutetium edotreotide) Lu177-DOTATOC for refractory Meningioma
 - ClinicalTrials.gov Identifier: IRB-24-005119, Start Date: March, 2024
 - Sponsor: ITM

CA-IX targeted PET imaging

- STARBURST: A prospective, open-label, phase 2 study to explore CAIX expression through 89Zirconium-labelled girentuximab deferoxamine (89Zr-girentuximab) PET/CT imaging in patients with solid tumors.
 - ClinicalTrials.gov Identifier: NCT05563272, Start Date: August 2024
 - Sponsor: Telix.

Co-Principal Investigator (Co-PI) and Co-Investigator (Co-I) of Industry Sponsored Research Trials

FAP-targeted PET Imaging

- FAPI-46 PDAC: A Phase 2, Multicenter, Single Arm, Open Label Non-Randomized Study of [68Ga]FAPI-46 PET in Patients With Resectable or Borderline Resectable Pancreatic Ductal Carcinoma
 - ClinicalTrials.gov Identifier: NCT05262855, Start Date: Apr, 2023
 - Sponsor: SOFIE, PI: Mark Girgis (UCLA Surgery)
- 18F-FAPI-74 GI: A Phase 2, Multicenter, Single Arm, Open Label, Non-Randomized Study of [18F]FAPI-74 PET in Patients With Gastrointestinal Cancers
 - ClinicalTrials.gov Identifier: NCT05262855, Start Date: Apr, 2024
 - Sponsor: SOFIE, PI: Mark Girgis (UCLA Surgery)

CA-IX targeted PET imaging

- ZIRCON: A Confirmatory, Prospective, Open-label, Multi-centre Phase 3 Study to Evaluate Diagnostic Performance of Zirconium-labelled Girentuximab to Non-invasively Detect ccRCC by PET/CT Imaging in Patients With Indeterminate Renal Masses
 - ClinicalTrials.gov Identifier: NCT03849118, Start Date: Dec, 2020
 - Sponsor: Telix, PI: Allan Pantuck (UCLA Urology)
- An Expanded Access Program for the Non-invasive Detection of Clear Cell Renal Cell Carcinoma (ccRCC) in Patients With Renal Masses Utilizing 89Zirconium-labelled Girentuximab (89Zr-DFO-girentuximab)
 - ClinicalTrials.gov Identifier: NCT06090331, Start Date: Mar, 2024
 - Sponsor: Telix, PI: Brian Shuch (UCLA Urology)

PSMA-targeted Therapy

- VISION: An International, Prospective, Open Label, Multicenter, Randomized Phase 3 Study of 177Lu-PSMA-617 in the Treatment of Patients With Progressive PSMA-positive Metastatic Castration-resistant Prostate Cancer (mCRPC)
 - ClinicalTrials.gov Identifier: NCT03511664, Start Date: Dec 7, 2018
 - Sponsor: Novartis, PI: Johannes Czernin (UCLA Nuclear Medicine)
- AMG160: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate
 - CancerClinicalTrials.gov Identifier: NCT03792841, Start Date: Dec 7, 2018
 - Sponsor: Amgen Inc, PI: Matthew Rettig (UCLA Medical Oncology)
- 177Lu-PSMA-617 Managed Access Program for mCRPC Patients
 - ClinicalTrials.gov Identifier: NCT04825652, Start Date: July 2021
 - Sponsor: Novartis, PI: Johannes Czernin (UCLA Nuclear Medicine)

SSTR-targeted Therapy

- RYZ101-301 ACTION-1: Study of RYZ101 Compared With SOC in Pts w Inoperable SSTR+ Well-differentiated GEP-NET That Has Progressed Following 177Lu-SSA Therapy (ACTION-1)
 - ClinicalTrials.gov Identifier: NCT05477576, Start Date: Aug, 2023
 - Sponsor: RayzeBio, PI: Martin Auerbach (UCLA Nuclear Medicine)
- RYZ101-101: Phase 1b single arm, open-label trial of RYZ101 in combination with carboplatin + etoposide + atezolizumab in subjects with somatostatin receptor expressing (SSTR+) extensive stage small cell lung cancer (ES-SCLC)
 - Study Number: NCT05595460, IRB#23-001276, Start Date: May, 2024
 - Sponsor: RayzeBio, PI: Jonathan Goldman (UCLA Medical Oncology)
- RYZ101-201 TRACY-01 Phase 1b/2 open-label trial of 225Ac-DOTATATE (RYZ101) alone and in combination with pembrolizumab in subjects with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2 (HER2)-negative, locally advanced and unresectable or metastatic breast cancer expressing somatostatin receptors (SSTRs) and progressed after antibody-drug conjugates and/or chemotherapy.
 - Study Number: NA, Start Date: May, 2024
 - Sponsor: RayzeBio, PI: Nikolaos Palaskas (UCLA Medical Oncology)

FAP-targeted Therapy

- LuMIERE: A Phase 1/2, Multicenter, Open label, Non randomized Study to Investigate Safety and Tolerability, Pharmacokinetics, Dosimetry, and Preliminary Activity of 177Lu FAP 2286 in Patients with an Advanced Solid Tumor.
 - ClinicalTrials.gov Identifier: NCT04939610, Start Date: August 2024
 - Sponsor: Novartis.
- CFXX489A12101 Phase 1 open-label, multi-center study to evaluate the safety, tolerability, dosimetry, and preliminary activity of 177Lu-NNS309 in patients with pancreatic, lung, breast and colorectal cancer
 - ClinicalTrials.gov Identifier: NA, Start Date: Dec 2024
 - Sponsor: Novartis.

GRPR-targeted Therapy

- A Phase I/II, Dose Finding and Optimization Study of [177Lu]Lu-NeoB in Combination With Capecitabine in Patients With GRPR+, ER+, HER2- Metastatic Breast Cancer After Progression on Previous Endocrine Therapy in Combination With a CDK4/6 Inhibitor..
 - ClinicalTrials.gov Identifier: NCT06247995, Start Date: August 2024
 - Sponsor: Novartis. PI: Kelly McCann (UCLA Breast Cancer Program)
- CAAA603C12101 Phase 1b Dose Finding Study Assessing Safety and Activity of [177Lu]Lu-NeoB in Combination with Radiotherapy and Temozolomide in Subjects with Newly Diagnosed Glioblastoma and as a Single Agent in Recurrent Glioblastoma.
 - ClinicalTrials.gov Identifier: NCT05739942, Start Date: August 2024
 - Sponsor: Novartis. PI: Tim Cloughesy (UCLA Neuro-Oncology Program)
- CAAA603B12101 177Lu]Lu-NeoB in Combination With Ribociclib and Fulvestrant in ER+, HER2- and GRPR+ Advanced Breast Cancer
 - ClinicalTrials.gov Identifier: NCT05870579, Start Date: August 2024
 - Sponsor: Novartis. PI: Aditya Bardia (UCLA Breast Cancer Program)

Blinded Independent Central Reader (BICR)

- An Open-label, Single-dose, Single Arm, Single-center Phase 3 Clinical Trial of 64Cu-DOTATATE (NETMedix™) PET-CT Scan for Imaging Patients With Known or Suspected Somatostatin Receptor-positive Neuroendocrine Tumors (NETs)
 - ClinicalTrials.gov Identifier: NCT03673943
 - Sponsor: **Radiomedix**, Inc.
 - Imaging: 64Cu-DOTATATE PET/CT
 - Number of scans to read: 60
 - October 2018 to January 2019
 - <https://pubmed.ncbi.nlm.nih.gov/31924723/>

- A Phase 3, Multi-Center, Open-Label Study to Assess the Diagnostic Performance and Clinical Impact of 18F-DCFPyL PET/CT Imaging Results in Men With Suspected Recurrence of Prostate Cancer (CONDOR)
 - ClinicalTrials.gov Identifier: NCT03739684
 - Sponsor: **Progenics Pharmaceuticals**, Inc.
 - Imaging: 18F-DCFPyL PET/CT
 - Number of scans to read: 240
 - June 2019 to January 2020
 - <https://pubmed.ncbi.nlm.nih.gov/33622706/>

- A Phase 1/2 Open-label, Multi-center, Safety and Tolerability Study of a Single Dose of 68Ga-PSMA-R2 in Patients With Biochemical Relapse (BR) and Metastatic Prostate Cancer (mPCa)
 - ClinicalTrials.gov Identifier: NCT03490032
 - Sponsor: **Advanced Accelerator Applications**
 - Imaging: 68Ga-PSMA-R2 PET/CT
 - Number of scans to read: 60
 - June 2020

- CONDOR-aPROMISE: Automated segmentation and quantification PROMISE
 - ClinicalTrials.gov Identifier: NCT03739684
 - Sponsor: **EXINI / Lantheus**
 - Imaging: 18F-DCFPyL PET/CT
 - Number of scans to read: 208
 - April – May 2021

- Study of Diagnostic Performance of [18F]CTT1057 for PSMA-positive Tumors Detection (GuideView)
 - ClinicalTrials.gov Identifier: NCT04838626, NCT04838613
 - Sponsor: **Novartis**
 - Imaging: F18-CTT1057 PET/CT
 - Number of scans to read: 447
 - April 2022 – Feb 2023

- SOLAR: Copper Cu64 PSMA I&T Injection in Patients with Histologically Proven Metastatic Prostate Cancer
 - ClinicalTrials.gov Identifier: NCT05653856
 - Sponsor: **Curium**
 - Imaging: Cu64 PSMA I&T
 - Number of scans to read: 72 (24 for Phase 1 and 48 for Phase 2)
 - Sep 2022 for Phase 1 and Mar-May 2023 for Phase 2

BIOPHARMA INDUSTRY CONSULTING ACTIVITIES

ADVISORY BOARD – CONSULTANT

- **Amgen**
Oct 2022 - PET tracer development KOL
- **Astellas**
Jan 2022 - Medical Virtual Seminar - PSMA PET
Feb 2023 - Prostate Virtual Advisory Board
May 2023 - Prostate Cancer Advisory Council Meeting
May 2024 – EMBARK Prostate Cancer Advisory Council Meeting
- **Bayer**
Feb 2023 - TRT strategy KOL Meeting
- **Blue Earth Diagnostics Inc.**
July 2019 - Virtual Advisory Council – Case
May 2023 - Advisory Board meeting, PSMA PET Imaging: What’s Next?
- **Coretag**
Aug 2024 - Necrosis Targeting Platform Technology KOL
- **Curium Pharma**
Apr 2020 - Prostate Cancer Investigational Products Advisory Board
Apr 2021 - Phase 3 radioligand therapy clinical development Advisory
2023-2024 -Data Safety Advisory Board ECLIPSE Trial
May 2024 - Internal Corporate Video Film Interview
- **DS Pharma**
Nov 2021 - MUC5AC Study Design Discussion
- **Fibrogen**
Jan 2024 - CD46 Advisory Board
- **GE Healthcare**
May 2020 - GalliProst Advisory Board Meeting
May 2022 - FAP medical advisory board meeting
Nov 2022 - Oncology Scientific Advisory Committee (SAC) meeting
- **Isoray**
Dec 2021 - KOL consultant Pb-212
- **Janssen Pharmaceuticals Inc.**
Dec 2019 - Radioconjugate Virtual Advisory Board
Mar 2021 - Prostate State of the Science Meeting
May 2021 - TMEFF2 Project Discussion
Jan 2022 - Hypoxia Therapeutic Strategy in Prostate Cancer Virtual Advisory Board
Jun 2022 - Advisory Board: What’s Next in Prostate Cancer? – Emerging Therapies
Apr 2023 - Global Prostate Cancer Virtual Advisory Board
- **Lantheus**
Apr 2021 - PyL for patient selection for LuPSMA
2022 - PYLARIFY Speaker Bureau
Jun 2023 - PYLARIFY AI (EXINI) Ad Board Meeting Chair person
- **Lightpointmedical**
Sept 2021 - Consultant PSMA Radioguided surgery

- **Novartis**
Dec 2022 - PSMAfore Virtual US Advisory Board
July 2023 - Novartis RLT Forum
July 2023 - PSMA Strategy Advisory Board
Aug 2023 - Next Generation RLT Administration Interview
Nov 2023 - PSMAfore Strategy Virtual US Advisory Board
Jan 2024 – FAP GI Advisory Board
Jul 2024 - PSMAcare steering committee
Jul 2024 - PSMA R2 actinium Ad Board
Aug 2024 – PLUVICTO marketing
- **Nucleus Radiopharma**
June 2024 – Inaugural Scientific Advisory Board
Aug 2024 – SAB meeting
- **Pfizer**
Mar 2023 - Pfizer KOL Series Webinar: Current and Future Advances in PSMA/Radioligand Landscape
- **POINT biopharma**
Nov 2020 - SPLASH study design Consultant
Apr 2021 - Analyst Call – FAP radiopharmaceutical development program
May 2021 - PNT655/FAPI Study Design Discussion
Sep 2021 - LuPNT6555 Advisory board videoconference
Feb 2022 - PSMA PET patient selection criteria for treatment with Lu-PSMA in SPLASH clinical trial: Advisory Discussion
Sep 2022 - ESMO prostate cancer advisory board meeting
Nov 2022 - POINT PNT2001 Advisory Board
July 2023 - FAP Development steering committee
- **Progenics Pharmaceuticals, Inc.**
June 2020 - Advisory Board Meeting
Nov 2020 - 18F-PyL Reader Training Module and consensus read meeting
- **Radiomedix**
2022-2024 - Data Safety Advisory Board ALPHAMEDIX-02 Trial
- **Radiopharm Theranostics**
2024 - RAD101 Study Protocol Review
- **Sanofi**
May 2022 - Expert Seminar Series - PSMA Theranostics
Oct 2022 - ASK THE EXPERT PSMA Theranostics
- **SIEMENS – Varian**
Feb 2023 - Comprehensive Cancer Care Strategy Advisory Board
May 2023 - Cancer 2035 Advisory Board - Radiomics, Treatment Response
- **SOFIE**
Oct 2022 - FAPI-46 Imaging reader manual
Aug 2024 - FAPI-74 registration trial
- **Telix**
Nov 2020 - Medical Education Steering Committee – Q&A-Telix PSMA Imaging Urologists' Webinar
Sept 2021 - Medical Education Steering Committee – Q&A- PSMA Interview - Sept 2021 <https://telixu.com/>
Feb 2023 - ASCO-GU HCP Advisory Board (TLXDOC-2573) ZIRCON
Jun 2023 - ZIRCON FDA Meeting – NDA
Oct 2023 - Visiting Professor Lecture - Carbonic Anhydrase IX Targeted PET imaging: ZIRCON and other studies.
Oct 2023 – RCC Lu177 Advisory Board
Nov 2023 - PSMA PET Surveillance Study / Biospy Study Design – KOL Advisory consulting call 1h
Aug 2024 - Reader Training CA-IX PET Speaker at Telix EAP IM Chicago Virtual - Aug 2024

SPEAKER BUREAU

- **Lantheus**
Promotional/educational campaign for Pylarify® - Dec. 2021-2022
- **Novartis**
Promotional/educational campaign for Pluvicto® - Dec 2021-2022

MEDICAL EDUCATION SPEAKER

- **GE HealthCare**
GEHC Theranostics Leadership Summit - Orsundsbro (Sweden) - Jun. 2024
- **IBA radiopharma**
Webinar Feb 2021
Webinar April 2021
- **Monrol**
Scientific Symposium – TWC June 2022
- **Novartis**
Novartis CME Diner Conference - CHU de Québec-Université Laval (Quebec City, Canada) - June 2024
Novartis CME Diner Conference - CHUM Centre hospitalier de l'Université de Montréal (Montreal, Canada) - June 2024
Nuclear Medicine Conference - MUHC - McGill University Health Centre (Montreal, Canada) - June 2024
Novartis 1st RLT Insider PLUVICTO launch – Sao Paulo (Brazil) - August 2024
- **Telix Pharmaceuticals**
SNMMI Annual Meeting Symposium - June 2020
AdMeTech Foundation Grand Rounds in Urology - Oct 2020
Medical Education Steering Committee – Q&A-Telix PSMA Imaging Urologists' Webinar - Nov 2020
Medical Education Steering Committee – Q&A- PSMA Interview - Sept 2021 <https://telixu.com/>
AUA Annual Meeting - Product Theater - San Antonio (TX, USA) The Future of Kidney Cancer Detection & Management – May 2024
SNMMI Annual Meeting – Dinner Symposium - Toronto (Canada) Next Frontier in Molecular Imaging in RCC – June 2024
Reader Training CA-IX PET <https://telixu.com/> - Jul 2024

EXPERT NETWORK CONSULTING INTERVIEWS

- | | | | |
|-----------------------------------|--------------------------|---|----------------|
| ▪ Alcimed | 2021-2024 | ▪ Health Science Communications HSCI | 2021 |
| ▪ AXIOM | 2019-2022-2023-2024 | ▪ Qual World | 2021 |
| ▪ BIONEST Partners | 2020 | ▪ REACH Market Research | 2023 |
| ▪ CB partners | 2020 | ▪ Ridgeback Capital - Morgan Stanley | 2024 |
| ▪ Clarivate DRG Consulting | 2021 | ▪ Slingshot Insights | 2023 |
| ▪ Envision Pharma Group | 2022 | ▪ Techspert.io | 2020-2022 |
| ▪ EVERSANA | 2023 | ▪ THIRD BRIDGE | 2022-2023-2024 |
| ▪ GLG consulting | 2020-2021-2022-2023-2024 | ▪ Two Labs Market Intelligence | 2021 |
| ▪ Guidepoint | 2020-2021-2022-2023-2024 | | |
| ▪ Health Advances | 2021 | | |

INVITED SPEAKER

INTERNATIONAL CONFERENCES

International Oncology Conferences

- 2018 Oct. **PCF Annual Scientific Retreat - Plenary Session - Carlsbad (CA, USA)**
Elucidating resistance to 177Lu-PSMA-617
- 2020 Feb **ASCO GU - Localized Prostate Cancer Plenary Session - San Francisco (CA, USA)**
PSMA PET: Who Should Undergo Advanced Imaging in the Current Era?
- 2020 Oct. **PROSCA/BLADDR - Global Congress on Prostate and Bladder – Virtual**
PSMA-PET: does it make a difference for patients at high-risk for de novo N1 disease?
- 2022 Jun. **ASCO Annual Meeting - Education Session GU Cancer – Chicago (IL, USA)**
Predictive Models for PSMA-Based Radioligand Therapy in Prostate Cancer
- 2024 May **AUA Annual Meeting – International Prostate Cancer Forum - San Antonio (TX, USA)**
mCRPC: Key Updates in Radioligand Therapy, PSMA Sensitive Disease
<https://www.urotoday.com/conference-highlights/aua-2024/aua-2024-prostate-cancer/151785-aua-2024-mcrpc-key-updates-in-radioligand-therapy-psma-sensitive-disease.html>
- 2024 May **AUA Annual Meeting - Product Theater - San Antonio (TX, USA)**
The Future of Kidney Cancer Detection & Management - Sponsored by: Telix Pharmaceuticals

International Nuclear Medicine and Imaging Conferences

- 2018 Jun. **SNMMI Annual Meeting - Philadelphia (PA, USA)**
Prostate Cancer Imaging Scientific Session – Moderator
- 2019 Jun. **SNMMI Annual Meeting - Anaheim (CA, USA)**
Prostate Cancer Imaging Scientific Session – Moderator
- 2020 Jul. **SNMMI Annual Meeting Virtual Edition - Satellite Symposium**
PSMA Imaging: Current Status and Prospects - Sponsored by Telix Pharmaceuticals
- 2020 Jul. **SNMMI Annual Meeting Virtual Edition – Drink and Think**
Prostate Imaging with PSMA PET and How it Plays into Other Imaging Modalities
- 2021 Jun. **SNMMI Annual Meeting Virtual Edition - Categorical Session: Correlative Imaging - Virtual**
Characterizing Bone Lesions in Prostate Cancer in Nuclear Medicine
- 2021 Jun. **SNMMI Annual Meeting Virtual Edition - Drink and Think**
FAP PET: Imaging of Fibroblast Activation Protein compared to FDG PET and other imaging modalities
- 2021 Nov. **RSNA Annual Meeting - Chicago (IL, USA)**
Case-based Review of Nuclear Medicine: PET/CT Workshop – Prostate (In Conjunction with SNMMI)
- 2022 Jun. **SNMMI Annual Meeting - Satellite Symposium – Vancouver (Canada)**
PSMA: the next frontier in Theranostics - transforming PCa care. Sponsored by Telix
- 2022 Jun. **SNMMI Annual Meeting - Satellite Symposium– Vancouver (Canada)**
FAP Ligands for Imaging and Therapy. Co- Sponsored by Clovis, POINT biopharma, SOFIE.
- 2022 Jun. **Theranostics World Congress - Wiesbaden (Germany)**
The Current and Future of Lutetium-177 PSMA Therapy – Sponsored by Monrol.
- 2022 Jun. **Theranostics World Congress - Wiesbaden (Germany)**
New PSMA PET criteria for patient selection and therapy response assessment to Lu-PSMA therapy.
- 2022 Nov. **ICPO Theranostics FAP Summit Virtual Event**
FAPi is not the new FDG

- 2022 Nov. **CHILI 5.0 Conference on Hybrid Imaging Live, ESHI society – Vienna (Austria)**
PSMA PET/CT for patient selection and monitoring of LuPSMA therapy
- 2023 Sep. **EANM annual congress - Clinical Oncology Track Featured Session: FAP-Imaging – Vienna (Austria)**
FAP-PET imaging for cancer patients - Introductory Talk
- 2023 Nov. **CHILI 6.0 Conference on Hybrid Imaging Live, ESHI society – Vienna (Austria)**
PSMA PET/CT in prostate cancer management
- 2024 Jun. **SNMMI Annual Meeting – Dinner Symposium - Toronto (Canada)**
Next Frontier in Molecular Imaging in RCC - Sponsored by: Telix Pharmaceuticals
- 2024 Jun. **GEHC Theranostics Leadership Summit – Orsundsbro (Sweden)**
Growing a theranostics program in a large academic center in the United States.

NATIONAL CONFERENCES

National Prostate Cancer Conferences

- 2019 Nov. **PCF PSMA Theranostics Scientific Working Group - New York (NYC, USA)**
Gallium vs Fluorine PSMA-PET: Will it Matter?
- 2020 Oct. **AdMeTech Virtual Global Summit on Prostate Cancer - Grand Rounds in Urology - Virtual**
Defining Non-Metastatic and Oligometastatic Prostate Cancer vs. Systemic Disease - Sponsored by Telix Pharmaceuticals
<https://grandroundsinurology.com/psma-pet-imaging-in-advanced-prostate-cancer/>
- 2021 Jul. **IPC31 - 31st Annual International Prostate Cancer Update - Snowbird (UTAH, USA)**
Current status of PSMA diagnostics – Ga68-PSMA-11
<https://grandroundsinurology.com/current-status-of-psma-diagnostics/>
<https://grandroundsinurology.com/panel-discussion-focus-on-psma/>
- 2021 Sep. **AdMeTech 5th Global Summit on Precision Dx and Tx of Prostate Cancer - Virtual**
Defining Non-Metastatic and Oligometastatic Prostate Cancer vs. Systemic Disease
- 2022 Mar. **IPC32 – 32nd Annual International Prostate Cancer Update - Snowbird (UTAH, USA)**
State of the Art Platinum Lecture: “How to Integrate PSMA PET Findings into Treatment Algorithms”
<https://grandroundsinurology.com/how-to-integrate-psma-pet-findings-into-treatment-algorithms/>
- 2022 Sep. **FOCAL Therapy Annual Meeting – Beverly Hills (CA, USA)**
PET Imaging for Selection of Focal Therapy Candidates
<https://grandroundsinurology.com/pet-imaging-for-selection-of-focal-therapy-candidates/>
- 2022 Sep. **AdMeTech 6th Global Summit on Precision Dx and Tx of Prostate Cancer - Virtual**
PSMA PET for improving patient selection for and outcomes of LuPSMA therapy
<https://grandroundsinurology.com/presentations-from-the-6th-global-summit-on-precision-diaqnosis-and-treatment-of-prostate-cancer-2/>
- 2023 Feb. **Inaugural US Prostate Cancer Conference USPROST8CON – SF Bay Area (CA, USA)**
Expert Perspectives on Controversies in Prostate Cancer Management
- 2024 Jan. **Inaugural UCSF-UCLA-PCF PSMA Conference – UCSF San Francisco (CA, USA)**
<https://radiology.ucsf.edu/blog/conference-convenes-experts-field-nuclear-medicine-advance-prostate-cancer-care>
- *PSMA PET selection of patients for PSMA RPT*
<https://www.urotoday.com/video-lectures/psma-ucsf-ucla-2024/video/mediaitem/3861-psma-pet-selection-of-patients-for-psma-radiopharmaceutical-therapy-presentation-jeremie-calais.html>
- *Imaging Response to PSMA RPT*
<https://www.urotoday.com/video-lectures/psma-ucsf-ucla-2024/video/mediaitem/3871-imaging-response-to-psma-radiopharmaceutical-therapy-presentation-jeremie-calais.html>
- *PSMA PET Tumor Board*

- 2024 Mar. **Specialized Program of Research Excellence (SPORE) in Prostate Cancer Multi-Institutional Retreat – LA (CA, USA)**
PSMA-targeted theranostics: PSMA-targeted imaging to improve PSMA-targeted therapy
- 2024 Mar. **US Prostate Cancer Conference USPCC – New York (NYC, USA)**
Point: For patients with BCR, post-RP, post-RT, or both, PSMA PET is the preferred standard-of-care, first-line imaging, and, therefore, there is no longer a role for conventional imaging.

National Radiation Oncology Conferences

- 2020 Sep. **Association of VA Hematology/Oncology Annual Meeting 2020 – Virtual**
Interest Group: VA National Radiation Oncology Program Efforts
PSMA PET/CT in prostate cancer staging and radiation treatment planning
- 2021 Oct **ASTRO CME Symposium - Chicago (IL, USA)**
Next Generation PSMA-targeted PET Imaging in the Detection of Prostate Cancer and Impact on Patient Management.

National Nuclear Medicine and Imaging Conferences

- 2019 Jan. **SNMMI Mid-Winter meeting - Plenary Session - Palm Springs (CA, USA)**
Prostate Cancer Theranostics
- 2019 Mar. **HCNMC Annual Meeting - Plenary Session - Vail (CO, USA)**
Prostate Cancer PET agents with PET/CT and PET/MRI
- 2022 Feb. **SNMMI Mid-Winter meeting Virtual Edition**
68Ga-FAPI-46 PET/CT in cancer patients: the UCLA experience
- 2022 Feb. **SNMMI Mid-Winter meeting Virtual Edition**
Incorporation of 177Lu-PSMA-617 Into the Management of Prostate Cancer
- 2022 Mar. **HCNMC Annual Meeting - Plenary Session – Sun Valley (ID, USA)**
Prostate Cancers Theranostics – A True Game-Changer
- 2023 Jan. **SNMMI Mid-Winter meeting - San Francisco (CA, USA)**
PSMA RPT: Clinical Trials and Practice. VISION trial and Beyond.
- 2024 Aug. **3rd Annual Targeted Radiopharmaceutical Summit US – San Diego (CA, USA)**
Early-Stage Clinical Session: Selecting Optimal Clinical Candidates & Keeping Clinical Design Patient Centric
Plenary Session: Reporting Data from Personalized Clinical Trials & Examining Impact on Efficacy
- 2024 Aug. **1st RLT Insider PLUVICTO launch NOVARTIS – Sao Paulo (Brazil)**
Patient Selection for Pluvicto: the role of PSMA PET/CT and potential biomarkers of response.

REGIONAL CONFERENCES

Regional Oncology Conferences

- 2023 May **Nebraska Oncology Society - Evening Speaker Series – Omaha (NE, USA)**
Updates on Theranostics
- 2024 Mar **DICOM (Martinique, France Outre-Mer)**
Cancer de la prostate et imageries de nouvelles générations: Optimisation du Circuit au Niveau Régional et Essais Cliniques
Quelle place pour le petPSMA dans la prise en charge du cancer de la prostate aujourd’hui et futures perspectives?

Regional Nuclear Medicine and Imaging

- 2022 Jul. **SNMMI Dinner Symposium – Dayton (OH, USA)**
The Role of PSMA Imaging and Therapy in Managing Prostate Cancer: The Nuclear Medicine Physician' Perspective
- 2022 Sep. **Pacific Southwest Physician Chapter SNMMI Virtual Meeting**
177Lu-PSMA therapy
- 2023 Nov. **WRSNM annual meeting - Distinguished Scientist Award Presentation – Vancouver (Canada)**
PSMA Theranostics for Prostate Cancer: From Research to Standard of Care

INVITED ACADEMIC LECTURES

- 2018 Nov. **USC Urology Grand Round - Los Angeles (CA, USA)**
PSMA Theranostics
- 2019 Apr. **UCLA JCCC Research Seminar Series - Los Angeles (CA, USA)**
PSMA Theranostics research program
- 2019 Nov. **UCLA Department of Medical and Pharmacology Retreat – Huntington Beach (CA, USA)**
PSMA Theranostics research program
- 2020 Oct. **UCLA Cancer Molecular Imaging, Nanotechnology, and Theranostics (CMINT) program seminar series - Los Angeles (CA, USA)**
Translational UCLA Theranostics Program – PSMA clinical research program
- 2021 Feb. **Scripps MD Anderson Cancer Center's Clinical Hematology and Oncology Conference 2021 - Virtual**
Practical Aspects of Novel Imaging Approaches in the Management of Prostate Cancer
- 2021 Oct. **Southern California KAISER Permanente Medical Group Urology Symposium - Virtual**
PSMA: prostate cancer imaging
- 2021 Dec **Nuclear Medicine Grand Rounds - Icahn School of Medicine Mount Sinai (NYC, USA)**
PSMA-PET imaging for prostate cancer
- 2022 Apr. **Hematology/Oncology Grand Rounds - Henry Ford Cancer Institute (Detroit, MI, USA)**
PSMA-Targeted PET Imaging and Theranostics for Prostate Cancer
- 2022 Apr. **UCLA JCCC Cancer Center Research Annual Retreat - Los Angeles (CA, USA)**
The UCLA molecular radio-theranostics program: From clinical research to the outpatient therapy center
- 2022 Apr. **Nuclear Medicine Grand Rounds - The Ohio State University (Columbus OH)**
Prostate Cancer Theranostics
- 2023 Apr. **HOAG Annual Oncologic PET/CT and Molecular Imaging and Therapy Course - Newport Beach (CA, USA)**
PSMA PET for Prostate Cancer: Development and Data
- 2023 Apr. **Daniel R. Biello Memorial Lecture, Mallinckrodt Institute of Radiology, Wash U. - St Louis (MO, USA)**
FAP-Targeted Imaging: Clinical Evidence and Pitfalls
- 2023 Apr. **Nuclear Medicine Conference, Mallinckrodt Institute of Radiology, Wash U. - St Louis (MO, USA)**
PSMA-Targeted Theranostics: VISION and Beyond
- 2024 Mar. **Colloque FPG-FC de Medecine Nucleaire - CHUV: Centre hospitalier universitaire vaudois (Lausanne, Suisse)**
FAP-Targeted PET imaging
- 2024 Apr. **Nuclear Medicine Grand Rounds - APHM CHU Timone (Marseille, France)**
FAP-Targeted Theranostics

- 2024 Jun. **Novartis CME Diner Conference - CHU de Québec-Université Laval (Quebec City, Canada)**
Lu177-PSMA-617 Therapy for Patients with mCRPC: Clinical Landscape in the US
- 2024 Jun. **Nuclear Medicine Conference - CHUM Centre hospitalier de l'Université de Montréal (Montreal, Canada)**
Lu177-PSMA-617 Therapy for Patients with mCRPC: Cases Review
- 2024 Jun. **Nuclear Medicine Conference - MUHC - McGill University Health Centre (Montreal, Canada)**
Lu177-PSMA-617 Therapy for Patients with mCRPC: Cases Review

VIRTUAL LECTURES

- 2020 Apr **PCF Global Journal Club Webinar – Q&A Panel List**
ProPSMA Lancet
- 2021 Jan. **SNMMI Clinical Trials Network Webinar**
The Approval of 68Ga-PSMA-11: What You Need to Know
- 2020 Nov. **Johnson and Johnson Innovation Scientific & Partnering Virtual Event**
The Future of Prostate Cancer Therapy, Theranostics - collaboration Janssen Oncology and PCF
- 2021 Jan. **The Pharma Imaging Network for Therapeutics and Diagnostics (PINTaD) Meeting - Virtual**
The Approval of 68Ga-PSMA-11
- 2021 Feb. **IBA RadioPharma Solutions Webinar**
Diagnostic efficacy of 68Ga-PSMA versus conventional imaging in prostate cancer settings/patients
- 2021 Apr. **IBA RadioPharma Solutions Webinar**
Impact of PSMA PET on management of patients with oligo metastatic prostate cancer
- 2021 Dec. **Urotoday PSMA-PET Academy - Virtual**
Understanding Physiological PSMA Biodistribution
<https://www.urotoday.com/video-lectures/psma-academy/video-2/2418-understanding-physiological-psma-biodistribution-jeremie-calais.html>
- 2023 Dec. **SNMMI/ACNM "Hot Topics" Webinar Series**
PSMA PET imaging

PATIENT FORUMS

- 2019 Mar **Prostate Forum of Orange County Patient Support Group - Fullerton (CA -USA)**
Using Gallium 68 PSMA PET Scanning to Locate Advanced Prostate Cancers.
- 2020 Sep. **Prostate Forum of Orange County Patient Support Group – Virtual**
Using Gallium 68 PSMA PET Scanning to Locate Advanced Prostate Cancers.
- 2021 Jun. **IPCSG Informed Prostate Cancer Support Group - Live Stream Webinar**
PSMA theranostics
<https://www.youtube.com/watch?v=2gp10-9k0HA>
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Theranotics treatments for cancer underway at UCLA Health
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PEER-REVIEW JOURNAL REVIEW ACTIVITIES

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▪ Associate Editor

The Journal of Nuclear Medicine

Since May 2020

▪ Guest Editor

European Urology Focus

2020

Special Issue - *PSMA and its influence in Urology*

▪ Reviewer

117 reviews total

The Journal of Nuclear Medicine

42 reviews (2016-2024)

European Journal of Nuclear Medicine and Molecular Imaging

20 reviews (2020-2021)

Journal of Clinical Oncology

6 reviews (2020-2023)

European Urology Focus

6 reviews (2020-2021)

European Urology Oncology

5 reviews (2020-2021-2024)

BioMed Central (BMC) Cancer

4 reviews (2018-2020)

American Journal of Roentgenology (AJR)

4 reviews (2020-2023)

The Journal of Urology

3 reviews (2020-2023)

BioMed Central (BMC) Medical Imaging

3 reviews (2020-2021)

Theranostics

3 reviews (2018-2020)

EJNMMI Research

3 reviews (2020)

American Journal of Respiratory and Critical Care Medicine

2 reviews (2022)

Cancer Research

2 reviews (2020-2021)

PNAS Proceedings of the National Academy of Sciences

2 reviews (2020-2021)

British Journal of Urology (BJU) International

2 reviews (2020-2021)

Radiology

1 review (2023)

European Urology

1 review (2023)

Urology

1 review (2023)

Nature Review Clinical Oncology

1 review (2022)

Frontiers in Oncology

1 review (2021)

Clinical Cancer Research

1 review (2020)

European Journal of Cancer

1 review (2020)

Molecular Imaging and Biology

1 review (2020)

Scientific Reports

1 review (2020)

The Lancet Oncology

1 review (2019)

Plos One

1 review (2018)

▪ Conference Abstracts Reviewer

SNMMI annual meeting

2018, 2019, 2020, 2021, 2022, 2023

TAT12 (Targeted Alpha Therapy) International Symposium - Cape Town

2022

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Redesigned Curricula, Stringent Licensing Criteria, and Integrated Independence Are Conditions for a Bright Future for Nuclear Medicine in the United States.
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BOOK CHAPTERS

1. Mahida B, **Calais, J.**, Rouzet F
Cardiovascular Implantable Electronic Device Infection.
In: Pelletier-Galarneau, M., Martineau, P. (eds) *FDG-PET/CT and PET/MR in Cardiovascular Diseases*. pp183-184
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ORAL COMMUNICATION ABSTRACT PRESENTER:

1. **J. Calais**, M.Chastan, A.Edet-Sanson, M.Baron, F.Callonec, S.Becker, S.Hapdey, B.Diologent, P.Vera
Comparaison des valeurs de la TEP/TDM au ¹⁸F-FDG et de l'IRM de diffusion pour l'évaluation ganglionnaire retro-péritonéale dans le cancer du col utérin.
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2. **J. Calais**, S.Thureau, B.Dubray, R.Modzelewski, I.Gardin, P.Vera
High FDG uptake areas on pre-radiotherapy PET/CT identifies preferential sites of local recurrence in non-small cell lung cancer patients
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3. P.Vera, **J. Calais**, R.Modzelewski, S.Hapdey, P.Gouel, H.Tilly, F.Jardin, S.Ruan, I.Gardin
Does enhanced CT influence the biological GTV measurement on FDG-PET images?
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4. **J. Calais**, D.Lussato, J.Menard, P.Merlet
Interet de la ¹⁸F-Choline et du ¹⁸F-FDG dans la caracterisation d'une metastase pulmonaire solitaire d'un adenocarcinome prostatique mimant une bronchocele stable depuis 3 ans.
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7. F. Bidault, S. Espinoza, A. Varoquaux, C. Cohen, N. Chartier, H. Bouhmar, N. Zhi, E. Gabiache, R. Seban, **J. Calais**, P. Blanc-Durand.
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8. **J. Calais**, J. Czernin, M. Eiber, WP. Fendler, J. Gartmann, A. Heaney, A. Hendifar, JR. Pisegna, JR. Hecht, E. Wolin, R. Slavik, P. Gupta, A. Quon, C. Schiepers, M. Allen-Auerbach, K. Herrmann.
Most intended management changes after ⁶⁸Ga-DOTATATE PET/CT are implemented.
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9. **J. Calais**, J. Czernin, W. Fendler, K. Herrmann, I. Rauscher, N. Hegemann, T. D. Poeppel, M. Cao, M. Eiber, N. Nickols
Impact of ⁶⁸Ga-PSMA-11 PET/CT on salvage radiotherapy planning in post-prostatectomy patients with early biochemical recurrence.
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10. **J. Calais**, J. Czernin, M. Cao, A. Kishan, J. Hegde, N. Shaverdian, K. Sandler, F-I Chu, C. King, M. Steinberg, I. Rauscher, N. Hegemann, T. Poeppel, P. Hetkamp, F. Ceci, K. Herrmann, W. Fendler, M. Eiber, N. Nickols.
⁶⁸Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: Impact on Salvage Radiotherapy Planning
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11. **J Calais**, W Fendler, M Eiber, M Lassmann, M Dahlbom, R Esfandiari, J Gartmann, K Nguyen, P Thin, K Herrmann, J Czernin, E Delpassand
RESIST-PC phase 2 trial: 177Lu-PSMA-617 radionuclide therapy for metastatic castrate-resistant prostate cancer
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+ Late Breaking Abstract +
12. **J Calais**, F Ceci, M Eiber, D Elashoff, T Grogan, M Dahlbom, R Slavik, J Gartmann, K Nguyen, V Lok, R Reiter, M Rettig, H Jadvar, T Bach-Gansmo, B Savir-Barush, C Nanni, C Rischpler, M Hofman, T Hope, W Fendler, J Czernin
68Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to 18F-Fluciclovine PET/CT in a prospective head-to-head comparative phase 3 study
AUA Chicago 2019 – American Urological Association Annual Meeting
+ Late Breaking Abstract +
13. **J Calais**, F Ceci, M Eiber, T Bach-Gansmo, C Nanni, B Savir-Baruch, M Hofman, T Hope, C Rischpler, D Elashoff, T Grogan, M Dahlbom, R Slavik, J Gartmann, R Reiter, M Rettig, H Jadvar, W Fendler, J Czernin
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14. **J Calais**, F Ceci, M Eiber, J Gartmann, K Nguyen, V Lok, D Elashoff, T Grogan, R Slavik, R Reiter, M Rettig, H Jadvar, T Bach-Gansmo, B Savir-Baruch, M Hofman, C Nanni, C Rischpler, T Hope, W Fendler, J Czernin.
68Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to 18F-Fluciclovine PET/CT in a prospective head to head comparative phase 3 study
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+ SNMMI Correlative Imaging Council Walter Wolf Young Investigator Award (YIA) +
+ SNMMI Early Career Professionals Committee Abstract Award - First Place Prize for Clinical Science +
15. **J Calais**, J Gartmann, WR Armstrong, P Thin, K Nguyen, V Lok, L Gosa, R Slavik, M Dahlbom, K Herrmann, M Eiber, WP Fendler, J Czernin.
Overall survival after 177Lu-PSMA-617 molecular radiotherapy in patients with metastatic castrate-resistant prostate cancer: Post-hoc analysis of a prospective phase II trial.
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Overall survival after 177Lu-PSMA-617 molecular radiotherapy in patients with metastatic castrate-resistant prostate cancer: Post-hoc analysis of a prospective phase II trial.
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1. **J Calais**, WR Armstrong, V Murthy, CL Heath, S Behr, F Barbato, F Ceci, A Farolfi, S Schwarzenboeck, M Unterrainer, H Zacho, MR Cooperberg, HG Nguyen, RE Reiter, S Holden, K Herrmann, WP Fendler, M Eiber, J Czernin, TA Hope.
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21. **J Calais**, M Eiber, A Iagaru, A Anand, K Sjostrand, A Bjartell, M Rettig, MJ Morris
Prospectively planned and Independent Validation of aPROMISE in a Phase III CONDOR Study for Rapid Lesion Detection and Standardized Quantitative Evaluation for 18F-DCFPyL (PSMA) Imaging in Prostate Cancer.
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Zirconium-labelled Girentuximab (89Zr-TLX250-CDx) PET/CT Imaging for non-invasive diagnosis of Clear Cell Renal Cell Carcinoma: results from the UCLA cohort of the ZIRCON trial
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A rapid efficient F-Choline PET/CT protocol used in a clinical routine practice in patients newly diagnosed of prostate cancer with Gleason score VII (4+3) VIII, IX, X, or with PSA up to 20ng/ml at initial staging.
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Apport de l'IRM de diffusion dans la pathologie hépatique
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9. **J.Calais**, F.Paycha
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The 70% of SUVmax threshold on pre radiotherapy PET/CT identifies the site of local recurrence in lung cancer
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12. **J. Calais**, C. Groult, J. Le Cloirec, S. Gaucher
Strategie d'exploration de l'amylose cardiaque en medecine nucleaire: interets respectifs de l'HMDP, de la MIBG et du ²⁰¹thallium
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13. **J. Calais**, A. Edet-Sanson, C. Dumant Forest, J. Le Cloirec
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14. E. Piekarski, F. Hyafil, N. Mikail, B. Mahida, J. Slama, E. Blanchet, **J. Calais**, H. Regaieg, R. De Paola Chequer, F. Rouzet, D. Le Guludec, K. BenAli.
Diagnostic value of ¹⁸F-FDG PET imaging patients with clinical suspicion of vasculitis
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15. **A. Chaput, J. Calais**, P. Robin, S. Thureau, D. Bourhis, R. Modzelewski, U. Schick, P. Vera, P.Y. Salaün, R. Abgral
Recherche d'une corrélation entre les zones les plus hypermétaboliques en TEP/TDM au ¹⁸FDG préthérapeutique (hotspots) et les sites préférentiels de récurrence locale après radiothérapie des cancers des VADS
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Correlation between areas of high FDG uptake on pre-treatment PET/CT and preferential sites of local relapse after chemo-radiotherapy for head and neck squamous cell carcinoma.
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Impact of ⁶⁸Ga-PSMA PET/CT on management of recurrent prostate cancer patients: the referring physician's perspective
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+ Late Breaking Abstract +
22. **J. Calais**, J. Czernin, M. Cao, A. Kishan, J. Hegde, N. Shaverdian, K. Sandler, F-I Chu, C. King, M. Steinberg, I. Rauscher, N. Hegemann, T. Poeppel, P. Hetkamp, F. Ceci, K. Herrmann, W. Fendler, M. Eiber, N. Nickols.
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(68)Ga-PSMA-11 PET/CT vs (18)F-Fluciclovine PET/CT: a case series in prostate cancer patients with biochemical recurrence
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25. W. Fendler, **J. Calais**, J. Gartmann, N. Nickols, R. Reiter, M. Rettig, R. Slavik, P. Gupta, A. Quon, M. Allen-Auerbach, K. Herrmann, J. Czernin, M. Eiber.
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26. W. Fendler, **J. Calais**, J. Gartmann, N. Nickols, R. Reiter, M. Rettig, R. Slavik, P. Gupta, A. Quon, M. Allen-Auerbach, K. Herrmann, J. Czernin, M. Eiber.
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29. **K. Pomykala**, W. Fendler, **J. Calais**, M. Eiber, J. Czernin.
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31. N Nickols, **J Calais**, A. Kishan , M Cao , W. Fendler, M Eiber, K Herrmann, F Ceci, R. Reiter, M. Rettig, J. Hegde, N Shaverdian, C. King, M. Steinberg, J Czernin
Potential impact of 68Ga-PSMA-11 PET/CT on prostate cancer definitive radiation therapy planning
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Comparison of (68)Ga-PSMA-11 PET/CT and (18)F-Fluciclovine PET/CT in recurrent prostate cancer.
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Octreoscan vs. DOTATATE PET: comparison of Krenning scoring
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40. D. Lubin, M. Allen-Auerbach, L. Gardner, **J. Calais**, J. Czernin, F. Ceci, A Quon.
177Lu-DOTATATE Radioligand Therapy in Patients Affected by Somatostatin-Receptor-Positive Neuroendocrine Tumors
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41. **J Calais**, F Ceci, K Nguyen, J Gartmann, M Eiber, RE Reiter, A Kishan, H Jadvar, WP Fendler, J Czernin
Prospective head-to-head comparison of 18F-fluciclovine and 68Ga-PSMA-11 PET/CT for localization of prostate cancer biochemical recurrence after primary prostatectomy.
ASCO GU San Francisco 2019 – Genitourinary Cancers Symposium
42. **J Calais**, J Czernin, WP Fendler, D Elashoff, NG Nickols
Randomized phase III trial of 68Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]
ASCO GU San Francisco 2019 – Genitourinary Cancers Symposium
43. N. Tan, N. Bavadian, **J. Calais**, U. Oyoyo, J.Kim, I. Turkbey, E. Mena, M. Davenport
Imaging of PSMA-targeted Radiotracers for the Detection of Prostate Cancer Biochemical Recurrence After Definitive Therapy: A Systematic Review and Meta-analysis
SAR Orlando 2019 - Annual Scientific Meeting of the Society of Abdominal Radiology
44. N. Tan, N. Bavadian, N. Ferguson, **J. Calais**, U. Oyoyo, M. Davenport
Comparative Effectiveness for 18-F Fluciclovine versus PSMA-targeted Radiotracers for Detection of Prostate Cancer Biochemical Recurrence After Definitive Therapy: A Systematic Review and Comparative Meta-analysis
SAR Orlando 2019 - Annual Scientific Meeting of the Society of Abdominal Radiology
+ Best Hot Topic in GU Scientific Paper Award +

45. BA Hadaschik, M Weber, A Iravani, MS Hofman, **J Calais**, J Czernin, H Ilhan, F Saad, EJ Small, MR Smith, P Perez, TA Hope, I Rauscher, A Londhe, A Lopez-Gitlitz, S Cheng, T Maurer, K Herrmann, M Eiber, WP Fendler
Prostate-specific membrane antigen positron-emission tomography (PSMA-PET) in high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC) SPARTAN-like patients (pts) negative by conventional imaging
EAU Barcelona 2019 - Annual Congress of European Association of Urology
46. B Hadaschik, M Weber, A Iravani, M Hofman, **J Calais**, J Czernin, H Ilhan, F Saad, E Small, M Smith, P Perez, T Hope, I Rauscher, A Londhe, A Lopez-Gitlitz, S Cheng, T Maurer, K Herrmann, M Eiber, W Fendler
Prostate-Specific Membrane Antigen Positron Emission Tomography (PSMA-PET) in high-risk nonmetastatic castration-resistant prostate cancer (NMCRPC) SPARTAN-like patients negative by conventional imaging.
AUA Chicago 2019 – American Urological Association Annual Meeting
47. A Pooli, T Sadun, D Johnson, C Lebacle, W Fendler, M Eiber, J Czernin, **J Calais**, R Reiter
The role of 68Ga-PSMA PET-CT in initial staging of treatment-naïve high risk prostate cancer.
AUA Chicago 2019 – American Urological Association Annual Meeting
48. **J Calais**, J Czernin, W Fendler, D Elashoff, N Nickols
Randomized prospective phase 3 trial of 68Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT].
ASCO Chicago 2019 – American Society of Clinical Oncology Annual Meeting
49. **J Calais**, W Fendler, M Eiber, M Lassmann, M Dahlbom, R Esfandiari, J Gartmann, K Nguyen, P Thin, V Lok, K Herrmann, J Czernin, E Delpassand
RESIST-PC phase 2 trial: 177Lu-PSMA-617 radionuclide therapy for metastatic castrate-resistant prostate cancer.
ASCO Chicago 2019 – American Society of Clinical Oncology Annual Meeting
50. **J Calais**, J Czernin, W Fendler, D Elashoff, N Nickols
Randomized Phase 3 Trial of 68Ga-PSMA-11 PET/CT Molecular Imaging for Prostate Cancer Salvage Radiotherapy Planning [PSMA-SRT]: Study Protocol
SNMMI Anaheim 2019 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
+ SNNMI 2019 Poster Award Nominee +
51. **K Pomykala**, J Czernin, **J Calais**.
Impact of Total Body 68Ga-PSMA-11 PET/CT on bone metastasis detection in Prostate Cancer Patients: should we go from Vertex to Toes ?
SNMMI Anaheim 2019 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
52. **K Pomykala**, M Jardon, J Czernin, J Williams, TR Grogan, **J Calais**.
Total-body 68Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients
ICIS 2019 Verona 2019 - International Cancer Imaging Society Annual Teaching Course
+ Best Poster Award +
53. **C Meyer**, M Dahlbom, J Czernin, S Vauclin, T Lindner, U Haberkorn, **J Calais**.
Biodistribution and radiation dosimetry study of 68Ga-FAPi-46 PET imaging in patients with various cancers.
EANM Barcelona 2019 - Annual Congress of the European Association of Nuclear Medicine
54. N Tan, U Oyoyo, N Bavadian, N Ferguson, A Mukkamala, **J Calais**, M Davenport
Comparative Effectiveness for 18-F Fluciclovine versus PSMA-targeted Radiotracers for Detection of Prostate Cancer Biochemical Recurrence after Definitive Therapy: A Systematic Review and Comparative Meta-analysis
RSNA Chicago 2019 - Radiological Society of North America Annual Meeting

55. WP Fendler, J Ferdinandus, **J Calais**, M Eiber, RR Flavell, A Mishoe, FY Feng, HG Nguyen, RE Reiter, MB Rettig, J Gartmann, R Smith, EJ Small, R Slavik, P Carroll, K Herrmann, J Czernin, TA Hope
Impact of 68Ga-PSMA-11 PET on the management of biochemically recurrent prostate cancer in a prospective single-arm clinical trial.
ASCO GU San Francisco 2020 – Genitourinary Cancers Symposium
56. **I Sonni**, M Eiber, WP Fendler, RM Alano, SS Vangala, AU Kishan, NG Nickols, MB Rettig, RE Reiter, J Czernin, **J Calais**.
Impact of 68Ga-PSMA-11 PET/CT on staging and management of prostate cancer patients in various clinical settings.
ASCO GU San Francisco 2020 – Genitourinary Cancers Symposium
57. TA Hope, WR Armstrong, V Murthy, R Juarez, CL Heath, S Behr, F Barbato, F Ceci, A Farolfi, S Schwarzenboeck, M Unterrainer, H Zacho, H Nguyen, M Cooperberg, P Carroll, R Reiter, S Holden, WP Fendler, S Zhu, M Eiber, K Herrmann, J Czernin, **J Calais**.
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
AUA 2020 Virtual Meeting - American Urological Association Annual Meeting
58. TA Hope, WR Armstrong, V Murthy, R Juarez, CL Heath, S Behr, F Barbato, F Ceci, A Farolfi, S Schwarzenboeck, M Unterrainer, H Zacho, H Nguyen, M Cooperberg, P Carroll, R Reiter, S Holden, WP Fendler, S Zhu, M Eiber, K Herrmann, J Czernin, **J Calais**.
Accuracy of 68Ga-PSMA-11 for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicenter prospective phase 3 imaging study.
ASCO 2020 Virtual Meeting – American Society of Clinical Oncology Annual Meeting
59. A Gafita, WP Fendler, H Wang, SK Sandhu, M Weber, R Esfandiari, J Czernin, H Rathke, I Rauscher, R Tauber, E Delpassand, WA Weber, K Herrmann, **J Calais**, M Eiber, MS Hofman
Efficacy and safety of 177Lu-PSMA radionuclide treatment in patients with diffuse bone marrow involvement: A multicenter retrospective study.
ASCO 2020 Virtual Meeting – American Society of Clinical Oncology Annual Meeting
60. **A Gafita, J Calais**, H Wang, M Weber, H Rathke, C Kratochwil, R Esfandiari, WR Armstrong, SK Sandhu, R Tauber, E Delpassand, U Haberkorn, WA Weber, K Herrmann, J Czernin, MS Hofman, WP Fendler, M Eiber.
Prognostic markers for overall survival and outcome to LuPSMA radionuclide treatment in patients with metastatic castration-resistant prostate cancer.
ASCO 2020 Virtual Meeting – American Society of Clinical Oncology Annual Meeting
61. **WR Armstrong**, P Thin, K Nguyen, RM Alano, KM. Booker, J Gartmann, V Lok, S Lira, J Czernin, AU Kishan, NG Nickols, **J Calais**.
Comparison of recurrence patterns after surgery and radiation therapy with 68Ga-PSMA-11 PET/CT in nonmetastatic castrate-sensitive prostate cancer patients: A single-center post-hoc retrospective analysis in 787 patients.
ASCO 2020 Virtual Meeting – American Society of Clinical Oncology Annual Meeting
62. **A. Gafita, J Calais**, W. Hui, M. Weber, H. Rathke, R. Esfandiari, W. Armstrong, C. Kratochwil, R. Tauber, E. Delpassand, U. Haberkorn, W. Weber, K. Herrmann, M. Hofman, J. Czernin, W. Fendler, M. Eiber.
Predictive factors and prediction nomograms for LuPSMA radioligand therapy in patients with metastatic castration-resistant prostate cancer: an international multicentre retrospective study.
SNMMI Virtual Meeting 2020 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
63. C. Meyer, A. Stuparu, L. Wei, C. Radu, **J Calais**, J. Czernin, M. Dahlbom, R. Slavik.
A combination isotope approach towards improved PSMA-targeted radioligand therapy in a murine model of prostate cancer
SNMMI Virtual Meeting 2020 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
64. A. Gafita, W. Fendler, W. Hui, S. Sandhu, M. Weber, R. Esfandiari, **J Calais**, I. Rauscher, H. Rathke, R. Tauber, E. Delpassand, W. Weber, K. Herrmann, J. Czernin, M. Eiber, M. Hofman.
Efficacy and safety of 177Lu-PSMA radionuclide treatment in patients with diffuse bone marrow involvement: a multicenter retrospective study.
SNMMI Virtual Meeting 2020 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
+++ 1st place Best Poster Award Clinical Oncology section +++

65. J. Ferdinandus, W. Fendler, J. Czernin, M. Eiber, R. Flavell, S. Behr, W. Katherine, C. Lawhn-Heath, M. Pampaloni, R. Reiter, M. Rettig, J. Gartmann, V. Murthy, R. Slavik, P. Carroll, K. Herrmann, **J Calais**, T. Hope.
Impact of 68Ga-PSMA-11 PET on the Management of recurrent Prostate Cancer in a Prospective Single-Arm Clinical Trial.
SNMMI Virtual Meeting 2020 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
66. **W. Armstrong**, P. Thin, R. Alano, K. Nguyen, K. Booker, J. Gartmann, V. Lok, S. Lira, I. Sonni, J. Czernin, **J Calais**.
Incidence of local prostate cancer recurrence by 68Ga-PSMA-11 PET/CT is higher after definitive Radiation Therapy than after Radical Prostatectomy: a single center post-hoc retrospective analysis of recurrence patterns of 787 patients.
SNMMI Virtual Meeting 2020 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
67. **WR Armstrong**, P Thin, R Alano, K Nguyen, K Booker, J Gartmann, V Lok, S Lira, I Sonni, J Czernin, NG Nickols, AU Kishan, **J Calais**
Comparison of recurrence patterns after surgery and radiation therapy with 68Ga-PSMA-11 PET/CT in non-metastatic castrate sensitive prostate cancer patients: a single center post-hoc retrospective analysis in 787 patients.
ASTRO 2020 Virtual Meeting - American Society for Radiation Oncology Annual Meeting – P4015
68. TM Ma, D Shabsovich, JE Juarez, P Thin, WR Armstrong, I Sonni, K Nguyen, V Lok, RE Reiter, MB Rettig, ML Steinberg, DD Yang, V Muralidhar, NR Parikh, NG Nickols, J Czernin, **J Calais**, AU Kishan
Impact of 68Ga-PSMA-11 PET/CT on Initial Staging of High-Risk Prostate Cancer Patients: Post-Hoc Analysis of a Prospective Single Center Experience
ASTRO 2020 Virtual Meeting - American Society for Radiation Oncology Annual Meeting – P0058
69. N Parikh, D Johnson, A Raldow, M Steinberg, J Czernin, N Nickols, **J Calais**, AU Kishan, T Royce
Cost-effectiveness of 68Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence
ASTRO 2020 Virtual Meeting - American Society for Radiation Oncology Annual Meeting – P1058
70. L Valle, EJ Lehrer, RJ Karnes, RE Reiter, M Rettig, **J Calais**, NG Nickols, DE Spratt, RT Dess, ML Steinberg, PL Nguyen, BJ Davis, N Zarosky, AU Kishan.
Meta-Analysis of Salvage Therapy Following Definitive Radiotherapy for Prostate Cancer
ASTRO 2020 Virtual Meeting - American Society for Radiation Oncology Annual Meeting – P4037
71. **J Calais**, WR Armstrong, AU Kishan, K Booker, J Czernin, NG Nickols
Impact of PSMA PET/CT on SRT planning: preliminary results from a randomized phase 3 trial.
ASTRO 2020 Virtual Meeting - American Society for Radiation Oncology Annual Meeting – P4003
72. **C Meyer**, D Mirando, T Adams, D Ranganathan, R Esfandiari, E Delpassand, J Czernin, **J Calais**, M Dahlbom
Patient-specific kidney absorbed doses in mCRPC patients treated with 177Lu-PSMA-617: a post-hoc analysis of a prospective phase 2 study
EANM 2020 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-772
73. A Gafita, W Fendler, W Hui, S Sandhu, M Weber, R Esfandiari, **J Calais**, I Rauscher, H Rathke, R Tauber, E Delpassand, W Weber, K Herrmann, J Czernin, M Eiber, M Hofman
Efficacy and safety of 177Lu-PSMA radionuclide treatment in patients with diffuse bone marrow involvement: a multicenter retrospective study.
EANM 2020 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-987
74. **A Gafita, J Calais**, H Wang, M Weber, H Rathke, C Kratochwil, R Esfandiari, W R Armstrong, S Sandhu, R Tauber, ES Delpassand, U Haberkorn, WA Weber, K Herrmann, J Czernin, MS Hofman, WP Fendler, M Eiber.
Prognostic markers for overall survival and outcome to LuPSMA radionuclide treatment in patients with metastatic castration-resistant prostate cancer
EANM 2020 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-979
75. **WR Armstrong**, P Thin, R Alano, K Nguyen, K Booker, J Gartmann, V Lok, S Lira, I Sonni, J Czernin, NG Nickols, AU Kishan, **J Calais**
Recurrence patterns after surgery and radiation therapy with 68Ga-PSMA-11 PET/CT in non-metastatic castrate sensitive prostate cancer patients: a single center post-hoc retrospective analysis.
EANM 2020 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-638

76. **J Calais**, WR. Armstrong, AU Kishan, KM Booker, D Elashoff, WP Fendler, J Czernin, NG. Nickols
Impact of PSMA PET/CT on SRT planning: Preliminary results from the randomized phase III trial NCT03582774.
ASCO GU Virtual Meeting 2021 – Genitourinary Cancers Symposium
77. **J Calais**, S Zhu, N Hirmas, M Eiber, BA Hadaschik, M Stuschke, K Herrmann, J Czernin, AU. Kishan, NG Nickols, D Elashoff, WP Fendler
Phase III randomized trial of PSMA PET prior to definitive radiation therapy for unfavorable intermediate-risk or high-risk prostate cancer [PSMA dRT]: Study protocol NCT04457245.
ASCO GU Virtual Meeting 2021 – Genitourinary Cancers Symposium
78. **I Sonni**, E Felker, AT Lenis, AE Sisk, S Bahri, M Auerbach, WR Armstrong, V Suvannarerg, T Tubtawee, T Grogan, D Elashoff, J Czernin, S Raman, RE Reiter, **J Calais**.
Head-to-head comparison of 68Ga-PSMA-11 PET/CT and mpMRI in the detection, intra-prostatic localization, and local extension of primary prostate cancer: A single-center imaging study with histopathology gold-standard.
ASCO GU Virtual Meeting 2021 – Genitourinary Cancers Symposium
<https://www.urotoday.com/conference-highlights/asco-gu-2021/prostate-cancer/127835-asco-gu-2021-head-to-head-comparison-of-68ga-psma-11-pet-ct-and-mpmri-in-the-detection-intra-prostatic-localization-and-local-extension-of-primary-prostate-cancer-a-single-center-imaging-study-with-histopathology-gold-standard.html>
<https://dailynews.ascopubs.org/doi/psma-pet-ct-and-mpmri-may-have-complementary-roles-prostate-cancer-staging-and>
<https://www.oncoamericas.com/en/68ga-psma-11-pet-ct-and-multiparametric-mri-in-primary-prostate-cancer/>
79. **C Zuo**, RR Huang, CE Mona, TL Lotan, L True, C Morrissey, J Czernin, **J Calais**, CE Magyar, H Ye
FAP is a Potential Theranostic Target for PSMA-negative Castration Resistant Prostate Cancer
USCAP annual meeting 2021 - United States and Canadian Academy of Pathology
80. K Chi, U Metser, J Czernin, **J Calais**, V Prasad, M Eiber, N Shore, J Jensen, N Fleshner, S Tagawa, O Sartor
Study Evaluating Metastatic Castrate Resistant Prostate Cancer (mCRPC) Treatment Using 177Lu-PNT2002 PSMA Therapy After Second-line Hormonal Treatment (SPLASH)
AACR Radiation Science and Medicine 2021 Annual Meeting
81. **CE Mona**, M Benz, F Hikmat, TG Grogan, K Lueckerath, AA Razmaria, R Riahi, R Slavik, MD Grigis, G Carlucci, KA Kelly, J Czernin, DW Dawson, **J. Calais**.
Validation of FAPI PET biodistribution by immunohistochemistry in patients with solid cancers: a prospective exploratory study
AACR Annual Meeting 2021 – American Association for Cancer Research - LB038
82. **J Calais**, S Zhu, N Hirmas, M Eiber, BA Hadaschik, M Stuschke, K Herrmann, J Czernin, AU. Kishan, NG Nickols, D Elashoff, WP Fendler
Phase 3 multicenter randomized trial of PSMA PET/CT prior to definitive radiation therapy for unfavorable intermediate-risk or high-risk prostate cancer [PSMA dRT]: Study Protocol
AACR Annual Meeting 2021 – American Association for Cancer Research - CT257
83. **CE Mona**, M Benz, F Hikmat, TG Grogan, K Lueckerath, AA Razmaria, R Riahi, R Slavik, MD Grigis, G Carlucci, KA Kelly, J Czernin, DW Dawson, **J. Calais**.
Validation of FAPI PET biodistribution by immunohistochemistry in patients with solid cancers: A prospective exploratory study.
ASCO 2021 Virtual Meeting – American Society of Clinical Oncology Annual Meeting
84. A Gafita, I Rauscher, M Weber, BA Hadaschik, H Wang, WR Armstrong, R Tauber, J Czernin, M Rettig, K Herrmann, **J Calais**, WA Weber, MR Benz, WP Fendler, M Eiber.
Interim PSMA PET/CT for response evaluation during LuPSMA treatment in mCRPC (INTERIM PET): An explorative, multicenter study.
ASCO 2021 Virtual Meeting – American Society of Clinical Oncology Annual Meeting
85. K Chi, U Metser, J Czernin, **J Calais**, V Prasad, M Eiber, N Shore, J Jensen, N Fleshner, S Tagawa, O Sartor
Study evaluating metastatic castrate resistant prostate cancer (mCRPC) treatment using 177Lu-PNT2002 PSMA therapy after second-line hormonal treatment (SPLASH).
ASCO 2021 Virtual Meeting – American Society of Clinical Oncology Annual Meeting

86. **C Meyer**, D Mirando, T Adams, J Czernin, **J Calais**, M Dahlbom
Patient-specific tumor dosimetry in mCRPC patients treated with 177Lu-PSMA-617
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
87. **C Meyer**, A Stuparu, K Lueckerath, L Nyiranshuti, J Czernin, M Dahlbom, **J Calais**, R Slavik
Preclinical evaluation of PSMA-TO1- a PSMA-targeting ligand with increased circulating half-life
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
88. **W Armstrong**, M Benz, F Ceci, G Polverari, T Donahue, Z Wainberg, A Quon, M Auerbach, M Girgis, K Herrmann, J Czernin, **J Calais**
18F-FDG PET/CT Combined Metabolic-Radiographic biomarker for Early Prediction of first line Chemotherapy Outcomes in PDAC: a single center prospective study
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
89. **CE Mona**, M Benz, F Hikmat, TG Grogan, K Lueckerath, AA Razmaria, R Riahi, R Slavik, MD Grigis, G Carlucci, KA Kelly, J Czernin, DW Dawson, **J. Calais**.
Validation of FAPi PET biodistribution by immunohistochemistry in patients with solid cancers: A prospective exploratory study.
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
+ Oncology, Basic Science Poster Award Winners, 2nd place +
+ Early-Career Professionals Abstract Award Winners, 1st Place Basic Science +
90. T Hope, C Graves, **J Calais**, E Ehman, G Johnson, D Thompson, QY Duh, C Seib, A Maya, J Gosnell, S Wen, S Roman, JA Sosa, W Kluijfhout, J Villanueva-Meyer, M Pampaloni, I Suh
Accuracy of 18F-fluorocholine PET for the detection of parathyroid adenomas: prospective single center study
SNMMI Virtual Meeting 2021 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
91. K Fizazi, K Hermann, BJ Krause, K Rahbar, KN Chi, MJ Morris, O Sartor, ST Tagawa, AT Kendi, N Vogelzang, **J Calais**, J Nagarajah, XX Wei, VS Koshkin, JM Beaugard, B Chang, M DeSilvio, RA Messmann, J de Bono.
Health-related quality of life, pain and safety outcomes in the phase 3 VISION study of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer
ESMO Paris 2021 – Annual Congress of the European Society for Medical Oncology
92. CP Smith, M Xiang, WR Armstrong, NG Nickols, ML Steinberg, RE Reiter, M Rettig, J Czernin, **J Calais**, AU Kishan
Patterns of Failure in Men With Radiorecurrent Prostate Cancer: A Post-Hoc Analysis of Two Prospective Ga-68-PSMA PET/CT Imaging Trials
ASTRO Chicago 2021 - American Society for Radiation Oncology Annual Meeting – P2595
93. TM Ma, M Xiang, D Tilki, RJ Karnes, BJ Stish, R Martinez-Monge, RD Tendulkar, EA Klein, PT Tran, J Tosoian, A Berlin, JD Tward, GS Merrick, DE Spratt, DJ Krauss, EM Horwitz, A Gafita, T Grogan, **J Calais**, AU Kishan.
Prognostic Significance of the Risk of Non-localized Disease on PSMA/PET: Comparative Performance of a Novel, PSMA/PET-Derived Risk Stratification Tool for High-Risk Prostate Cancer in a Large, Multi-Institutional Cohort
ASTRO Chicago 2021 - American Society for Radiation Oncology Annual Meeting – OP 97
94. **Gafita A, Calais J**, Grogan TR, Hadaschik B, Wang H, Weber M, Sandhu S, Kratochwil C, Esfandiari R, Tauber R, Zeldin A, Rathke H, Armstrong WR, Robertson A, Thin P, D'Alessandria C, Rettig MB, Delpassand ES, Haberkorn U, Elashoff D, Herrmann K, Czernin J, Hofman MS, Fendler WP, Eiber M.
Nomograms to predict outcomes after 177Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study.
EANM 2021 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-0171
95. A. Gafita, I. Rauscher, M. Weber, B. Hadaschik, H. Wang, WR Armstrong, R. Tauber, TR Grogan, J. Czernin, MB Rettig, K. Herrmann, **J. Calais**, WA Weber, MR Benz, WP Fendler, M Eiber.
Development of a novel framework for treatment response evaluation using PSMA-PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP): an international multicenter study
EANM 2021 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-0896

96. **C. Meyer**, V. Prasad, A. Stuparu, G. Glatting, P. Kletting, J. Miksch, C. Solbach, K. Lueckerath, L. Nyiranshuti, S. Zhu, J. Czernin, M. Dahlbom, **J. Calais**, A. Beer, R. Slavik.
Comparison of PSMA-TO-1 and PSMA-617 labelled with 68Ga, 177Lu and 225Ac: a first in-human translational study
EANM 2021 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-0113
97. Fendler WP, Ferdinandus J, Farolfi A, Washington S, Mohammad O, Pampaloni MH, Scott PJ, Rodnick M, Viglianti BL, Eiber M, Herrmann K, Czernin J, Armstrong WR, **Calais J**, Hope TA, Piert MA.
PSMA PET validates higher rates of metastatic disease for European Association of Urology Biochemical Recurrence Risk Groups: an international multicenter study.
EANM 2021 Virtual Meeting - Annual Congress of the European Association of Nuclear Medicine - OP-0169
98. **J Crane**, DS Graham, C Mona, SD Nelson, A Samiei, D Dawson, S Dry, J Crompton, M Benz, J Czernin, FC Eilber, T Graeber, **J Calais**, NC Federman.
Fibroblast Activation Protein expression in Sarcomas.
CTOS Virtual Annual Meeting 2021 - Annual Meeting of the Connective Tissue Oncology Society -P121 – ID#1818938
99. T Cloughesy, B Ellingson, A Gafita, S Chun, E Filka, P Nghiemphu, A Lai, S Green, J Tsang, Y Jingwen, **J Calais**, I Sonni, G Li, D Nathanson.
Evaluating metabolic alterations in patients with EGFR activated recurrent glioblastoma (RGBM) by inhibiting EGFR with osimertinib
SNO Boston 2021 – Annual Meeting of the Society for Neuro-Oncology - CTNI-14
100. **M Hotta**, K Nguyen, P Thin, WR Armstrong, A Gafita, MR Benz, J Czernin, AU Kishan, NG Nickols, **J Calais**.
Kinetics of PSMA PET uptake in prostate cancer lesions after radiation therapy: A single-center retrospective study.
ASCO GU San Francisco 2022 – Genitourinary Cancers Symposium
101. **M Hotta**, A Gafita, V Murthy, MR. Benz, I Sonni, I Burger, M Eiber, L Emmett, A Farolfi, WP Fendler, MS Hofman, TA Hope, C Kratochwil, J Czernin, **J Calais**.
Predicting the outcome of mCPRC patients after Lu-177 PSMA therapy using semiquantitative and visual criteria in baseline PSMA PET: An international multicenter retrospective study.
ASCO GU San Francisco 2022 – Genitourinary Cancers Symposium
102. **M Hotta**, A Gafita, J Czernin, **J Calais**.
Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy.
ASCO GU San Francisco 2022 – Genitourinary Cancers Symposium
103. A Gafita, I Rauscher, M Weber, BA Hadaschik, H Wang, WR Armstrong, R Tauber, T Grogan, J Czernin, MB Rettig, K Herrmann, **J Calais**, WA Weber, MR. Benz, WP Fendler, M Eiber.
Novel framework for treatment response evaluation using PSMA-PET/CT in patients with metastatic castration resistant prostate cancer (RECIP): An international multicenter study.
ASCO GU San Francisco 2022 – Genitourinary Cancers Symposium
104. **Kupperman D, Calais J**, Brisbane W, Tran E, Herbert L, Benz M, Czernin J, Marks L.
Prostate biopsy targeted to Prostate Specific Membrane Antigen (PSMA) foci - MP09-20
AUA New Orleans 2022 – American Urological Association Annual Meeting
105. N Nickols, G Berenji, N Kane, K Sjostrand, A Anand, C Smith, **J Calais**, MB Rettig.
Quantitative Piflufolostat-F18 (PSMA) Scan indices as a response imaging-biomarker to androgen deprivation therapy in veterans with newly diagnosed metastatic prostate cancer. - PD35-04
AUA New Orleans 2022 – American Urological Association Annual Meeting
106. L Djaïleb, WR. Armstrong, D Thompson, A Gafita, A Farolfi, A Rajagopal, R Juarez, M Cooperberg, P Carroll, S Washington, J Czernin, RE Reiter, TA Hope, **J Calais**.
Predictive value of extra-prostatic disease Detection by pre-operative PSMA-PET for biochemical recurrence free survival in patients treated with Radical Prostatectomy and Pelvic Lymph Node Dissection: follow-up analysis of a Multicenter Prospective Phase 3 Imaging Trial.
ASCO Chicago 2022 – American Society of Clinical Oncology Annual Meeting

107. **M Hotta**, A Gafita, V Murthy, MR. Benz, I Sonni, I Burger, M Eiber, L Emmett, A Farolfi, WP Fendler, MS Hofman, TA Hope, C Kratochwil, J Czernin, **J Calais**.
Predicting the outcome of mCPRC patients after Lu-177 PSMA therapy using semiquantitative and visual criteria in baseline PSMA PET: An international multicenter retrospective study.
ASCO Chicago 2022 – American Society of Clinical Oncology Annual Meeting
108. **WR Armstrong**, AU Kishan, KM Booker, WP Fendler, TA Hope, NG Nickols, J Czernin, **J Calais**.
Impact of PSMA PET/CT on prostate cancer salvage radiotherapy management: Results from the prospective randomized phase 3 trial [PSMA SRT NCT03582774].
ASCO Chicago 2022 – American Society of Clinical Oncology Annual Meeting
109. **M Hotta**, K Nguyen, P Thin, WR Armstrong, A Gafita, MR Benz, J Czernin, AU Kishan, NG Nickols, **J Calais**.
Kinetics of PSMA PET uptake in prostate cancer lesions after radiation therapy: A single-center retrospective study.
ASCO Chicago 2022 – American Society of Clinical Oncology Annual Meeting
110. N Vaishampayan, MJ Morris, BJ Krause, NJ Vogelzang, AT Kendi, LT Nordquist, **J Calais**, J Nagarajah, TM Beer, G El-Haddad, M Brackman, M Desilvio, RA Messmann, AO Sartor, K Fizazi.
177Lu-PSMA-617 in PSMA-positive metastatic castration-resistant prostate cancer: Prior and concomitant treatment subgroup analyses of the VISION trial.
ASCO Chicago 2022 – American Society of Clinical Oncology Annual Meeting
111. **M Hotta**, A Gafita, J Czernin, **J Calais**.
Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy.
ASCO Chicago 2022 – American Society of Clinical Oncology Annual Meeting
112. **M Hotta**, A Gafita, V Murthy, MR. Benz, I Sonni, I Burger, M Eiber, L Emmett, A Farolfi, WP Fendler, MS Hofman, TA Hope, C Kratochwil, J Czernin, **J Calais**.
PSMA PET tumor-to-Salivary Glands ratio (PSG score) to predict response to Lu-177 PSMA radioligand therapy: an international multicenter retrospective study.
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Kinetics of PSMA PET uptake in prostate cancer lesions after radiation therapy: A single-center retrospective study.
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114. P Kuo, DC Yoo, R Avery, M Seltzer, **J Calais**, J Nagarajah, W Weber, W Fendler, M Hofman, B Krause, A Catafau, E Kpamegan, M Brackman, A T Kendi.
Reader agreement of [68Ga]Ga-PSMA-11 PET/CT scan interpretation to determine patient eligibility for [177Lu]Lu-PSMA-617 radioligand therapy: a VISION sub-study
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115. **I Sonni**, A Dal Pra, DP O'Connell, M Benz, K Nguyen, SM Yoon, J Deng, C Smith, N Nickols, TR Grogan, M Cao, A Kishan, **J Calais**.
PSMA PET mapping of postoperative local recurrence and impact on prostate fossa contouring guidelines for salvage radiation therapy
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116. N Nickols, A Anand, K Sjostrand, G Berenji, N Kane, C Smith, S Duriseti, **J Calais**, M Rettig.
Quantitative Assessment of PSMA PET Response to Androgen Deprivation in Veterans with Treatment Naïve Castration Sensitive Prostate Cancer
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117. **C Meyer**, A Allmann, J Allmann, M Eiber, J Czernin, M Dahlbom, **J Calais**.
Extrapolating organ and tumor doses for 225Ac-PSMA-I&T radionuclide therapy in patients with mCPRC
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118. **C Meyer**, D Mirando, J Czernin, **J Calais**, M Dahlbom,
Kidney and tumor radiation absorbed doses in mCRPC patients treated with 177Lu-PSMA-617: a preliminary analysis of the RESIST-PC phase 2 trial
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119. **L Djaïleb**, **WR Armstrong**, D Thompson, K Nguyen, A Gafita, A Farolfi, A Rajagopal, R Juarez, M Cooperberg, P Carroll, S Washington, J Czernin, RE Reiter, TA Hope, **J Calais**.
Predictive value of extra-prostatic disease detection by pre-operative PSMA-PET for biochemical recurrence free survival in patients with Radical Prostatectomy: follow-up analysis of a Multicenter Prospective Phase 3 Imaging Trial.
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120. **V Murthy**, E Appiah-Kubi, K Nguyen, P Thin, M Hotta, A Gafita, I Sonni, **J Calais**.
Changes in Quantitative PSMA PET Metrics and PSA Progression-Free Survival following Initiation of Androgen Deprivation Therapy in Prostate Cancer Patients: a retrospective single-center study
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121. **A Gafita**, V Murthy, P Thin, K Nguyen, J Czernin, **J Calais**,
Prognostic value of end-of-treatment 68Ga-PSMA-11 PET/CT in patients treated with 177Lu-PSMA radioligand therapy: a retrospective, single-center analysis.
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122. **M Hotta**, A Gafita, J Czernin, **J Calais**.
Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy.
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123. **I Sonni**, A Dal Pra, D O'Connell, M Benz, K Nguyen, S Yoon, J Deng, CP Smith, NG Nickols, M Cao, AU Kishan, **J Calais**.
PSMA PET/CT–Based Atlas for Prostatic Bed Recurrence of Prostate Cancer after Radical Prostatectomy: Clinical Implications for Salvage Radiation Therapy
AdMeTech 6th Global Summit on Precision Dx and Tx of Prostate Cancer.
+++ First Place Winner of the Abstract Competition +++
124. **WR Armstrong**, AU Kishan, K Booker, WP Fendler, T Hope, NG Nickols, J Czernin, **J Calais**.
Impact of PSMA PET/CT on Prostate Cancer Salvage Radiotherapy Management: Results from the Prospective Randomized Phase 3 Trial [PSMA SRT NCT03582774].
ASTRO San Antonio 2022 - American Society for Radiation Oncology Annual Meeting
125. **I Sonni**, A Dal Pra, D O'Connell, M Benz, K Nguyen, S Yoon, J Deng, CP Smith, NG Nickols, M Cao, AU Kishan, **J Calais**.
PSMA PET/CT–Based Atlas for Prostatic Bed Recurrence of Prostate Cancer after Radical Prostatectomy: Clinical Implications for Salvage Radiation Therapy.
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126. **M Hotta**, K Nguyen, P Thin, WR Armstrong, A Gafita, M Benz, I Sonni, J. Czernin, NG Nickols, AU Kishan, **J Calais**.
Kinetics and Patterns of PSMA PET Uptake in Prostate Cancer after Radiation Therapy: A Single Center Retrospective Study.
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127. **K Herrmann**, BJ Krause, K Rahbar, KN Chi, MJ Morris, O Sartor, ST Tagawa, AT Kendi, N Vogelzang, **J Calais**, J Nagarajah, XX Wei, V Koshkin, J Beauregard, B Chang, M DeSilvio, RA Messmann, J de Bono, K Fizazi.
Health-related quality of life (HRQoL), pain and safety outcomes in the phase 3 VISION study of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer OP-161
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128. **P Kuo**, DC Yoo, R Avery, M Seltzer, **J Calais**, J Nagarajah, WA Weber, WP Fendler, MS Hofman, BJ Krause, A Catafau, E Kpamegan, M Brackman, AT Kendi.
VISION read criteria of 68Ga-PSMA-11 PET scans for patient eligibility to 177Lu-PSMA-617 therapy: a simple and reproducible methodology OP-380
EANM 2022 Barcelona - Annual Congress of the European Association of Nuclear Medicine

129. L Djaileb, W Armstrong, D Thompson, K Nguyen, A Gafita, A Farolfi, M Hotta, A Rajagopal, R Juarez, M Cooperberg, P Carroll, S Washington, J Czernin, R Reiter, T Hope, **J Calais**.
Predictive value of extra prostatic disease detection by PSMA PET for BCR free survival in patient by radical prostatectomy: follow up analysis of a multicenter prospective phase 3 imaging trial OP-639.
EANM 2022 Barcelona - Annual Congress of the European Association of Nuclear Medicine
130. A Gafita, I Rauscher, W Fendler, V Murthy, W Hui, W Armstrong, K Herrmann, WA Weber, **J Calais**, M Eiber, M Weber, M Benz.
Measuring response in metastatic castration-resistant prostate cancer using PSMA PET/CT: Comparison of RECIST 1.1, aPCWG3, aPERCIST, PPP, and RECIP 1.0 criteria OP-830.
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131. **P Thin**, M Hotta, A Gafta, **J Calais**, I Sonni.
When to Repeat Imaging after a Negative PSMA PET Scan in Patients with Recurrent Prostate Cancer under Active Surveillance: A Single-Center Retrospective Study OP-832.
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133. **A Farolfi**, L Djaileb, M Hotta, A Gafita, M Benz, J Czernin, D Kuppermann, LS Marks, **J Calais**.
PSMA-targeted prostate biopsy: a single-center retrospective analysis EPS-229
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Incidental Uptake on FAPI PET/CT imaging: Physiologies, Pathologies, and Pitfalls.
RSNA 2022 Annual Meeting Chicago - Radiological Society of North America Annual Meeting - NMMIEE-15
135. AJ Pantuck, **J Calais**, K Chamie, A Drakaki, A Chin, H Ye, M Auerbach, J Czernin, B Shuch.
Results of 89Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma: the UCLA experience
AAGUS 2023 Jacksonville - American Association of Genitourinary Surgeons
136. LM. Gudenkauf, M Chavez, M Maconi, C Geiss, A Seyedroudbari, P Thin, A Hoogland, K Nguyen, LB. Oswald, HSL Jim, G El-Haddad, WP Fendler, K Herrmann, D Cella, J Czernin, MS Hofman, AP Dicker, **J Calais**, ST Tagawa, BD Gonzalez
Developing a novel patient-reported outcome measure for patients with prostate cancer receiving radionuclide therapy: The FACT-RNT.
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137. LF Valle, **J Calais**, LS Marks, S Raman, RE Reiter, M Rettig, J Shen, J Czernin, AB Weiner, ML Steinberg, NG Nickols, AJ Chang, PC Boutros, HH Ye, M Hotta, RR Huang, AU Kishan
Radiographic-pathologic concordance in the workup of locally radiorecurrent prostate cancer.
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177Lu-PSMA-617 dans le cancer de la prostate métastatique résistant à la castration PSMA positif : analyse des traitements antérieurs et concomitants – VISION
JFMN 2023 Paris - Journées Francophones de Médecine Nucléaire DOI: 10.1016/j.mednuc.2023.01.033
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141. **D Kuppermann, J Calais**, E Tran, S Gonzalez, M Delfin, L Marks
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144. **PG Maliha**, M Hotta, A Farolfi, A Limon, R Alano, G Carlucci, K Booker, K Nguyen, P Thin, M Benz, M Auerbach, J Czernin, **J Calais**.
FAPI PET uptake patterns after invasive medical interventions or cancer therapy: a single center retrospective analysis
JCC 2023 Annual Retreat of UCLA Jonsson Comprehensive Cancer Center – Lushkin Center
145. **Z Ells**, A Farolfi, RE Reiter, NM Donin, JD Shirk, JJ H Zhang, AB Weiner, **J Calais**, M Dahlbom.
Potential value of 3D Volume Rendering using PSMA PET/CT to improve surgical planning for salvage lymph node resection: the UCLA initial experience
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146. **L Unterrainer**, A Farolfi, F Rosar, CS Denis, L Emmett, I de Kouchkovsky, TA Hope, M Hotta, A Gafita, L Djaileb, J Czernin, **J Calais**.
Early changes of PSMA PET signal after initiation of androgen receptor signaling inhibitors in mCRPC: first results of a retrospective international multicenter study.
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147. **CP Smith**, WR Armstrong, KJ Clark, J Moore, M Roberts, A Farolfi, RE Reiter, M Rettig, J Shen, L Valle, NG Nickols, ML Steinberg, J Czernin, AU Kishan, **J Calais**.
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Do bone scans over-stage disease compared to PSMA PET? An international multicenter retrospective study with blinded independent readers.
ASCO Chicago 2023 - American Society of Clinical Oncology Annual Meeting
149. **LM Unterrainer**, A Farolfi, F Rosar, CS Denis, L Emmett, I de Kouchkovsky, TA Hope, M Hotta, A Gafita, L Djaileb, J Czernin, **J Calais**.
Early changes of PSMA PET signal after initiation of androgen receptor signaling inhibitors in mCRPC: An international multicenter retrospective study.
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Head-to-head comparison of 68Ga-PSMA-11 PET with 99mTc-MDP bone scan for detection of bone disease in patients with prostate cancer with biochemical progression during ADT: A single center prospective study.
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151. **WR Armstrong**, KJ Clark, CP Smith, P Thin, L Djaileb, MR Benz, RE Reiter, M Rettig, J Czernin, NG Nickols, AU Kishan, **J Calais**.
PSMA PET findings in an “EMBARK-like” cohort of patients with high-risk non-metastatic hormone-sensitive prostate cancer: A single center post-hoc retrospective analysis.
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Pre-surgical 68Ga-PSMA-11 PET for biochemical recurrence risk assessment: A surrogate of pelvic lymph node dissection? Follow-up analysis of a multicenter prospective phase 3 imaging trial.
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Prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) disease extent and overall survival (OS) in patients (pts) with high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC): An international multicenter retrospective study.
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FAPI PET uptake patterns after invasive medical interventions or cancer therapy: a single center retrospective analysis
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
155. **I Sonni**, A Gafita, R Alano, S Lira, J Shen, A Drakaki, TR Grogan, M Rettig, J Czernin, **J Calais**.
Effects of novel androgen receptor signaling inhibitors on PSMA PET signal intensity in patients with castrate-resistant prostate cancer: a prospective exploratory serial imaging study
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
156. L Djaileb, WR Armstrong, A Gafita, A Farolfi, A Rajagopal, TR Grogan, K Nguyen, M Benz, M Hotta, M Unterrainer, R Juarez, M Cooperberg, S Washington, RE Reiter, M Eiber, K Herrmann, WP Fendler, J Czernin, T Hope, **J Calais**, D Thompson, F Barbato, F Ceci, S Schwarzenböck, HD Zacho, PR Carroll.
Pre-surgical 68Ga-PSMA-11 PET for biochemical recurrence risk assessment: a surrogate of Pelvic Lymph Node Dissection? Follow-up analysis of a Multicenter Prospective Phase 3 Imaging Trial.
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157. A Farolfi, WR Armstrong, L Djaileb, A Gafita, M Hotta, M Auerbach, WP Fendler, M Rettig, M Eiber, M Hofman, B Hadaschik, K Herrmann, J Czernin, **J Calais**, M Benz.
Inter-institutional differences and common ground in 177Lu-PSMA radionuclide therapy: International survey in 95 theranostic centers
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
158. **L Unterrainer**, A Farolfi, F Rosar, L Emmett, CS Denis, T Hope, M Hotta, I de Kouchkovsky, L Djaileb, A Gafita, J Czernin, **J Calais**.
Early changes of PSMA PET signal after initiation of androgen receptor signaling inhibitors in mCRPC: an international multicenter, retrospective analysis.
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
159. **J Calais**, M Benz, F Jiang, D Thompson, R Juarez, MH Pampaloni, WR Armstrong, F Barbato, PK Gupta, M Auerbach
WP Fendler, T Hope.
Do Bone Scans Over Stage Disease Compared to PSMA PET? An international multicenter retrospective study with blinded independent readers.
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
160. **Z Ells**, A Farolfi, RE Reiter, NM Donin, JD Shirk, JJ H Zhang, AB Weiner, **J Calais**, M Dahlbom.
Potential value of 3D Volume Rendering using PSMA PET/CT to improve surgical planning for salvage lymph node resection: the UCLA initial experience
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting

161. **A Castellanos Rieger**, A Farolfi, C Smith, J Czernin, M Rettig, **J Calais**.
PSMA PET prognostic value for outcome of pre-chemotherapy post-ARSI CRPC patients: a single center retrospective analysis
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
162. **M Jafarvand**, A Farolfi, M Benz, L Djaileb, R Mei, J Czernin, LS Marks, **J Calais**.
PSMA PET/CT for prostate cancer patients after focal therapy: a single center retrospective analysis
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
163. **Z Ells**, C Meyer, M Dahlbom, A Farolfi, JJ H Zhang, A Gafita, G Carlucci, JD Shirk, J Czernin, RE Reiter, **J Calais**.
Determining the optimal time interval between 99mTc-PSMA-I&S administration and radioguided pelvic lymph node dissection in patients with prostate cancer pelvic lymph node metastasis: results from a prospective exploratory study
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
164. **A Gafita**, R Alano, M Rettig, J Shen, WR Armstrong, TR Grogan, ST Liu, M Benz, J Czernin, **J Calais**.
Head-to-head comparison of 68Ga-PSMA-11 PET with 99mTc-MDP bone scan for detection of bone disease in prostate cancer patients with biochemical progression during ADT: a single center prospective study
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
165. **A Gafita**, L Djaileb, I Rauscher, WP Fendler, B Hadaschik, K Herrmann, **J Calais**, SP Rowe, M Rettig, M Eiber, M Weber, M Benz, A Farolfi.
Practical RECIP: Visual assessment of Response Evaluation Criteria In PSMA-PET/CT in metastatic castration-resistant prostate cancer.
SNMMI Chicago 2023 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
166. I Sonni, DH Kim, A Ter-Pogosyan, T Grogan, N Barroso, P Ahuja, **J Calais**, A Sisk, S Raman
Association of aggressive prostate cancer features on whole-mount pathology with quantitative measures on PSMA PET - OP-034
EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
167. I Sonni, S Doddipalli, M Deol, D Ban, H Kim, T Grogan, N Barroso, P Ahuja, Y Zong, A Sisk, **J Calais**, R Reiter, S Raman
In-depth analysis of PSMA PET/CT and mpMRI discrepancies in prostate cancer detection with histopathology gold standard.
EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
168. L. Djaileb, W. Armstrong, D. Thompson, A. Gafita, A. Farolfi, T. Grogan, M. Cooperberg, P. Carroll, S. Washington, R. Reiter, J. Czernin, H. Thomas, **J. Calais**
Pre-surgical 68Ga-PSMA-11 PET for biochemical recurrence risk assessment: a surrogate of Pelvic Lymph Node Dissection? Follow-up analysis of a Multicenter Prospective Phase 3 Imaging Trial.
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169. A. Farolfi, W. Armstrong, L. Djaileb, A. Gafita, M. Hotta, M. Auerbach, L. Unterrainer, WP Fendler, M. Rettig, M. Eiber, M. Hofman, B. Hadaschik, K. Herrmann, J. Czernin, **J. Calais**, M. Benz
Inter-institutional differences and common ground in 177Lu-PSMA radionuclide therapy: International survey in 95 theranostic centers
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170. R. Seifert, L. Emmett, K. Herrmann, B. Hadaschik, **J. Calais**, S. Fanti, TA Hope, M. S. Hofman, M. Eiber, W. P. Fendler
The Updated Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE V2.0) Framework for Standardized Reporting of PSMA-PET
EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
171. I. Sonni, A. Gafita, RM Alano, S. Lira, L. Unterrainer, J. Shen, A. Drakaki, T. Grogan, MB Rettig, J. Czernin, **J. Calais**
Effects of novel androgen receptor signaling inhibitors on PSMA PET signal intensity in patients with castrate resistant prostate cancer: a prospective exploratory serial imaging study
EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
172. P. Jeanjean, S. Kwock, T. Cloughesy, **J. Calais**, J. Czernin, G. Carlucci, D. Nathanson, C. Mona, E. Besserer-Offroy
Radioligand Therapy in GBM: Fibroblast Activation Protein (FAP) Promises
EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine

173. **Z. Ells**, L. Unterrainer, D. Sennung, R. Alano, K. Booker, C. Felix, A. Daley, A. Farolfi, J. Czernin, M. Dahlbom, A. Kishan, **J. Calais**
 Dosimetry estimates of ¹⁷⁷Lu-PNT2002 in oligorecurrent prostate cancer: preliminary dosimetry results from a randomized phase 2 trial (LUNAR)
 EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
174. **L. Unterrainer**, TA Hope, H. Ndlovu, F. Barbato, W. P. Fendler, K. Herrmann, M. Sathekge, J. Czernin, **J. Calais**
 From CHARTED low- and high-volume disease to PSMA PET imaging volume in mHSPC patients: an international multicenter retrospective study
 EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
175. **A. Gafita**, R. Alano, M. Rettig, J. Shen, W. Armstrong, T. R. Grogan, S. Liu, M. R. Benz, J. Czernin, **J. Calais**
 Head-to-head comparison of ⁶⁸Ga-PSMA-11 PET with ^{99m}Tc-MDP bone scan for detection of bone disease in prostate cancer patients with biochemical progression during ADT: a single center prospective study
 EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
176. **A. Gafita**, L. Djaileb, I. Rauscher, WP Fendler, B. Hadaschik, J. Czernin, K. Herrmann, SP Rowe, **J. Calais**, M. Rettig, M. Eiber, M. Weber, M. R. Benz, A. Farolfi;
 Assessment of Response Evaluation Criteria in PSMA PET/CT (RECIP 1.0) in Metastatic Castration-Resistant Prostate Cancer
 EANM 2023 Vienna - Annual Congress of the European Association of Nuclear Medicine
177. **J. Nikitas**, JA Proudfoot, E Davicioni, **J. Calais**, H Nagar, A Kishan
 Predictive Value of Genomic Classifier Scores and Transcriptomic Data for Prostate Cancer Distant Metastasis Risk: a multicenter retrospective study
 ASTRO 2023 San Diego - Annual Meeting of the American Society for Radiation Oncology
178. **EG Selles**, JD Subiela, A Maldonado, F Lopez, BS Moreno, BD Delgado León, V Gomez Dos Santos, JA Ovide, LE Ortega Polledo, D Gonzalez, F Guerrero, FJ Burgos Revilla, A Kishan, **J. Calais**, F Counago.
 Clinical usefulness of PSMA PET/CT imaging in patients with suspected recurrence of prostate cancer after primary RT with PSA below the Phoenix criteria threshold: Systematic review and meta-analysis.
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 PSMA PET Guided Salvage Radiotherapy Among Prostate Cancer Patients in the Post-Prostatectomy Setting: A Single Center Post-Hoc Analysis.
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180. **L. Unterrainer**, TA Hope, W. P. Fendler, H. Ndlovu, F. Barbato, M. Sathekge, K. Herrmann, J. Czernin, **J. Calais**
 Low- and high-volume disease in mHSPC: From CHARTED to PSMA PET
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 Molecular correlates with PSMA expression in primary prostate cancer
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Pre-surgical 68Ga-PSMA-11 PET for biochemical recurrence risk assessment: A surrogate of pelvic lymph node dissection? Follow-up analysis of a multicenter prospective phase 3 imaging trial.
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188. LM Gudenkauf, V Murthy, EC. Lam, X Li, L Gardner, ST. Tagawa, AP. Dicker, D Cella, J Czernin, **J Calais**, BD. Gonzalez.
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189. A Gafita, L Djaileb, I Rauscher, WP. Fendler, BA. Hadaschik, SP. Rowe, K Herrmann, **J Calais**, M Rettig, M Eiber, M Weber, MR. Benz, A Farolfi.
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Systemic and tumor-directed therapy for oligorecurrent metastatic prostate cancer (SATURN): Primary endpoint results of a phase II clinical trial.
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191. **J Nikitas**, EC. Lam, KM Booker, WP. Fendler, M Eiber, BA. Hadaschik, K Herrmann, N Hirmas, H Lanzafame, M Stuschke, J Czernin, ML. Steinberg, NG Nickols, AU Kishan, **J Calais**.
Update from the PSMA-dRT trial: A randomized phase III trial of PSMA-PET prior to definitive radiation therapy for unfavorable intermediate-risk or high-risk prostate cancer.
ASCO GU San Francisco 2024 – Genitourinary Cancers Symposium. Abstract 438246
192. WG. Brisbane, MT. Topoozian, **J Calais**, MK. Delfin, L Kwan, SR. Gonzalez, LS. Marks
Can PSMA-targeted prostate biopsy detect cancer when MRI-guided biopsy is negative? PD50-04
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Correlating prostate-specific membrane antigen with molecular pathways in treatment naïve prostate cancer PD42-05
AUA 2024 San Antonio - American Urological Association Annual Meeting
<https://doi.org/10.1097/01.JU.0001008560.54103.65.05>
194. **V Murthy**, A Voter, K Nguyen, M Auerbach, S Caputo, E Ledet, O Akerele, A Moradi Tuchayi, C Lawhn Heath, M Carducci, M Pomper, C Paller, J Czernin, L Solnes, T Hope, O Sartor, **J Calais**, A Gafita
Efficacy and toxicity of 177Lu-PSMA-617 for metastatic castration-resistant prostate cancer in a real-world setting: Results from the U.S. Expanded Access Program and comparisons with phase 3 VISION data.
ASCO Chicago 2024 - American Society of Clinical Oncology Annual Meeting

195. **Z Ells**, T Grogan, J Czernin, M Dahlbom, **J Calais**
 Dosimetry of Lutetium-177 PSMA-targeted radiopharmaceutical therapies for prostate cancer patients: A comparative systematic review and meta-analysis.
 ASCO Chicago 2024- American Society of Clinical Oncology Annual Meeting
196. **V Murthy**, O Lokre, T Perk, P Thin, K Nguyen, L Chen, A Gafita, J Czernin, **J Calais**
 Exploring the prognostic value of the TRAQinform Profile applied to end-of-treatment PSMA PET/CT in patients with mCRPC and treated with 177Lu-PSMA radioligand therapy: A retrospective, single-center analysis.
 ASCO Chicago 2024 - American Society of Clinical Oncology Annual Meeting
197. **J Nikitas**, AC Castellanos Rieger, A Farolfi, AU Kishan, NG Nickols, ML Steinberg, J Czernin, **J Calais**
 Prostate-specific membrane antigen PET/CT-guided, metastasis-directed radiotherapy for oligometastatic castration-resistant prostate cancer.
 ASCO Chicago 2024 - American Society of Clinical Oncology Annual Meeting
198. **V Murthy**, O Lokre, T Perk, L Chen, P Thin, K Nguyen, S Lira, R Alano, A Gafita, J Czernin, **J Calais**
 Baseline PSMA PET/CT as a predictive biomarker for toxicity and patient-reported outcomes in mCRPC patients undergoing 177Lu-PSMA radioligand therapy.
 ASCO Chicago 2024 - American Society of Clinical Oncology Annual Meeting
199. **A Holzgreve**, A Delker, Z Ells, J Brosch-Lenz, S Zhu, S Lira, J Nikitas, T Grogan, D Elashoff, L Unterrainer, M Dahlbom, M Auerbach, J Czernin, **J Calais**
 A randomized phase 2 trial in progress of flexible and extended dosing of 177Lu-PSMA-617 molecular radioligand therapy in mCRPC (FLEX-MRT).
 ASCO Chicago 2024 - American Society of Clinical Oncology Annual Meeting
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200. **Z Ells**, T Grogan, J Czernin, M Dahlbom, **J Calais**
 Dosimetry of Lutetium-177 PSMA-targeted radiopharmaceutical therapies for prostate cancer patients: a comparative systematic review and meta-analysis
 SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
201. **J Hong**, **J Calais**, M Benz, M Auerbach, A Salavati
 Comparative analysis of large language models: ChatGPT and Google Bard answer non-expert questions related to the diagnostic and therapeutic applications of prostate-specific membrane antigen (PSMA) in patients with prostate cancer
 SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
202. **J Nikitas**, AC Castellanos Rieger, A Farolfi, AU Kishan, NG Nickols, ML Steinberg, J Czernin, **J Calais**
 Prostate-Specific Membrane Antigen PET/CT-Guided, Metastasis-Directed Radiotherapy for Oligometastatic Castration-Resistant Prostate Cancer
 SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
203. **V Murthy**, O Lokre, T Perk, P Thin, K Nguyen, L Chen, A Gafita, J Czernin, **J Calais**
 Exploring the Prognostic Value of Machine Learning Models Applied to End-of-Treatment PSMA PET/CT in mCRPC Patients Treated with 177Lu-PSMA Radioligand Therapy Using the TRAQinform Profile: A Retrospective, Single-Center Analysis
 SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
204. **M Hotta**, G Kim, V Rerkpichaisuth, G Fishbein, J Czernin, E Volkmann, S Weigt, **J Calais**
 Correlation of FAPI PET signal with immunohistochemistry in explanted lung tissue from transplanted patients with refractory interstitial lung diseases: preliminary results of a prospective exploratory study
 SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
+++ General Clinical Specialties Poster Award Winner, 2nd place +++
205. **S Esfahani**, M Morris, O Sartor, M Frydenberg, S Fanti, **J Calais**, N Vapiwala
 Standardized Template for Clinical Reporting PSMA PET/CT Scans
 SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting

206. **Z Ells**, V Ludwig, A Weiner, C Meyer, D Sennung, G Carlucci, A Farolfi, J Czernin, M Dahlbom, R Reiter, **J Calais**
99mTc-PSMA-I&S radioguided salvage lymphadenectomy for prostate cancer: preliminary clinical results from a prospective trial
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207. **V Murthy**, O Lokre, T Perk, L Chen, P Thin, K Nguyen, S Lira, R Alano, A Gafita, J Czernin, **J Calais**
Baseline PSMA PET/CT as a Predictive Biomarker for Hematologic Toxicity and Patient-Reported Outcomes in mCRPC Patients Undergoing 177Lu-PSMA Radioligand Therapy
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208. J Zahner, A Delker, A Holzgreve, M Unterrainer, Z Ells, M Tiling, G Sheikh, M Zacherl, E Berg, C Aydogdu, SC Kunte, P Bartenstein, G Böning, **J Calais**, C Stief, J Casuscelli, L Unterrainer
Influence of androgen receptor signaling inhibitors on absorbed doses in mCRPC patients undergoing 177Lu-PSMA-617 therapy: First dosimetry results
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Update from the PSMA-dRT trial: A randomized phase III trial of PSMA-PET/CT prior to definitive radiation therapy for unfavorable intermediate-risk or high-risk prostate cancer
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210. **A Holzgreve**, A Delker, Z Ells, J Brosch-Lenz, S Zhu, S Lira, J Nikitas, T Grogan, D Elashoff, L Unterrainer, M Dahlbom, M Auerbach, J Czernin, **J Calais**
Clinical trial protocol: A randomized phase 2 trial of FLEXible and extended dosing of 177Lu-PSMA-617 Molecular Radioligand Therapy (FLEX-MRT)
SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
211. L Valle, E Felker, V Ludwig, **J Calais**, L Marks, W Brisbane, S Raman, R Reiter, M Rettig, J Shen, J Czernin, M Steinberg, N Nickols, A Chang, P Boutros, H Ye, M Hotta, RR Huang, A Kishan
Comparison of MRI and PSMA PET with histopathology in patients with suspected Locally Radiorecurrent Prostate Cancer: a single center retrospective analysis
SNMMI Toronto 2024 - Society of Nuclear Medicine and Molecular Imaging Annual Meeting
212. **V Murthy**, A Voter, K Nguyen, M Auerbach, S Caputo, E Ledet, O Akerele, A Moradi Tuchayi, C Lawhn Heath, M Carducci, M Pomper, C Paller, J Czernin, L Solnes, T Hope, O Sartor, **J Calais**, A Gafita
Efficacy and toxicity of 177Lu-PSMA-617 for metastatic castration-resistant prostate cancer in a real-world setting: Results from the U.S. Expanded Access Program and comparison with phase 3 VISION data
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213. EY. Yu, V Narayan, G Esposito, R Szmulewitz, Y Lu, M Lilly, **J Calais**, G Bratslavsky, M Vasanaawala, G Ulaner, F Pouliot, D David Laidley, N Fleshner, F Saad, JC Provost, I Teslenko, M Dionne, A Koo, S Alam, VA. DiPippo, N Kishore Rawat, Y Menda
A phase 2 trial of prostate-specific membrane antigen (PSMA)-targeted radioligand therapy with 131I-LNTH-1095 plus enzalutamide vs enzalutamide monotherapy in chemotherapy-naïve patients whose piflufolastat F 18-avid metastatic castration-resistant prostate cancer progressed on abiraterone: ARROW
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214. O Sartor, Di Maria Jiang, M Smoragiewicz, MR. Zibelman, A Flechon, G El-Haddad, G Abikhzer, F Saad, RF. Tutrone, ST. Tagawa, U Metsler, **J Calais**, AR Hansen, W Wu, J Jensen, C Trieu, NE. Fleshner, I Teslenko, JC Provost, KN. Chi, on behalf of the SPLASH Trial Investigators.
SPLASH study primary endpoint and overall survival (OS) analysis: First results from a randomized, phase III, pivotal trial of 177Lu-PNT2002 radioligand therapy in PSMA-positive mCRPC following progression on an androgen-receptor pathway inhibitor (ARPI)
ESMO Barcelona 2024 - Annual Congress of the European Society for Medical Oncology

Titre : Recherche Clinique et Translationnelle en Radiotheranostique

Mots clés : cancer; radiopharmaceutique; TEP/TDM; TEMP/TDM; radiothérapie; imagerie médicale; essai clinique;

La radiothéranostique peut être défini comme l'utilisation combinée d'un agent radiopharmaceutique d'imagerie (radiotracer) et d'un agent radiopharmaceutique thérapeutique (radiothérapie interne vectorisée) ayant la même cible moléculaire. L'imagerie ciblée permet d'estimer la biodistribution individualisée du traitement radiopharmaceutique pour chaque patient. Suite au succès de la translation clinique et des autorisations aux Etats-Unis et en Europe des thérapies radiopharmaceutiques ciblant le SSTR (Lu177-DOTATATE) pour les tumeurs neuroendocrines et le PSMA (Lu177-PSMA-617) pour le cancer de la prostate métastatique, le marché des radiopharmaceutiques est en plein essor. Profitant de l'essor de la radiothéranostique, j'ai eu l'occasion de diriger en tant qu'investigateur principal de nombreuses études de recherche clinique et translationnelle à l'Université de Californie à Los Angeles (UCLA) (de la phase 0 à la phase 3) en utilisant l'imagerie et/ou la thérapie aux radionucléides.

Ce manuscrit de l'Habilitation à Diriger des Recherches (HDR) vise à présenter mes contributions scientifiques depuis mon arrivée à UCLA en 2016 à travers une sélection de publications dont j'ai été le superviseur. Pour ce manuscrit, ceux-ci ont été arbitrairement regroupés en 3 sujets de recherche : (1) Translation clinique de l'imagerie TEP ciblant FAP; (2) Essais cliniques randomisés d'imagerie TEP ciblant le PSMA; (3) Explorer au-delà de l'utilisation approuvée des radiothéranostique ciblant le PSMA.

Il existe de nombreuses perspectives de recherche pour améliorer l'utilisation des radiothéranostiques ciblant FAP et PSMA. De multiples autres cibles moléculaires (CA-IX, SSTR, GRPR, GPC3) et applications (dosimétrie, intelligence artificielle) sont à l'étude et de nombreux essais cliniques sont actuellement menés (phase 0 à phase 3). Les grands groupes pharmaceutiques investissent massivement dans le marché des radiopharmaceutiques. L'exploitation de ce dynamisme de l'industrie et de ce flux d'investissements peut permettre à la communauté de la médecine nucléaire d'offrir aux patients atteints de cancer et à leurs médecins un maximum de techniques radiopharmaceutiques innovantes.

Title : Clinical and Translational Research in Radiotheranostics

Keywords : cancer; radiopharmaceutical; PET/CT; SPECT/CT; radiotherapy; medical imaging; clinical trial;

Radiotheranostics can be defined as the combined use of a radiopharmaceutical imaging agent (radiotracer) and a radiopharmaceutical therapeutic agent having the same molecular target. Targeted imaging enables the estimation of the individualized biodistribution of the radiopharmaceutical drug for each patient. Following the successful clinical translation and approvals in the United States and in Europe of radiopharmaceutical therapies targeting SSTR (Lu177-DOTATATE) for neuroendocrine tumors and more importantly PSMA (Lu177-PSMA-617) for metastatic prostate cancer, the radiopharmaceutical market is booming. Taking advantage of the rise of radiotheranostics, I had the opportunity to lead as principal investigator numerous clinical and translational research studies at the University of California, Los Angeles (UCLA) (from phase 0 to phase 3) using targeted radionuclide imaging and/or therapy.

This manuscript of Accreditation to Supervise Research (Habilitation à Diriger des Recherches (HDR)) aims at presenting my scientific contributions since joining UCLA in 2016 with a focus on selected publications in which I served as supervisor. For this manuscript, these were arbitrarily grouped in 3 research topics: (1) Clinical Translation of FAP-PET imaging; (2) Randomized Trials of PSMA PET imaging trials powered for clinical outcome; (3) Exploring Beyond the approved use of PSMA theranostics.

There are many research perspectives for improving the use of FAP-targeted and PSMA-targeted radiotheranostics. Multiple other molecular targets (CA-IX, SSTR, GRPR, GPC3) and applications (dosimetry, artificial intelligence) are being studied and numerous clinical trials are currently being conducted (phase 0 to phase 3). There are massive financial investments from major pharmaceutical groups into the radiopharmaceutical market. Leveraging this industry dynamism and flow of investments can enable the nuclear medicine community to offer cancer patients and their doctors a maximum of innovative radiopharmaceutical techniques.