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Théranostique ciblant le PSMA : de la recherche clinique a la norme de soins standards

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PSMA-targeted theranostics: From research to standard-of-care

*Théranostique ciblant le PSMA:
de la recherche clinique à la norme de soins standards*

Thèse de doctorat de l'université Paris-Saclay

Ecole doctorale n°575 : electrical, optical, bio : physics and engineering (EOBE)
Spécialité de doctorat : Physique et imagerie médicale
Graduate School : Sciences de l'ingénierie et des systèmes.
Réfèrent : Faculté des sciences d'Orsay

Thèse préparée au sein de l'unité mixte de recherche
Laboratoire d'Imagerie Translationnelle en Oncologie
(LITO, U1288 Inserm, Institut Curie),
sous la direction d'**Irène Buvat**, directrice de recherche

Thèse soutenue à Paris, le 18 décembre 2023, par

Jeremie CALAIS

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Titre : Théranostique ciblant le PSMA: de la recherche clinique à la norme de soins standard

Mots Clés : Théranostique; PSMA; TEP/TDM; Thérapie par radionucléides; Radiothérapie Moléculaire

Résumé : L'objectif de ce manuscrit de thèse de doctorat par Validation des Acquis de l'Expérience (VAE) est de mettre en évidence les principales études de recherche menées à UCLA qui ont conduit à l'implémentation clinique des techniques théranostiques ciblant le PSMA aux États-Unis. Le manuscrit est divisé en 2 parties: l'imagerie et la thérapie.

Dans la première partie sont fournis les essais pivots d'efficacité diagnostique utilisés pour l'autorisation par la FDA du 68Ga-PSMA-11 (Article #1: Performance diagnostique de la TEP-PSMA pour la localisation de la récurrence du cancer de la prostate: un essai clinique d'imagerie prospective multicentrique de phase 3 (n=635), PMID 30920593; Article #2: Performance diagnostique de la TEP-PSMA pour la détection des métastases ganglionnaires pelviennes avant prostatectomie radicale et curage ganglionnaire pelvien: un essai clinique d'imagerie prospective multicentrique de phase 3 (n=764), PMID 34529005), des études comparatives comparant la TEP-PSMA aux techniques d'imagerie standard (Article #3: TEP/TDM à la 18F-Fluociclovine et au 68Ga-PSMA-11 chez les patients présentant une récurrence biochimique après prostatectomie avec un taux de PSA $\leq 2,0$ ng/ml: un essai d'imagerie comparative prospectif monocentrique (n=50), PMID 31375469; Article #4: Comparaison de la TEP/TDM-PSMA et de l'IRMmp avec référence par histopathologie dans la détection, la localisation intra-prostatique et la détermination de l'extension locale du cancer primitif de la prostate: résultats dans une cohorte monocentrique d'un essai prospectif (n=74), PMID 34649942) et une étude montrant un impact significatif sur la prise en charge (Article #5: Cartographie par TEP/TDM-PSMA de la récurrence biochimique du cancer de la prostate après prostatectomie radicale chez 270 patients avec un taux de PSA < 1,0 ng/ml: Impact sur la planification de la radiothérapie de rattrapage (n=270), PMID 29123013) qui a conduit à un essai randomisé visant à montrer une amélioration des

résultats cliniques grâce à la TEP PSMA (Article #6: Essai randomisé prospectif de phase 3 de radiothérapie de rattrapage du cancer de la prostate guidée par TEP-PSMA [PSMA-SRT] (n=193), PMID 30616601; Article #7: Mise à jour de l'essai PSMA-SRT NCT03582774: un essai randomisé prospectif de phase 3 de radiothérapie de rattrapage du cancer de la prostate guidée par TEP-PSMA (n=193), PMID 33386288).

Dans la deuxième partie sont présentés les résultats du premier essai de phase 2 de la thérapie au 177Lu-PSMA aux USA qui a précédé l'essai VISION (Article #8: Essai prospectif de phase 2 de radiothérapie moléculaire au 177Lu-PSMA-617 pour cancer de la prostate métastatique résistant à la castration (RESIST-PC): Résultats d'efficacité de la cohorte UCLA (n=43), PMID 34016732; Article #9: Tolérance et sécurité de la radiothérapie moléculaire au 177Lu-PSMA-617: résultats de l'essai prospectif multicentrique de phase 2 RESIST-PC NCT03042312 (n=64), PMID 34272322), des études rétrospectives multicentriques visant à affiner les critères de sélection TEP-PSMA (Article #10: Suivi des patients négatifs au PSMA par critères TEP PSMA de l'essai VISION traités par 177Lu-PSMA: une analyse rétrospective multicentrique (n=301), PMID 35273096; Article #11: Ratio tumeur/glande salivaire par TEP-PSMA pour prédire la réponse à la thérapie par 177Lu-PSMA: une étude rétrospective multicentrique internationale (n=237), PMID 36997329; Article #12: Nomogrammes pour prédire les résultats après traitement au 177Lu-PSMA chez les patients atteints d'un cancer de la prostate métastatique résistant à la castration: une étude rétrospective internationale multicentrique (n=270), PMID 34246328) et une revue narrative des mécanismes de résistance à la thérapie au 177Lu-PSMA (Article #13: Prédicteurs de réponse et utilisation dans le monde réel de la radiothérapie moléculaire ciblée du cancer de la prostate: PSMA et au-delà. PMID 35609224).

Title : PSMA-targeted theranostics: from research to standard-of-care

Keywords : Theranostics; PSMA; PET/CT; Radionuclide Therapy; Molecular Radiotherapy.

Abstract : The aim of this manuscript for PhD by Accreditation of Prior Learning is to highlight the key research studies conducted at UCLA which lead to the clinical implementation of PSMA-theranostics in the US. The manuscript is divided in 2 parts: imaging and therapy.

In the first part are provided the pivotal trials of diagnostic efficacy used for the FDA approval of 68Ga-PSMA-11 (Article #1: Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective multicenter single-arm phase 3 clinical trial (n=635), WP Fendler et al. JAMA Oncol 2019 PMID 30920593; Article #2: 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 (n=764), TA Hope et al. JAMA Oncol 2021 PMID 34529005), head-to-head comparison trials comparing PSMA-PET to standard-of-care imaging techniques (Article #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 (n=50), J Calais et al. Lancet Oncol 2019 PMID 31375469; Article #4: 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 (n=74), I Sonni et al. J Nucl Med 2022 PMID 34649942) and a study showing significant impact on management (Article #5: 68Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: impact on salvage radiotherapy planning (n=270), J Calais et al. J Nucl Med 2018 PMID 29123013) that lead to a randomized imaging trial powered for clinical outcome (Article #6: Randomized prospective phase 3 trial of 68Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning

[PSMA-SRT] (n=193), J Calais et al. BMC cancer 2019 PMID 30616601; Article #7: Update from PSMA-SRT Trial NCT03582774: a randomized phase 3 imaging trial of prostate-specific membrane antigen positron emission tomography for salvage radiation therapy for prostate cancer recurrence powered for clinical outcome (n=193), J Calais et al. Eur Urol Focus PMID 33386288).

In the second part are provided the results of the first phase 2 trial of 177Lu-PSMA therapy in the US that preceded the VISION trial (Article #8: Prospective phase 2 trial of PSMA-targeted molecular Radiotherapy with 177Lu-PSMA-617 for metastatic Castration-resistant Prostate Cancer (RESIST-PC): Efficacy results of the UCLA cohort (n=43), J Calais et al. J Nucl Med 2021 PMID 34016732; Article #9: Safety of PSMA-targeted molecular radioligand therapy with 177Lu-PSMA-617: results from the prospective multicenter phase 2 trial RESIST-PC NCT03042312 (n=64), J Calais et al. J Nucl Med 2021 PMID 34272322), multicenter retrospective studies aiming at refining the PSMA-PET selection criteria (Article #10: Outcome of patients with PSMA PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy: a multicenter retrospective analysis (n=301), M Hotta et al. J Nucl Med 2022 PMID 35273096; Article #11: PSMA-PET tumor-to-salivary gland ratio to predict response to 177Lu-PSMA radioligand therapy: an international multicenter retrospective study (n=237), M Hotta et al. J Nucl Med 2023 PMID 36997329; Article #12: Nomograms to predict outcomes after 177Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicenter, retrospective study (n=270), A Gafita et al. Lancet Oncol 2021 PMID 34246328) and a narrative review of the mechanisms of resistance to 177Lu-PSMA therapy (Article #13: Predictors and real-world Use of prostate-specific radioligand therapy: PSMA and Beyond. A Gafita et al. Am Soc Clin Oncol Educ Book 2022 PMID 35609224).

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TABLE OF CONTENTS

Résumé (FRA)	page 2
Abstract (ENG)	page 3
Acknowledgments	page 4
Table of contents	page 5
List of Tables and Figures	page 6
Abbreviations	pages 7-8
Synthèse en Français (FRA)	pages 9-19
Perspectives (FRA)	pages 20-23
Main Manuscript (ENG)	page 24
Introduction	pages 25-31
Part One PSMA-PET imaging	page 32
Article 1: Pivotal study of PSMA-PET for Biochemical recurrence	pages 37-55
Article 2: Pivotal study of PSMA-PET for Primary Staging	pages 56-66
Article 3: Comparison of PSMA-PET vs Fluciclovine PET	pages 67-96
Article 4: Comparison of PSMA-PET vs MRI	pages 97-108
Article 5: PSMA-PET Mapping recurrence after RP for SRT planning	pages 109-121
Article 6: PSMA-SRT trial study protocol	pages 122-134
Article 7: PSMA-SRT trial update	pages 135-139
Part Two PSMA Radionuclide Therapy	page 140
Article 8: RESIST-PC trial Efficacy	pages 143-159
Article 9: RESIST-PC trial Safety	pages 160-175
Article 10: Outcomes of VISION PET screen failure patients	pages 177-183
Article 11: Outcomes of patients after LuPSMA therapy by PSG score	pages 184-216
Article 12: Nomograms for LuPSMA therapy	pages 217-248
Article 13: LuPSMA therapy Resistance mechanisms review	pages 249-268
References	pages 269-273
Serment des Docteurs (FRA)	page 275
Doctors Oath (ENG)	page 275

LIST OF TABLES AND FIGURES

TABLES

<u>Table 1:</u>	page 33
Clinical research studies of PSMA-PET/CT conducted at UCLA since 2016.	
<u>Table 2:</u>	page 142
Clinical studies of PSMA radionuclide therapy conducted at UCLA since 2017.	

FIGURES

<u>Figure 1:</u>	page 25
Prostate cancer stages and progression (<i>Adapted from RJ Rebello et al. Nature Reviews 2021</i>).	
<u>Figure 2:</u>	page 27
PSMA = target for theranostics (<i>Adapted from Maurer T et al, Nat Rev Urol, 2016</i>).	
<u>Figure 3:</u>	page 28
Chemical structures of the main PSMA-targeting small molecules ligands (<i>Adapted from G Capasso et al. European Journal of Medicinal Chemistry, 2024</i>).	
<u>Figure 4:</u>	page 29
Biodistribution of the main PSMA PET ligands (<i>Adapted from Seifert et al. Eur Urol. 2023</i>).	
<u>Figure 5:</u>	page 34
Number of PSMA-PET scans performed at UCLA between 2016 and 2020.	
<u>Figure 6:</u>	page 35
Going from research to an approved and reimbursed procedure. Timeline of the FDA approval of 68Ga-PSMA-11 produced by UCLA and UCSF.	

ABBREVIATIONS

ADT:	Androgen Deprivation Therapy
AE:	Adverse Event
ARSI:	Androgen Receptor Signaling Inhibitor
AUA:	American Urological Association
BCR:	Biochemical Recurrence
BICR:	Blinded Independent Central Reader
CMC:	Chemistry Manufacturing and Controls
CRPCm:	Cancer de la prostate métastatique résistant à la castration
CT:	Computed tomography
CTCAE:	Common Terminology Criteria for Adverse Events
CTV:	Clinical Target Volume
dRT :	Definitive Radiotherapy
EAU:	European Association of Urology
ECOG:	Eastern Cooperative Oncology Group Scale
EI:	Effet indésirable
ESMO:	European Society for Medical Oncology
FDA:	United States Food and Drug Administration
FDG:	Fluorodeoxyglucose
FOLH1:	Folate hydrolase 1
GBq:	Gigabecquerel
GCPII:	Glutamate carboxypeptidase II
HAS:	Haute Autorité de Santé
HR:	Hazard ratio
IAANG:	Inhibiteur de l'axe androgénique de nouvelle génération
IC _{95%} :	Intervalle de confiance à 95%
IIT:	Investigator Initiated Trial
IND:	Investigational New Drug
IQR:	Interquartile range
IRMmp:	Imagerie par Résonance Magnétique Multiparamétrique
JAMA:	Journal of American Medical Association
LDH:	Lactate dehydrogenase
mCRPC:	Metastatic resistant prostate cancer
MIP:	Maximum intensity Projection
mL:	Millilitre
mpMRI:	Multiparametric Magnetic Resonance Imaging
MSG:	Monosodium Glutamate
NAAG:	N-acetylaspartylglutamate
NCCN:	National Comprehensive Cancer Network
NDA:	New Drug Application
ng:	Nanogramme
NPV:	Negative Predictive Value
OR:	Odds Ratio
OS:	Overall survival
PARP:	Poly (ADP-ribose) polymerase
PET:	Positron emission tomography
PFS:	Progression free survival
PPV:	Positive Predictive Value
PSA:	Prostate Specific Antigen
PSMA:	Prostate Specific Membrane Antigen
PSG:	PSMA to salivary glands ratio
RNT:	Radionuclide therapy

RP:	Radical Prostatectomy
ROI:	Region of interest
SD:	Standard deviation
SBRT:	Stereotactic Body Radiation Therapy
Se:	Sensitivity
SF:	Screen failure
SG:	Survie globale
SNMMI:	Society of Nuclear Medicine and Molecular Imaging
Spe:	Specificity
SPECT:	Single-photon emission computed tomography
SRT:	Salvage Radiotherapy
SUV:	Standardized uptake value
TEP:	Tomographie par émission de positons
TDM:	Tomodensitométrie
UCSF:	University of California San Francisco
UCLA:	University of California Los Angeles
VAE:	Validation des Acquis de l'Expérience
VOI :	Volume of Interest
VPP:	Valeur Prédictive Positive

SYNTHESE EN FRANÇAIS

Introduction

La théranostique est l'utilisation combinée d'un agent d'imagerie et d'un agent thérapeutique ayant la même cible moléculaire. L'antigène membranaire spécifique de la prostate (PSMA) est fortement surexprimé par la plupart (90%) des cancers de la prostate. Étant donné que 95 % de la molécule de PSMA est extracellulaire, elle est accessible pour la liaison d'anticorps ou de ligands de faible poids moléculaire. Les niveaux élevés de surexpression du PSMA dans le cancer de la prostate font du PSMA une excellente cible théranostique pour le cancer de la prostate : rapport signal sur bruit élevé pour l'imagerie et indice thérapeutique élevé pour le traitement. Entre 2015 et 2020, plusieurs molécules ciblant le PSMA ont été développées et testées pour des applications d'imagerie et de thérapie en médecine nucléaire. La tomographie par émission de positrons couplée à la tomodensitométrie ciblant le PSMA (TEP/TDM-PSMA) et le traitement par radiothérapie moléculaire ciblant le PSMA sont depuis devenus la norme de soins depuis 2020 et sont inclus dans les recommandations de pratiques cliniques internationales.

University of California Los Angeles (UCLA) a été un site pionnier pour les premiers essais cliniques de théranostique ciblant le PSMA aux États-Unis. La TEP-PSMA et la radiothérapie moléculaire ciblant le PSMA sont maintenant utilisées en routine clinique à UCLA chez les patients ayant un cancer de la prostate. L'objectif de ce manuscrit de Thèse de doctorat par Validation des Acquis de l'Expérience (VAE) est de mettre en évidence les études clés menées à UCLA qui ont eu un impact majeur sur l'implémentation clinique de la théranostique ciblant le PSMA aux États-Unis. Le manuscrit est divisé en 2 parties : l'imagerie TEP-PSMA et la thérapie par radionucléides ciblant le PSMA.

Première partie : Imagerie TEP-PSMA

Le premier essai clinique de TEP-PSMA approuvé par la FDA (Food and Drug Administration) aux USA en 2016 a été conçu pour la localisation de la récurrence biochimique du cancer de la prostate après traitement initial. En 2019, UCLA et University of California San Francisco (UCSF) ont soumis conjointement une demande d'autorisation de mise sur le marché (NDA : New Drug Application). Et en décembre 2020, la FDA a approuvé le Gallium-68 PSMA-11 (Ga-68PSMA-11) manufacturé à UCLA et à UCSF (1). Il s'agissait du premier radiotraceur TEP ciblant le PSMA à être approuvé aux USA. Les indications approuvées sont le bilan initial des patients ayant un cancer de la prostate candidats à un traitement initial potentiellement curatif par chirurgie ou radiothérapie chez qui l'on soupçonne des métastases et les patients ayant une suspicion de récurrence après un traitement initial sur la base d'un taux sérique élevé d'antigène prostatique spécifique (PSA). Deux études pivotales démontrant les performances diagnostiques de la TEP/TDM-PSMA ont été utilisées pour la soumission du NDA : une pour l'indication de récurrence biochimique et une pour l'indication de stadification initiale.

Étude pivotale de la TEP-PSMA pour la récurrence biochimique (WP Fendler et al. JAMA Oncol 2019 (2))

Dans cet essai prospectif mono-bras non-aveugle mené à UCSF et à UCLA, 635 patients atteints d'un cancer de la prostate biochimiquement récidivant après prostatectomie radicale (n=262, 41%), radiothérapie définitive (n=169, 27%) ou les deux (n=204, 32%) ont réalisé une TEP au 68Ga-PSMA-11. La présence de lésions suspectes de cancer de la prostate a été analysée en aveugle par patient et par région par 3 spécialistes en imagerie TEP. Les lésions suspectes ont été validées par référence histopathologique et référence composite. Les critères d'évaluation étaient la valeur prédictive positive (VPP), le taux de détection, la reproductibilité entre lecteurs.

Au total, 635 patients ont été recrutés avec un âge médian de 69 ans (44-95 ans). Par patient, la VPP était de 0,84 (IC_{95%} 0,75-0,90) par validation histopathologique (critère d'évaluation principal, n=87) et de 0,92 (IC_{95%} 0,88-0,95) par référence composite (n=217). La TEP-PSMA a localisé une lésion de cancer de la prostate récidivant chez 475 des 635 patients (75%). Les taux de détection (i.e. de positivité) augmentaient significativement avec le taux de PSA : 38% pour <0,5 ng/mL (n=136), 57% pour 0,5 à <1,0 ng/mL (n=79), 84% pour 1,0 à <2,0 ng/mL (n=89), 86% pour 2,0 à <5,0 ng/mL (n=158) et 97% pour >5,0 ng/mL (n=173, P<0,001). La reproductibilité entre lecteurs était substantielle (Fleiss κ , 0,65-0,78). Les traitements ablatifs guidés par TEP-PSMA ont entraîné une baisse de PSA de ≥ 50 % chez 31/39 patients (80%).

Nous avons établi des taux de détection, une valeur prédictive positive, une reproductibilité inter-lecteurs élevés de la TEP au 68Ga-PSMA-11 pour la localisation du cancer de la prostate biochimiquement récidivant dans un essai multicentrique prospectif. Le critère d'évaluation principal a été atteint : la TEP au 68Ga-PSMA-11 a démontré une valeur prédictive positive de 84 % à 92 % avec un taux de détection global de 75 %.

Étude pivotale de la TEP-PSMA pour la stadification initiale (TA Hope et al. JAMA Oncol 2021 (3))

Dans cet essai d'imagerie prospectif multicentrique non-aveugle mono-bras mené à UCSF et à UCLA, 764 patients atteints d'un cancer de la prostate de risque intermédiaire ou élevé (critères du NCCN) et candidat à une prostatectomie radicale ont réalisé une TEP au 68Ga-PSMA-11 pour bilan initial de décembre 2015 à décembre 2019. Le critère d'évaluation principal était la sensibilité et la spécificité de la détection des métastases ganglionnaires pelviennes en comparaison à la référence par histopathologie, par patient et par région. Chaque examen TEP a été lu en aveugle par 3 spécialistes en imagerie TEP indépendants, et une règle de majorité a été utilisée pour l'analyse centrale.

Au total, 764 patients ont été recrutés (âge médian [écart interquartile IQR], 69 [63-73] ans) et 277 des 764 (36%) ont ensuite subi une prostatectomie avec curage ganglionnaire (cohorte d'analyse d'efficacité) après la TEP-PSMA. D'après les comptes-rendus cliniques d'histopathologie, 75 des 277 patients (27%) présentaient des métastases ganglionnaires pelviennes. La TEP au 68Ga-PSMA-11 a détecté des lésions suspectes d'extension ganglionnaire pelvienne, ganglionnaire extra-pelvienne et métastatique osseuse chez 40/277 (14%), 2/277 (1%) et 7/277 (3%) des patients, respectivement. La sensibilité, la spécificité, la VPP et la VPN pour la détection des métastases ganglionnaires pelviennes étaient respectivement de 0,40 (IC_{95%} 0,34-0,46), 0,95

(IC_{95%} 0,92-0,97), 0,75 (IC_{95%} 0,70-0,80) et 0,81 (IC_{95%} 0,76-0,85).

L'étude était conduite en non-aveugle et les résultats de la TEP-PSMA ont été utilisés pour la décision de traitement. Ainsi, les patients avec une maladie plus étendue visualisée par TEP-PSMA ont subi des traitements autres que la prostatectomie radicale, ce qui représente un impact majeur de l'examen sur les soins aux patients. Sur les 764 patients, 487 (64%) n'ont pas subi de prostatectomie, dont 108 qui ont été perdus de vue. Les patients suivis ont plutôt subi une radiothérapie (262 sur 379 [69%]), un traitement systémique (82 sur 379 [22%]), une surveillance (16 sur 379 [4%]) ou d'autres traitements (19 sur 379 [5%]).

Dans cet essai d'imagerie diagnostique prospectif multicentrique de phase 3 mené chez 277 patients en bilan initial d'un cancer de la prostate à risque intermédiaire ou élevé, la sensibilité et la spécificité par patient de la TEP-PSMA de la détection des métastases ganglionnaires pelviennes en comparaison à l'histopathologie étaient respectivement de 0,40 et 0,95.

Comparaison avec la TEP à la fluciclovine (J Calais et al. Lancet Oncol. 2019 (4))

Nous avons comparé la nouvelle technique d'imagerie TEP-PSMA à la technique de référence aux USA pour la localisation des récidives biochimiques (TEP à la F18-Fluciclovine, AXUMIN®, Blue Earth Diagnostics). La F18-fluciclovine est un traceur métabolique TEP à base d'acides aminés qui a été approuvé par la FDA en 2016 et est recommandé par le NCCN.

Il s'agissait d'une étude comparative prospective, monocentrique, non-aveugle et à un seul bras, réalisée à UCLA. Les patients présentant une récidive biochimique du cancer de la prostate après une prostatectomie radicale et des taux de PSA allant de 0,2 à 2,0 ng/mL sans traitement de rattrapage préalable étaient éligibles. Les patients ont réalisé une TEP-fluciclovine (test de référence) et une TEP-PSMA (test d'index) dans un intervalle de 15 jours maximum. Le taux de détection de la récidive biochimique par patient et par région anatomique était le critère d'évaluation principal. L'analyse de puissance statistique a démontré qu'un échantillon de 50 patients était nécessaire pour montrer une différence de 22% des taux de détection en faveur de la TEP-PSMA (test de supériorité). Chaque examen TEP a été lu en aveugle par 3 spécialistes en imagerie TEP indépendants, et une règle de majorité a été utilisée pour l'analyse centrale.

Entre février 2018 et septembre 2018, 143 patients ont été considérés pour inclusion, et 50 ont été recrutés dans l'étude. Le suivi médian était de 8 mois (IQR 7-9). Les taux de détection par patient étaient significativement plus faibles avec la TEP-Fluciclovine (13/50 [26%; IC_{95%} 15-40]) qu'avec la TEP-PSMA (28/50 [56%; IC_{95%} 41-70]), avec un odds ratio (OR) de 4,8 (IC_{95%} 1,6-19,2; p=0,0026). Les taux de détection dans la région des ganglions pelviens étaient significativement plus faibles avec la TEP-Fluciclovine (4/50 [8%; IC_{95%} 2-19]) qu'avec la TEP-PSMA (15/50 [30%; IC_{95%} 18-45]), OR 12,0 [IC_{95%} 1,8-513,0], p=0,0034; ainsi que pour toute lésion extra-pelvienne (0/50 [0%; IC_{95%} 0-6]) vs 8/50 [16%; IC_{95%} 7-29]; OR non estimable [IC_{95%} non estimable], p=0,0078).

Les résultats de cette comparaison prospective ont fourni des preuves en faveur de l'utilisation préférentielle de la TEP-PSMA pour la prise en charge des patients présentant une récidive biochimique avec de faibles

concentrations de PSA ($\leq 2,0$ ng/mL). L'imagerie TEP-PSMA est désormais incluse dans les recommandations d'experts internationales et nationales (exemple : NCCN, AUA, EAU, ESMO, HAS).

Comparaison avec l'IRM (I Sonni et al. J Nucl Med. 2022 (5))

L'IRM multiparamétrique (IRMmp) est la technique d'imagerie de référence pour la détection et l'évaluation de l'extension intra-prostatique du cancer de la prostate. Le rôle de la TEP/TDM-PSMA par rapport à l'IRMmp dans l'évaluation des foyers de cancer intra-prostatique n'est pas bien défini. L'objectif de notre étude était de comparer les performances diagnostiques de la TEP/TDM-PSMA, de l'IRMmp et de la fusion de l'IRMmp+TEP/TDM-PSMA dans la détection, la localisation intra-prostatique et la détermination de l'extension locale du cancer primitif de la prostate, en utilisant 3 spécialistes en imagerie masqués et indépendants pour chaque modalité, et avec histopathologie comme standard de référence. Cette étude a été menée sur une sous-cohorte de patients inscrits à l'essai pivot de UCLA soumis à la FDA. Les patients ont été inclus s'ils avaient réalisé à UCLA un bilan initial avec TEP/TDM-PSMA et IRMmp, et avaient ensuite subi une prostatectomie radicale à UCLA.

L'analyse finale a inclus 74 patients ayant un cancer de la prostate (14 [19%] à risque NCCN intermédiaire et 60 [81%] à risque élevé). Le taux de détection (analyse lésionnelle) était de 85 %, 83 % et 87 % pour la TEP/TDM-PSMA, l'IRMmp et la fusion TEP/TDM-PSMA+IRMm, respectivement. La différence de l'aire sous la courbe entre la fusion TEP/TDM-PSMA+IRMm et les 2 modalités d'imagerie seules pour la délimitation de la localisation tumorale (analyse segmentaire) était statistiquement significative ($P < 0,001$) mais pas entre la TEP/TDM-PSMA et l'IRMmp ($P = 0,093$). L'IRMmp a surpassé la TEP/TDM-PSMA dans la détection de l'extension extra-capsulaire ($P = 0,002$) et de l'invasion des vésicules séminales ($P = 0,001$). Dans l'analyse segmentaire, une fiabilité modérée a été observée chez les lecteurs de TEP PSMA et d'IRMmp par coefficients de corrélation intra-classe (0,53 à 0,64). Pour l'évaluation de la détection de l'extension extra-capsulaire et de l'invasion des vésicules séminales, une fiabilité médiocre a été constatée chez les lecteurs de TEP/TDM-PSMA et une fiabilité faible à modérée a été constatée chez les lecteurs d'IRMmp.

La TEP/TDM-PSMA et l'IRMmp ont une précision similaire dans la détection et la localisation intra-prostatique des foyers de cancer de la prostate. L'IRMmp était plus performante dans l'identification de l'extension extra-capsulaire et de l'invasion des vésicules séminales. L'utilisation combinée des 2 modalités conduit à une meilleure localisation du cancer, mais n'améliore pas significativement les taux de détection. Dans la mesure du possible, la TEP/IRM-PSMA ou la fusion de la TEP/TDM-PSMA et de l'IRMmp devrait être utilisée car elle améliore la délimitation de l'étendue de la tumeur.

Impact de la TEP-PSMA sur la radiothérapie de rattrapage (J Calais et al. J Nucl Med 2018 (6))

Nous avons évalué l'impact de la TEP/TDM-PSMA sur la prise en charge des patients ayant un cancer de la prostate à l'aide d'une cohorte de patients éligibles à la radiothérapie de rattrapage.

Les contours des volumes cibles pour la radiothérapie de rattrapage du cancer de la prostate récidivant après

une prostatectomie radicale sont généralement établis en l'absence de récurrence visible de la maladie. La TEP/TDM-PSMA peut détecter les lésions de récurrence avec une sensibilité supérieure à celle de l'imagerie standard à des taux de PSA faibles, quand la radiothérapie de rattrapage est indiquée. Notre objectif était de cartographier par TEP/TDM-PSMA les sites de récurrence biochimique après une prostatectomie radicale et de déterminer la fréquence à laquelle les volumes cibles anatomo-cliniques (CTV) ne couvrent pas les sites de récurrence définis par TEP/TDM-PSMA.

Cette analyse rétrospective multicentrique inclut 270 patients ayant réalisé une TEP/TDM-PSMA dans 4 établissements pour récurrence biochimique après prostatectomie, sans radiothérapie préalable, avec un taux de PSA <1 ng/mL. Les CTV incluant la loge prostatique et les aires ganglionnaires pelviennes ont été délimités sur TDM par un radiothérapeute masqué à la TEP-PSMA. Les images TEP/TDM-PSMA ont été analysées par un médecin nucléaire. Les investigateurs ont évalué le recouvrement par les CTV des lésions détectées par TEP/TDM-PSMA.

Le taux médian de PSA au moment de la TEP/TDM-PSMA était de 0,48 ng/mL (0,03 à 1 ng/mL). 132 des 270 patients (49%) ont eu au moins une lésion détectée par TEP/TDM-PSMA. 52 des 270 (19%) présentaient au moins une lésion détectée par TEP/TDM-PSMA qui n'était pas couverte par les CTV, 33 des 270 (12%) présentaient des lésions extra-pelviennes, et 19 sur 270 (7%) présentaient des lésions intra-pelviennes non couvertes par les CTV. Les 2 localisations de lésions détectées par TEP/TDM-PSMA les plus courantes non couvertes par les CTV étaient les métastases osseuses (23/52, 44%) et les ganglions péri-rectaux (16/52, 31%). Dans cette étude rétrospective, la TEP/TDM-PSMA a identifié des sites de récurrence non couverts par les CTV chez 52 des 270 patients (19%) avec une récurrence biochimique et un taux de PSA <1,0 ng/mL. Cette étude suggère un impact potentiel majeur de la TEP/TDM-PSMA sur la planification de la radiothérapie de rattrapage. Nous avons émis l'hypothèse que cet impact majeur de la TEP/TDM-PSMA sur la sélection des patients et la planification de la radiothérapie de rattrapage peut améliorer les résultats de la radiothérapie de rattrapage. Ceci a motivé le lancement d'un essai prospectif randomisé.

Essai randomisé de radiothérapie de rattrapage guidée par TEP/TDM-PSMA (J Calais et al. BMC Cancer 2019 (7)).

L'objectif de l'essai clinique PSMA-SRT NCT03582774 est d'évaluer le taux de réussite de la radiothérapie de rattrapage pour récurrence après prostatectomie avec et sans planification basée sur la TEP/TDM-PSMA.

193 patients ont été randomisés pour radiothérapie de rattrapage sans TEP/TDM-PSMA (bras témoin, n=90) ou pour radiothérapie de rattrapage avec TEP/TDM-PSMA (bras expérimental, n=103). Le critère d'évaluation principal est le taux de réussite de la radiothérapie de rattrapage, mesuré par le taux de survie sans progression biochimique après le début de la radiothérapie de rattrapage. La progression biochimique est définie par un taux de PSA >0,2 ng/mL et en augmentation. Le rapport de randomisation de 1:1,13 suppose qu'environ 13 % des sujets randomisés dans le bras expérimental ne seront pas traités par radiothérapie de rattrapage en raison de métastases extra-pelviennes détectées par TEP/TDM-PSMA. Ces patients ne seront pas inclus dans l'analyse

du critère d'évaluation principal, mais seront tout de même suivis pour les critères secondaires. Le choix de traiter la loge prostatique seule ou avec les ganglions lymphatiques pelviens, avec ou sans hormonothérapie, est choisi par le radiothérapeute. Le radiothérapeute peut modifier le plan de radiothérapie en fonction des résultats de la TEP/TDM-PSMA. Toute autre modalité d'imagerie approuvée (y compris la TEP-fluciclovine) était autorisée pour la planification de la radiothérapie de rattrapage dans les deux bras si elle est effectuée dans le cadre de routine clinique standard. Les patients seront suivis jusqu'à ce que l'une ou l'autre des conditions suivantes se produise : 5 ans après la date de début de la randomisation, progression biochimique, diagnostic de maladie métastatique, initiation de tout traitement de rattrapage supplémentaire, décès. Le recrutement de l'essai a été achevé en 2020 et l'analyse finale est prévue pour 2025.

Deuxième partie: Traitement par radiothérapie moléculaire au Lu177-PSMA

En 2017, UCLA a co-initié le premier essai clinique prospectif aux États-Unis de radiothérapie moléculaire au Lutetium-177-PSMA-617 (RESIST-PC, NCT03042312) avec Excel Diagnostics à Houston, au Texas. Il s'agissait d'une étude de phase 2 bi-centrique chez des patients atteints d'un cancer de la prostate métastatique résistant à la castration (CPRCm) de stade avancé. RESIST-PC (NCT03042312) était un essai prospectif multicentrique de phase 2. Les patients atteints d'un CPRCm progressant après ≥ 1 inhibiteur de l'axe androgénique de nouvelle génération (IAANG), n'ayant jamais reçu de chimiothérapie ou ayant reçu ≥ 1 régime de chimiothérapie, présentant une fonction médullaire suffisante, une fonction rénale normale et une expression suffisante du PSMA par les lésions tumorales étaient éligibles. Les patients ont été randomisés (1:1) en 2 groupes d'activité (6,0 ou 7,4 GBq) et ont reçu jusqu'à 4 cycles de traitement 177Lu-PSMA toutes les 8 semaines.

Entre-temps, Novartis acquérait les droits de développement clinique et de commercialisation du PSMA-617 afin d'élargir son portfolio de radiopharmaceutiques à la suite du succès de l'acquisition du Lutetium-177-DOTATATE (Lutathera®) (8). Novartis préparant le lancement de l'essai pivot multicentrique international (VISION; NCT03511664), l'essai RESIST-PC a été jugé non aligné avec la stratégie globale de l'entreprise. L'étude a été clôturée en 2018 avant d'atteindre la population cible de 200 patients. En raison de conflits de propriété des données, l'analyse de l'efficacité de l'essai RESIST-PC n'a été effectuée que pour le site de UCLA. L'analyse de la tolérance et de sécurité a été réalisée pour les deux sites avec le soutien de Novartis. Par la suite, ces résultats des deux sites d'étude ont été utilisés pour l'autorisation de mise sur le marché du Lu177-PSMA-617.

Résultats d'efficacité de l'essai RESIST-PC (J Calais et al. J Nucl Med 2021 (9))

L'objectif de cette étude était de déterminer le profil d'efficacité de 2 niveaux d'activité (6,0 vs 7,4 GBq) de 177Lu-PSMA-617 chez des patients ayant un CPRCm. Le critère d'évaluation principal était l'efficacité du 177Lu-PSMA-617 mesurée par le taux de réponse (RR) de du PSA après 2 cycles (baisse de $\geq 50\%$ par rapport

à la valeur initiale). Les critères d'évaluation secondaires comprenaient le RR du PSA (baisse de $\geq 50\%$) à tout moment (meilleure réponse) et la survie globale (SG).

Nous rapportons ici les résultats d'efficacité uniquement de la cohorte UCLA (n=43). Les RR du PSA après 2 cycles et à tout moment étaient de 11/40 (28%, IC_{95%} 15-44), 6/13 (46%, IC_{95%} 19-75) et 5/27 (19%, IC_{95%} 6-38), et 16/43 (37%, IC_{95%} 23-53), 7/14 (50%, IC_{95%} 23-77) et 9/29 (31%, IC_{95%} 15-51) dans l'ensemble de la cohorte, le groupe 6,0 GBq, et le groupe 7,4 GBq, respectivement (P=0,12 et P=0,31). La SG médiane était de 14,0 mois (IC_{95%} 10,1-17,9), 15,8 mois (IC_{95%} 11,8-19,4) et 13,5 mois (IC_{95%} 10,0-17,0) dans l'ensemble de la cohorte, le groupe 6,0 GBq et le groupe 7,4 GBq, respectivement (p=0,87). La SG a été plus longue chez les patients qui ont connu une baisse du PSA de $\geq 50\%$ à tout moment que chez ceux qui n'en ont pas connu: médiane, 20,8 contre 10,8 mois (p=0,005).

Résultats de tolérance et de sécurité de l'essai RESIST-PC (J Calais et al. J Nucl Med 2021 (10))

L'objectif de cette analyse était de rendre compte du profil de tolérance du 177Lu-PSMA-617 dans la cohorte bi-centrique de 64 patients inclus dans l'essai RESIST-PC NCT03042312. Le critère d'évaluation principal a été évalué en recueillant et classant les événements indésirables (EI) à l'aide des critères de toxicité CTCAE (Common Terminology Criteria for Adverse Events). Les patients ont été suivis jusqu'à la progression de la maladie, le décès, les EI graves ou intolérables, l'arrêt de l'étude par le promoteur, le retrait du patient, la perte de suivi ou 24 mois après le premier cycle.

L'étude a été clôturée prématurément en raison du transfert de propriété de Lu177-PSMA-617, à 71 des 200 patients prévus. Au total, 64 patients (90,1%) ont reçu au moins 1 cycle de 177Lu-PSMA-617 : 28 (36%) dans le bras 6,0 GBq et 41 (64%) dans le bras 7,4 GBq. Il y avait 10 (43,5%), 19 (46,5%) et 29 (45,3%) patients qui ont complété 4 cycles de 177Lu-PSMA-617 dans le bras 6,0 GBq, le bras 7,4 GBq et au total, respectivement. Les EI liés au traitement, tous grades confondus, étaient la sécheresse buccale (47,8%; 63,4%; 57,8%, respectivement), la fatigue (56,5%; 51,2%; 53,1%, respectivement), les nausées (52,2%; 43,9%; 46,9%, respectivement) et la diarrhée (13,0%; 31,7%; 25,0%, respectivement). Les fréquences de tous les autres EI étaient comparables entre les 2 groupes (avec une différence de 10%). Des EI graves, possiblement liés au traitement, ont été rapportés chez 5 patients (7,8%) au total (aucun n'a été considéré comme probablement ou définitivement lié au traitement): hématome sous-dural de grade 4 (n=1), anémie de grade 3 (n=1), thrombocytopenie de grade 4 (n=1), hémorragie gastro-intestinale de grade 3 (n=1) et lésion rénale aiguë de grade 3 (n=1). Il n'y avait pas de modification cliniquement significative des constantes vitales et des électrocardiogrammes acquis avant et après l'injection dans les 2 groupes de traitement. Aucune tendance à l'augmentation de la créatinine n'a été notée.

Malgré l'hétérogénéité de la population étudiée et l'arrêt prématuré de l'étude, le profil d'efficacité du 177Lu-PSMA semblait favorable et comparable entre les 2 régimes d'activité (6,0 et 7,4 GBq) avec une SG globale de 14 mois dans une population de patients avec un CPRCm avancé. Le 177Lu-PSMA-617 s'est avéré sûr et bien

toléré à 6,0 et 7,4 GBq par cycle administré à des intervalles de 8 semaines, avec des effets secondaires facilement gérés avec un support médical standard.

Plus tard, l'essai multicentrique randomisé de phase 3 VISION (11) a confirmé les résultats d'études antérieures, rapportant une amélioration significative des patients recevant le ¹⁷⁷Lu-PSMA-617 +/- le standard de traitement autorisé dans le protocole (STD) (n=551) par rapport au STD seul (n=280) en termes de SG (médiane, 15,3 contre 11,3 mois), de survie sans progression radiographique (médiane 8,7 contre 3,4 mois), et de réponse biochimique. De plus, il a pu être démontré que le ¹⁷⁷Lu-PSMA-617 retardait le temps jusqu'à la dégradation de la qualité de vie et de la douleur. L'essai VISION a été mené sur 84 sites (52 en Amérique du Nord et 32 en Europe), dont UCLA et Excel Diagnostics. En utilisant les résultats de l'essai VISION, Novartis a obtenu avec succès l'approbation de la FDA en 2022 sous le nom de ¹⁷⁷Lu-vipivotide tetraxetan (Pluvicto®) (12). Pluvicto® a été approuvé par la FDA pour le traitement des patients atteints d'un CPRCm exprimant le PSMA en progression après traitement par IAANG et chimiothérapie à base de taxanes. Il est important de noter que les patients doivent être sélectionnés par imagerie TEP-PSMA. Les lésions sont considérées comme positives si leur signal TEP-PSMA est supérieur à celui du foie et négatives si inférieur ou égal à celui du foie. Les patients sont éligibles si au moins une lésion tumorale est jugée positive et si toutes les lésions mesurables par imagerie anatomique TDM sont également positives (critères de taille : lésion viscérale ≥ 1 cm de petit axe, ganglions lymphatiques $\geq 2,5$ cm de petit axe, lésion osseuse a composante lytique ≥ 1 cm de petit axe). Les patients sont considérés inéligibles si toutes les lésions sont négatives au PSMA ou si une lésion plus grande que les critères de taille TDM est négative au PSMA. Dans l'essai VISION, le taux d'exclusion selon ces critères était de 12,6%: 126/1003 ont été exclus par TEP-PSMA pour un total de 831 patients finalement inclus. À la suite des doutes concernant la nécessité de l'évaluation pré-thérapeutique par TEP de l'expression de la cible, nous avons mené une étude pour évaluer le devenir des patients atteints d'un CPRCm et traités par ¹⁷⁷Lu-PSMA qui auraient été exclus de l'essai VISION (SF, screen failure) sur la base des critères TEP/TDM-PSMA.

Résultats du Lu177-PSMA chez les patients négatifs au PSMA (M Hotta et al. J Nucl Med 2022 (13))

Nous avons mené une étude de cohorte rétrospective multicentrique sur 301 patients atteints d'un CPRCm traité par ¹⁷⁷Lu-PSMA. Les patients ont été classés en groupes éligibles (VISION-PET-E) et SF (VISION-PET-SF) sur la base des critères TEP de l'essai VISION appliqués sur la TEP/TDM-PSMA pré-thérapeutique. Les taux de réponse biochimique, la survie sans progression biochimique et la SG ont été comparés.

Sur 301 patients, 272 (90,4%) et 29 (9,6%) étaient respectivement VISION-PET-E et VISION-PET-SF. Les patients VISION-PET-SF présentaient un taux de baisse du PSA de $\geq 50\%$ (21% contre 50%, $p=0,005$) et une survie sans progression du PSA (2,1 contre 4,1 mois, $p=0,023$) plus faible que les patients VISION-PET-E et avaient tendance à avoir une survie globale plus courte (9,6 contre 14,2 mois $p=0,16$).

Cette étude a montré que les patients VISION-PET-SF avaient de moins bons résultats que les patients VISION-PET-E. Cependant, d'autres améliorations dans les critères de sélection des patients pour la thérapie au ¹⁷⁷Lu-

PSMA sont nécessaires pour optimiser les résultats, car les patients ne répondent pas uniformément.

Score PSG pour prédire la réponse à la thérapie LuPSMA (M Hotta et al. J Nucl Med 2023 (14))

Nous avons ensuite tenté d'affiner les critères de sélection TEP-PSMA à l'aide du MIP-3D (3-dimensional maximum intensity projection) de la TEP-PSMA pré-thérapeutique. Nous avons émis l'hypothèse que l'utilisation des glandes salivaires au lieu du foie comme organe de référence peut permettre une stratification plus sélective des patients.

Cette étude de cohorte multicentrique rétrospective a inclus 237 patients avec un CPRCm traités par 177LuPSMA. Un score quantitatif PSG (qPSG) (rapport du SUV moyen du volume tumoral corps entier sur celui des glandes parotides) a été calculé de manière semi-automatique sur la TEP-PSMA pré-thérapeutique. Les patients ont été divisés en 3 groupes : score élevé (qPSG >1,5), intermédiaire (qPSG = 0,5-1,5) et faible (qPSG <0,5). Dix spécialistes en imagerie TEP indépendants ont classé les patients en 3 groupes en fonction d'un score visuel PSG (vPSG) appliqué sur le MIP de la TEP-PSMA pré-thérapeutique comme suit: élevé (>80% des lésions ont un signal plus élevé que celui des glandes parotides), intermédiaire (ni faible ni élevé) et faible (>80% des lésions ont un signal plus faible que celui des glandes parotides).

Le nombre de patients classés dans les groupes élevé, intermédiaire et faible étaient respectivement de 56 (23,6%), 163 (68,8%) et 18 (7,6%) pour le score qPSG et 106 (44,7%), 96 (40,5%) et 35 (14,8%) pour le score vPSG. La reproductibilité inter-lecteur du score vPSG était substantielle (Fleiss pondéré k, 0,68). Le taux de baisse du PSA de ≥ 50 % était meilleur chez les patients ayant un score PSG plus élevé (élevé vs intermédiaire vs faible, 69,6% vs 38,7% vs 16,7% par qPSG [P<0,001] et 63,2% vs 33,3% vs 16,1%, par vPSG [P< 0,001], respectivement). La médiane de survie sans progression biochimique des groupes élevé, intermédiaire et faible était de 7,2, 4,0 et 1,9 mois (P<0,001) selon le score qPSG, et de 6,7, 3,8 et 1,9 mo (P<0,001) selon le score vPSG, respectivement. La SG médiane des groupes élevé, intermédiaire et faible était de 15,0, 11,2 et 13,9 mois (P=0,017) selon le score qPSG, et de 14,3, 9,6 et 12,9 mois (P=0,018), selon le score vPSG, respectivement.

Le score PSG était le pronostic de la réponse biochimique et la SG après thérapie au 177Lu-PSMA. Le score PSG visuel évalué sur les images MIP de la TEP-PSMA pré-thérapeutique a donné une reproductibilité substantielle et une valeur pronostique comparable au score quantitatif.

Des nomogrammes pour prédire les résultats du traitement par LuPSMA (A Gafita et al. Lancet Oncol. 2021 (15))

Avec les différentes options thérapeutiques disponibles pour le traitement de seconde ou troisième ligne des patients avec un CPRCm de stade avancé, il existe un besoin d'identifier les patients ayant un CPRCm les plus susceptibles de bénéficier d'un certain traitement. Notre objectif était de développer des nomogrammes pour prédire les résultats du traitement par LuPSMA chez les patients atteints de CPRCm. Nous avons émis l'hypothèse qu'une combinaison de paramètres cliniques et dérivés de la TEP-PSMA peut aider à la prise de décision clinique et à la sélection des candidats pour ce traitement.

Dans cette étude rétrospective multicentrique, étaient inclus des patients avec CPRCm traités par Lu177-PSMA entre 2014 et 2019 dans six hôpitaux et centres universitaires en Allemagne, aux États-Unis et en Australie. Les patients éligibles étaient des patients avec CPRCm traités avec 6,0 à 8,5 GBq de Lu177-PSMA une fois toutes les 6 à 8 semaines, pendant un maximum de 4-6 cycles, et avaient des données cliniques et une TEP/TDM-PSMA pré-thérapeutiques, ainsi que de résultats de survie disponibles. 18 variables pré-thérapeutiques clinico-pathologiques et TEP/TDM-PSMA ont été testées. Les critères de jugement principaux pour les nomogrammes étaient la survie globale et la survie sans progression du PSA. Les nomogrammes pour chaque résultat ont été calculés à partir de modèles de régression de Cox. La performance du modèle a été mesurée en examinant la discrimination (indice-C de Harrell), l'étalonnage (tracés d'étalonnage) et l'utilité (stratification des patients en groupes à faible risque et à haut risque). Les modèles ont été validés en interne et en externe sur une cohorte de validation.

Sur 414 patients considérés, 270 (65%) étaient éligibles et ont été répartis en cohortes de développement (n=196) et de validation (n=74). La durée médiane du suivi était de 21,5 mois (IQR 13,3-30,7). L'indice-C du modèle de survie globale était de 0,71 (IC_{95%} 0,69-0,73). Des indice-C similaires ont été obtenus lors de la validation interne (0,71 [0,69-0,73]) et externe (0,72 [0,68-0,76]). L'indice-C du modèle de survie sans progression du PSA était de 0,70 (IC_{95%} 0,68-0,72). Des indice-C similaires ont été obtenus lors de la validation interne (0,70 [0,68-0,72]) et externe (0,71 [0,68-0,74]). Par rapport aux patients à haut risque, les patients à faible risque avaient une survie globale significativement plus longue dans la cohorte de validation (24,9 mois [IC_{95%}16,8-27,3] vs 7,4 mois [IC_{95%}4,0-10,8]; p<0,0001) et une survie sans progression du PSA (6,6 mois [IC_{95%} 6,0-7,1] vs 2,5 mois [IC_{95%}1,2-3,8]; p=0,022).

Ces nomogrammes sont prédictifs des résultats de la thérapie au Lu177-PSMA pourraient aider à la conception d'essais cliniques et à la prise de décision clinique individuelle, en particulier dans les établissements où Lu177-PSMA est introduit comme une nouvelle option thérapeutique. Pour permettre une mise en œuvre clinique immédiate à grande échelle, un calculateur de risque en ligne a été développé et est disponible en ligne (<https://www.uclahealth.org/nuc/nomograms>). Ces modèles peuvent être testés et mis à jour au fur et à mesure que de nouvelles données d'essais cliniques deviennent disponibles.

Améliorations potentielles pour la thérapie LuPSMA et domaines de recherche futurs (A Gafita et al. ASCO 2022 educational book (16))

Malgré les résultats positifs de l'essai VISION, jusqu'à 30% des patients présentent une résistance inhérente à la radiothérapie moléculaire ciblant le PSMA au Lu177-PSMA-617, et une résistance acquise est inévitable chez tous les patients. Par conséquent, des stratégies visant à accroître l'efficacité de la thérapie par radionucléides à base de PSMA font l'objet d'études cliniques et sont décrites dans cette revue.

Des améliorations dans les critères de sélection des patients sont nécessaires pour optimiser les résultats, car les patients ne répondent pas uniformément. L'ajout de la TEP/TDM au FDG pour la sélection des patients peut permettre d'augmenter les réponses thérapeutiques chez les patients sélectionnés de manière plus

sélective. Des facteurs prédictifs de la réponse au ^{177}Lu -PSMA ont été identifiés et incorporés dans les nomogrammes pour faciliter le processus de sélection des patients et devraient être testés.

Les mécanismes de résistance à la radiothérapie moléculaire ciblant le PSMA comprennent une expression tumorale faible ou hétérogène du PSMA, l'incapacité à délivrer une dose létale de rayonnement aux sites métastatiques, le microenvironnement tumoral et la radiorésistance biologique tumorale.

L'association de la radiothérapie moléculaire à base de PSMA avec des agents potentiellement synergiques (par exemple, les thérapies ciblées inhibiteurs de points de contrôle immunitaires, inhibiteurs de PARP, les anti-androgènes, l'inhibiteur de CDK-4/6, ou chimiothérapies bases de taxanes) ou l'utilisation d'émetteurs alpha au lieu de beta peut potentiellement améliorer les réponses thérapeutiques. Des cibles biologiques autres que le PSMA sont actuellement à l'étude pour des applications théranostiques potentielles dans le cancer de la prostate.

Cet article conclut ce manuscrit pour le doctorat par validation des acquis de l'expérience.

PERSPECTIVES

Perspectives en imagerie TEP PSMA

La TEP ciblant le PSMA est désormais une technique approuvée et remboursée pour les patients ayant un cancer de la prostate. Les indications validées pour la TEP PSMA sont le bilan initial des cancers de la prostate à haut risque, le bilan de récurrence et la sélection des patients pour traitement par radiothérapie moléculaire ciblant le PSMA. De nouvelles indications potentielles sont à l'étude comme le ciblage des biopsies intra-prostatiques.

Des critères standardisés d'interprétation ont été proposés comme par exemple PROMISE, PSMA-RADS, E-PSMA, PRIMARY (pour l'analyse intra-prostatique), PSG-score (pour l'évaluation corps entier du niveau d'expression ou encore RECIP (pour l'évaluation corps entier de la réponse thérapeutique). Cependant, ces critères n'ont pas été validés dans des études prospectives multicentriques conçues pour l'amélioration de la survie. De plus, il existe encore une large variation dans la qualité d'interprétation des TEP PSMA et la communication des résultats aux uro-oncologues dans la communauté en dehors des centres experts (faux positifs dans l'analyse de l'envahissement ganglionnaire ou osseux, notamment). Des efforts supplémentaires de standardisation sont requis pour pouvoir homogénéiser l'utilisation de l'information obtenue par TEP PSMA.

L'imagerie TEP PSMA crée de nouvelles stadifications de la maladie. Des patients classés M0 par imagerie conventionnelle peuvent être reclassifiés M1 (« upstaging ») par imagerie TEP PSMA et vice versa (« downstaging »). Il est clairement démontré que l'utilisation de la TEP PSMA change la prise en charge des patients. Cependant, les recommandations cliniques et les algorithmes de traitement sont basés sur des stadifications définies par imagerie conventionnelle (RECIST, PCWG). A ce jour, il n'existe pas suffisamment de données permettant de démontrer comment utiliser les nouvelles informations TEP PSMA au bénéfice de l'amélioration de la survie des patients et sans augmentation de la toxicité (« overtreatment »). L'implémentation de l'imagerie TEP PSMA dans les essais thérapeutiques randomisés multicentriques (pour l'inclusion et le suivi) permettra de générer les données nécessaires pour optimiser les algorithmes de traitements et les recommandations cliniques en fonction de la stadification TEP PSMA.

En plus de l'information qualitative de stadification, la TEP PSMA permet aussi de délivrer une information quantitative corps entier, telle que le volume tumoral total exprimant le PSMA (mL), ou l'intensité moyenne d'expression du PSMA au sein du volume tumoral total (SUV). Ces paramètres quantitatifs, et d'autres, ont le potentiel d'être utilisés comme biomarqueurs pour affiner la sélection des patients pour un traitement donné ou l'évaluation de la réponse thérapeutique aux traitements systémiques. Cependant, la segmentation manuelle du volume tumoral corps entier est chronophage et il n'existe pas encore de méthode unanimement

validée et acceptée. Ces facteurs ont limité jusqu'à présent la génération des données cliniques reproductibles à grande échelle qui permettraient de démontrer la valeur diagnostique, pronostique et prédictive des paramètres quantitatifs corps entier obtenus par TEP PSMA. De multiples techniques d'intelligence artificielle sont en cours de développement et d'évaluation clinique pour offrir des solutions automatisées pour obtenir ces paramètres sans ralentir le workflow clinique. Leur implémentation dans les centres de médecine nucléaire est limitée par le grand nombre d'algorithmes proposés (reproductibilité), leur compatibilité avec les systèmes existants, l'accès informatique aux données patients (sécurité) et surtout l'absence d'impact clinique démontré (efficacité diagnostique, amélioration de la survie des patients).

Les améliorations techniques des scanners (TEP numérique, TEP grand champ corps-entier) permettront peut-être d'augmenter la sensibilité de l'imagerie TEP aux ligands ciblant le PSMA. En outre, de multiples radiopharmaceutiques TEP visant à un meilleur rapport signal-sur-bruit, via une captation tumorale plus élevée (par exemple, le ligand SAR-bis-PSMA, dimérisé avec 2 points d'attache au PSMA), ou via la possibilité d'imagerie tardive pour réduire le signal des organes sains ou le signal urinaire (par exemple en utilisant le Zirconium-89 ou le Cuivre-64) sont en cours de développement clinique.

Perspectives en radiothérapie moléculaire ciblant le PSMA

Le traitement par radiothérapie moléculaire ciblant le PSMA est désormais approuvé et remboursé. L'indication validée est le traitement des patients atteints d'un CPRCm en progression après hormonothérapie inhibitrice de la voie des androgènes et chimiothérapie, et positif par TEP PSMA.

De multiples questions restent ouvertes.

La place de la thérapie au Lu177-PSMA-617 dans la séquence des traitements systémiques pour le CPRCm (multiples options) n'est pas encore définie et des études cliniques comparant des séquences thérapeutiques seraient utiles.

Les critères de sélection des patients par imagerie TEP peuvent être affinés. L'utilisation de paramètres quantitatifs TEP (e.g. volume tumoral total exprimant le PSMA, valeur moyenne de l'expression tumorale mesurée par le SUVmean) est une voie potentielle de recherche. L'utilisation combinée de la TEP au FDG et de la TEP au PSMA est une pratique courante en Australie ou en Allemagne. La TEP au FDG permet de détecter plus de lésions négatives au PSMA que la TDM, notamment dans le foie ou la moelle osseuse. Les lésions de phénotype discordant, i.e. positives au FDG et négatives au PSMA représentent un facteur de mauvais pronostic. Cependant, l'utilisation combinée de la TEP au FDG et de la TEP au PSMA est complexe d'un point de vue financier, logistique (2 visites nécessaires) et d'interprétation.

Le nombre total/maximum de cycles de thérapie au Lu177-PSMA-617, l'intervalle entre les cycles, l'activité

injectable administrée par cycle, les seuils de sécurité pour les paramètres de fonctions médullaire et rénale ont été dérivés de manière empirique (programme d'usage compassionnel du Lu177-PSMA-617 en Allemagne, expérience clinique avec les radiopharmaceutiques commercialement approuvés tels que 177-Lutetium-DOTATATE, 223-Radium, ou 90-Yttrium-ibritumomab-tiuxetan). Plusieurs rapports de patients traités avec plus de 6 cycles suggèrent un profil de sécurité favorable et un bénéfice sur la progression de la maladie tumorale. Néanmoins, le profil de toxicité d'un usage prolongé du LuPMSA617 reste à évaluer dans des études prospectives, tout comme la toxicité à long-terme ou tardive (≥ 12 mois) qui reste mal connue.

Il n'existe pas de critères standardisés de réponse et de discontinuation. Les pratiques sont hétérogènes. La décision doit être basée sur les paramètres cliniques, biochimiques, d'imagerie et sur les autres options de prise en charge disponibles. Des propositions de critères standardisés d'imagerie nucléaire ciblée au PSMA pour l'évaluation de la réponse thérapeutique ont été proposées (PPP, RECIP, RE-SPECT) et devraient être testés dans des essais cliniques.

L'imagerie TEMP (tomographie par émission mono-photonique) post-thérapeutique du Lu177-PSMA-617 offre la possibilité de visualiser la biodistribution du radiopharmaceutique spécifique à chaque patient et d'estimer la quantité de dose de radiation délivrée dans les lésions et organes sains. Ces données individualisées pourraient permettre de modifier le schéma d'administration pour chaque patient (activité injectée, intervalle inter-cycle) afin de maximiser le profil d'effet antitumoral ou de sécurité. Cependant, il n'existe pas encore de méthode de référence pour chacune des étapes de calcul allant de l'activité détectée par les scanners TEMP jusqu'à l'estimation du dépôt de dose en Gray (modèles de scanner TEMP, paramètres d'acquisition de l'image, paramètres de reconstruction de l'image, méthodes de segmentation, software, méthodes d'ajustement de courbe d'activité, algorithmes de modélisation et calcul de la dose). Cette hétérogénéité des pratiques combinée à l'absence de collection systématique des données de toxicité n'a pas permis jusqu'ici d'évaluer la corrélation entre la dose calculée de radiothérapie interne vectorisée et les indices cliniques. Les seuils de toxicité actuellement employés sont dérivés de patients ayant reçu de la radiothérapie externe entre les années 1950 et 1990. De plus, l'impact de la modification du schéma d'administration (activité injectée, intervalle inter-cycle) et de la dose estimée reste non établi. Des études de standardisation, les multiples techniques d'intelligence artificielle en cours de développement et l'implémentation de protocoles de dosimétrie dans les essais thérapeutiques avec un suivi clinique systématisé pourraient permettre d'homogénéiser les pratiques et de générer des données cliniques qui permettraient de démontrer un impact sur la survie des patients.

D'autres radiopharmaceutiques à visée thérapeutique ciblant le PSMA sont aussi en développement.

L'utilisation de radionucléides émetteurs alpha permet un dépôt d'énergie jusqu'à 100 fois supérieur à celui des particules bêta sur une distance beaucoup plus courte (nanomètres versus millimètres pour les particules bêta). L'Actinium-225 est celui qui a été le plus utilisé jusqu'ici, mais sa production à grande échelle n'est pas

encore établie. D'autres émetteurs alpha sont à l'étude comme l'Astatatine-211, le Plomb-212 ou le Terbium-149. A noter que le développement de générateurs de Plomb-212 pourrait permettre à des équipes de radiomarquer le radiopharmaceutique sur site de manière indépendante comme avec le Gallium-68. Les résultats préliminaires de la thérapie à l'Ac225-PSMA-617 sont prometteurs et montrent une très forte activité antitumorale. Cependant la toxicité, notamment au niveau des glandes salivaires, demeure un problème non résolu.

L'anticorps J591 ciblant le PSMA et pouvant être radiomarqué avec du Lutetium-177 ou de l'Actinium-225 ne démontre pas de captation dans les glandes salivaires et pourrait représenter une alternative au PSMA-617. Des travaux pré-cliniques rapportent une captation tumorale plus élevée et un temps de rétention plus long qu'avec le PSMA-617. En revanche, le temps de circulation sanguine de Lu177-J591 est long et la toxicité médullaire et sanguine est plus importante que celle du Lu177-PSMA-617. Des essais cliniques testant le Lu177-J591 (limité à 2 cycles) sont en cours (PROSTACT).

De multiples essais thérapeutiques en cours tentent d'évaluer la thérapie au Lu177-PSMA-617 à un stade plus précoce : avant la chimiothérapie (ex : PSMAfore, SPLASH, PSMAAddition), au stade hormono-sensible (ex : PSMAAdditon), oligo-métastatique (ex : LUNAR) ou même en néo-adjuvant (ex : LuTectomy). Plus le volume à traiter est faible, plus le profil de tolérance et de toxicité est doit être évalué précisément (espérance de vie longue, disponibilité du Lu177-PSMA-617 aux tissus sains compte tenu de la captation tumorale limitée, , effets à distance de la cible). La toxicité à long-terme ou tardive (≥ 12 mois) reste mal connue et le risque de néphropathie ou de myélodysplasie est à monitorer avec attention dans les populations exposées au Lu177-PSMA-617 à un stade de maladie précoce.

A noter que le traitement par radiothérapie moléculaire ciblant le PSMA chez des patients à faible volume tumoral et/ou microscopique serait potentiellement efficace en utilisant des émetteurs alphas (énergie délivrée sur des nanomètres versus des millimètres pour les particules bêta). En revanche, le profil de toxicité salivaire de l'alpha thérapie avec le ligand PMSA-617 n'est pas acceptable dans cette population. Le développement de ligands ciblant le PSMA avec un meilleur index thérapeutique est requis pour traiter ce type de patients.

De multiples essais cliniques sont en cours pour tester l'association de la radiothérapie moléculaire ciblant le PSMA avec des agents potentiellement synergiques tels que les thérapeutiques ciblant le récepteur aux androgènes, des radio-sensibilisateurs (par exemple, les thérapies ciblées inhibiteurs de points de contrôle immunitaires, les inhibiteurs de PARP, ou des chimiothérapies) ou l'immunothérapie.

Enfin d'autres cibles biologiques que le PSMA sont actuellement à l'étude pour des applications théranostiques potentielles dans le cancer de la prostate telles que STEAP1 (Six transmembrane epithelial antigen of the prostate 1), HK2 (Human-kallikrein-2 hK2), PSA (KLK3) ou encore DLL3 (Delta-like ligand 3) pour le cancer de la prostate neuroendocrine.

MAIN MANUSCRIPT

INTRODUCTION

Prostate Cancer

The prostate gland is a male reproductive accessory organ located beneath the bladder and surrounding the urethra. The main function of the prostate is to contribute essential secretions to semen which formulate ejaculate and maintain sperm viability. The cells within the prostate gland frequently give rise to tumors, most often in the mid-to-late stage of life.

Prostate cancer is the most common cancer diagnosis in men and a leading cause of cancer-related morbidity and mortality (17,18). It can exist along a wide spectrum of aggressiveness and severity, from indolent, very-low-risk, localized prostate cancer to life-threatening, very-high-risk, metastatic prostate cancer.

Prostate cancer is usually diagnosed by prostate biopsy prompted by a blood test to measure prostate-specific antigen levels and/or digital rectal examination.

Most cancers at diagnosis are localized and fully contained within the prostate gland (organ-confined disease, 80%). A minority of patients have local positive lymph nodes (locoregional metastasis, 15%) or distant metastasis (5%) at diagnosis. The 5-year overall survival of patients with localized disease is 60–99%, whereas that of patients with distant metastases is 30–40% (17,18).

Treatment options vary, depending on stage and grade of the tumor as well as patient characteristics, such as age, comorbidity, and personal preferences (17,19).

Treatment for localized disease includes active surveillance, radical prostatectomy or definitive radiotherapy as curative approaches. Failure after initial therapy or recurrence are usually diagnosed based on serum PSA levels or imaging. As prostate cancer is hormone dependent, androgen-deprivation therapy (ADT) is the first-line therapy commonly offered to patients with advanced disease. Men whose disease relapses after prostatectomy are treated with salvage radiotherapy and/or androgen deprivation therapy (ADT) for local relapse. Once the disease spreads outside the prostate, in the lymph nodes, bone or visceral organs, patients are treated with systemic therapies (17,19).

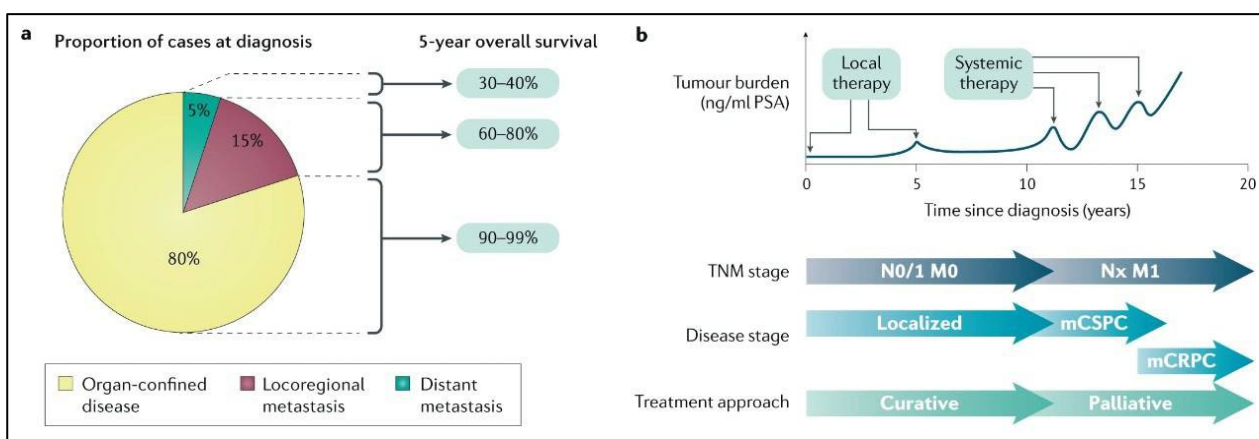


Figure 1: Prostate cancer stages and progression (Adapted from RJ Rebello et al. Nature Reviews 2021 (17)).

Advanced prostate cancer often progresses despite androgen deprivation and is then considered castration-resistant and incurable. Chemotherapy, bone-directed therapy (such as zoledronic acid or denosumab), second generation androgen axis inhibitors such as abiraterone, enzalutamide, darolutamide or apalutamide, radionuclide therapy, immunotherapy, or a combination of these treatments may also be used for advanced prostate cancer both in the castration sensitive and castration resistant settings.

For a newly diagnosed patient in a given clinical state, especially early in the disease, the spectrum of appropriate therapeutic options may range from no intervention to multimodality therapy. Accurate assessment of the extent of disease (e.g., metastatic vs. localized prostate cancer) is essential for guiding treatment decisions.

PSMA

In 1987, Horoszewicz et al. described a prostate-specific antigen which later became designated Prostate Specific Membrane Antigen (PSMA) (20). This type II transmembrane protein is also known as folate hydrolase 1 (FOLH1), glutamate carboxypeptidase II (GCPII) or N-acetylaspartylglutamate (NAAG). Despite its designation, PSMA was subsequently found to be expressed in other tissues such as renal proximal tubules, digestive system, non-myelinic nerves, salivary and lacrimal glands as well as in the neovasculature in many solid tumors (21). PSMA is expressed by prostate epithelial cells but more importantly, it is highly overexpressed by PC cells in more than 85% of prostate cancer samples across many independent immunohistochemistry studies (22). The function of PSMA in PC remains unclear but seems related to the folate and glutamate metabolism (23). Higher PSMA expression carries prognostic value and has been associated with disease aggressiveness' and poor outcomes (21–23).

PSMA-targeted theranostics for prostate cancer

Theranostics is the combined use of an imaging and therapeutic agent with the same molecular target. Since 95% of the PSMA molecule is extracellular, it is accessible for binding of antibodies or low-molecular-weight ligands. The high levels of PSMA overexpression in prostate cancer makes PSMA an excellent prostate cancer theranostic target: high lesion-to- background ratio for imaging and high therapeutic index for therapy.

A number of PSMA-targeting small molecule and antibody agents have been developed and tested for imaging by single photon emission computerized tomography (SPECT) and PET, and for radionuclide therapy (RNT) applications (Figure 2).

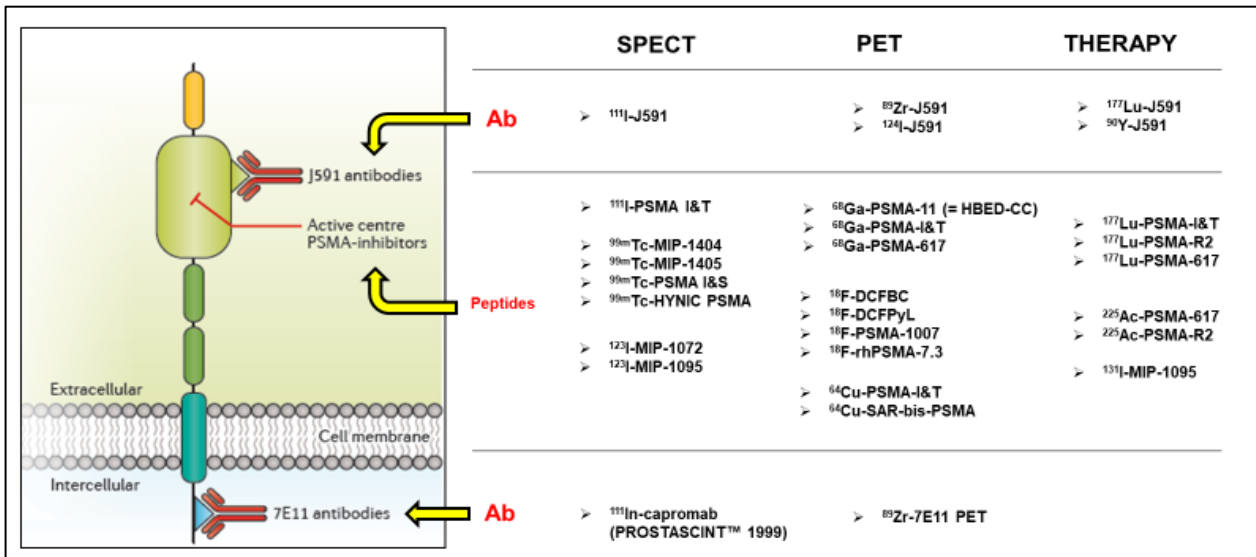


Figure 2: PSMA = target for theranostics (Adapted from Maurer T et al, Nat Rev Urol, 2016 (24))

PSMA-targeted imaging for prostate cancer

There was a first attempt to image PSMA with gamma scintigraphy via a monoclonal antibody labeled with Indium-111: ProstaScint® (7E11-C5) (25–27), FDA approved in 1996. However, 7E11-C5 targets an intracellular epitope of PSMA which provided low quality images and its clinical use was abandoned.

Successful demonstration of clinical targeting of the external portion of PSMA began with the development of the humanized J591 antibody (28). First gamma planar scintigraphy images obtained with ^{111}In -J591 and ^{177}Lu -J591 demonstrated the ability of a PSMA targeting agent to accurately target bone and soft tissue PC lesions in patients with metastatic PC (28,29). However, because of the relatively long clearance time of antibodies, the ideal imaging time to provide the highest tumor-to-background ratio was 7 days post-injection.

In contrast, small molecule ligands that bind to PSMA may be preferable to antibodies as PET imaging agents due to their rapid clearance kinetics, that allow a higher practicability for clinical imaging use (ability to read images within 1 to 2 hours as opposed to days with antibodies).

The first-in-human PET image of a PSMA small molecule ligand was performed in Heidelberg, Germany in 2012 (30). Within the last years, multiple different PSMA-targeting small molecules, most sharing the same glutamate-urea-lysine binding motif but slightly differing in their linker-chelate, were developed (Figure 3) (31).

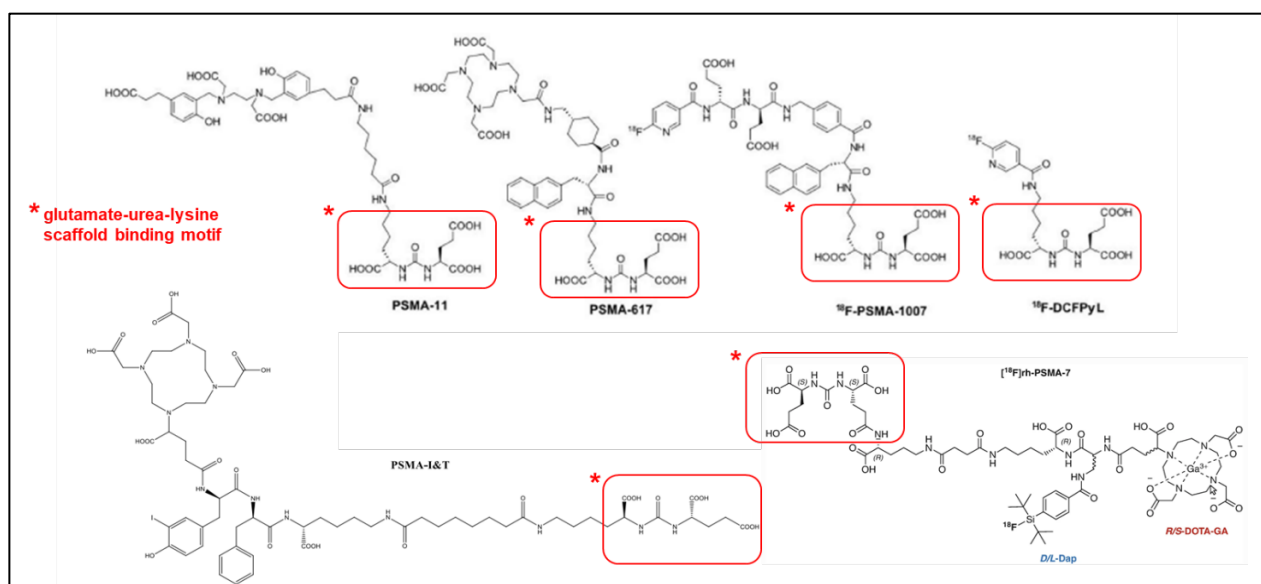


Figure 3: chemical structures of the main PSMA-targeting small molecule ligands (*Adapted from G Capasso et al. European Journal of Medicinal Chemistry, 2024 (32)*)

These small molecules can be radiolabeled with positron-emitter isotopes such as Gallium-68 (68Ga), Fluor-18 (18F) or Copper-64 (64Cu). These positron-emitters differ in their half-lives (68Ga: 68 min 18F: 110 min, 64Cu 12.7 h), their maximum positron energy as well as different synthesis methods.

Fluor-18 is obtained via a cyclotron and can be produced on a large scale on-demand. Its half-life of 110 minutes enables central production and distribution to satellite sites. Therefore 18F-based agents are suitable for commercial development. The rights for the clinical development of the main F18 compounds (18F-DCFPyL, 18F-rhPSMA7.3, 18F-PSMA-1007) were acquired by commercial entities. Even if some university hospitals with a cyclotron performed F18-PSMA PET scans in the early clinical research studies, most of the clinical data on PSMA PET was generated using Ga68-PSMA-11.

Gallium-68 is obtained by natural decay of the father element Germanium-68 from a generator. Many nuclear medicine structures have the capacity to acquire a Germanium-68/Gallium-68 generator and perform the radiolabeling on-site independently. PSMA-11 (or HBED-CC) was not patented and free-of-use. As such, 68Ga-PSMA-11 has been widely used at independent academic centers internationally and data from dozens of thousands of patients have been published despite a lack of industry support.

Of note, ligands PSMA-617 and PSMA-I&T used for Lu177-PSMA therapy can also be labeled with Gallium-68. Some centers use them for PET imaging. However, the uptake of PSMA-617 and PSMA-I&T in tumor lesions is slower than that of PSMA-11, which is less optimal to match the Gallium-68' short half-life of 68 minutes (33,34),

68Ga-PSMA-11 (manufactured by UCLA-UCSF, or as Illuccix®, Telix or as Locametz®, Novartis), 18F-DCFPyL (PYLARIFY®, Lantheus) and 18F-rhPSMA7.3 (POSLUMA®, Blue Earth Diagnostics) have been approved by FDA since 2020 (Figure 4).

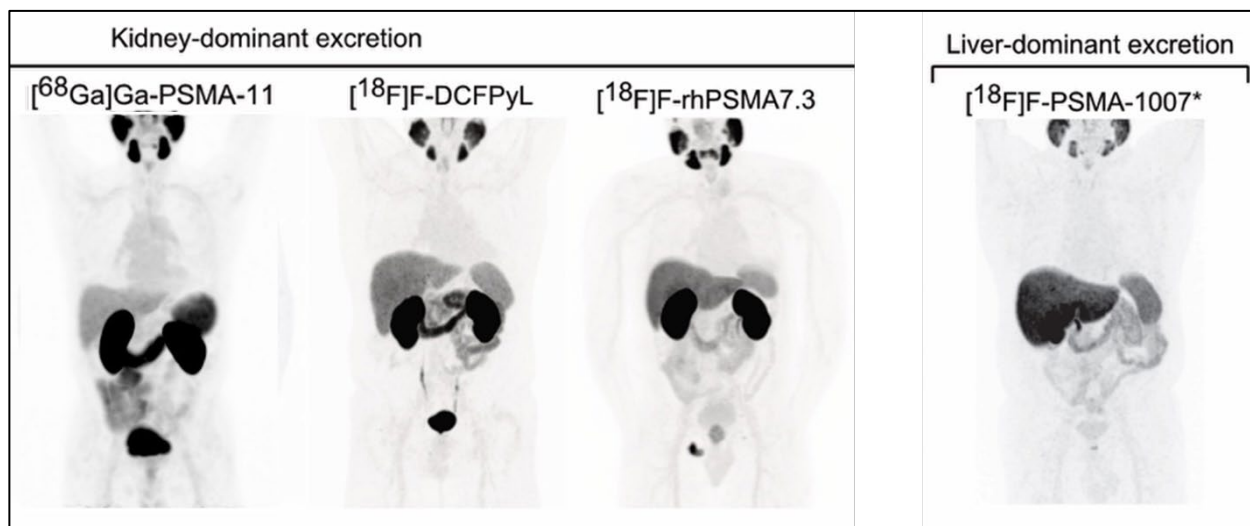


Figure 4: Biodistribution of the main PSMA PET ligands (adapted from Seifert et al. *Eur Urol.* 2023 (35))

Despite a huge amount of data published on PSMA PET, there are only limited head-to-head or matched-pair comparative data between the PSMA PET ligands. Prospective head-to-head comparative trials are costly and risky for the companies (high risk of failure). Overall, the FDA-approved PSMA ligands are considered to have similar diagnostic efficacy and are grouped as a class (PSMA PET) by clinical guidelines (36). Of note, studies suggest that F18-PSMA-1007 and rhPSMA-7.3 are superior to 68Ga-PSMA-11 and 18F-DCFPyL for the analysis of the prostate fossa or the areas surrounding the bladder because of their lower and slower urinary excretion. On the other hand, F18-based PSMA PET tracers, especially F18-PSMA-1007, exhibit higher uptake in benign bone lesions than 68Ga-PSMA-11, leading to more false positive and/or equivocal findings, especially in the ribs (36)

The NCCN guidelines recommend the use of the FDA-approved PSMA-targeting PET radioligands as a first-line imaging tool for initial staging of a newly diagnosed intermediate and high-risk / very high-risk PC, the detection of biochemical recurrence, as work-up for progression in recurrent PC and to select patients for PSMA-targeted radionuclide therapy (19). Similarly, the AUA, EAU, ESMO, HAS and other expert societies recommend PSMA-PET imaging in their guidelines.

PSMA-targeted radionuclide therapy for prostate cancer

As with imaging, the first efforts at PSMA-targeted radionuclide therapy were utilizing antibodies.

The therapeutic counterpart of ProstaScint, 90Y-capromab pendetide (7E11-C5.3), failed clinical trials due to unacceptable bone marrow toxicity without clinical response. Phase 1 trials of single dose of 90Y-J591 and 177Lu-J591 provided first clinical evidence of anti-tumor activity with PSA response and symptomatic improvement of bone pain and served to validate PSMA as a clinically addressable and potentially valuable target (29,37). The dose-limiting toxicity was myelotoxicity, primarily thrombocytopenia, attributed to the long circulating time of the antibody and resulting marrow exposure. 177Lu- J591 has been licensed by Telix.

A phase 3 randomized registration trial is underway (ProstACT Global). The first clinically studied small molecule therapeutic PSMA-targeting agent was labeled with Iodine-131: 131I-MIP-1095 (38). A multicenter phase II study (ARROW, NCT03939689) is evaluating 131I-MIP-1095 plus enzalutamide compared to enzalutamide alone in patients with mCRPC who have progressed under abiraterone. However, Iodine-131 emits high energy gamma rays and requires more radiation safety precautions than Lutetium-177. Therefore, Lutetium-177 was the beta-emitting radionuclide of choice for the clinical development of PSMA-targeted radioligand therapy. 177Lu-PSMA-617 is the most investigated PSMA ligand for the treatment of mCRPC. After the first patient was treated with 177Lu-PSMA-617 in 2014 (39), many clinical reports and phase 2 trials demonstrated promising results with significant treatment responses and low-grade toxicities (40–43). The administration scheme of 177Lu-PSMA-617 (amount of injected peptide or ligand [nmol], amount of injected activity [GBq – mCi], time interval between each cycle or fractionation, and number of cycles) derives from prior empirical clinical compassionate use of 177Lu-PSMA-617 in Germany and prospective trials using other established molecular radionuclide therapy agents (177Lu-DOTATATE, 223Radium, 90Yttrium-ibritumomab-tiuxetan) (44–46). The selected 8-wk interval between treatment cycles was based on established hematologic safety considerations (blood count nadir at 3–6 wk after molecular radionuclide therapy administration) reported in the above-mentioned randomized prospective phase 3 trials (1,7,8). The 6.0- and 7.4-GBq activity regimens were chosen following the NETTER-1 trial experience (45). The amount of injected activity (GBq - mCi) is mainly limited by the bone marrow and kidney dose limits used in external beam radiation therapy (47). The phase 2 RESIST-PC trial attempted to compare two levels of injected activity of 177Lu-PSMA-617: 6.0 GBq vs 7.4 GBq. Unfortunately, there were no conclusions possible due to early study termination. Overall, 177Lu-PSMA-617 administered at up to 4 cycles at 8-wk intervals was safe and well tolerated at 6.0 and 7.4 GBq per cycle. Side effects were easily managed with standard medical support.

The phase III, multicenter VISION trial confirmed the results of the earlier studies, reporting a significant improvement in patients undergoing 177Lu-PSMA-617 plus standard-of-care compared to standard-of-care alone in overall survival (median, 15.3 vs. 11.3 months) and radiographic progression-free survival (median 8.7 vs. 3.4 months), and PSA response were also improved with 177Lu-PSMA-617 (11). Additionally, it 177Lu-PSMA-617 delayed time to worsening of pain and health-related quality of life (48).

177Lu-PSMA-617 was approved by the FDA in 2022 as 177Lu-vipivotide tetraxetan (Pluvicto®) (12) for men with progressing mCRPC after docetaxel and ≥ 1 ARSI and with PSMA-positive disease following the VISION trial results. Pluvicto® should be given once every 6 weeks for 4 cycles (injected activity 7.4 GBq / cycle) with the potential to increase up to 6 cycles based on patient response and tolerance. The NCCN guidelines recommends 177Lu-PSMA-617 therapy accordingly as a treatment option for mCRPC after Docetaxel (19). A pre therapeutic PSMA-PET/CT is required to show at least one tumoral lesion with PSMA-uptake above

than the one of the liver (assessed visually) and the absence of PSMA-negative lesions (uptake equal or below the one of the liver) measurable by CT (bone with soft tissue component ≥ 1.0 cm, lymph node ≥ 2.5 cm and solid organ ≥ 1.0 cm).

Another small molecule PSMA inhibitor under clinical development is ^{177}Lu -PSMA-I&T: two multicenter phase III studies (SPLASH (NCT04647526) and ECLIPSE (NCT05204927)) are underway.

Objective of the manuscript

UCLA was an instrumental pioneer site for the early clinical trials of PSMA-targeting theranostics in the USA. PSMA-PET and PSMA therapy are now implemented at UCLA in clinical routine. At UCLA I had the opportunity to conduct the initial research studies, then the pivotal studies that led to FDA approvals and finally oversee the implementation of PSMA-PET imaging and ^{177}Lu -PSMA therapy in clinical routine.

The aim of this manuscript for PhD by Accreditation of Prior Learning is to highlight the key studies conducted at UCLA that had a major impact on the clinical implementation of PSMA-theranostics in the US.

Manuscript organization

The manuscript is divided in 2 parts: PSMA-PET imaging and PSMA Radionuclide Therapy.

In the first part are provided the pivotal phase 3 trials of diagnostic efficacy used for the FDA approval of ^{68}Ga -PSMA-11, head-to-head comparison trials comparing a new imaging technique (PSMA-PET) to the standard technique (Fluciclovine and MRI) and a multicenter study that led to a randomized imaging trial powered for clinical outcome.

In the second part are provided the results of the first phase 2 trial of ^{177}Lu PSMA therapy in the US that preceded the VISION trial, multicenter studies aiming at refining the PET selection criteria and an overview on the mechanisms of resistance to ^{177}Lu PSMA therapy.

Part One: PSMA-PET imaging

The first reported clinical use of PSMA-PET was a case report published in 2012 by the Heidelberg team, Germany (30). Very rapidly, in view of these very impressive images and positive early experience, the nuclear medicine and uro-oncology community had a huge interest to bring and try this new PET tracer at their institutions and for their patients.

Under the initiative of Johannes Czernin, head of the Nuclear Medicine Division at UCLA, we built a clinical research program of PSMA-targeted theranostics. Experienced German colleagues (Ken Herrmann, Wolfgang Fendler, Matthias Eiber) joined the UCLA group for a few years to initiate the first PSMA studies. With the help our Heidelberg colleagues who provided all the non-clinical pharmacology /toxicology dosimetry data of 68Ga-PSMA-11 required for an Investigational New Drug (IND) and also Thomas Hope at UCSF we obtained a research IND in 2016 (IND#130649). The first PSMA-PET clinical trial approved was designed for the localization of biochemical recurrence (or BCR) of prostate cancer after initial therapy. Then we subsequently used this IND to initiate many other research studies, to cover other indications, clinical needs and try to answer other clinical questions. There was no external funding source for these studies. We were granted by the FDA the right to charge patients for investigational drugs under IND (Title 21 of the Code of Federal Regulation Section (CFR) 312.8) (49). This cost-recovery mechanism is allowed if one can provide evidence that the drug has a potential clinical benefit, demonstrate that the data from the clinical trial would be essential for approval, and that the clinical trial could not be conducted without charging patients because there is no other funding. Johannes Czernin provided the infra-structure and the department funds to develop this research program and hire all the people needed. The table 1 lists the clinical studies of PSMA-PET scans conducted at UCLA since 2016.

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

Table 1: clinical research studies of PSMA-PET/CT conducted at UCLA since 2016.

Very rapidly, we observed a strong interest in this new technique by the physicians and patients. The referring uro-oncologists quickly adopted this imaging technique at UCLA. The impact at the tumor board was very impressive with images and cases unseen before. More importantly, as there were not many sites providing this procedure at this time, we received many external referrals from outside of UCLA, nationally and even internationally. Figure 2 depicts the number of PSMA-PET scans performed at UCLA between October 2016 and October 2023.

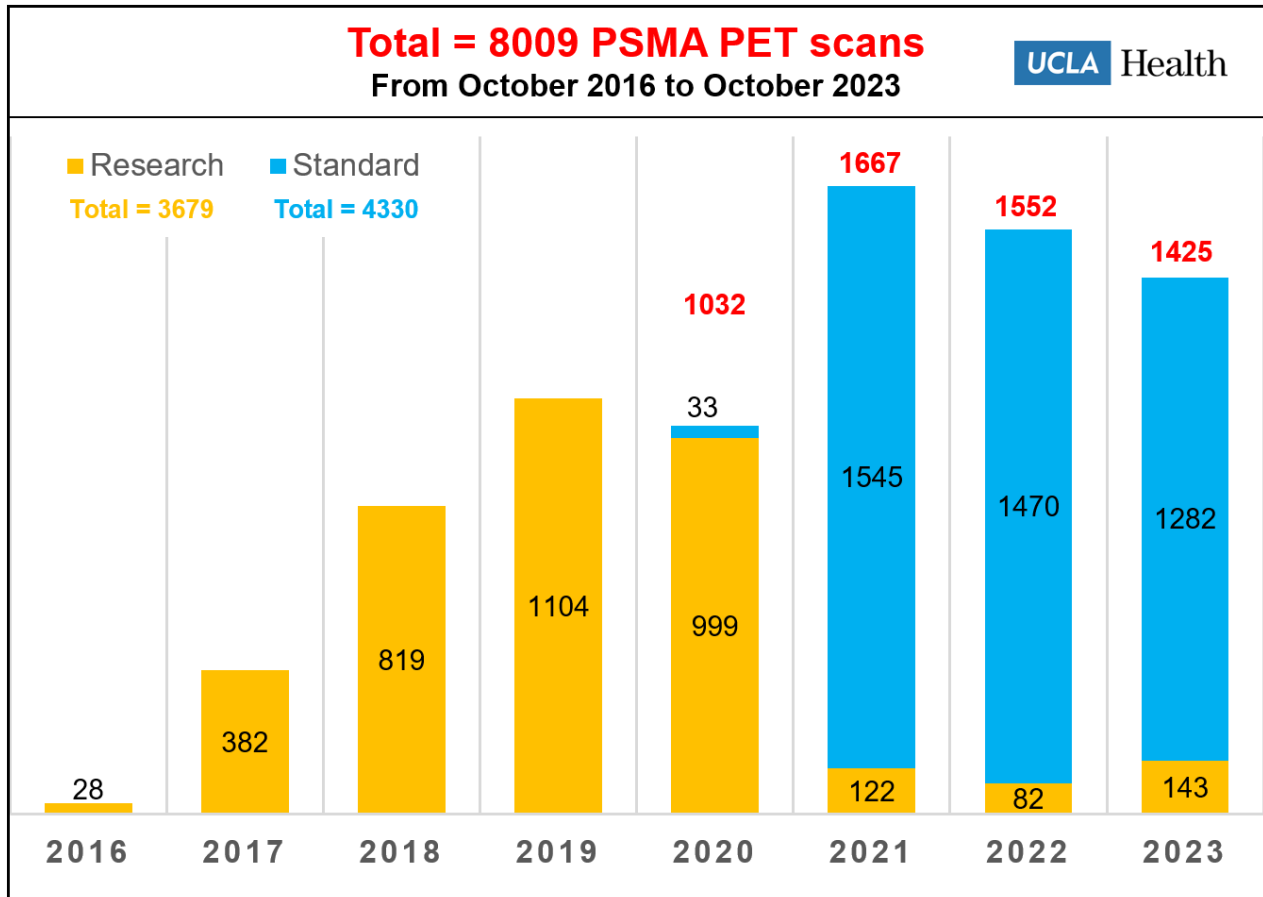


Figure 5: number of PSMA-PET scans performed at UCLA October 2016 and October 2023.

In 2017, we started to consider merging datasets with our collaborator Thomas Hope at UCSF who had the same IND research study protocols. The aim was to assess if the quality of the data collected so far was sufficient to go to the next level: to apply for a New Drug Application (NDA). NDAs are usually conducted by industry with sufficient manpower and financial resources. There were only few prior examples of successful academic NDAs (ex: C-11 choline (2012) at Mayo Clinic, Ga-68-DOTATOC (2019) at University of Iowa, F-18 fluorodopa (2019) at Feinstein Institutes for Medical Research). We used a consulting company to help us to build a pre-NDA meeting request package. In August 2018, we received positive feedback from the FDA at the pre-NDA meeting that led us to think this was potentially feasible. FDA was also willing to allow 2 paired NDAs one for UCLA one for UCSF which led to a very productive academic collaboration. Figure 6 shows the 68Ga-PSMA-11 timeline until FDA approval in December 2020.

This was a unique regulatory approach. There were two separate NDAs: UCSF NDA #212643 and UCLA NDA #212642. They both shared the same clinical and non-clinical information however they were separate because of the site-specific CMC (Chemistry Manufacturing and Controls) modules sections. They had a similar package insert; but a different vial label because of the site-specific CMC. As it was not feasible for us to generate the data, we used it for the non-clinical pharmacology, toxicology and clinical dosimetry sections from existing literature (505(b)(2) NDA pathway).

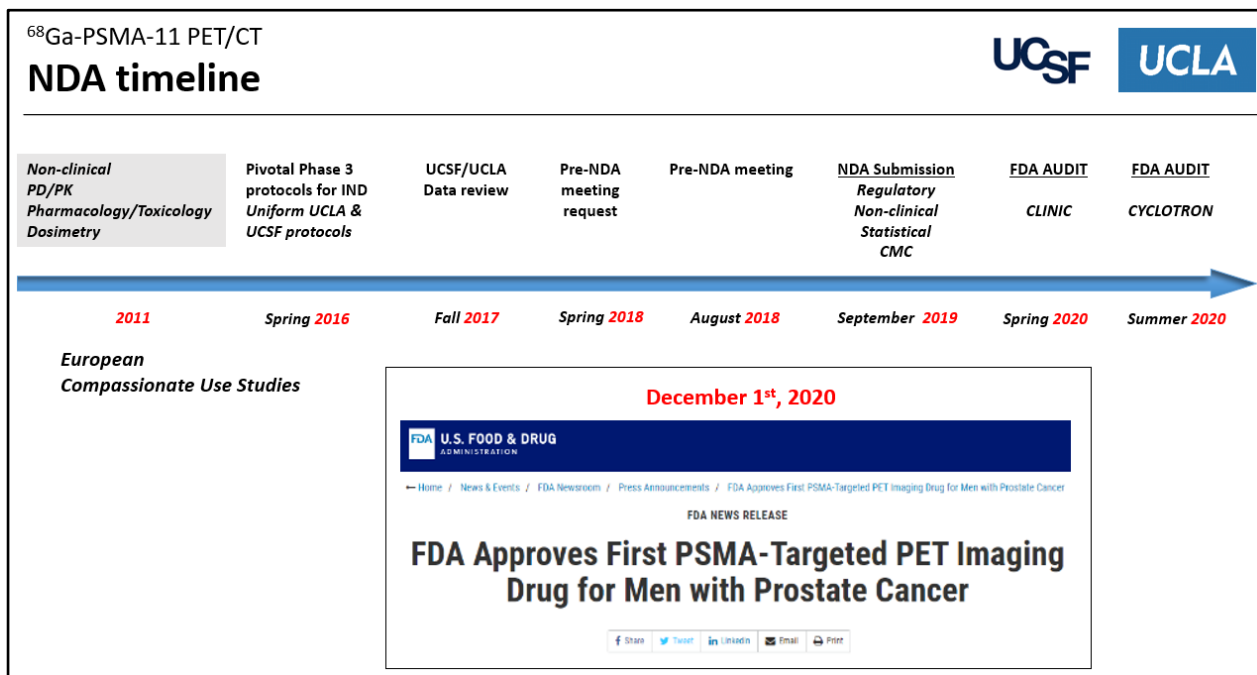


Figure 6: Timeline of the FDA approval of 68Ga-PSMA-11 produced by UCLA and UCSF

On December 1st 2020, the U.S. Food and Drug Administration approved Gallium-68 PSMA-11 (Ga-68 PSMA-11) produced at UCLA and UCSF (1). This was the first diagnostic agent approved for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer. The approved indications were patients with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy with suspected metastasis who are candidates for initial definitive therapy and patients with suspected recurrence based on elevated serum prostate specific antigen (PSA) level. The FDA package insert and prescribing information are provided here.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212642s000lbl.pdf

Of note, the 4 other commercial PSMA-PET agents since then approved by the FDA (Ga-68 PSMA-11 as Illuccix® by Telix or as Locametz®, by Novartis), 18F-DCFPyL (PYLARIFY®, Lantheus) and 18F-rhPSMA-7.3 (POSLUMA®, Blue Earth Diagnostics) have all the same indications.

UCSF and UCLA can distribute 68Ga-PSMA-11 only within their institutions. We waived market exclusivity: any site can potentially file an ANDA application (Abbreviated NDA) as long as they demonstrate they can manufacture 68Ga-PSMA-11 the same way it was performed by UCLA or UCSF.

We used 2 pivotal study datasets for the NDA submission: one for the Biochemical Recurrence indication (n=635, UCLA NCT02940262 (n=250) and UCSF NCT03353740 (n=385)) and one for the Initial Staging indication (n=277, UCLA NCT03368547 (n=130), UCSF NCT02611882, NCT02919111 (n=147)). These studies demonstrate the diagnostic efficacy performances of the new diagnostic nuclear medicine tracer and are presented below.

Article #1:

Assessment of ⁶⁸Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A prospective Multicenter Single-Arm Phase 3 Clinical Trial (n=635)

In the BCR setting, true negative and false negative PET imaging findings cannot be verified. Patients have the diagnosis of biochemical recurrence after initial definitive therapy based on elevated serum PSA levels. The scan here aims at localizing the source(s) of the PSA production. PSMA-PET scan is a whole-body imaging modality: unless by autopsy, the analysis of all regions negative by PSMA-PET is impossible. As such, Sensitivity ($TP/TP+FN$) and Specificity ($TN/TN+FP$) cannot be assessed. However, obtaining verification of the positive findings pinpointed by the scan using biopsy or follow-up is possible. Therefore, we can document true positive and false positive numbers. Hence, the primary endpoint for BCR trial was the positive predictive value (PPV) on a per-patient and per-region basis of ^{68}Ga -PSMA-11 PET for detection and tumor location confirmed by histopathology. Our hypothesis for success definition was a PPV of 70% or more. Following our sample size and power analysis, we needed close to 110 patients with pathology confirmation. This is challenging to obtain in the biochemical recurrence setting (few patients undergo biopsies in clinical practice). The FDA was able to recognize that limitation and agreed on a pre-defined composite reference standard: other confirmation could be obtained with histopathology, PSA decrease after focal therapy without ADT, or correlation with other imaging modality. We used 3 blinded independent central readers (BICR) for the image analysis.

The UCLA-UCSF *BCR* (Biochemical Recurrence) study met the primary endpoint and was published in *JAMA oncology* as provided below.

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JAMA Oncology | Original Investigation

Assessment of ^{68}Ga -PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer

A Prospective Single-Arm Clinical Trial

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 Supplemental content

IMPORTANCE In retrospective studies, ^{68}Ga -PSMA-11 positron emission tomographic (PET) imaging improves detection of biochemically recurrent prostate cancer compared with conventional imaging.

OBJECTIVE To assess ^{68}Ga -PSMA-11 PET accuracy in a prospective multicenter trial.

DESIGN, SETTING, AND PARTICIPANTS In this single-arm prospective trial conducted at University of California, San Francisco and University of California, Los Angeles, 635 patients with biochemically recurrent prostate cancer after prostatectomy (n = 262, 41%), radiation therapy (n = 169, 27%), or both (n = 204, 32%) underwent ^{68}Ga -PSMA-11 PET. Presence of prostate cancer was recorded by 3 blinded readers on a per-patient and per-region base. Lesions were validated by histopathologic analysis and a composite reference standard.

MAIN OUTCOMES AND MEASURES Endpoints were positive predictive value (PPV), detection rate, interreader reproducibility, and safety.

RESULTS A total of 635 men were enrolled with a median age of 69 years (range, 44-95 years). On a per-patient basis, PPV was 0.84 (95% CI, 0.75-0.90) by histopathologic validation (primary endpoint, n = 87) and 0.92 (95% CI, 0.88-0.95) by the composite reference standard (n = 217). ^{68}Ga -PSMA-11 PET localized recurrent prostate cancer in 475 of 635 (75%) patients; detection rates significantly increased with prostate-specific antigen (PSA): 38% for <0.5 ng/mL (n = 136), 57% for 0.5 to <1.0 ng/mL (n = 79), 84% for 1.0 to <2.0 ng/mL (n = 89), 86% for 2.0 to <5.0 ng/mL (n = 158), and 97% for ≥ 5.0 ng/mL (n = 173, $P < .001$). Interreader reproducibility was substantial (Fleiss κ , 0.65-0.78). There were no serious adverse events associated with ^{68}Ga -PSMA-11 administration. PET-directed focal therapy alone led to a PSA drop of 50% or more in 31 of 39 (80%) patients.

CONCLUSIONS AND RELEVANCE Using blinded reads and independent lesion validation, we establish high PPV for ^{68}Ga -PSMA-11 PET, detection rate and interreader agreement for localization of recurrent prostate cancer.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: [NCT02940262](https://clinicaltrials.gov/ct2/show/study/NCT02940262) and [NCT03353740](https://clinicaltrials.gov/ct2/show/study/NCT03353740).

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Treatment of patients with biochemically recurrent prostate cancer is guided by disease location and extent. Major guidelines recommend computed tomography (CT), magnetic resonance imaging (MRI), and/or bone scintigraphy at biochemical recurrence. However, these guidelines acknowledge limited sensitivity at low prostate-specific antigen (PSA) levels.¹⁻³ Novel positron emission tomography (PET) radiotracers promise to overcome this limitation, most recently with the approval of ¹⁸F-fluciclovine.^{2,4,5} Among the various PET probes available, ⁶⁸Ga-labeled ligands of the prostate-specific membrane antigen (PSMA) were associated with unprecedented accuracy and effect on treatment in several meta-analyses of retrospective studies.⁶⁻⁸ Although ⁶⁸Ga-PSMA-11 PET has been used extensively on a compassionate use basis and reported in numerous retrospective case series outside of the United States, prospective data are lacking.

Here we report findings from a prospective multicenter trial investigating the positive predictive value (PPV), detection rate, reproducibility, and safety of ⁶⁸Ga-PSMA-11 PET imaging in patients with biochemically recurrent prostate cancer.

Methods

Patients

This is a single-arm prospective multicenter trial. Conduction and data acquisition under separate but clinically identical Investigational New Drug (IND) protocols (attached in the [Supplement](#)) was defined at baseline. Patients were recruited at the University of California, Los Angeles (UCLA, [NCT02940262](#)) and the University of California, San Francisco (UCSF, [NCT03353740](#)). Patients were eligible if they had a history of histopathology-proven prostate adenocarcinoma and biochemical recurrence. Biochemical recurrence was defined as a PSA of 0.2 or more ng/mL measured more than 6 weeks after prostatectomy or a PSA of 2 or more ng/mL rise above nadir following radiation therapy (ASTRO-Phoenix consensus definition).⁹ Patients were enrolled irrespective of prior conventional imaging findings. Exclusion criteria were investigational therapy for prostate cancer, inability to tolerate a PET scan, and another concurrent malignant condition.

Study Design

The Standards for Reporting of Diagnostic Accuracy (STARD) checklist is included in [Supplement 1](#); the STARD flow diagram is shown in [Figure 1](#). The study was initiated, planned, conducted, analyzed, and published by the investigators. No financial support was received from commercial entities. The study was approved by local institutional review boards at UCSF and UCLA, and written informed consent was obtained from all patients. Data were collected in a central REDCap database.

PET Imaging

⁶⁸Ga-PSMA-11 was produced with harmonized release criteria (included in the clinical trial protocol in [Supplement 2](#)). Scans were acquired in accordance with the international guideline.¹⁰ In brief, patients received an average of 5.1 (stan-

Key Points

Question What is the accuracy of ⁶⁸Ga-PSMA-11 positron emission tomographic (PET) imaging for localization of recurrent prostate cancer?

Findings In this prospective single-arm trial of 635 men, ⁶⁸Ga-PSMA-11 PET demonstrated 84% to 92% positive predictive value at 75% overall detection rate in patients with biochemically recurrent prostate cancer and median prostate-specific antigen of 2.1 ng/mL. Agreement among 3 readers of the PET images was substantial.

Meaning ⁶⁸Ga-PSMA-11 PET has high positive predictive value, detection rate, and interreader agreement for localization of recurrent prostate cancer; ⁶⁸Ga-PSMA-11 PET provides early detection of metastases and contributes highly relevant information in a biochemical recurrence setting.

dard deviation, 1.1) mCi of ⁶⁸Ga-PSMA-11 and 20 mg of furosemide at a mean (SD) 64 (13) min before the scan. Furosemide was given to 588 (93%) of 635 patients to minimize pelvic scatter artifacts. Whole-body PET was acquired starting from pelvis to vertex. Depending on patient weight and bed position, emission time was 2 to 5 minutes per bed position. The UCLA investigators performed PET and or computed tomographic (CT) imaging. The UCSF investigators performed PET/CT or PET/MRI based on availability and contraindications. For PET/CT, a diagnostic CT was obtained with the use of a standard protocol (80 to 100 mA, 120 kV) before the PET scan. Intravenous iodinated contrast was administered to 613 (97%) patients.

For PET/MRI, an abbreviated pelvis PET/MRI was obtained following a whole-body protocol after the PET scan, and the PET/MRI protocol was reported previously.¹¹

The PET scan was reconstructed by ordered subset expectation maximization (OSEM)-based algorithms. Data from the CT or MRI scan were used for attenuation correction. All imaging devices used underwent successful American College of Radiology Accreditation.

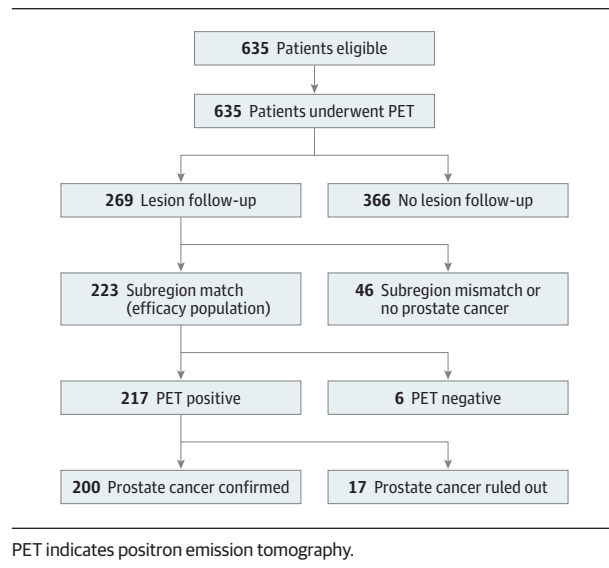
Safety

Patients were monitored for adverse events during and for 2 hours after radiotracer administration. Heart rate and blood pressure were assessed before and after injection of the radiotracer. Patients were also contacted by phone to assess for the development of delayed adverse events.

Image Interpretation

The cases were divided randomly between 9 readers, not involved in study design and data acquisition, to obtain 3 independent reads per patient (O.S., L.E., H.Z., H.I., A.W., C.R., M.E., I.B., H.S.). Readers with more than 5 years PET/CT experience were assigned to PET/CT, readers with more than 5 years PET/MRI experience were assigned to PET/MRI data sets. At baseline, all readers were trained by reviewing 30 PSMA PET biochemical recurrence cases from a previously published data set.¹² Training cases were reviewed in a blinded fashion before the reference standard was revealed. Correct

Figure 1. STARD Flow Diagram for the Efficacy Cohort with Composite Validation



quantification and image display was confirmed for the local workstations. Images were interpreted by visual criteria published previously.¹³ In brief, any focal tracer uptake higher than the surrounding background and not associated with physiological uptake was considered suspicious for malignant abnormality. Stage and PSMA expression were categorized in accordance with Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) guidelines.¹⁴

Data sets for reader interpretation included whole-body PET (attenuation corrected and noncorrected), whole-body postcontrast CT, or whole-body postgadolinium T1 and pelvic T2 MRI. Readers were provided recent PSA level and type of primary therapy (prostatectomy vs radiation therapy), but were blind to all other information. Presence of prostate cancer (positive vs negative) was recorded for 4 regions (prostate bed, pelvic nodes, extrapelvic nonbone, bone), and a total of 21 subregions. Findings were entered directly into the central database. For analysis, majority vote was used in cases of reader disagreement.

Lesion Validation

All patients were followed up for histopathologic analysis, conventional imaging (CT, MRI, and/or bone scan) or serum PSA after focal salvage therapy acquired during clinical routine. Combination of (in descending priority) histopathologic analysis, imaging, and PSA follow-up after local/focal therapy was taken as composite reference standard. Validation was performed by the unblinded local investigators after reviewing images and reports, following prespecified criteria of the study protocol included in Supplement 2. In patients with follow-up, positive ⁶⁸Ga-PSMA-11 PET findings were validated as true or false-positive results. Regions negative on ⁶⁸Ga-PSMA-11 PET, but with subsequently confirmed prostate cancer by histopathologic analysis, were considered false-negative results. True negative was not defined.

Statistical Analysis

The primary endpoint was positive predictive value (PPV) on a per-patient and per-region basis of ⁶⁸Ga-PSMA-11 PET for detection of tumor location confirmed by histopathologic analysis. The null hypothesis was that the true PPV is 0.50, whereas the alternative hypothesis was that the true PPV is at least 0.70. Enrollment was completed when 114 patients had biopsy and/or surgery follow-up, fulfilling protocol requirements for analysis of the per-patient-based primary endpoint (≥ 107 patients with biopsy and/or surgery follow-up, 90% power, 1-sided .01 significance level). The study was ended before target accrual of 1500 patients to allow for analysis of the primary endpoint for FDA New Drug Application (NDA) submission.

Secondary endpoints were per-patient and per-region PPV confirmed by composite validation, per-patient and per-region sensitivity (SE) confirmed by histopathologic validation, per-patient detection rate stratified by PSA and PSA doubling time, inter-reader agreement, and safety. Impact on treatment was reported previously for a subset of the UCLA cohort.¹⁵ Detection rate was defined as proportion of patients with PSMA PET positive results, independent of the reference standard. The PPV confidence interval (CI) in the region-based analysis was calculated using logistic random-effects models.¹⁶ All other PPV and SE confidence intervals were calculated using the Wilson score method.¹⁷ Detection rates were compared by χ^2 analysis with a 2-sided significance level of .05. Interreader agreement was determined by Fleiss' κ and interpreted by criteria of Landis and Koch.¹⁸ For logistic random-effects models, SPSS statistical software was used (version 24, IBM Inc). Other statistical analyses were performed with R statistical software (version 3.5.1, R Foundation).

Results

Baseline Characteristics and Follow-up

From September 2016 through October 2017, a total of 635 patients were enrolled (n = 250 [39%] at UCLA; n = 385 [61%] at UCSF). Table 1 shows the clinical characteristics of all patients and the efficacy endpoint cohorts separately. Patients underwent either PET/CT (n = 443 [70%]) or PET/MRI (n = 192 [30%]).

Of 635 patients, 269 (42%) had composite follow-up at a median duration of 9 months. Of the 635 patients, 114 (18%) had histopathologic follow-up. Forty-six of 269 patients (17%) were excluded from efficacy analysis based on PET vs follow-up location mismatch (on a subregion basis) or absence of prostate cancer both on PET and histopathologic analysis (true negative not defined in the study protocol). Thus, efficacy cohorts were 223 patients with composite validation and 93 patients with histopathologic validation (eFigure 1 in Supplement 1).

Detection Rate and Accuracy

Based on independent reads, PET detection rate among all patients was 75%. Detection rate stratified by PSA is given in Table 2 and shown in Figure 2. Two patients with prior PSA levels of 0.2 or more at enrollment but less than 0.2 ng/mL at time of imaging

Table 1. Characteristics of the Patients at Baseline

Characteristic	No. (%)		
	All Patients (N = 635)	Efficacy Cohort	
		Composite (N = 223)	Histopathologic (N = 93)
Age, median (range), y	69 (44-95)	70 (49-88)	71 (49-88)
Initial therapy			
Prostatectomy only	262 (41)	60 (27)	22 (24)
Radiation therapy only	169 (27)	80 (36)	50 (54)
Prostatectomy and salvage radiation therapy	204 (32)	83 (37)	21 (23)
Other prior therapy			
Local salvage therapy	85 (13)	35 (16)	9 (10)
Androgen deprivation	244 (38)	110 (49)	31 (33)
Abiraterone/enzalutamide	15 (2)	13 (6)	1 (1)
Chemotherapy	14 (2)	12 (5)	1 (1)
Bone-targeted treatment	6 (1)	6 (3)	0 (0)
Other	32 (5)	19 (9)	3 (3)
Time from initial therapy to PET, y			
Median (range)	5 (0-33)	6 (0-29)	6 (0-29)
<5	309 (49)	97 (43)	34 (37)
≥5	307 (48)	118 (53)	57 (61)
Not available	19 (3)	8 (4)	2 (2)
Gleason score			
<8	378 (60)	128 (57)	68 (73)
≥8	202 (32)	82 (37)	21 (23)
Not available	55 (9)	13 (6)	4 (4)
PSA, median (range), ng/mL ^a	2.1 (0.1-1154.0)	3.5 (0.1-1154.0)	3.9 (0.1-70.6)
PSA doubling time, median (range), mo ^b	6 (0->120)	6 (1->120)	10 (1-73)

Abbreviations: PSA, prostate-specific antigen; PET, positron emission tomography.

^a Most recent before PET.

^b Determined in accordance with Pound et al.¹⁹

Table 2. ⁶⁸Ga-PSMA-11 PET Detection Rate on a Patient Basis

Stratification	No.	PET-Positive Results, No. (%)	χ ² P Value
All patients	635	475 (75)	
PSA			
<0.5	136	52 (38)	<.001
0.5- <1.0	79	45 (57)	
1.0- <2.0	89	75 (84)	
2.0- <5.0	158	136 (86)	
≥5.0	173	167 (97)	
PSA doubling time, mo ^a			
<6	248	191 (77)	.80
≥6	245	182 (74)	
Not available	142	102 (72)	
PSA nadir after prostatectomy ^b			
<0.1	230	146 (63)	.18
≥0.1	111	81 (73)	
Not available	125	92 (74)	

Abbreviations: PSA, prostate-specific antigen; PET, positron emission tomography.

^a Determined in accordance with Pound et al.¹⁹

^b Determined in accordance with Bianchi et al.²⁰

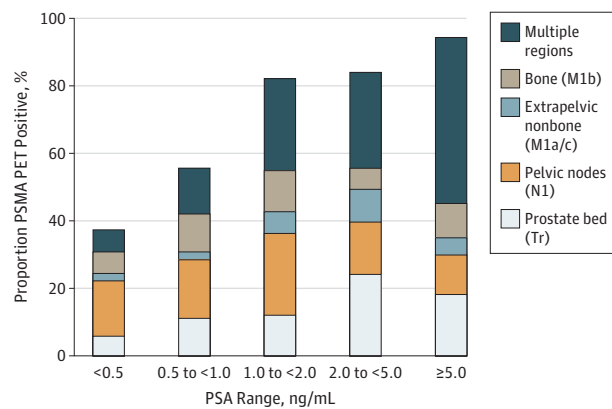
had negative PET results. There was a significant increase in detection rate across the predefined PSA ranges: 38% for <0.5 ng/mL (n = 136); 57% for 0.5 to <1.0 (n = 79), 84% for 1.0 to <2.0 ng/mL (n = 89), 86% for 2.0 to <5.0 ng/mL (n = 158), and 97% for ≥5.0 ng/mL (n = 173) (P < .001). The PSA doubling time and PSA nadir were not significantly associated with PET detection rate. In patients with PSA levels of 1 ng/mL or higher, disease was spread more often to multiple regions and less often

confined to the pelvis (Figure 2). Minimum, median, and maximum PSMA expression score of positive lesions was 1, 2, and 3, respectively, for each of the 4 regions.¹⁴

In total, 223 patients had lesion validation (n = 217 PET positive, n = 6 PET negative). The PPV/SE contingency tables are shown in eFigure 1 in Supplement 1.

In cases with composite validation, 200 of 217 (92%) PET-positive patients and 229 of 249 (92%) PET-positive regions

Figure 2. Detection Rate on a Patient Basis Stratified by PSA and Region



Abbreviations: Tr indicates prostate bed only; N1, pelvic nodes only; M1, extrapelvic only. Proportion of patients with ⁶⁸Ga-PSMA-11 PET positive findings were stratified by PSA range and region of disease in accordance with PROMISE.¹⁴

were characterized as true positive. This resulted in a ⁶⁸Ga-PSMA-11 PET PPV of 0.92 (95% CI, 0.88-0.95) (Table 3). In PET-positive patients with histopathologic validation (n = 87), PPV was 0.84 on a per-patient and per-region basis (primary endpoint; 95% CI, 0.75-0.90 and 95% CI, 0.76-0.91, respectively) (Table 3).

In cases with histopathologic validation, 73 of 79 (92%) confirmed patients and 76 of 84 (90%) confirmed regions were PET positive resulting in an SE of 0.92 (95% CI, 0.84-0.96) on a per-patient and 0.90 (95% CI, 0.82-0.95) on a per-region basis (Table 3). eFigure 2 in Supplement 1 demonstrates examples for PET true and false-positive findings. Detection rate and PPV for individual readers are given in eTable 1 in Supplement 1.

There were 8 regions where findings of PET were judged negative by the blinded readers but biopsy and/or surgery confirmed prostate cancer (PET false-negative, eFigure 1C in Supplement 1). Biopsy and/or surgery was triggered by local reads based on faint focal uptake (n = 4, mean maximum standardized uptake value [SUV_{max}], 5.1), CT/MRI lesions (n = 3; mean size, 0.9 cm), or clinical suspicion (n = 1). Details for PET false-negative regions are given in eTable 2 in Supplement 1.

PSA Response to Focal Salvage Therapy in the Validation Data set

The association of PET with tumor control was not the focus of this study; however, PSA response was collected as part of the lesion validation in 39 patients with focal therapy. Patient characteristics are given in eTable 3 in Supplement 1. Radiation therapy, surgery, or cryoablation was performed for PET lesions in 20 (51%), 16 (41%), or 3 (8%) of 39 patients, respectively. Treatment was not standardized. Patients were identified during follow-up file review by confirming lesion removal and/or targeting in absence of systemic therapy. Surgical specimens confirmed prostate cancer in 16 of 16 (100%) patients. eFigure 3 in Supplement 1 presents a waterfall plot of best PSA response stratified by type of focal therapy. The PSA

follow-up was recorded at a median duration of 6 months (range 1-12 months) after treatment.

Following focal therapy to PET lesions, any PSA decline was seen in 36 of 39 patients (92%). PSA decline was 50% or higher in 31 (80%) patients (PET true positive). In 10 (26%) of these patients, PSA was undetectable.

PET Disease Extent and Reader Agreement

The PET disease extent, categorized by PROMISE is given in eTable 4 in Supplement 1. Prostate cancer was localized in the pelvis only in 219 of 635 patients (35%). Of the 635 patients, 256 (40%) had extrapelvic disease, including nodal/soft tissue metastases (105 [17%]), bone metastases (104 [16%]), or involvement of both (47 [7%]). Inter-reader agreement was substantial for all 4 regions (prostate bed, κ = 0.65; 95% CI, 0.61-0.70; pelvic nodes, κ = 0.73; 95% CI, 0.69-0.78; extrapelvic soft tissue, κ = 0.70; 95% CI, 0.65-0.74; bone, κ = 0.78; 95% CI, 0.73-0.82).

Safety

There was no grade 2 or higher event (eTable 5 in Supplement 1). Grade 1 events were noted in 15 of 635 (2%) patients after the PET scan. None of the events required intervention.

Discussion

Prospective proof of accuracy of a new diagnostic test is prerequisite for approval and reimbursement. This prospective multicenter trial demonstrates high accuracy, reproducibility, and safety of ⁶⁸Ga-PSMA-11 PET in patients with biochemically recurrent prostate cancer. The primary endpoint (PPV \geq 0.70) was met: the positive predictive value for prostate cancer localization ranged from 0.84 to 0.92. The overall detection rate was 75% with significant correlation with PSA. There were no notable adverse events.

There are a number of strengths of this study in comparison to prior retrospective trials evaluating ⁶⁸Ga-PSMA-11 PET. Our prospective study is strengthened by a large cohort size, implementation of blinded reads, and independent lesion validation. Image interpretation was defined by a statistical consensus of trained, international readers randomly assigned to the data sets. Validation of findings was performed locally based on predefined reference standard criteria.

The detection rate reported in this prospective trial falls within the 95% confidence interval of a meta-analysis of previously published detection rates.⁷ In 2015, Eiber et al²¹ and Afshar-Oromieh et al²² reported somewhat higher detection rates, likewise associated with PSA at biochemical recurrence. In their studies, findings were summarized retrospectively in an unblinded manner, which may have led to a higher confidence for prostate cancer detection. Detection rate was similar in a recent expanded cohort of more than 1000 patients.²³

Afshar-Oromieh et al²² and smaller trials employed pathologic correlation in part of their patient cohorts. In line with our findings, ⁶⁸Ga-PSMA-11 PET PPV for localization of prostate cancer was consistently 0.80 or more.^{21,22,24-28} We demonstrate in this prospective multicenter trial that

Table 3. ⁶⁸Ga-PSMA-11 PET Accuracy

Validation Group	Total Regions/Patients, No.	No. (%)		PPV or SE (95%CI)
		Confirmed	Ruled Out	
Positive Predictive Value				
Composite validation				
PET positive (per-patient)	217	200 (92)	17 (8)	0.92 (0.88-0.95)
PET positive (per-region)	249	229 (92)	20 (8)	0.92 (0.88-0.95)
Histopathologic validation				
PET positive (per-patient)	87	73 (84)	14 (16)	0.84 (0.75-0.90)
PET positive (per-region)	90	76 (84)	14 (16)	0.84 (0.76-0.91)
Sensitivity				
Histopathologic findings				
Confirmed (per-patient)	79	73 (92) ^a	6 (8) ^b	0.92 (0.84-0.96)
Confirmed (per-region)	84	76 (90) ^a	8 (10) ^b	0.90 (0.82-0.95)

Abbreviations: PET, positron emission tomography; PPV, positive predictive value; SE, sensitivity.

^a PET positive.

^b PET negative.

⁶⁸Ga-PSMA-11 PET positivity identifies with very high likelihood of prostate cancer. High rates of biochemical response ($\geq 80\%$) in patients with PET-directed focal therapy indicates potential value of the PET information for treatment planning. However, this study focuses on the diagnostic performance of ⁶⁸Ga-PSMA-11 PET. The PSA response was recorded as part of the lesion validation only. The association of PET with tumor control needs to be carefully weighed against potential morbidity and complexity of salvage procedures in clinical trials on patient outcomes.²⁹

Overall, PET false-positive lesions were reported in few patients, most often in the prostate or prostate bed (11 of 17 patients [65%]). False-positive reports may be owing to urinary tracer excretion, inflammation, or posttherapeutic remodeling.³⁰

Half of PET false-negative lesions demonstrated faint tracer uptake. Unblinded local reads, guided by clinical need, triggered biopsy and/or surgery, whereas blinded consensus was negative. Low or absent PSMA expression, small lesion size, and adjacent uptake in the urinary bladder (5 of 8 lesions were in the prostate bed) may have resulted in false-negative findings.^{30,31}

We demonstrate substantial reproducibility of the PET interpretations across 9 randomly assigned international readers for all 4 evaluated regions. Reproducibility is similar to previous findings of our group,¹² which identified optimal experience level and allowed creation of a reader training, which was implemented in this prospective study. High reproducibility of ⁶⁸Ga-PSMA-11 PET interpretation is in line with findings for the approved ⁶⁸Ga-somatostatin-receptor PET.^{32,33} ⁶⁸Ga-PSMA-11 PET Fleiss' κ values (0.65 to 0.78) were higher than those reported for the recently approved ¹⁸F-fluciclovine PET (0.36 to 0.57).³⁴

Limitations

Development of a reference standard in patients with biochemically recurrent prostate cancer is challenging. In

patients with low PSA levels (304 [48%] of our patients had PSA levels lower than 2 ng/mL), positive lesions are frequently subcentimeter and difficult to biopsy. Therefore, performing biopsies in this population is frequently not possible or bears high risk of target mismatch. Furthermore, previous retrospective studies document high accuracy of ⁶⁸Ga-PSMA-11 PET, and so mandated biopsy of PET-positive and PET-negative regions was deemed both not feasible and unethical by the investigators. Instead, lesion validation was based on a composite reference standard comprised of histopathologic analysis, PSA levels, and imaging data acquired during clinical routine. As anticipated, owing to current guideline recommendations, few patients received biopsy and/or surgery or imaging under first-line treatment for biochemical recurrence.^{2,3} This may have introduced a selection bias for the lesion validation. Other factors may have negatively impacted the accuracy of the reference standard: size criteria with potentially limited sensitivity and specificity were applied. Based on our validation framework, true negative lesions were not defined and specificity as well as negative predictive value were not determined. ¹⁸F-fluciclovine PET, which may have complemented the reference standard, was not approved at the time of study initiation. Comparison of ⁶⁸Ga-PSMA-11 vs ¹⁸F-fluciclovine PET is currently under investigation in a subsequent trial at UCLA (ClinicalTrials.gov identifier, [NCT03515577](https://clinicaltrials.gov/ct2/show/study/NCT03515577)).

Conclusions

We established high detection rates, positive predictive value, inter-reader reproducibility, and safety of ⁶⁸Ga-PSMA-11 PET for localization of biochemically recurrent prostate cancer in a prospective multicenter trial. The primary endpoint was met: ⁶⁸Ga-PSMA-11 PET demonstrated 84% to 92% positive predictive value at 75% overall detection rate.

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Study supervision: Fendler, Calais, Eiber, Rischpler, Czernin, Hope.

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Supplementary Online Content

Fendler WP, Calais J, Eiber M. Assessment of ^{68}Ga -PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial [published online March 28, 2019]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.0096

eFigure 1. Contingency tables for Positive Predictive Value (PPV) and Sensitivity (SE).

eFigure 2. Examples of true positive (A-D) and false positive (E-H) PET/CT Findings.

eFigure 3. Best PSA response following Focal Therapy to PET lesions.

eTable 1. Positive Predictive Value (PPV) among individual Readers.

eTable 2. PET false negative regions.

eTable 3. Characteristics of the Patients with PSA response following Focal Therapy.

eTable 4. miTNM Stage by PSMA PET.

eTable 5. Safety.

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Contingency tables for Positive Predictive Value (PPV) and Sensitivity (SE). In total, 223 patients had validation (n=217 PET positive, n=6 PET negative). Data are shown separately for **(A)** PET positive with composite versus **(B and C)** PET positive/negative with histopathology validation on per-patient and per-region basis. *LL denotes lower limit, UL denotes upper limit.

A Composite validation

	N	Confirmed	Ruled-out	PPV	95% CI LL*	95% CI UL*
PET positive (per-patient)	217	200	17	0.92	0.88	0.95
PET positive (per-region)	249	229	20	0.92	0.88	0.95

B Histopathology validation (per-patient)

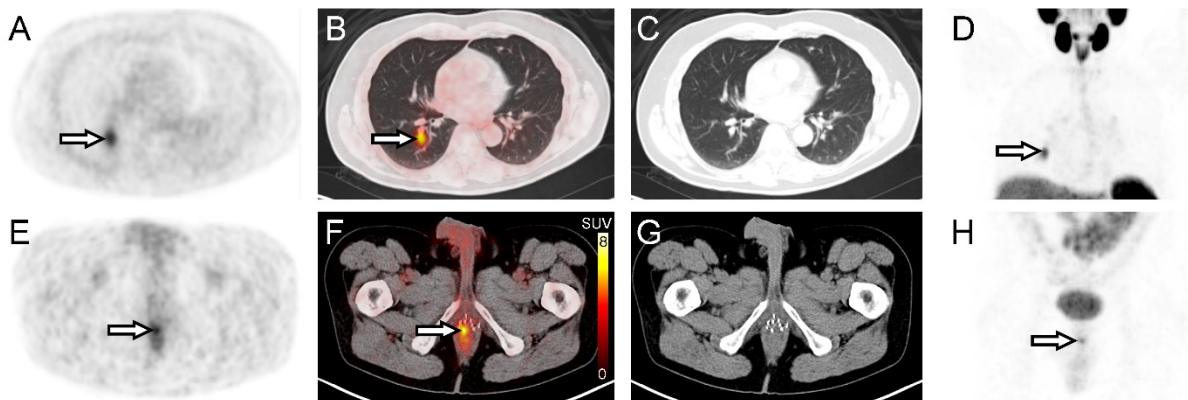
	N	Confirmed	Ruled-out	PPV	95% CI LL*	95% CI UL*
PET positive	87	73	14	0.84	0.75	0.90
PET negative	6	6	not defined			
	SE	0.92				
	95% CI LL*	0.84				
	95% CI UL*	0.96				

C Histopathology validation (per-region)

	N	Confirmed	Ruled-out	PPV	95% CI LL*	95% CI UL*
PET positive	90	76	14	0.84	0.76	0.91
PET negative	8	8	not defined			
	SE	0.90				
	95% CI LL*	0.82				
	95% CI UL*	0.95				

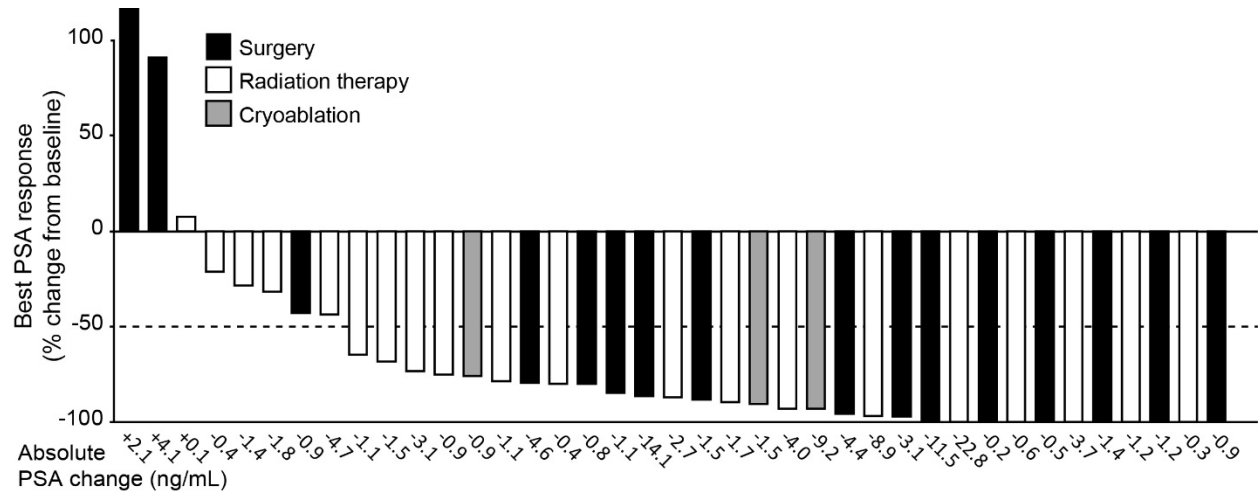
eFigure 2. Examples of true positive (A-D) and false positive (E-H) PET/CT Findings.

⁶⁸Ga-PSMA-11 PET (A, E), PET/CT (B, F), CT (C, G) and PET maximum intensity projection images (D, H) are shown. (A-D) Lung metastasis was diagnosed based on focal right lower lobe uptake (arrow). Abnormal mucosa was noted on bronchoscopy and endobronchial biopsy confirmed invasion by prostate cancer. (E-H) Focal uptake (arrow) led to suspicion of local recurrence after brachytherapy. Ten core biopsy of the uptake area was negative for prostate cancer.



eFigure 3. Best PSA response following Focal Therapy to PET lesions.

Best PSA response of individual patients (n=39) is shown as percent change from baseline (bars) and given as absolute change in ng/mL. Patients were stratified by treatment.



eTable 1. Positive Predictive Value (PPV) among individual Readers.

Reader	N datasets read		Detection rate (%)	PPV			
	PET/CT	PET/MRI		Composite validation (per-patient)	Histopathology validation (per-patient)	Composite validation (per-region)	Histopathology validation (per-region)
1	235	0	82	0.97	0.95	0.95	0.95
2	237	0	81	0.95	0.88	0.95	0.88
3	236	0	78	0.94	0.91	0.93	0.91
4	237	0	78	0.93	0.86	0.91	0.87
5	231	0	74	0.95	0.91	0.94	0.91
6	37	144	91	0.89	0.77	0.90	0.77
7	42	147	76	0.87	0.76	0.88	0.77
8	34	144	70	0.82	0.64	0.83	0.64
9	37	144	75	0.92	0.88	0.93	0.88

eTable 2. PET false negative regions confirmed by histopathology.

No	Subregion	CT	MRI	PET	Biopsy/Surgery triggered by
1	Prostate bed	no lesion	n/a	SUV _{max} 7.2	PET local read
2	Prostate bed	no lesion	n/a	no lesion	Clinical suspicion
3	Prostate bed	n/a	1.0 cm	no lesion	MRI local read
4	Left seminal vesicle	no lesion	n/a	SUV _{max} 5.5	PET local read
5	Left seminal vesicle	no lesion	n/a	SUV _{max} 3.3	PET local read
6	Mesorectal nodes	0.5 cm	n/a	no lesion	CT local read
7	Retroperitoneal nodes	no lesion	n/a	SUV _{max} 4.5	PET local read
8	Lung	1.3 cm	n/a	no lesion	CT local read

Abbreviation: n/a, not available

eTable 3. Baseline Characteristics of the Patients with PSA response following Focal Therapy (N=39).

Characteristic		N	(%)
Age (years)	Median (Range)	65 (49-82)	
Initial therapy			
	Prostatectomy only	23	59
	Radiation therapy only	8	21
	Prostatectomy and Salvage Radiation therapy	8	21
Other prior therapy			
	Local salvage therapy	5	13
	Androgen deprivation	11	28
	Abiraterone/Enzalutamide	1	3
PET findings			
	No disease*	5	13
	Prostate bed (Tr)	9	23
	Pelvic nodes (N1)	17	44
	Extrapelvic non-bone (M1a/c)	2	5
	Multiple regions	6	15
Type of focal therapy			
	Radiation therapy	20	51
	Surgery‡	16	41
	Cryoablation	3	8
Follow-up duration for PSA response (months)	Median (Range)	6 (1-12)	
Time from initial therapy to PET (years)	Median (Range)	5 (0-19)	
	<5	19	49
	≥5	19	49
	Not available	1	3
T stage			
	<T3	13	33
	≥T3	11	28
	Not available	15	38
Gleason Score			
	<8	23	59
	≥8	14	36
	Missing data	2	5
PSA (ng/mL)**	Median (Range)	1.9 (0.2-21.4)	
PSA doubling time (months)†	Median (Range)	7 (1-45)	
	<6 months	12	31
	≥6 months	22	56
	Not available	5	13

*positive local reads triggered therapy. **most recent before PET. †determined in accordance with Pound et al ¹. ‡Histopathology confirmed prostate cancer in 16 of 16 (100%) patients.

eTable 4. miTNM Stage by PSMA PET.

miTNM stage	N=635	N	%
M0			
	TON0M0	160	25
	TrN0M0	99	16
	TON1M0	105	17
	TrN1M0	15	2
M1			
	TON0M1	107	17
	TON1M1	96	15
	TrN0M1	28	4
	TrN1M1	25	4
M1 subgroups			
	Any M1	256	40
	M1a/c only	105	17
	M1b only	104	16
	Multiple M1	47	7

miTNM stage in accordance with PROMISE². Abbreviation: Tr, prostate bed; N1, pelvic nodes; M1, extrapelvic.

eTable 5. Safety.

System Organ Class	Frequency					
	Grade 1	%	Grade 2	%	Grade ≥3	%
Any	15	2	0	0	0	0
Gastrointestinal Disorders						
Nausea	2	0	0	0	0	0
Diarrhea	3	0	0	0	0	0
Dysphagia	1	0	0	0	0	0
Nervous System Disorders						
Headache	2	0	0	0	0	0
Dizziness	1	0	0	0	0	0
Paresthesia	1	0	0	0	0	0
Insomnia	1	0	0	0	0	0
Skin and subcutaneous Tissue Disorders						
Rash	1	0	0	0	0	0
General Disorders and Administration Site Conditions						
Fatigue	1	0	0	0	0	0
Injection site pruritus	1	0	0	0	0	0
Cardiac and Renal Disorders						
Renal calculi	1	0	0	0	0	0

References

1. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281(17):1591-1597.
2. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. *J Nucl Med*. 2018;59(3):469-478.

Article #2:

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 (n=764).

In the primary staging setting, the determination of pelvic nodal invasion is crucial for staging. Here because patients undergo pelvic nodal dissection all true and false negative numbers can be obtained. The primary endpoint of this trial was the diagnostic efficacy performances (Se, Spe, PPV, NPV) of 68Ga-PSMA-11 PET for the detection of regional nodal metastases compared to histopathology at radical prostatectomy on a per patient basis and using nodal regional correlation (left/right/other) in patients with intermediate to high-risk prostate cancer. Our hypothesis for success definition was a Sensitivity of 65% of PSMA-PET. For this, we needed 61 patients with nodal disease per pathology to have sufficient statistical power. We used 3 blinded independent central readers (BICR) for the image analysis.

The UCLA-UCSF *Pre-RP* (Pre-Radical Prostatectomy) study was published in *JAMA oncology* and is provided below.

Of note, the sensitivity was 40% and the study did not meet the primary endpoint.

However, a high proportion (64%) of patients did not undergo prostatectomy. The study was open label and the PSMA-PET results were used for treatment decisions. As such, patients with more extensive disease on PET underwent treatments other than prostatectomy which represents a major impact of the scan on patient care.

It is also important to highlight the limitation of the spatial resolution of PET: 90% of the lymph nodes with a tumor deposit of 5 mm (short axis) can be detected by PSMA-PET whereas only 50% of the lymph nodes with a tumor deposit of 2 mm (short axis) are detected by PSMA-PET (50). Micrometastases induce false negative findings. If a PSMA-PET scan is negative for pelvic nodal disease, it means either the patient has no disease, or the disease is too small to be seen. Therefore, a PSMA-PET scan negative for extra-prostatic disease (N0 M0) must not preclude loco-regional therapy (pelvic nodal dissection or irradiation) if intended for cure. A PSMA-PET scan negative for extra-prostatic disease (N0 M0) is prognostic of better outcome after local therapy. In a 3-yr follow-up study of the surgical cohort evaluated in our UCLA-UCSF *Pre-RP* trial, we demonstrated how presurgical PSMA-PET can improve the risk stratification before RP (51).

JAMA Oncology | Original Investigation

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

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IMPORTANCE The presence of pelvic nodal metastases at radical prostatectomy is associated with biochemical recurrence after prostatectomy.

OBJECTIVE To assess the accuracy of prostate-specific membrane antigen (PSMA) ⁶⁸Ga-PSMA-11 positron emission tomographic (PET) imaging for the detection of pelvic nodal metastases compared with histopathology at time of radical prostatectomy and pelvic lymph node dissection.

DESIGN, SETTING, AND PARTICIPANTS This investigator-initiated prospective multicenter single-arm open-label phase 3 imaging trial of diagnostic efficacy enrolled 764 patients with intermediate- to high-risk prostate cancer considered for prostatectomy at University of California, San Francisco and University of California, Los Angeles from December 2015 to December 2019. Data analysis took place from October 2018 to July 2021.

INTERVENTIONS Imaging scan with 3 to 7 mCi of ⁶⁸Ga-PSMA-11 PET.

MAIN OUTCOMES AND MEASURES The primary end point was the sensitivity and specificity for the detection of pelvic lymph nodes compared with histopathology on a per-patient basis using nodal region correlation. Each scan was read centrally by 3 blinded independent central readers, and a majority rule was used for analysis.

RESULTS A total of 764 men (median [interquartile range] age, 69 [63-73] years) underwent 1 ⁶⁸Ga-PSMA-11 PET imaging scan for primary staging, and 277 of 764 (36%) subsequently underwent prostatectomy with lymph node dissection (efficacy analysis cohort). Based on pathology reports, 75 of 277 patients (27%) had pelvic nodal metastasis. Results of ⁶⁸Ga-PSMA-11 PET were positive in 40 of 277 (14%), 2 of 277 (1%), and 7 of 277 (3%) of patients for pelvic nodal, extrapelvic nodal, and bone metastatic disease. Sensitivity, specificity, positive predictive value, and negative predictive value for pelvic nodal metastases were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85), respectively. Of the 764 patients, 487 (64%) did not undergo prostatectomy, of which 108 were lost to follow-up. Patients with follow-up instead underwent radiotherapy (262 of 379 [69%]), systemic therapy (82 of 379 [22%]), surveillance (16 of 379 [4%]), or other treatments (19 of 379 [5%]).

CONCLUSIONS AND RELEVANCE This phase 3 diagnostic efficacy trial found that in men with intermediate- to high-risk prostate cancer who underwent radical prostatectomy and lymph node dissection, the sensitivity and specificity of ⁶⁸Ga-PSMA-11 PET were 0.40 and 0.95, respectively. This academic collaboration is the largest known to date and formed the foundation of a New Drug Application for ⁶⁸Ga-PSMA-11.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: [NCT03368547](https://clinicaltrials.gov/ct2/show/study/NCT03368547), [NCT02611882](https://clinicaltrials.gov/ct2/show/study/NCT02611882), and [NCT02919111](https://clinicaltrials.gov/ct2/show/study/NCT02919111)

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← Invited Commentary
page 1642

+ Supplemental content

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Accurate staging in prostate cancer is key to planning initial treatments. In patients who undergo radical prostatectomy, the presence of pelvic lymph node metastases at time of surgery is correlated with biochemical failure.¹ However, conventional imaging used for staging, including computed tomography (CT), bone scan, and magnetic resonance imaging (MRI), is limited for the detection of metastatic disease, especially for nodal disease.² Therefore, improved detection of metastatic disease prior to definitive therapy is needed.

Molecular imaging using positron emission tomography (PET) improves the detection of metastatic disease, particularly in patients with biochemical recurrence after definitive therapy. Both carbon-11 choline and fluorine-18 fluciclovine are approved by the US Food and Drug Administration (FDA) for imaging of patients with biochemical recurrence and have shown higher detection rates compared with conventional imaging.^{3,4} These agents have also been evaluated, but to a lesser extent, at time of initial staging.⁵

PET imaging targeting the prostate-specific membrane antigen (PSMA) was shown to outperform existing PET imaging agents in patients with biochemical recurrence.^{6,7} For initial staging before definitive therapy, PSMA PET leads to increased diagnostic accuracy and a high management change rate.⁸ Furthermore, PSMA PET has shown promise for detection of pelvic nodal metastasis at initial staging, with an initial retrospective analyses reporting a sensitivity of 66% when using histopathology reference.⁹

In this multicenter study, we set out to prospectively assess the diagnostic accuracy of ⁶⁸Ga-PSMA-11 PET for the detection of pelvic nodal metastases at initial staging in patients with intermediate- to high-risk prostate cancer using 3 blinded independent central readers and a histopathology reference standard. We hypothesized that ⁶⁸Ga-PSMA-11 PET increases the sensitivity for pelvic nodal metastases detection from 46% to 65%.

Methods

Study Design and Participants

This was a prospective multicenter open-label single-arm phase 3 trial of diagnostic efficacy performed at 2 institutions: University of California, Los Angeles (UCLA) (NCT03368547; trial protocol in Supplement 1) and University of California, San Francisco (UCSF) (NCT02611882 and NCT02919111; trial protocol in Supplement 2). The study was conducted under separate but identical Investigational New Drug applications (IND Nos. 127621 and 130649) and was approved by local institutional review boards (IRBs) at UCSF (IRB No. 15-17570) and UCLA (IRB No. 16-001684). Patients were eligible if they had histopathology-proven prostate adenocarcinoma, were planning to undergo a radical prostatectomy, and had intermediate- to high-risk disease as determined by at least 1 of the following: elevated prostate-specific antigen (PSA) level (PSA >10 ng/mL; to convert to µg/L, multiply by 1.0), T-stage (T2b or greater), Gleason score (Gleason score >6), or other risk factors. Results of prior conventional imaging did not influence

Key Points

Question What is the sensitivity and specificity of prostate-specific membrane antigen (PSMA) ⁶⁸Ga-PSMA-11 positron emission tomographic (PET) imaging for the detection of nodal metastases in men with intermediate- to high-risk prostate cancer?

Findings In this prospective single-arm diagnostic imaging trial that included 764 men with intermediate- to high-risk prostate cancer who underwent a ⁶⁸Ga-PSMA-11 PET scan, 277 of whom subsequently underwent radical prostatectomy, the sensitivity and specificity for pelvic nodal metastases were 0.40 and 0.95, respectively, compared with histopathology.

Meaning In men with intermediate- to high-risk prostate cancer, ⁶⁸Ga-PSMA-11 PET imaging may miss small pelvic nodal metastases, and therefore a PSMA PET scan negative for pelvic nodal metastasis does not indicate that a pelvic nodal dissection is not required; these data were the foundation of a New Drug Application for ⁶⁸Ga-PSMA-11.

eligibility. Any prostate cancer therapy prior to prostatectomy was an exclusion criterion, including androgen deprivation therapy, neoadjuvant chemotherapy, radiotherapy, or any other focal ablation techniques. Written informed consent was obtained from all patients. Prescreening failure patients were not tracked prior to enrollment and imaging. Data were collected in a central REDCap database. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Procedures

⁶⁸Ga-PSMA-11 PET Imaging

All patients underwent a single ⁶⁸Ga-PSMA-11 PET study. 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 guidelines.¹⁰ Target injected activity was 185 MBq (5 mCi) (allowed range, 111-259 MBq [3-7 mCi]), and patients received a mean (SD) of 196 (35) MBq (5.3 [0.9] mCi). Target uptake period was 60 minutes (allowed range, 50-100 minutes), and image acquisition began a mean (SD) of 65 (12) minutes after injection. Patients were imaged using either a PET/CT or PET/MRI; 152 patients were imaged using PET/MRI (63 in the surgical cohort and 89 in the nonsurgical cohort). For PET/CT, a diagnostic CT scan (200-240 mAs, 120 kV) with 5-mm slice thickness was performed. For PET/MRI, an abbreviated pelvis PET/MRI was obtained followed by a whole-body MRI.¹¹ 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). Intravenous contrast media (iodinated or gadolinium) was administered in 703 of 764 patients (94%).

Image Interpretation

Each ⁶⁸Ga-PSMA-11 PET study was read locally by board-certified nuclear medicine physicians with access to all medical information to generate clinical reports. The ⁶⁸Ga-PSMA-11 PET images and report were sent to the referring physician, and treatment decisions were allowed to be based on the PET results. Patients who did not undergo prostatectomy were not included in the primary efficacy population and did not undergo central imaging review.

Each imaging study of the primary efficacy population (patients who underwent radical prostatectomy) was read by 3 blinded independent central readers, not involved in study design and data acquisition. In total, 6 blinded readers (F.B., F.C., A.F., S.M.S., M.U., and H.D.Z.) were used from outside institutions and were required to complete a training on 30 cases from a previously published data set.¹² Anonymized data sets for reader interpretation included attenuation-corrected PET images and contrast-enhanced CT or T1-weighted images postgadolinium and small field of view pelvic T2 images. Diffusion and dynamic contrast-enhanced images were not provided to readers for PET/MRI. Images were interpreted by visually using PROMISE (Prostate Cancer Molecular Imaging Standardized Evaluation) criteria: focal tracer uptake higher than surrounding background and not attributable to physiological uptake or known pitfall is considered suspicious for malignant neoplasm.¹³ Readers assessed the presence of prostate cancer (positive vs negative) for 5 regions: prostate bed (T), pelvic lymph nodes (N), extrapelvic nodes (M1a), bone (M1b), or other organ (M1c). Pelvic lymph nodes were subdivided by side and location (left, right, other). Other included perivesical, perirectal, and presacral areas. Findings were entered by the readers directly into the central REDCap database. For analysis, a centralized per-region majority rule was generated by the local investigators.

Safety

Vital signs were recorded before and after radiotracer injection. Patients were monitored for self-reported adverse events up to 2 hours after injection. Finally, patients were contacted by phone 1 to 3 days to evaluate for delayed adverse events.

Follow-up and Histopathology Correlation

Patients were followed up after imaging by unblinded local investigators, who collected subsequent management. In patients who underwent prostatectomy after imaging, the surgical pathology report was obtained. The surgical approach was not standardized, and no resection template was required. The investigators coded the histopathology reference standard as negative or positive for pelvic lymph node metastasis. The size, number, and location (left, right, and other for perivesical, perirectal and presacral areas) of the pelvic lymph nodes were recorded.

Regions positive on imaging reads, based on majority rule, and positive on pathology were considered true positive (TP); regions positive on imaging without corresponding positive pathology finding were considered false positives (FPs); regions

negative on imaging but positive on pathology were considered false negatives (FNs); and regions negative on imaging and pathology were considered true negatives (TNs). If a patient had a TP region, the patient was considered TP on the patient level. Patients were subsequently classified as FP, FN, and TN based on regional results.

Outcomes

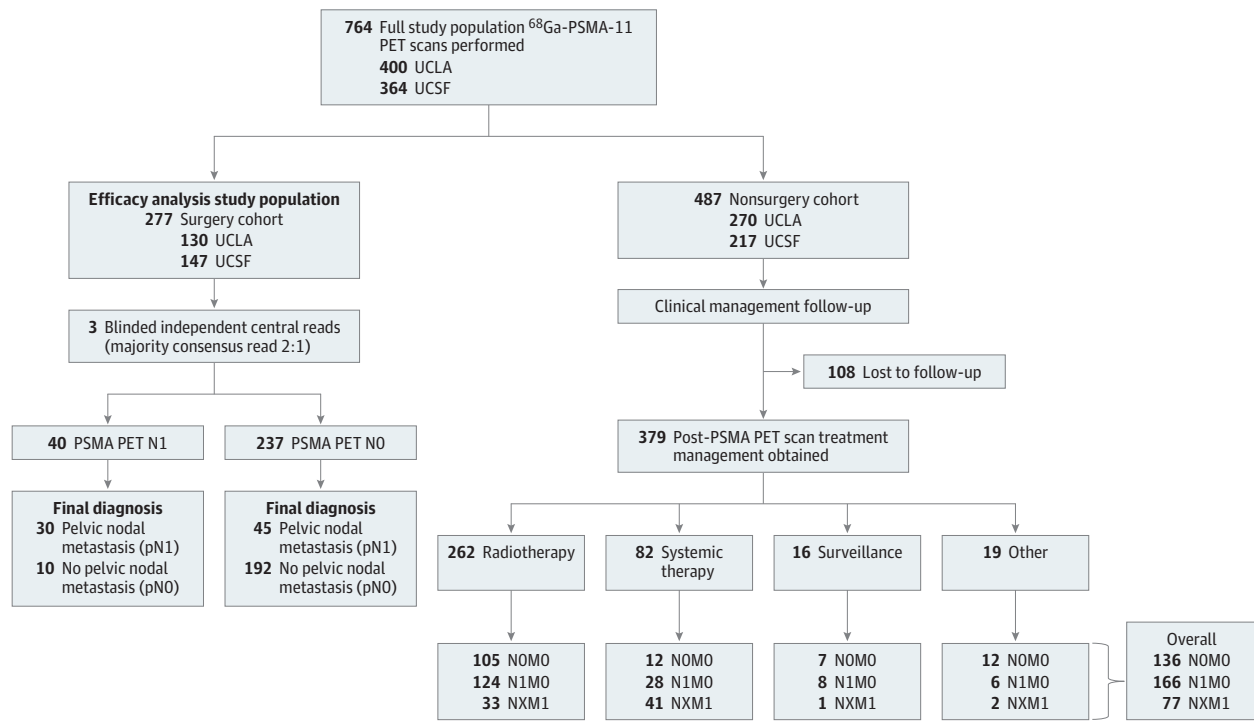
The primary end points of the study were the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ⁶⁸Ga-PSMA-11 PET for the detection of regional nodal metastases compared with pathology at radical prostatectomy on a per-patient basis using nodal regional correlation (left, right, other).

Statistical Analysis

Based on a retrospective analysis, the hypothesis was an increase in sensitivity for pelvic nodal metastasis detection from 46% to 65%.⁹ A statistical power analysis established prospectively that a sample size of 68 patients with positive nodal metastases per histopathology provides at least 80% power and a significance level of .01. We required 226 patients to undergo prostatectomy with the assumption that 30% of patients with intermediate- to high-risk prostate cancer would have pelvic lymph nodes metastasis at prostatectomy (pN1). Initially we estimated that 25% of patients would not undergo prostatectomy, therefore requiring a total sample size of 302 patients. Based on an interim preliminary analysis, the sample size was increased because a lower percentage of patients underwent prostatectomy (123 of 325 [38%]). The interim analysis was unplanned and performed in 2018 for the purpose of a pre-New Drug Application meeting with the FDA. The data from the unplanned interim analysis included blinded reads and correlation with pathologic results. These results are available in the prescribing information for ⁶⁸Ga-PSMA-11.¹⁴

Descriptive statistics were used, including median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. Confidence intervals were calculated using the Wilson score method. Wilcoxon sum rank test was used to compare the distributions of age and PSA between the 2 cohorts; and χ^2 test was used to assess if grade, low/high PSA level, and D'Amico risk were different between the 2 cohorts. A 2-sample *t* test was used to test the difference in average nodal sizes between positive and negative lesions. A χ^2 test was used to determine the association of Gleason score, PSA level, D'Amico risk, and node size with accuracy measurements. Specifically, to assess the outcome of PSA level on sensitivity, we compared the proportion of TP among the positive patients between low PSA level (<11 ng/mL) vs high PSA level (>11 ng/mL) by χ^2 test. We performed a similar analysis for node size, using a 1-cm cut point. Interreader agreement was determined by Fleiss' κ and interpreted by criteria of Landis and Koch by region.¹⁵ A *P* value less than .05 was considered significant. Statistical analyses were performed with R, version 3.5.1 (R Foundation).

Figure. CONSORT Flow Diagram



PET indicates positron emission tomography; PSMA, prostate-specific membrane antigen; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.

Table 1. Baseline Characteristics

Characteristic	No. (%)			P value
	Total	Surgery cohort	Nonsurgery cohort	
No. (%)	764 (100)	277 (36)	487 (64)	NA
Age, median (IQR), y	69 (63-73)	67 (61-71)	70 (65-75)	<.001
PSA, median (IQR), ng/mL	11.4 (6.7-21.2)	11.1 (6.5-18.0)	11.9 (6.8-24.0)	.07
≥20	202 (26)	59 (21)	143 (29)	.73
ISUP grade group ^a				
1	30 (4)	8 (3)	22 (5)	.65
2	128 (17)	49 (18)	79 (22)	
3	151 (20)	59 (21)	92 (19)	
4	186 (25)	63 (23)	123 (26)	
5	264 (35)	98 (35)	166 (34)	
D'Amico risk ^a				
Intermediate	166 (22)	49 (18)	117 (24)	.12
High	590 (78)	225 (81)	365 (75)	

Abbreviations: IQR, interquartile range; ISUP, International Society of Uro pathology; NA, not applicable; PSA, prostate-specific antigen.
SI conversion factor: To convert PSA to µg/L, multiply by 1.0.
^a Numbers do not add up to 764 because of patients with missing data variables.

Results

From December 2015 to December 2019, a total of 764 patients (median [IQR] age, 69 [63-73] years) were enrolled at UCSF (n = 364) and UCLA (n = 400). Prescreen failure patients were not tracked prior to enrollment and imaging. The study CONSORT flowchart is shown in the Figure. Of the 764 patients, 277 (36%) underwent prostatectomy after imaging and were included in the primary analysis. The baseline

characteristics for the surgery and nonsurgery cohorts are provided in Table 1. Of the 277 prostatectomies, 215 (78%) occurred at UCSF or UCLA.

Surgery Cohort: Efficacy Analysis Population

A total of 75 of 277 patients (27%) had regional pelvic node metastasis found on pathology (pN1). Pelvic nodal involvement was unilateral, bilateral, and in other in 45 of 75 (60%), 47 of 75 (63%), and 17 of 75 (23%), respectively (eTable 1 in Supplement 3). A total of 4683 nodes were removed, with a median

Table 2. ⁶⁸Ga-PSMA-11 Test Characteristics for the Composite 3 Blinded Reads and Overall Majority Rule Read

Test characteristic	Read 1	Read 2	Read 3	Majority read
True positive	30	33	29	30
False positive	13	16	15	10
True negative	189	186	187	192
False negative	45	42	46	45
Sensitivity ^a	0.40 (0.30-0.51)	0.44 (0.33-0.55)	0.39 (0.28-0.50)	0.40 (0.30-0.51)
Specificity ^a	0.94 (0.89-0.96)	0.92 (0.88-0.95)	0.93 (0.88-0.95)	0.95 (0.91-0.97)
PPV ^a	0.70 (0.55-0.81)	0.67 (0.53-0.79)	0.66 (0.51-0.78)	0.75 (0.60-0.86)
NPV ^a	0.81 (0.75-0.85)	0.82 (0.76-0.86)	0.80 (0.75-0.85)	0.81 (0.76-0.85)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PSMA, prostate-specific membrane antigen.

^a 95% CIs in parentheses.

(IQR) of 17 (10-22) nodes per patient. In 15 of 277 patients (5.5%), no lymph nodes were reported in the pathology report. The median (IQR) size of the largest positive lymph node on pathology per patient was 6 (3-10) mm.

Based on the majority reads, ⁶⁸Ga-PSMA-11 PET was positive in 40 of 277 (14%), 2 of 277 (1%), and 7 of 277 (3%) patients for pelvic nodal, extrapelvic nodal, and bone disease. On a per-patient level, the sensitivity, specificity, PPV, and NPV of ⁶⁸Ga-PSMA-11 PET based on the majority reads were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85). Results for individual readers are provided in **Table 2**. In a post hoc analysis that excluded the 15 patients with no nodes on pathology, the sensitivity, specificity, PPV, and NPV were 0.41 (95% CI, 0.36-0.47), 0.95 (95% CI, 0.91-0.97), 0.74 (95% CI, 0.69-0.79), and 0.82 (95% CI, 0.76-0.86).

We retrospectively reviewed patients characterized as having FPs and obtained their postsurgery follow-up; 5 of 10 (50%) patients had PSA persistence after surgery, and a postsurgery ⁶⁸Ga-PSMA-11 PET scan showed the same PET-positive lymph nodes as the presurgery scan. Consequently, it is highly likely that these nodes were not removed, and therefore the histopathology reference standard might have been inaccurate. If one were to consider these nodes as TP lesions, the sensitivity, specificity, and PPV would be 0.44 (95% CI, 0.33-0.55), 0.97 (95% CI, 0.94-0.99), and 0.88 (95% CI, 0.74-0.95).

Additionally, we performed a post hoc retrospective analysis to determine if PSA level, Gleason score, D'Amico risk, and node size were associated with the sensitivity, specificity, PPV, and NPV of ⁶⁸Ga-PSMA-11 PET (eTable 2 in **Supplement 3**). Larger pelvic lymph node metastasis size (>10 mm) was associated with higher sensitivity of ⁶⁸Ga-PSMA-11 PET for the detection of pelvic nodal metastases. True-positive and FN pelvic lymph node metastasis measured an average of 1.1 cm and 0.6 cm, respectively ($P = .01$). There was insufficient evidence to conclude that Gleason score, PSA level (categorized) and D'Amico risk were associated with sensitivity.

Interreader Variability

On a per-region level, interreader agreement was substantial for right-sided nodes ($\kappa = 0.61$; 95% CI, 0.55-0.67) and left-sided nodes ($\kappa = 0.66$; 95% CI, 0.60-0.71). For other nodes, there was moderate interreader agreement ($\kappa = 0.52$; 95% CI, 0.46-0.58).

Nonsurgery Cohort

Of the 764 patients, 487 (64%) did not undergo prostatectomy, of which 108 patients had no follow-up data. In the nonsurgery cohort, the unblinded local reads were positive for pelvic lymph node disease (N1), extrapelvic lymph node disease (M1a), and bone metastatic disease (M1b) in 252 of 487 (52%), 47 of 487 (10%), and 62 of 487 (13%), respectively. In the subset of patients with follow-up, the majority of nonsurgery patients underwent radiotherapy (262 of 379 [69%]), followed by systemic therapy (82 of 379 [22%]), surveillance (16 of 379 [4%]), or other treatments (19 of 379 [5%]). If we break down the nonsurgery cohort into NOMO, N1MO, and NXM1 based on local reads, the rate of radiotherapy was higher with NOMO and N1MO vs NXM1 (77% [105 of 136] and 75% [124 of 166] vs 43% [33 of 77]), and the rate of systemic therapy was higher with NXM1 vs NOMO and N1MO (53% [41 of 77] vs 9% [12 of 136] and 16% [28 of 166]) (Figure).

Safety Evaluation

There was no grade 2 or higher adverse event. Grade 1 events were reported in 44 of 764 patients (6%), and none required intervention. The most common adverse events were diarrhea ($n = 16$ of 764 [2%]) and fatigue ($n = 6$ of 764 [1%]). Rash and nausea were reported by 4 patients apiece. These events were not considered to be related to the study drug and possibly were related to contrast administration.

Discussion

In this multicenter prospective phase 3 imaging trial using 3 blinded independent central readers, the sensitivity and specificity of ⁶⁸Ga-PSMA-11 PET for the detection of pelvic nodal metastases compared with histopathology were 0.40 and 0.95, respectively. To our knowledge, this study is the largest prospective study using PSMA PET at time of initial staging and was conducted in a cohort of 277 patients with intermediate-to-high-risk prostate cancer. The results of this study were used to support the FDA approval of ⁶⁸Ga-PSMA-11 PET at initial staging.¹⁶

Recent studies comparing ⁶⁸Ga-PSMA-11 with pelvic nodal dissection reported similar sensitivities of 0.42 ($n = 97$), 0.41 ($n = 117$), and 0.38 ($n = 208$).¹⁷⁻¹⁹ Additionally, the multicenter OSPREY trial of ¹⁸F-DCFPyL, which was per-

formed in 252 patients, reported a sensitivity ranging from 0.31 to 0.42 across the 3 blinded independent central readers.²⁰ These recent reports using blinded reads are in line with our results.

It should be noted that the sensitivity of 85% reported in the ProPSMA study⁸ is not comparable to our results: the reported sensitivity was for any metastasis and based on a composite end point with multiple criteria other than histopathology, including the presence and number of metastasis, other imaging modalities, symptoms, or changes in lesion size and PSA level. In ProPSMA, 83 of 126 men (66%) who underwent prostatectomy had pelvic node sampling, and only 14 of 295 patients (4.7%) had pelvic nodes confirmed by histology. The sensitivity and specificity in patients with histologic verification was not provided but would be much lower than 85%.

The study did not meet the predefined threshold sensitivity of 0.65.⁹ Early promising results of ⁶⁸Ga-PSMA-11 were not reproducible as summarized by a recent meta-analysis reporting a weighted sensitivity of 59%, but with a wide range of 23% to 100%.²¹ Most of these early studies were small single-center retrospective studies and did not use blinded independent central readers. It has been documented that wide disease spectrum, nonconsecutive recruitment, open-label reading of tests, and retrospective data collection are associated with higher estimates of diagnostic accuracy.²² We used a centralized majority rule, which decreases the sensitivity compared with consensus reads, which can introduce a non-independent, nonmasked major bias. Additionally, unblinded local reads are guided by clinical need and tend to be more sensitive.²³

Although our study had a lower sensitivity than our predefined threshold, it did demonstrate a high specificity (0.95). It is clear that if the ⁶⁸Ga-PSMA-11 PET is positive, then disease is present. On the other hand, the NPV was 0.81, indicating that 20% of patients who underwent prostatectomy with a negative PET will have nodes on pathology. For this reason, it is important that surgeons do not use a negative PET to forgo a pelvic nodal dissection. Prospective trials based on PSMA PET findings are warranted. Additionally, the sensitivity estimates of the blinded independent readers were similar, and

the interreader agreement was substantial (>0.6), confirming the high reproducibility of PSMA PET imaging.^{12,23}

Limitations

One limitation of our study is the high proportion (64%) of patients who did not undergo prostatectomy, which introduced a bias that likely lowered the reported sensitivity because patients with larger size and number of nodes were treated with nonsurgical approaches. The cause of this is that our study was open label, and the PSMA PET results were used for treatment decision. As such, patients with more extensive disease on PET underwent treatments other than prostatectomy. In the non-surgery cohort, 52% were PSMA PET N1, while in the surgery cohort, only 14% were PSMA PET N1. This removed patients with pelvic nodes metastasis that were more easily detected by PSMA PET from the surgery cohort. This illustrates the rapid clinical acceptance of PSMA PET by uro-oncologists. Even when PSMA PET was a nonapproved research procedure, the referring urologists changed their management from surgery because of disease upstaging. However, this limitation is also a strength of our study, as our sensitivity and specificity rates likely reflect the performance of PSMA PET imaging in the context of guiding urologists in their radical prostatectomies; these metrics reflect real-world practice.

Finally, the histopathology reference standard was not accurate because in 5 patients, PSMA PET-positive lymph nodes were not removed and were considered as FPs. Additionally, 5% of the surgery cohort had no nodes reported in the pathology report, potentially missing additional sites of disease.

Conclusions

In this multicenter prospective phase 3 diagnostic imaging trial in 277 patients with intermediate- to high-risk prostate cancer prior to prostatectomy, the sensitivity and specificity of ⁶⁸Ga-PSMA-11 PET for the detection of pelvic nodal metastases compared with histopathology on a patient level were 0.40 and 0.95, respectively. This academic collaboration is the largest to date and formed the foundation of a New Drug Application for ⁶⁸Ga-PSMA-11.

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Conflict of Interest Disclosures: Dr Hope reported grants from National Cancer Institute (National Institutes of Health [NIH]) and Prostate Cancer Foundation during the conduct of the study; grants from Clovis Oncology and Philips; and personal fees from Curium, Blue Earth Diagnostics, and Ipsen outside the submitted work. Dr Eiber reported personal fees and a cooperation project from Blue Earth Diagnostics and personal fees from Progenics and Point Biopharma outside the submitted work; in addition, Dr Eiber had a patent for rhPSMA issued Scintomics/Blue Earth Diagnostics. Dr Behr reported grants from Commercialization Transition Track (Small Business Innovation Research NIH grant), personal fees from Progenics (honorarium), and personal fees from AAA Novartis (scientific advisory board) outside the submitted work. Dr Zhang reported personal fees from Smith-Kettlewell Eye Research Institute and Raydiant Oximetry, Inc outside the submitted work. Dr Schwarzenböck reported grants from Novartis and personal fees from ABX CRO outside the submitted work. Dr Cooperberg reported personal fees from Janssen, Astellas, AstraZeneca, Dendreon, Merck, Bayer, Foundation Medicine, and Veracyte outside the submitted work. Dr Carroll reported personal fees from Progenics (advisory board) during the conduct of the study; and serving on an advisory board for Nutcracker Therapeutics and receiving personal fees for serving on an advisory board for Insightec outside the submitted work. Dr Herrmann reported research grants from Theragnostics; personal fees from Bayer (speakers bureau, advisory board), Sofie Biosciences (board member, consultant), SIRTEX (speakers bureau), Adacap/Novartis (advisory board, consultant, speakers bureaus), Curium (advisory board, consultant), BTG/BSC (research, advisory board, speakers bureau), Ipsen (advisory board), Siemens Healthineers (speakers bureau, advisory board), GE Healthcare (advisory board), Amgen (advisory board, consultant), Y-mAbs Therapeutics (data monitoring committee), Aktis Oncology (consultant), and Pharma 15 (board member); and nonfinancial support from ABX (consultant) outside the submitted work. Dr Czernin reported being founder and shareholder of Trethera Corporation and Sofie Biosciences. Dr Fendler reported personal fees from RadioMedix, Bayer, Parexel, and BTG outside the submitted work. Dr Calais reported grants from Progenics for Pyl Research Access Program, investigator-initiated trial NCT04457245; personal fees (consultant) from POINT Biopharma, Curium Pharma, GE Healthcare, Blue Earth Diagnostics, Janssen Pharmaceuticals, and Progenics; personal fees (blinded independent central reader) from Advanced Accelerator Applications, Radiomedix, Progenics, and Exini; and personal fees (speaker fees) from IBA

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Invited Commentary

Prostate-Specific Membrane Antigen Positron Emission Tomography and the New Algorithm for Patients With Prostate Cancer Prior to Prostatectomy

Joseph R. Osborne, MD, PhD; Neil H. Bander, MD; Scott T. Tagawa, MD, MS

After several decades of development of prostate-specific membrane antigen (PSMA) as a biomarker for prostate cancer, a recent series of studies have defined its diagnostic clinical significance in patients with prostate cancer, including prior to radical prostatectomy, as in the diagnostic imaging study by Hope et al¹ in this issue of



Related article page 1635

JAMA Oncology. Importantly, these data comport with a similarly designed prospective trial evaluating PSMA positron emission tomography (PET) diagnostic performance of a similar agent (¹⁸F-DCFPyL) in cohort A of the OSPNEY trial.² There is a clear message from both trials: clinicians taking care of patients with high-risk prostate cancer being assessed for prostatectomy can use a positive PET scan as a true positive (0.95 [95% CI, 0.92-0.97]¹ vs 0.98 [95% CI, 0.94-0.99] in the OSPNEY trial²), whereas a negative scan cannot be used to exclude disease or inform nodal dissection (both studies had a diagnostic sensitivity near 40%). One methodologic issue to mention is that clinicians were not blinded to PSMA PET results, and patients with evidence of extraprostatic disease may not have gone on to surgery. Post hoc analysis of these “negative” PET studies in both investigations also have a common message. Both demonstrate that many of the false-negative studies are found in patients who have pathologically PSMA-positive lymph nodes that are smaller than 1.0 cm or 0.5 cm, below the resolution of this technology. These truly micrometastatic lesions may have a better prognosis than those identified by imaging and lead to the hypothesis that these are likely the patients with long-term benefit from surgical resection.

In addition, false-positive scans have been described, but not all false-positive scans are actually correctly categorized as such. Hope et al¹ describe a subset of patients with positive ⁶⁸Ga-PSMA-11 imaging results with negative pathology of dissected lymph nodes. These patients then had persistent de-

tectable postoperative prostate-specific antigen as well as positive postoperative PSMA imaging results. These cases might be better characterized as false-negative lymph node dissections. An additional area of ongoing research is PSMA-radioguided surgery using intraoperative probes to assist with identification of areas to resect beyond typical lymph node dissection templates.³

The study by Hope et al¹ provided the context for US Food and Drug Administration approval of ⁶⁸Ga-PSMA-11 PET and has provided a road map for how preintervention PSMA PET imaging will guide the appropriateness of radical prostatectomy for the referring urologists. As such, these results are practice changing for the nuclear medicine physicians, urologists, and medical oncologists who will manage this cohort of patients. While there are radiochemical and practical differences between ⁶⁸Ga-PSMA-11 and ¹⁸F-DCFPyL, in the clinic, both present notable improvements over previously standard imaging modalities. The similar positive and negative predictive values across studies suggest that ⁶⁸Ga-PSMA will not be inferior to ¹⁸F-PSMA for this and probably any other diagnostic task. It is likely that a large number of patients would need to be assessed in a head-to-head study to see meaningful differences. It is possible that novel tracers or imaging techniques might lead to advances in the future.

There were many published studies and meta-analyses that hinted at the qualities and value of a variety of PSMA PET agents in these patients,^{4,5} but to our knowledge, this is the first for ⁶⁸Ga-PSMA-11 with a real-world prospective design that simulated a viable practice pattern. The prior designed prospective clinical trial (proPSMA)⁶ was an important step, but it included composite end points and a small number of patients who underwent prostatectomy with pathologically positive lymph nodes, which likely affected the reported sensitivity of

Article #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 (n=50)

In the following study, we compared the new imaging technique (PSMA-PET) to the reference technique by standard-of-care for biochemical recurrence localization (18F-Fluciclovine PET, AXUMIN®, Blue Earth Diagnostics). 18F-fluciclovine is an amino-acid metabolic PET tracer which was FDA approved in 2016 and recommended by NCCN guidelines.

In a patient population with low PSA levels (<2.0 ng/ml), our hypothesis for success definition was a 22% difference in detection rates in favor of PSMA. For such a difference a sample size of 50 patients was needed. Each PET scan was interpreted by three independent masked readers.

Primary and secondary endpoints were met: PSMA-PET/CT detection rates at the patient level, and at the regional level for pelvic lymph node regions and for extra-pelvic metastasis were more than twice as high as those for 18F-fluciclovine PET/CT.

The results of this prospective head-to-head comparison study provided evidence to use PSMA-PET preferentially when PET/CT imaging is considered for subsequent treatment management decisions in patients with biochemical recurrence and low PSA concentrations (≤ 2.0 ng/mL). The NCCN, AUA, EAU and ESMO now all recommend PSMA-PET imaging in their guidelines.

The study was published in *The Lancet Oncology* and is provided below.

¹⁸F-fluciclovine PET-CT and ⁶⁸Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial



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Summary

Background National Comprehensive Cancer Network guidelines consider ¹⁸F-fluciclovine PET-CT for prostate cancer biochemical recurrence localisation after radical prostatectomy, whereas European Association of Urology guidelines recommend prostate-specific membrane antigen (PSMA) PET-CT. To the best of our knowledge, no prospective head-to-head comparison between these tests has been done so far. The aim of this study was to compare prospectively paired ¹⁸F-fluciclovine and PSMA PET-CT scans for localising biochemical recurrence of prostate cancer after radical prostatectomy in patients with low prostate-specific antigen (PSA) concentrations (<2.0 ng/mL).

Methods This was a prospective, single-centre, open-label, single-arm comparative study done at University of California Los Angeles (Los Angeles, CA, USA). Patients older than 18 years of age with prostate cancer biochemical recurrence after radical prostatectomy and PSA levels ranging from 0.2 to 2.0 ng/mL without any prior salvage therapy and with a Karnofsky performance status of at least 50 were eligible. Patients underwent ¹⁸F-fluciclovine (reference test) and PSMA (index test) PET-CT scans within 15 days. Detection rate of biochemical recurrence at the patient level and by anatomical region was the primary endpoint. A statistical power analysis demonstrated that a sample size of 50 patients was needed to show a 22% difference in detection rates in favour of PSMA (test for superiority). Each PET scan was interpreted by three independent masked readers and a consensus majority interpretation was generated (two vs one) to determine positive findings. This study is registered with ClinicalTrials.gov, number NCT02940262, and is complete.

Findings Between Feb 26, 2018, and Sept 20, 2018, 143 patients were screened for eligibility, of whom 50 patients were enrolled into the study. Median follow-up was 8 months (IQR 7–9). The primary endpoint was met; detection rates were significantly lower with ¹⁸F-fluciclovine PET-CT (13 [26%; 95% CI 15–40] of 50) than with PSMA PET-CT (28 [56%; 41–70] of 50), with an odds ratio (OR) of 4.8 (95% CI 1.6–19.2; $p=0.0026$) at the patient level; in the subanalysis of the pelvic nodes region (four [8%; 2–19] with ¹⁸F-fluciclovine vs 15 [30%; 18–45] with PSMA PET-CT; OR 12.0 [1.8–513.0], $p=0.0034$); and in the subanalysis of any extrapelvic lesions (none [0%; 0–6] vs eight [16%; 7–29]; OR non-estimable [95% CI non-estimable], $p=0.0078$).

Interpretation With higher detection rates, PSMA should be the PET tracer of choice when PET-CT imaging is considered for subsequent treatment management decisions in patients with prostate cancer and biochemical recurrence after radical prostatectomy and low PSA concentrations (≤ 2.0 ng/mL). Further research is needed to investigate whether higher detection rates translate into improved oncological outcomes.

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Introduction

Treatment of patients with biochemical recurrence of prostate cancer is guided by disease location and extent.^{1,2} Whole-body PET-CT imaging can depict increased L-amino-acid-transporter-1 (LAT1) activity with ¹⁸F-fluciclovine or overexpressed cell-surface proteins such as prostate-specific membrane antigen (PSMA) with ⁶⁸Ga-PSMA-11. Both ¹⁸F-fluciclovine and PSMA PET-CT localise biochemical recurrence with higher

detection rates and sensitivity than conventional imaging (eg, CT, bone scanning, and MRI) and choline PET-CT.^{3,4} For biochemical recurrence localisation, National Comprehensive Cancer Network (NCCN) guidelines recommend the Food and Drug Administration-approved ¹⁸F-fluciclovine PET-CT, whereas European Association of Urology guidelines recommend PSMA PET-CT.^{1,2} Preliminary reports suggest superior detection rates of PSMA PET-CT compared with ¹⁸F-fluciclovine PET-CT.⁵

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See Online for appendix

Research in context

Evidence before this study

Two PET-CT imaging tests for detection and localisation of prostate cancer tumour sites in patients with biochemical recurrence have been introduced in Europe and the USA. ¹⁸F-fluciclovine exploits upregulated amino acid transporter activity whereas the second test targets the prostate-specific membrane antigen (PSMA). It is unknown which test performs better, especially in patients with biochemical recurrence at low PSA concentrations (≤ 2.0 ng/mL) in whom focused salvage therapy could potentially be curative. We did PubMed searches for publications in English comparing ¹⁸F-fluciclovine and PSMA PET-CT at any date using the keywords (“Fluciclovine” AND “PSMA”) OR (“FACBC” AND “PSMA”) on March 13, 2017, Oct 21, 2017, and Nov 19, 2018. No prospective direct comparison between the two PET-CT imaging tests was found.

Added value of this study

Superiority of one over the other test can only be established in a prospective head-to-head comparative study, which, to the

best of our knowledge, has not been done previously. Our study is prospective, using paired studies in the same cohort of patients, and findings are based on external independent masked reads.

Implications of all the available evidence

The collective data from this prospective comparative imaging trial and published studies suggest higher detection rates and reliability of PSMA PET-CT than ¹⁸F-fluciclovine PET-CT in patients with biochemical recurrence and low serum PSA concentrations. Thus, PSMA-targeted PET-CT imaging should become the standard of care in these patients. Whether early detection of biochemical recurrence sites by PET-CT imaging affects patient outcome is the subject of ongoing randomised phase 3 clinical trials (NCT03582774 and NCT03762759).

However, these imaging tests have not been compared prospectively and directly.

Here, we present a prospective head-to-head comparison between ¹⁸F-fluciclovine and PSMA PET-CT for localising biochemical recurrence after radical prostatectomy in patients with low prostate-specific antigen (PSA) concentrations (≤ 2.0 ng/mL). Validation of imaging findings is rarely available in patients with biochemical recurrence. Therefore, assessments of true test sensitivity and specificity for biochemical recurrence detection is difficult, if not impossible. In this setting, the most relevant performance parameter is the detection rate (the proportion of patients with PET-positive findings) that approximates the test sensitivity for prostate cancer detection.⁶ Although some false-positive findings have been reported (eg, mistaken identification of ganglia and ribs trauma as prostate cancer),⁷⁻⁹ the positive predictive value (PPV) of PSMA PET-CT with experienced readers is high (>85%).^{6,10} Hence, we aimed to compare the detection rates of ¹⁸F-fluciclovine and PSMA PET-CT, at the patient level and by anatomical region (pelvic and extra-pelvic localisations). Based on published data^{3,11-15} the hypothesis was a detection rate difference of at least 22% between the two tests in favour of PSMA.

Methods

Study design and participants

This was a prospective, single-centre, open-label, single-arm comparative imaging study done at University of California Los Angeles (UCLA; Los Angeles, CA, USA) using external, anonymised, masked, and independent interpretations of 50 consecutive paired ¹⁸F-fluciclovine and PSMA PET-CT studies. The study was done under an investigational new drug approval protocol

(IND#130649; appendix pp 18–41), approved by the local institutional review board (IRB#17–001885).

Inclusion criteria were histopathologically proven prostate cancer; biochemical recurrence after radical prostatectomy with PSA values of 0.2–2.0 ng/mL at the time of imaging; no previous salvage therapies (including salvage radiotherapy or salvage lymph node dissection); ¹⁸F-fluciclovine and PSMA PET-CT done within 15 days of each other; no change in prostate cancer treatment between the two scans; ability to understand and sign the written informed consent form; age older than 18 years; and Karnofsky performance status of at least 50. Patients were enrolled irrespective of previous conventional imaging findings. Informed written and oral consent was obtained from all patients.

Procedures

All patients had standard-of-care ¹⁸F-fluciclovine and investigational PSMA PET-CT according to guidelines within a maximum time interval of 15 days between the two scans.^{16,17} Patients were asked to fast for more than 4 h and avoid substantial exercise for more than 24 h before ¹⁸F-fluciclovine tracer administration. ⁶⁸Ga-PSMA-11 (Glu-NH-CO-NH-Lys-(Ahx)-[⁶⁸Ga(HBED-CC)]) was used as the PSMA ligand¹⁸ and was obtained from the Biomedical Cyclotron Facility at UCLA. Oral and intravenous CT-contrast was administered for both tests unless obtained at outside institutions or contra-indicated. A 5-mm slice thickness CT scan was used. All PET images acquired from pelvis to vertex were corrected for attenuation, dead time, random events, and scatter. The time per bed position was based on patient weight.¹⁹

PET-CT scans were each interpreted by three independent masked experts (¹⁸F-fluciclovine experts were TB-G, CN, and BS-B; PSMA experts were MSH, TAH,

and CR) who were not involved in study design or data acquisition. The fluciclovine experts did not read the PSMA scans and the PSMA experts did not read the fluciclovine scans. Details of PET-CT experience of each reader are in the appendix (p 1).

Each reader was masked to the interpretations of the five other readers. Anonymised datasets included CT and attenuation-corrected PET images, prostate cancer history, and a spreadsheet with interpretation guidelines (appendix p 17). Readers were instructed to first characterise PET lesions as suspicious or non-suspicious for prostate cancer lesions. CT correlates of the PET-positive lesions were then analysed for disease localisation and to rule out pitfalls.⁷⁻⁹ Readers assessed the presence of prostate cancer (positive *vs* negative) for five regions according to interpretation guidelines:^{7,20,21} prostate bed (T), pelvic lymph nodes (N), extrapelvic nodes (M1a), bone (M1b), or other organ (M1c).

In cases of reader disagreement, regions were rated on the basis of a consensus majority rule (2:1). PET-CT scans were considered positive if any of the five regions were rated positive by a 2:1 majority.

All patients were followed for subsequent biopsies, imaging studies, PSA measurements, and disease management. Treatment decisions were not standardised and were made at the discretion of the referring physician on the basis of all available clinical information, including the non-masked local reports of both PET scans and any other imaging findings. If available, PET-positive regions were categorised by the non-masked UCLA investigators as true or false positive by a composite reference standard (appendix p 41). This composite reference standard included histopathology, follow-up imaging, or PSA decrease after PET-positive lesion-directed therapy without systemic therapy or without whole-pelvic lymph node radiotherapy. PET-negative regions by majority consensus but with subsequently confirmed prostate cancer were considered false negatives. True negative was not defined.

Outcomes

The primary outcome was the detection rate (proportion of patients with PET-positive findings) of ¹⁸F-fluciclovine (reference test) and PSMA PET-CT (index test) for the identification of tumour locations, at the patient level and by anatomical region. The secondary outcomes were detection rates of ¹⁸F-fluciclovine and PSMA PET-CT stratified by PSA value (0.2–0.5 ng/mL *vs* 0.51–1.0 ng/mL *vs* 1.01–2.0 ng/mL); the positive predictive value and sensitivity of ¹⁸F-fluciclovine and PSMA PET-CT in patients with available lesion validation by the composite reference standard; and the inter-reader agreement of ¹⁸F-fluciclovine and PSMA PET-CT studies.

Statistical analysis

Based on published data, detection rates at the patient level for biochemical recurrence localisation at PSA

concentrations of 2 ng/mL or less are 21–59% (estimated mean 47%) for ¹⁸F-fluciclovine PET-CT^{3,11,12} and 61–82% (estimated mean 69%) for PSMA PET-CT.^{13–15} A statistical power analysis established prospectively that a sample size of 50 patients provides at least 86% power to detect the expected difference of 22% between detection rates at the patient level in favour of PSMA PET-CT (test for superiority) assuming a one-sided α of 0.05 (one-sided McNemar exact conditional test).

Descriptive statistics (median and IQR) or frequencies and percentages were computed to summarise demographic, clinical, pathological, and imaging characteristics. Detection rates per patient, per region, and sensitivity of index and reference tests based on majority consensus reads were compared using the two-sided McNemar's test for paired proportions (with odds ratios [ORs] and 95% CIs; Clopper-Pearson Exact method) and two-sided Fisher's exact test for independent proportions. These analyses were also done after stratifying the population by PSA concentrations (<0.5 *vs* 0.51–1.00 *vs* 1.01–2.00 ng/mL). Fleiss multirater κ statistics were computed to assess inter-reader agreement between reviewers for each imaging modality (¹⁸F-fluciclovine and PSMA). Pairwise κ coefficients were used to compare reader performance for the index and reference tests.

To establish the degree of lesion PET-tracer uptake, a post-hoc semiquantitative analysis was done in the subset of patients with concordant PSMA and ¹⁸F-fluciclovine positive findings. The maximum standardised uptake value (SUV_{max}) of each PET-positive lesion was measured by local investigators. Background organ SUV_{mean} was established by placing 3D volumes of interest on the right liver lobe, the descending aorta at the carina level, and the pelvic muscle closest to the lesion. Lesion-to-background ratios were then calculated. The paired *t* test was used to compare SUV_{max} and lesion-to-background ratios.

To establish which other factors might be associated with lesion detection after accounting for PET tracer (¹⁸F-fluciclovine *vs* PSMA), a post-hoc analysis was done with multivariable mixed-effects logistic regression models using SAS, version 9.4. The following variables were tested with the outcome of a positive PET scan: PET tracer, ongoing androgen deprivation therapy, history of adjuvant androgen deprivation therapy, history of adjuvant radiotherapy, risk group, PSA doubling time (higher *vs* lower than median), PSA velocity, ¹⁸F-fluciclovine uptake time (≤ 3 min *vs* > 3 min) and ¹⁸F-fluciclovine with contrast-enhanced CT. Because of sample size limitations, two predictor variables at a time were tested rather than a single full model with all terms: PET tracer (¹⁸F-fluciclovine *vs* PSMA) and each other variable was tested separately.

All other statistical analyses were done in R, version 3.5.1. To overcome the statistical limitation of multiple testing in a sample of modest size, an additional post-hoc Benjamini–Hochberg step-up procedure was

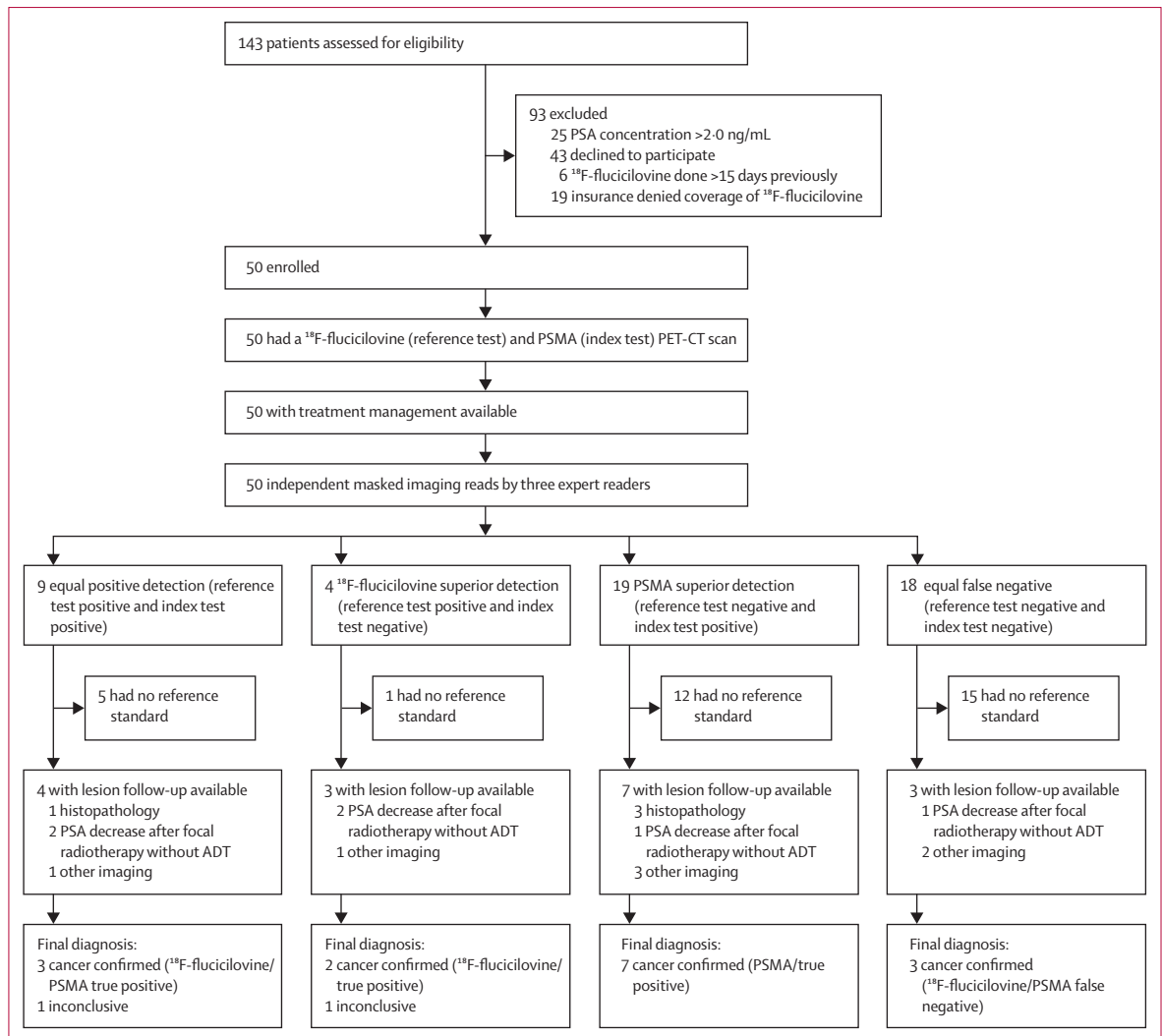


Figure 1: Trial profile

The reference standard included histopathology, follow-up imaging, or PSA concentration decrease after PET-positive lesion-directed therapy without systemic therapy or without whole-pelvic lymph node radiotherapy. Patients without a reference standard were not excluded from primary and safety analyses; this was only used for the positive predictive value and sensitivity analyses.

done to obtain the overall false-discovery rate associated with the 0.05 significance level.

This study is registered on ClinicalTrials.gov, number NCT02940262.

Role of the funding source

There was no funding for this study. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Results

Patient were enrolled between Feb 26, 2018, and Sept 20, 2018. 143 patients were assessed for eligibility, of whom 93 were excluded (19 of these could not be included in the study because their insurance denied coverage of ^{18}F -fluciclovine PET-CT) and 50 were enrolled

(figure 1). Demographics and clinical characteristics of the study population are presented in table 1. Median PSA concentration at enrolment was 0.48 ng/mL (IQR 0.38–0.83). The median time interval between the two scans was 6 days (IQR 2–8). 21 (42%) of 50 patients had ^{18}F -fluciclovine PET-CT after PSMA PET-CT and 29 (58%) had ^{18}F -fluciclovine PET-CT before PSMA PET-CT.

Scanner devices and iterative algorithms used for PET image reconstruction are listed with the technical parameters in the appendix (p 2). Standard-of-care ^{18}F -fluciclovine PET-CT was done at UCLA in 38 (76%) of 50 and at other institutions in 12 (24%) patients. Investigational PSMA PET-CT was done at UCLA in all 50 patients. For ^{18}F -fluciclovine PET-CT, intravenous CT contrast was administered in 35 (70%) of 50 patients

All patients (n=50)	
National Comprehensive Cancer Network risk group	
Intermediate	17 (34%)
High	14 (28%)
Very high	5 (10%)
Regional (N1)	11 (22%)
Not available	3 (6%)
PSA at initial diagnosis, ng/mL	
<10	25 (50%)
10–20	9 (18%)
>20	3 (6%)
Not available	13 (26%)
Histopathological TNM stage	
pT2	18 (36%)
pT3a	12 (24%)
pT3b	5 (10%)
pN1	11 (22%)
Not available	4 (8%)
International Society of Urological Pathologists grade group	
1	3 (6%)
2	16 (32%)
3	15 (30%)
4	5 (10%)
5	8 (16%)
Not available	3 (6%)
Pelvic lymph node dissection	
Margins positive (R1)	13 (26%)
Adjuvant radiotherapy	6 (12%)
Adjuvant androgen deprivation therapy	10 (20%)
PSA persistence (never undetectable after surgery)	12 (24%)
PSA recurrence (became undetectable after surgery then increased to detectable levels)	38 (76%)
Ongoing androgen deprivation therapy	7 (14%)
Age, years	68 (64–74)
Time from radical prostatectomy to PET, years	3 (1–8)
Last PSA concentration before PET, ng/mL	0.48 (0.38–0.83)
PSA doubling time, months	4 (3–16)
PSA velocity, ng/mL per year	0.3 (0.1–1.2)
Data are n (%) or median (IQR). PSA=prostate-specific antigen.	

Table 1: Demographic and clinicopathological characteristics

and oral CT contrast was administered in 37 (74%) patients; for PSMA PET-CT, intravenous CT contrast was administered in 48 (96%) patients and oral CT contrast in 49 (98%) of 50 patients. The median injected activity was 381 MBq (IQR 359–407) for ^{18}F -fluciclovine and 200 MBq (192–204) for PSMA. PET images were acquired after a median uptake period of 2 min (IQR 1–3) for ^{18}F -fluciclovine and 61 min (57–66) for PSMA.

The subsequent patient management of the entire cohort after a median follow-up of 8 months (IQR 7–9) is summarised in the appendix (p 3). Focal therapy (metastasis surgery and metastasis stereotactic body

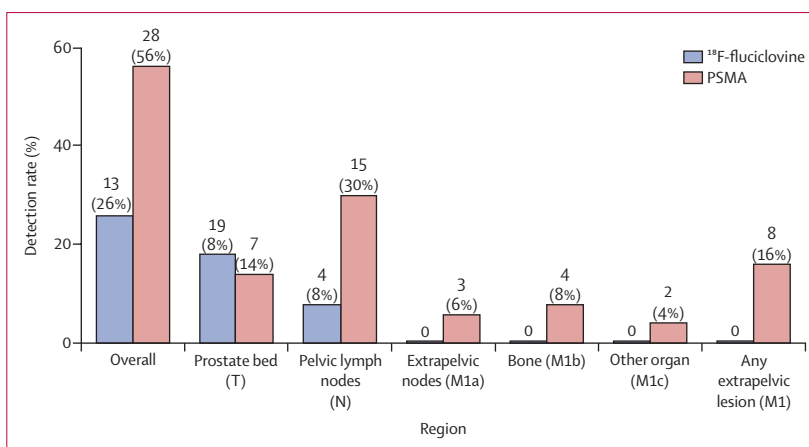


Figure 2: Detection rates per region and per patient (majority consensus reads)
PSMA=prostate-specific membrane antigen.

radiation therapy) was applied to PET-positive lesions in 15 (30%) of 50 patients, 30 (60%) patients received androgen deprivation therapy, and nine (18%) were managed with active surveillance. No patients were lost to follow-up or excluded from analysis.

Individual reader interpretations and the majority consensus are detailed in the appendix (pp 4–7). 18 (36%) of 50 patients had equal false-negative detection, nine (18%) had equal positive detection, four (8%) had ^{18}F -fluciclovine superior detection, and 19 (38%) had PSMA superior detection (figure 1, appendix p 8).²⁰ The contingency tables are in the appendix (pp 9–10).

The detection rates of biochemical recurrence per patient were significantly lower with ^{18}F -fluciclovine (13 [26%; 95% CI 15–40] of 50) than with PSMA PET-CT (28 [56%; 41–70] of 50), with an OR of 4.8 (95% CI 1.6–19.2; $p=0.0026$; figure 2).

To assess potential bias, a post-hoc analysis was done, confirming the differences in the patient-level detection rates of biochemical recurrence between the reference and index tests in the 38 patients with ^{18}F -fluciclovine PET-CT obtained at UCLA (12 [32%; 95% CI 18–49] of 38 with ^{18}F -fluciclovine vs 21 [55%; 38–71] of 38 with PSMA; OR 3.3 [1.0–13.7], $p=0.049$), the 12 patients with ^{18}F -fluciclovine PET-CT obtained at other institutions (one [8%; 0–38] of 12 with ^{18}F -fluciclovine vs seven [58%; 28–85] of 12 with PSMA; OR not estimable, $p=0.031$), and the 35 patients in whom both studies were done with contrast-enhanced CT (11 [31%; 17–49] of 35 with ^{18}F -fluciclovine vs 20 [57%; 40–74] of 35 with PSMA; OR 4.0 [1.08–22.1], $p=0.035$). Additionally, we found no significant difference between the patient-level detection rates of ^{18}F -fluciclovine PET-CT obtained at UCLA and at other institutions (12 [32%; 17–51] of 38 at UCLA vs one [8%; 0–38] of 12 at other institutions; difference 23% [95% CI 7–41], $p=0.15$) or those done with versus without intravenous contrast (11 [31%; 17–49] of 35 vs two [13%; 2–40] of 15; difference 18% [10–37], $p=0.29$).

	PSMA	¹⁸ F-fluciclovine	p value
Detection at the patient level			
Overall	0.67 (0.51 to 0.83)	0.20 (0.04 to 0.36)	0.0020
Detection at the regional level			
Prostate bed (T)	0.65 (0.49 to 0.81)	0.43 (0.27 to 0.59)	0.046
Pelvic lymph nodes (N)	0.76 (0.60 to 0.92)	0.05 (-0.11 to 0.21)	<0.0001
Extrapelvic nodes (M1a)	0.60 (0.44 to 0.76)	-0.02 (-0.18 to 0.14)	0.0025
Bone (M1b)	0.46 (0.30 to 0.62)	-0.03 (-0.19 to 0.13)	0.0051
Other organ (M1c)	0.65 (0.49 to 0.81)	-0.01 (-0.17 to 0.15)	0.016
Any extrapelvic lesion (M1)	0.60 (0.44 to 0.76)	-0.07 (-0.23 to 0.09)	<0.0001

Data are the multi-rater κ statistic (95% CI). Negative κ statistics signify less observed agreement than that expected by chance. 95% CIs overlapping with zero indicate that the observed agreement was statistically indistinguishable from chance agreement. PSMA=prostate-specific membrane antigen.

Table 2: Inter-reader measures of agreement

¹⁸F-fluciclovine detection rates of biochemical recurrence were significantly lower than PSMA detection rates for the pelvic lymph node region (N; four [8%; 95% CI 2–19] of 50 with ¹⁸F-fluciclovine vs 15 [30%; 18–45] of 50 with PSMA; OR 12.0 [95% CI 1.8–513.0], $p=0.0034$) and for any extrapelvic lesions (M1; none [0–6] of 50 vs eight [16%; 7–29] of 50; OR non-estimable [95% CI non-estimable], $p=0.0078$; figure 2). No significant differences were detected for the individual extrapelvic lesion locations (M1a, M1b, and M1c), possibly because patient numbers were too small. Detection rates for prostate bed recurrence (T) did not differ significantly between the tests (nine [18%; 9–31] of 50 vs seven [14%; 6–27] of 50; OR 0.6 [0.1–3.1], $p=0.73$).

In the 26 patients with PSA concentrations of 0.2–0.5 ng/mL, detection rates were seven (27%; 95% CI 12–48) for ¹⁸F-fluciclovine versus 12 (46%; 27–67) with PSMA; for the 18 with concentrations 0.51–1.00 ng/mL, rates were five (28%; 10–53) versus 12 (67%; 41–87); and for the six with concentrations 1.01–2.00 ng/mL, detection rates were one (17%; 0–64) versus four (67%; 22–96; appendix pp 11–12). No significant difference was detected between these subgroups in the analysis by patient or region (appendix p 12).

Inter-reader agreement was significantly lower for ¹⁸F-fluciclovine (κ values ≤ 0.20) than for PSMA (κ values ≥ 0.60) at the patient level ($p=0.0020$) and per region ($p\leq 0.016$) except for the prostate bed region (table 2; pairwise κ is in the appendix p 13).

PET findings were validated in 15 (30%) of 50 patients (five (38%) of 13 with ¹⁸F-fluciclovine-positive findings and ten (36%) of 28 with PSMA-positive findings). Reference standard included histopathology ($n=4$), follow-up imaging ($n=7$), and PSA decreases after PET-directed focal therapy without androgen deprivation therapy ($n=4$; appendix p 14). Five other patients had imaging follow-up (MRI or CT) but without lesion validation because follow-up scans were negative. As anticipated, only a minority of patients (16 [32%] of 50) had surgery ($n=3$), biopsy ($n=1$), or further imaging

($n=12$) for lesion verification. No false-positive findings occurred with either tracer in the 15 patients in whom lesions were verified (positive predictive value of 100% for both ¹⁸F-fluciclovine and PSMA findings). Per-patient sensitivity was 33% (95% CI 15–58; five true positives and ten false negatives) for ¹⁸F-fluciclovine and 66% (42–85; ten true positive and five false negative) for PSMA PET-CT (OR 3.5 [95% CI 0.67–34.5], $p=0.18$).

The post-hoc semiquantitative analysis of lesion PET tracer uptake was done in seven patients: three concordantly positive pelvic lymph nodes and four local recurrences (appendix p 15). The mean lesion SUV_{max} was 8.21 (SD 4.05) for PSMA versus 3.73 (0.85) for ¹⁸F-fluciclovine ($p=0.013$) and lesion-to-background ratios were 1.68 (SD 1.16) versus 0.52 (0.16) for liver ($p=0.0052$); 6.83 (3.60) versus 2.44 (0.60) for blood pool ($p=0.0085$); and 25.39 (15.3) versus 3.69 (1.87) for muscle ($p=0.021$); all significantly higher for PSMA than ¹⁸F-fluciclovine PET-CT.

A summary of the post-hoc multivariable logistic regression analysis is in the appendix (p 16). The only significant predictor for test positivity was the PET tracer used (¹⁸F-fluciclovine vs PSMA; ORs 3.56–3.88; $p<0.05$). Neither ¹⁸F-fluciclovine uptake time (≤ 3 min vs >3 min) nor the administration of intravenous contrast for CT imaging were confounding factors.

The Benjamini–Hochberg step-up procedure indicated that the 0.05 significance level provided a 7% false-discovery rate control (data not shown), suggesting that the observed statistical differences were generally not artefacts of multiple hypothesis testing.

Discussion

PSMA PET-CT detects biochemical recurrence sites at low PSA concentrations more frequently and with higher reader agreement than ¹⁸F-fluciclovine PET-CT. The primary endpoint of this study was met ($\geq 22\%$ difference between the detection rates at the patient level) in this highly relevant population of patients with early biochemical recurrence in whom focused salvage therapy can be potentially curative. Detection rates per patient, for pelvic lymph nodes, and for any extrapelvic metastasis were more than twice as high with PSMA than with ¹⁸F-fluciclovine. The inter-reader agreement was consistently higher for PSMA than ¹⁸F-fluciclovine PET-CT.

Differences in detection rates between ¹⁸F-fluciclovine and PSMA PET-CT in similar patient cohorts have been previously reported: they averaged around 45% for ¹⁸F-fluciclovine^{3,11,12} and 65% for PSMA PET-CT.^{6,10,13–15} Inter-reader agreement was also consistently higher for PSMA than for ¹⁸F-fluciclovine PET-CT.^{5,22} These differences were now corroborated prospectively in the same cohort of post-radical prostatectomy biochemical recurrence patients with low PSA concentrations.

Detection rates for both the index and reference tests were lower in our study than those reported previously, probably because of the retrospective nature of most

previous studies with heterogeneous patient populations and absence of masked image interpretation by multiple readers in some studies. One prospective study¹⁰ reported PSMA PET-CT detection rates in patients with low PSA concentrations similar to those reported in our study. Most of our cohort (44 [88%] of 50) had PSA concentrations of 1.0 ng/mL or less. ¹⁸F-fluciclovine detection rates for similar populations ranged from 41% in a retrospective study without masked readers¹² to 21% in a prospective study with two independent readers.³ Thus, our detection rate of 26% is well within the expected range.³ Detection rates stratified by PSA concentrations were not significantly different between index and reference test. These findings might be because of the low number of patients in each PSA subgroup in our analysis. With more patients included, ¹⁸F-fluciclovine might have been non-inferior to PSMA PET-CT at higher PSA concentrations (eg, >1.5 ng/mL), although this notion is speculative.

Several factors might account for the superiority of PSMA PET-CT in patients with early biochemical recurrence. First, overexpression of PSMA results in high tracer uptake. SUV_{max} was two times higher and lesion-to-background ratios were seven times higher for concordantly PET-positive lesions with PSMA than ¹⁸F-fluciclovine. Expression and activity of LAT1, which is responsible for transport of ¹⁸F-fluciclovine into tumour cells, is high in advanced castrate-resistant prostate cancer but low in early castrate-sensitive prostate cancer.²³ By contrast, PSMA expression is increased 100–1000 times in both castrate-sensitive and castrate-resistant prostate cancer.^{24,25} Equally important, PSMA expression in non-target tissues is very low. By contrast, amino acid transporters are important contributors to muscle protein anabolism and LAT1 expression is associated with skeletal muscle microvasculature.²⁶ Blood pool activity is high at early imaging timepoints and remains high over time.²⁷ Subsequently, ¹⁸F-fluciclovine becomes highly distributed throughout skeletal muscles.²⁷ Thus, both target and background characteristics favour lesion detectability with PSMA PET-CT. The favourable lesion-to-background ratio explains the high agreement among PSMA readers. This advantage of PSMA over ¹⁸F-fluciclovine might be less pronounced in patients with more advanced disease, higher PSA concentrations,¹² and castrate-resistant disease,²³ or in the 5–10% of patients whose lesions exhibit low or no PSMA expression.^{24,25}

PSMA PET-CT detected pelvic lymph node metastases more frequently and with greater reader confidence than ¹⁸F-fluciclovine PET-CT. This finding is important because biochemical recurrence is most frequently associated with pelvic lymph node involvement and accurate detection of pelvic disease is crucial for planning local, potentially curative treatment.

No extrapelvic metastases were detected with ¹⁸F-fluciclovine PET-CT, whereas PSMA PET-CT detected extrapelvic oligometastatic disease in eight (16%) of

50 patients. Lesion validation was available in four of these patients and prostate cancer was confirmed in all of them (appendix p 14). Unusual lesion locations became evident in our study. These regions included the penis, the inguinal canal or spermatic cord, and inguinal lymph nodes (appendix p 14). Notably, ablative therapies might benefit patients when disease is still oligometastatic.^{28,29}

Obtaining a firm reference standard in biochemical recurrence of prostate cancer is challenging. NCCN guidelines recommend observation or ADT with or without salvage radiotherapy and histological confirmation of the PET-positive lesions when feasible.¹ In patients with low PSA concentrations, PET-positive lesions are rarely targeted with biopsies because they are often small and difficult to reach anatomically (deep pelvic or abdominal lymph nodes or bone lesions without a CT correlate). Notably, 15 (30%) of 50 of the patients received PET-positive metastasis-directed focal therapy on the basis of the local non-masked clinical reads. As anticipated, only a minority of patients had surgery, biopsy, or further imaging for lesion verification. Thus, specificity and negative predictive value could not be established and lesion validation was only available in five (38%) of 13 patients with positive findings by ¹⁸F-fluciclovine and ten (36%) of 28 patients with positive findings by PSMA (appendix p 14).

The term detection rate used in this and many previous reports is not entirely correct because false-positive findings have been reported.^{7–9} However, the majority consensus rule (2:1) might have led to lower sensitivity but higher specificity than clinical routine interpretations,¹⁰ thus explaining the positive predictive value of 100% for both scans in the subset of patients with lesion validation. Furthermore, high positive predictive values of PSMA (>85%) reported in a meta-analysis that included only patients with biochemical recurrence with histopathological verification⁶ and a prospective multicentre phase 3 trial¹⁰ justify the use of detection rates rather than positivity rates. In this study, probably because of small patient numbers with lesion validation (n=15), the sensitivity of the two scans did not differ significantly. Larger cohorts would be required to formally address this question.

This study has several limitations. Technical parameters might have been confounding factors and could have potentially introduced a bias. ¹⁸F-fluciclovine uptake time was shorter than that recommended by guidelines.¹⁶ This might have affected pelvic image quality via higher blood pool activity at the time of imaging, and thus T and N staging, but not the extrapelvic (M) staging. Some ¹⁸F-fluciclovine PET-CT scans were done without intravenous CT-contrast application. However, the differences were also confirmed in the subset of patients who had both ¹⁸F-fluciclovine and PSMA PET-CT scans with intravenous CT contrast. A post-hoc multivariate analysis of potential confounding factors revealed no

effect of the tracer uptake time or the use of intravenous CT contrast. Only the PET tracer used (^{18}F -fluciclovine or PSMA) was predictive of PET scan positivity.

PSMA readers had recorded a higher number of PSMA scan reads than the ^{18}F -fluciclovine readers had recorded of ^{18}F -fluciclovine scan reads. This difference is probably because of the more frequent clinical use of PSMA, especially in Europe. However, care was taken to select well-trained readers with extensive publication and clinical track records for both scans. Thus, a qualification bias as a confounding factor is highly unlikely.

A high rate of change in management of patients with recurrence after PSMA or ^{18}F -fluciclovine PET-CT has been reported.^{30,31} Our study was not designed to assess the effect of ^{18}F -fluciclovine or PSMA on patient management or outcome. Because both tests were done in the same patient cohort within 2 weeks, the independent effect of the tests could not be established. The effect of PET imaging findings on patient outcome is still unknown. In a randomised trial of patients with recurrent oligometastatic disease, androgen deprivation therapy-free survival was longer with PET-positive metastasis-directed therapy than with surveillance alone.²⁹ However, whether or not PET-positive metastasis-directed therapy improves progression-free or overall survival remains unclear.²⁸ Furthermore, inappropriate management due to false positive findings cannot be ruled out. Even if PSMA PET-CT detects sites of recurrence earlier than ^{18}F -fluciclovine PET-CT, the implications on hard clinical endpoints remain uncertain. Randomised clinical trials of standard salvage radiotherapy versus PSMA PET-CT-based salvage radiotherapy (NCT03582774) and ^{18}F -fluciclovine versus PSMA PET-CT-based salvage radiotherapy (NCT03762759), both powered for outcome, are ongoing.

This prospective head-to-head comparison between ^{18}F -fluciclovine and PSMA PET-CT in 50 patients with post-radical prostatectomy biochemical recurrence and PSA concentrations of 2.0 ng/mL or less shows superior detection rates and reader agreement with PSMA PET-CT than with ^{18}F -fluciclovine. Primary and secondary endpoints were met: PSMA PET-CT detection rates at the patient level, and at the regional level for pelvic lymph node regions and for extra-pelvic metastasis were more than twice as high as those for ^{18}F -fluciclovine PET-CT. However, because the PET findings could not be validated by a gold reference standard in two-thirds of patients, neither sensitivity nor specificity could be established. Nevertheless, the results of this prospective head-to-head comparison indicate that PSMA should be the PET tracer of choice when PET-CT imaging is considered for subsequent treatment management decisions in patients with biochemical recurrence and low PSA concentrations (≤ 2.0 ng/mL).

Contributors

JCz was the principal investigator. JCa, FC, ME, WPF, and JCz did the literature search and conceived and designed the study. JG, KN, VL,

and JCz provided administrative support. JCa, FC, JG, KN, VL, RS, MD, RER, MBR, AUK, and HJ collected and assembled the data. JCa, DE, TG, TB-G, MSH, TAH, CN, CR, BS-B, and JCz analysed and interpreted the data. JCa, FC, ME, WPF, TAH, DE, TG, and JCz wrote the manuscript. All authors approved the manuscript. JCa and JCz are accountable for all aspects of the work.

Declaration of interests

JCa reports personal fees from Progenics Pharmaceuticals and RadioMedix and is a consultant for Blue Earth Diagnostics outside the submitted work. JCz is a founder, board member, and holds equity in Sofie Biosciences and Trethera Therapeutics, serves on the medical advisory board of Actinium, and is a member of the VISION trial steering committee, a clinical trial sponsored by Endocyte, outside the submitted work. WPF is a consultant for Endocyte and Ipsen and reports personal fees from Radiomedix Inc outside the submitted work. ME reports grants from ABX advanced biochemical compounds and Blue Earth Diagnostics, is a consultant for Progenics Pharmaceuticals and Janssen, and has a patent rhPSMA issued, outside the submitted work. TB-G reports grants and personal fees from Blue Earth Diagnostics outside the submitted work. BS-B reports grants and personal fees from Blue Earth Diagnostics and personal fees from Phillips outside the submitted work. CN reports grants and personal fees from Blue Earth Diagnostics outside the submitted work. TAH reports grants from Advanced Accelerator Applications and personal fees from GE Healthcare, Progenics Pharmaceuticals, Curium, and Ipsen outside the submitted work. MBR reports grants and non-financial support from Novartis, personal fees and non-financial support from Johnson & Johnson, non-financial support from Merck, Medivation, and Astellas, and has a patent "Inhibitors of the N-terminal Domain of the Androgen Receptor" pending, outside the submitted work. MSH reports grants and personal fees from Endocyte, Ipsen, and Sanofi Genzyme outside the submitted work. CR received speaker fees from GE Healthcare outside the submitted work. AUK reports personal fees from Varian Medical Systems, ViewRay, and Janssen Pharmaceuticals outside the submitted work. HJ is an investigator for ImaginAb and Subtle Medical outside the submitted work. All other authors declare no competing interests.

Data sharing

Deidentified data collected for the study have been made available to other researchers for purposes of reproducing the results and are available to others in the FACBC-PSMA PUBLIC Master Table Database Appendix.

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For the deidentified data see https://www.researchgate.net/publication/333059173_FACBC-PSMA_PUBLIC_Master_Table_Database_Appendix

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Calais J, Ceci F, Eiber M, et al. ^{18}F -fluciclovine PET-CT and ^{68}Ga -PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol* 2019; published online July 31. [http://dx.doi.org/10.1016/S1470-2045\(19\)30415-2](http://dx.doi.org/10.1016/S1470-2045(19)30415-2).

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLES

Supplemental Table 1: Expert readers background and experience

NM : Nuclear medicine physician; RAD: Radiologist.

Reader	Institution	Specialty	Software	PET/CT reading experience (years)	FACBC or PSMA reading experience (years)	Number of FACBC or PSMA reads	Number of FACBC or PSMA publications
T Bach-Gansmo	Oslo, NOR	NM	Syngo Via	13	5	350	9
M Hofman	Melbourne, AU	NM	MIM	14	4	2000	20
T Hope	UCSF, USA	NM + RAD	OsiriX	7	4	1000	8
C Nanni	Bologna, ITA	NM + RAD	GE AW	16	2	150	7
C Rischpler	Essen, GER	NM	Syngo Via	5	5	3000	5
B Savir-Baruch	Chicago, USA	NM	Hermes	10	10	400	14

Supplemental Table 2: PET/CT imaging technical parameters

OSEM: ordered subset expectation maximization; i: iteration; s: subset;

		FACBC		PSMA	
Institution					
	UCLA	38 (76%)		50 (100%)	
	Outside	12 (24%)		-	
Scanner Device					
	Siemens Biograph64 TruePoint	23 (46%)		28 (56%)	
	Siemens Biograph64 mCT	21 (42%)		22 (44%)	
	Siemens Emotion Duo	2 (4%)		-	
	GE Discovery MI	1 (2%)		-	
	GE Discovery RX	1 (2%)		-	
	GE Discovery ST	1 (2%)		-	
	GE Discovery STE	1 (2%)		-	
Contrast					
	Oral	37 (74%)		49 (98%)	
	IV	35 (70%)		48 (96%)	
Reconstruction Algorithm and Parameters					
	3D OSEM (2i, 21s), Gaussian Filter 5.0, pixel 4.07x4.07 mm	19 (38%)		28 (54%)	
	3D OSEM (2i, 24s), Gaussian Filter 5.0, pixel 4.07x4.07 mm	19 (38%)		22 (44%)	
	2D OSEM (2i, 8s), Gaussian Filter 5.0, pixel 5.31x5.31 mm	3 (6%)		-	
	PSF TOF (2i, 21s), pixel 4.07x4.07 mm	2 (4%)		-	
	PSF (3i, 21s), pixel 4.07x4.07 mm	4 (8%)		-	
	GE 3D-IR, pixel 5.47x5.47 mm	2 (4%)		-	
	GE QCFX, pixel 2.73x2.73 mm	1 (2%)		-	
		Median	IQR	Median	IQR
Injected Activity (MBq)		381	359-407	200	192-204
Uptake time (min)		2	1-3	61	57-66
Time-per-bed-position (min)		3.0	2.8-4.0	3.0	2.8-4.0

Supplemental Table 3: Treatment Management after the 2 PET/CT scans (median follow-up of 8 months)

SRT: salvage radiation therapy; SBRT: stereotactic body radiation therapy; LN: lymph node; ADT: androgen deprivation therapy; Abi: abiraterone; Enza: Enzalutamide.

Treatment Management	n (%)
Metastasis Surgery	3 (6%)
Metastasis SBRT	2 (4%)
Prostate Fossa SRT	4 (8%)
Prostate Fossa SRT + Whole-Pelvic LN RT	1 (2%)
Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT	1 (2%)
ADT	7 (14%)
ADT + Abi/Enza	2 (4%)
ADT + Prostate Fossa SRT	10 (20%)
ADT + Prostate Fossa SRT + Metastasis SBRT	1 (2%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT	2 (4%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT	3 (6%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT + Abi/Enza	2 (4%)
ADT + Metastasis SBRT	3 (6%)
Surveillance	9 (18%)

Supplemental Table 5: Detailed reads per-patient of the 6 expert readers

Bottom row indicate the detection rates.

UCLA #	PSMA positivity			FACBC positivity			PSA
	R1	R2	R3	R4	R5	R6	
UCLA #013	0	0	0	0	0	0	0.2
UCLA #014	0	0	0	0	0	0	0.2
UCLA #032	0	0	0	0	0	1	0.23
UCLA #026	1	1	1	1	0	1	0.26
UCLA #043	0	0	1	1	1	1	0.28
UCLA #015	1	1	1	0	0	0	0.29
UCLA #022	1	1	1	1	0	0	0.29
UCLA #025	0	0	0	0	0	0	0.3
UCLA #041	0	0	0	0	0	0	0.3
UCLA #044	1	0	1	1	0	1	0.35
UCLA #018	1	1	1	1	1	0	0.36
UCLA #007	0	0	0	0	0	1	0.37
UCLA #049	1	1	1	0	0	0	0.38
UCLA #027	0	0	1	0	0	1	0.38
UCLA #003	1	1	1	1	0	0	0.39
UCLA #019	1	1	1	1	1	0	0.39
UCLA #028	0	0	1	1	0	1	0.39
UCLA #009	1	1	1	0	1	0	0.4
UCLA #017	0	0	0	0	0	1	0.4
UCLA #010	1	1	1	1	1	1	0.43
UCLA #020	0	1	0	0	0	1	0.43
UCLA #050	1	1	1	1	0	0	0.43
UCLA #004	1	1	1	0	0	1	0.45
UCLA #035	0	0	0	0	0	0	0.46
UCLA #042	0	0	0	1	0	1	0.46
UCLA #012	0	0	0	0	0	0	0.5
UCLA #008	1	1	1	0	1	1	0.54
UCLA #030	0	0	0	0	0	0	0.54
UCLA #040	0	0	1	1	1	0	0.55
UCLA #047	0	0	1	0	0	0	0.56
UCLA #016	0	0	0	0	0	0	0.6
UCLA #033	0	0	0	0	0	0	0.6
UCLA #039	1	1	1	1	0	1	0.6
UCLA #023	1	0	1	1	0	0	0.62
UCLA #031	1	1	1	1	1	1	0.68
UCLA #021	1	1	1	1	1	1	0.72
UCLA #045	1	1	1	1	0	0	0.78
UCLA #002	1	1	1	0	0	1	0.84
UCLA #011	0	0	0	1	1	1	0.84
UCLA #046	1	1	1	1	1	1	0.84
UCLA #036	1	1	1	1	0	0	0.9
UCLA #001	1	1	1	0	0	1	0.91
UCLA #024	1	0	1	0	0	1	0.97
UCLA #005	1	1	1	0	1	0	1
UCLA #034	1	1	1	0	0	0	1.1
UCLA #037	1	1	1	0	0	1	1.29
UCLA #038	1	0	1	1	0	1	1.44
UCLA #029	0	0	1	0	0	0	1.57
UCLA #006	0	0	0	0	0	0	2
UCLA #048	1	0	1	0	0	0	2
	28	24	34	21	12	23	
	56%	48%	68%	42%	24%	46%	

Supplemental Table 6: Detailed majority consensus reads per-region and per-patient of the 50 patients

Bottom row indicate the detection rates.

	PSMA Tr	FACBC Tr	PSMA N	FACBC N	PSMA M1a	FACBC M1a	PSMA M1b	FACBC M1b	PSMA M1c	FACBC M1c	PSMA scan	FACBC scan	PSA
UCLA #013	0	0	0	0	0	0	0	0	0	0	0	0	0.20
UCLA #014	0	0	0	0	0	0	0	0	0	0	0	0	0.20
UCLA #032	0	0	0	0	0	0	0	0	0	0	0	0	0.23
UCLA #026	0	0	1	1	0	0	0	0	0	0	1	1	0.26
UCLA #043	0	0	0	1	0	0	0	0	0	0	0	1	0.28
UCLA #015	0	0	0	0	1	0	0	0	0	0	1	0	0.29
UCLA #022	1	0	0	0	0	0	0	0	0	0	1	0	0.29
UCLA #025	0	0	0	0	0	0	0	0	0	0	0	0	0.30
UCLA #041	0	0	0	0	0	0	0	0	0	0	0	0	0.30
UCLA #044	0	0	0	0	0	0	1	0	0	0	1	0	0.35
UCLA #018	0	1	1	0	0	0	0	0	0	0	1	1	0.36
UCLA #007	0	0	0	0	0	0	0	0	0	0	0	0	0.37
UCLA #049	0	0	1	0	0	0	0	0	0	0	1	0	0.38
UCLA #027	0	0	0	0	0	0	0	0	0	0	0	0	0.38
UCLA #003	1	0	0	0	0	0	0	0	0	0	1	0	0.39
UCLA #019	0	1	1	0	0	0	0	0	0	0	1	1	0.39
UCLA #028	0	1	0	0	0	0	0	0	0	0	0	1	0.39
UCLA #009	0	0	1	0	0	0	0	0	0	0	1	0	0.40
UCLA #017	0	0	0	0	0	0	0	0	0	0	0	0	0.40
UCLA #010	0	0	1	1	0	0	0	0	0	0	1	1	0.43
UCLA #020	0	0	0	0	0	0	0	0	0	0	0	0	0.43
UCLA #050	0	0	0	0	0	0	1	0	0	0	1	0	0.43
UCLA #004	0	0	1	0	0	0	0	0	0	0	1	0	0.45
UCLA #035	0	0	0	0	0	0	0	0	0	0	0	0	0.46
UCLA #042	0	1	0	0	0	0	0	0	0	0	0	1	0.46
UCLA #012	0	0	0	0	0	0	0	0	0	0	0	0	0.50
UCLA #008	0	0	1	0	0	0	0	0	0	0	1	0	0.54
UCLA #030	0	0	0	0	0	0	0	0	0	0	0	0	0.54
UCLA #040	0	0	0	0	0	0	0	0	0	0	0	0	0.55
UCLA #047	0	0	0	0	0	0	0	0	0	0	0	0	0.56
UCLA #016	0	0	0	0	0	0	0	0	0	0	0	0	0.60
UCLA #033	0	0	0	0	0	0	0	0	0	0	0	0	0.60
UCLA #039	0	0	1	1	0	0	0	0	0	0	1	1	0.60
UCLA #023	0	0	0	0	0	0	1	0	0	0	1	0	0.62
UCLA #031	1	1	0	0	0	0	0	0	0	0	1	1	0.68
UCLA #021	1	1	1	0	0	0	0	0	0	0	1	1	0.72
UCLA #045	0	0	1	0	1	0	0	0	0	0	1	0	0.78
UCLA #002	0	0	0	0	1	0	0	0	1	0	1	0	0.84
UCLA #011	0	1	0	0	0	0	0	0	0	0	0	1	0.84
UCLA #046	1	1	0	0	0	0	0	0	0	0	1	1	0.84
UCLA #036	0	0	1	0	0	0	0	0	0	0	1	0	0.90
UCLA #001	0	0	1	0	0	0	0	0	0	0	1	0	0.91
UCLA #024	0	0	0	0	0	0	1	0	0	0	1	0	0.97
UCLA #005	0	0	0	0	0	0	0	0	1	0	1	0	1.00
UCLA #034	1	0	0	0	0	0	0	0	0	0	1	0	1.10
UCLA #037	0	0	1	0	0	0	0	0	0	0	1	0	1.29
UCLA #038	1	1	0	0	0	0	0	0	0	0	1	1	1.44
UCLA #029	0	0	0	0	0	0	0	0	0	0	0	0	1.57
UCLA #006	0	0	0	0	0	0	0	0	0	0	0	0	2.00
UCLA #048	0	0	1	0	0	0	0	0	0	0	1	0	2.00
TOTAL	7	9	15	4	3	0	4	0	2	0	28	13	
	14%	18%	30%	8%	6%	0%	8%	0%	4%	0%	56%	26%	

Supplemental Table 7: Summary of the detection rates per-readers, majority consensus and average

	Expert Reader 1/4	Expert Reader 2/5	Expert Reader 3/6	Majority Consensus	Average
T = Local Recurrence					
PSMA	14%	12%	22%	14%	16%
FACBC	22%	14%	14%	18%	17%
N = Pelvic LN					
PSMA	30%	32%	36%	30%	33%
FACBC	12%	8%	34%	8%	18%
M1a = Extra-Pelvic LN					
PSMA	6%	4%	6%	6%	5%
FACBC	0%	6%	0%	0%	2%
M1b = Bone					
PSMA	8%	2%	14%	8%	8%
FACBC	10%	0%	0%	0%	3%
M1c = Visceral Metastasis					
PSMA	4%	2%	6%	4%	4%
FACBC	0%	4%	0%	0%	1%
Any M					
PSMA	16%	8%	24%	16%	16%
FACBC	10%	10%	0%	0%	7%
Patient = Scan					
PSMA	56%	48%	68%	56%	57%
FACBC	42%	24%	46%	26%	37%

Supplemental Table 8: Paired PET/CT findings of the consensus majority reads (TNM score)

	FACBC	PSMA	n (%)	Cancer Confirmed
Equal false negative (n=18)	T0 N0 M0	T0 N0 M0	18 (36%)	3
Equal positive detection per-patient (n=9)	T+ N0 M0	T+ N0 M0	3 (6%)	3
	T+ N0 M0	T0 N1 M0	3 (6%)	0
	T0 N1 M0	T0 N1 M0	3 (6%)	0
FACBC superior detection per-patient (n=4)	T+ N0 M0	T0 N0 M0	3 (6%)	2
	T0 N1 M0	T0 N0 M0	1 (2%)	0
PSMA superior detection per-patient (n=19)	T0 N0 M0	T+ N0 M0	3 (6%)	0
	T0 N0 M0	T0 N1 M0	8 (16%)	4
	T0 N0 M0	T0 N1 M1a	1 (2%)	0
	T0 N0 M0	T0 N0 M1a	1 (2%)	0
	T0 N0 M0	T0 N0 M1b	4 (8%)	1
	T0 N0 M0	T0 N0 M1c	1 (2%)	1
	T0 N0 M0	T0 N0 M1a M1c	1 (2%)	1

Supplemental Table 9: Contingency table of the consensus majority reads per-patient

Full Analysis Population (n=50)			Lesion Validation Population (n=15)		
	FACBC -	FACBC +		FACBC -	FACBC +
PSMA -	18	4	PSMA -	3	2
PSMA +	19	9	PSMA +	7	3
<i>p=0.0026</i>			<i>p=0.18</i>		

Supplemental Table 10: Contingency tables of the consensus majority reads per-region for the 50 patients

Tr: Prostate fossa local recurrence

Tr			N			M1a			M1b			M1c			Any M		
FACBC neg.		FACBC pos.	FACBC neg.		FACBC pos.	FACBC neg.		FACBC pos.	FACBC neg.		FACBC pos.	FACBC neg.		FACBC pos.	FACBC neg.		FACBC pos.
PSMA neg.	38	5	PSMA neg.	34	1	PSMA neg.	47	0	PSMA neg.	46	0	PSMA neg.	48	0	PSMA neg.	42	0
PSMA pos.	3	4	PSMA pos.	12	3	PSMA pos.	3	0	PSMA pos.	4	0	PSMA pos.	2	0	PSMA pos.	8	0
<i>p=0.73</i>			<i>p=0.0034</i>			<i>p=0.25</i>			<i>p=0.13</i>			<i>p=0.50</i>			<i>p=0.0078</i>		

Supplemental Table 11: Detection rates per-patient and per-region stratified by PSA category (majority consensus reads)

Region	PET Tracer	< 0.5 (n=26)	0.51-1.00 (n=18)	1.01-2.00 (n=6)
T	<i>PSMA</i>	2 (8%)	3 (16%)	2 (33%)
	<i>FACBC</i>	4 (15%)	4 (22%)	1 (17%)
N	<i>PSMA</i>	7 (27%)	6 (33%)	2 (33%)
	<i>FACBC</i>	3 (12%)	1 (6%)	0 (0%)
M1a	<i>PSMA</i>	1 (4%)	2 (11%)	0 (0%)
	<i>FACBC</i>	0 (0%)	0 (0%)	0 (0%)
M1b	<i>PSMA</i>	2 (8%)	2 (11%)	0 (0%)
	<i>FACBC</i>	0 (0%)	0 (0%)	0 (0%)
M1c	<i>PSMA</i>	0 (0%)	2 (11%)	0 (0%)
	<i>FACBC</i>	0 (0%)	2 (11%)	0 (0%)
Any M	<i>PSMA</i>	3 (12%)	5 (28%)	0 (0%)
	<i>FACBC</i>	0 (0%)	0 (0%)	0 (0%)
PET/CT scan	<i>PSMA</i>	12 (46%)	12 (67%)	4 (67%)
	<i>FACBC</i>	7 (27%)	5 (28%)	1 (17%)

Supplemental Table 12: Contingency tables of the majority consensus reads stratified by PSA category (<0.5 / 0.5-1.0 / 1.0-2.0 ng/ml)

Most recent PSA 0.20-0.50 (n=26)	Tr	FACBC		N	FACBC		M1c	FACBC	
	PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
	No	20	4		No	18	1	No	26
Yes	2	0		Yes	5	2	Yes	0	0
		p=0.687			p=0.219			p=NA	
Distant LN	PSMA	FACBC		M1b	FACBC		Positivity	FACBC	
	PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
	No	25	0	No	24	0	No	11	3
Yes	1	0		Yes	2	0	Yes	8	4
		p=1.00			p=0.500			p=0.227	

Most recent PSA 0.51-1.00 (n=18)	Tr	FACBC		N	FACBC		M1c	FACBC	
	PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
	No	14	1		No	12	0	No	16
Yes	0	3		Yes	5	1	Yes	2	0
		p=1.00			p=0.063			p=0.500	
Distant LN	PSMA	FACBC		M1b	FACBC		Positivity	FACBC	
	PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
	No	16	0	No	16	0	No	5	1
Yes	2	0		Yes	2	0	Yes	8	4
		p=0.500			p=0.500			p=0.039	

Most recent PSA 1.01-2.00 (n=6)	Tr	FACBC		N	FACBC		M1c	FACBC	
	PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
	No	4	0		No	4	0	No	6
Yes	1	1		Yes	2	0	Yes	0	0
		p=1.00			p=0.500			p=NA	
Distant LN	PSMA	FACBC		M1b	FACBC		Positivity	FACBC	
	PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
	No	6	0	No	6	0	No	2	0
Yes	0	0		Yes	0	0	Yes	3	1
		p=NA			p=NA			p=0.250	

Supplemental Table 13: Pairwise Individual
Measures of agreement *Kappa* 95% Confidence
intervals

PSMA (pairwise Kappa, 95% CI)			FACBC (pairwise Kappa, 95% CI)		
R1 vs R2	R1 vs R3	R2 vs R3	R4 vs R5	R4 vs R6	R5 vs R6
0.91 (0.63, 1.19)	0.59 (0.32, 0.87)	0.50 (0.23, 0.78)	0.59 (0.32, 0.87)	0.46 (0.18, 0.74)	0.17 (-0.11, 0.45)
0.86 (0.58, 1.14)	0.77 (0.50, 1.05)	0.64 (0.37, 0.92)	0.11 (-0.17, 0.39)	0.15 (-0.12, 0.43)	-0.15 (-0.42, 0.13)
0.79 (0.51, 1.07)	0.65 (0.37, 0.92)	0.37 (0.09, 0.65)	-0.03 (-0.31, 0.25)	NA	-0.03 (-0.31, 0.25)
0.37 (0.09, 0.65)	0.69 (0.42, 0.97)	0.18 (-0.09, 0.46)	-0.05 (-0.33, 0.22)	-0.05 (-0.33, 0.22)	NA
0.66 (0.38, 0.93)	0.79 (0.51, 1.07)	0.48 (0.20, 0.76)	-0.02 (-0.30, 0.26)	NA	-0.02 (-0.30, 0.26)
0.76 (0.48, 1.04)	0.75 (0.47, 1.02)	0.51 (0.23, 0.78)	0.32 (0.04, 0.60)	0.19 (-0.09, 0.47)	0.08 (-0.20, 0.35)

Supplemental Table 14 : Details of the 15 patients with lesion validation

Tr: local recurrence; REI: right external iliac; LEI : left internal iliac; ING: inguinal; RCI: right common iliac; LII: left internal iliac;

Patient #	PSA	FACBC scan	FACBC Final Diagnosis	PSMA scan	PSMA Final Diagnosis	Region Validated	Lesion Validated	Validation Procedure	Management
UCLA #002	0.84	T0 N0 M0	FN	T0 N0 M1a M1c	TP	M1a	R ING LN	Histopathology (biopsy)	SRT Prostate fossa + SRT Pelvis + LN SBRT + ADT
UCLA #004	0.37	T0 N0 M0	FN	T0 N1 M0	TP	N1	LEI LN	Histopathology	Surgery
UCLA #046	0.84	Tr N0 M0	TP	Tr N0 M0	TP	T	Rectal mass	Histopathology	Surgery
UCLA #008	0.54	T0 N0 M0	FN	T0 N1 M0	TP	N1	REI LN	Histopathology	Surgery
UCLA #001	0.83	T0 N0 M0	FN	T0 N1 M0	TP	N1	LII LN	PSA after focal RT no ADT	LN SBRT
UCLA #042	0.46	Tr N0 M0	TP	T0 N0 M0	FN	T	Prostate Fossa	PSA after focal RT no ADT	SRT Prostate fossa
UCLA #031	0.68	Tr N0 M0	TP	Tr N0 M0	TP	T	Prostate Fossa	PSA after focal RT no ADT	SRT Prostate fossa
UCLA #025	0.30	T0 N0 M0	FN	T0 N0 M0	FN	T	Prostate Fossa	PSA after focal RT no ADT	SRT Prostate fossa
UCLA #029	1.57	T0 N0 M0	FN	T0 N0 M0	FN	M1b	Pubis	Follow-up imaging (bone scan +CT)	M1b SBRT + ADT
UCLA #030	0.54	T0 N0 M0	FN	T0 N0 M0	FN	M1b	T7	Follow-up imaging (MRI)	Surveillance
UCLA #023	0.62	T0 N0 M0	FN	T0 N0 M1b	TP	M1b	T11	Follow-up imaging (MRI)	Surveillance
UCLA #049	0.38	T0 N0 M0	FN	T0 N1 M0	TP	N1	LO LN	Follow-up imaging (MRI)	SRT Prostate fossa + SRT Pelvis + ADT
UCLA #011	0.84	Tr N0 M0	TP	T0 N0 M0	FN	T	Prostate Fossa	Follow-up imaging (MRI)	SRT Prostate fossa + ADT
UCLA #005	1.00	T0 N0 M0	FN	T0 N0 M1c	TP	M1c	Penis	Follow-up imaging (MRI)	ADT
UCLA #038	1.44	Tr N0 M0	TP	Tr N0 M0	TP	T	Prostate Fossa	Follow-up imaging (Ultrasound)	ADT

Supplemental Table 15: Semi-quantitative analysis and lesion-to-background ratios

L/B: lesion-to-background ratio; Values are mean.

Concordant Lesion	n=	FACBC			PSMA				
		Lesion SUVmax	L/B Liver	L/B Aorta	L/B muscle	Lesion SUVmax	L/B Liver	L/B Aorta	L/B muscle
Pelvic LN (N)	3	3.13	0.50	2.18	3.65	5.60	0.94	4.35	13.03
Prostate fossa (T)	4	4.17	0.55	2.71	3.73	10.18	2.24	8.69	34.67
All concordant lesions	7	3.73	0.52	2.44	3.69	8.21	1.68	6.83	25.39

Supplemental Table 16: Summary of multivariable logistic regression mixed effects 9-model with the outcome of positive PET scan.

ADT: androgen deprivation therapy; RT: radiation therapy; RP: radical prostatectomy; NCCN: national comprehensive cancer network.

Model	Covariates	OR (95% CI)	p-value
1	PET Scan tracer (FACBC vs PSMA)	3.88 (1.59-9.45)	0.0036
	on-going ADT	1.49 (0.41-5.41)	0.54
2	PET Scan tracer (FACBC vs PSMA)	3.56 (1.47-8.65)	0.0060
	history of adjuvant ADT	1.18 (0.30-4.15)	0.87
3	PET Scan tracer (FACBC vs PSMA)	3.63 (1.48-8.89)	0.0057
	history of adjuvant RT	0.38 (0.08-1.92)	0.24
4	PET Scan tracer (FACBC vs PSMA)	3.65 (1.38-9.65)	0.010
	PSA doubling time > median	0.87 (0.29-2.63)	0.81
5	PET Scan tracer (FACBC vs PSMA)	3.68 (1.39-9.79)	0.010
	PSA Velocity	1.28 (0.68-2.42)	0.437
6	PET Scan tracer (FACBC vs PSMA)	3.58 (1.42-9.04)	0.0081
	NCCN risk group		0.29
	High vs Intermediate	0.41 (0.11-4.49)	0.17
	N1 vs Intermediate	1.40 (0.37-5.25)	0.61
	Very high vs Intermediate	0.45 (0.07-2.75)	0.38
7	PET Scan tracer (FACBC vs PSMA)	3.73 (1.55-8.93)	0.0040
	time RP to PET	1.00 (0.99-1.01)	0.87
8	PET Scan tracer (FACBC vs PSMA)	3.73 (1.56-8.94)	0.0040
	Uptake time > 3 min	1.21 (0.35-4.20)	0.76
9	PET Scan tracer (FACBC vs PSMA)	3.77 (1.57-9.10)	0.0039
	administration of IV CT-contrast	1.68 (0.58-4.86)	0.33

PSMA vs AXUMIN
PET READING SPREADSHEET GUIDELINES

1. Rate the quality of each PET/CT scan as follow : 3 = good quality; 2 = fair quality; 1 = poor quality.
 - a. If poor quality (=1), please explain why: CT artefacts, low resolution CT, low tracer activity, high background activity, bladder activity etc ...
2. Determine if IV contrast has been administrated: yes =1; no =0.
3. Determine if oral contrast has been administrated: yes =1; no =0.
4. Rate the prostate bed analysis as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
 - a. If positive, measure the SUVmax of the prostate bed lesion (if possible with a 3D VOI).
 - b. If positive, specify if there is CT correlate: yes =1; no =0.
 - c. If positive and with CT correlate, measure the long axis (mm) of the prostate bed lesion
5. Rate the pelvic lymph nodes analysis (below aorto-iliac bifurcation) as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
 - a. If positive, specify the number of positive pelvic lymph node(s)
If positive, specify the localization as follow: RII/LII/RO/LO/REI/LEI/PR/PS/Other (please specify)
RII= right internal iliac, LII= left internal iliac, RO= right obturator, LO= left obturator, REI= right external iliac, LEI=left external iliac, PR= peri-rectal, PS= pre-sacral.
If multiple, separate each positive pelvic lymph node by " / "
 - b. If positive, measure the SUVmax of the positive pelvic lymph node(s) (if possible with a 3D VOI).
If multiple, separate each value by " / " (same order than in column AD)
 - c. If positive, measure the short axis (mm) of the positive pelvic lymph node(s).
If multiple, separate each value by " / " (same order than in column AD)
6. Rate the extra-pelvic lymph nodes analysis (above aorto-iliac bifurcation) as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
 - a. If positive, specify the number of positive pelvic lymph node(s)
 - b. If positive, specify the localization as follow: ABD/SD/ING/Other (please specify)
ABD= abdominal, SD= supra-diaphragmatic, ING= inguinal.
If multiple, separate each positive pelvic lymph node by " / "
 - c. If positive, measure the SUVmax of the positive extra-pelvic lymph node(s) (if possible with a 3D VOI).
If multiple, separate each value by " / " (same order than in column AI)
 - d. If positive, measure the short axis (mm) of the positive extra-pelvic lymph node(s)
If multiple, separate each value by " / " (same order than in column AI)
7. Rate the skeletal analysis as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
 - a. If positive, specify the number of positive bone lesion
 - b. If positive, specify the bone lesion anatomic localization.
If multiple, separate each positive bone lesion by " / "
 - c. If positive, measure the SUVmax of the positive bone lesion(s) (if possible with a 3D VOI).
If multiple, separate each value by " / " (same order than in column AN)
 - d. If positive, specify the CT correlate as follow: NO/SCL/LY/MIX
If multiple, separate each positive bone lesion by " / " (same order than in column AN).
NO=None, SCL= sclerotic, LY= Lytic, MIX= Mixed.
 - e. If positive and with CT correlate, measure the long axis (mm) of the positive bone lesion(s).
If multiple, separate each value by " / " (same order than in column AN).
8. Rate the visceral metastasis analysis as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
 - a. If positive, specify the number of positive visceral lesion
 - b. If positive, specify the visceral lesion anatomic localization.
If multiple, separate each positive visceral lesion by " / "
 - c. If positive, measure the SUVmax of the positive visceral lesion(s) (if possible with a 3D VOI).
If multiple, separate each value by " / " (same order than in column AS)
 - d. If positive, measure the long axis (mm) of the positive visceral lesion(s).
If multiple, separate each value by " / " (same order than in column AS).
9. Rate the whole body PET/CT scan analysis as negative (=0) or positive (=1).
If equivocal findings note these in column AX. You must choose here between 0 and 1.
10. Note any equivocal findings or other remarks (AX)

Article #4:

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 (n=74)

In the following study, we compared the new imaging technique (PSMA-PET) to the reference technique by standard-of-care for intra-prostatic tumor staging i.e. multiparametric magnetic resonance imaging (mpMRI).

This study was conducted on a sub-cohort of patients enrolled in the UCLA pivotal trial submitted to the FDA for primary staging. Patients were included if they underwent initial staging with both PSMA-PET/CT and mpMRI at our institution and subsequently underwent radical prostatectomy at our institution. The aim of our study was to evaluate how PSMA-PET/CT performs in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer of primary prostate cancer in comparison to mpMRI using 3 independent masked readers for each modality and with histopathology as the gold standard.

The 2 imaging modalities showed similar accuracy in the detection and localization of intraprostatic lesions. The combined use of the two led to better cancer localization but did not significantly improve detection rates.

The study was published in *The Journal of Nuclear Medicine* on the Cover page as featured article and is provided below.

IMPACT FACTOR
10.057

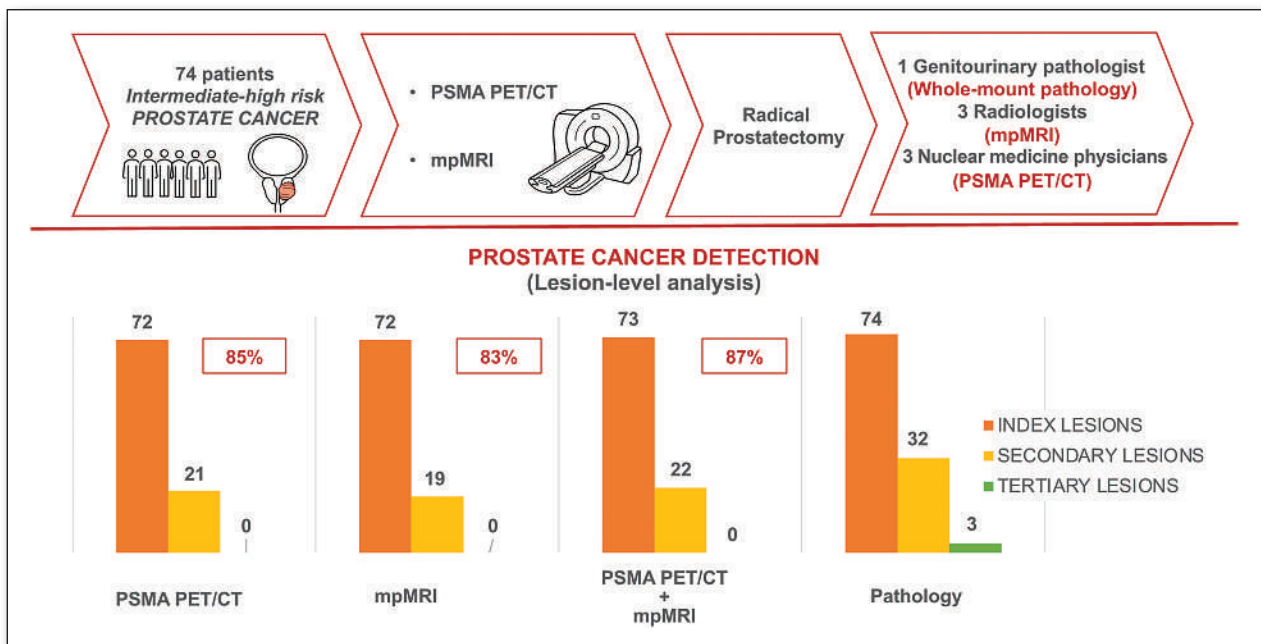
#1 NUCLEAR MEDICINE,
MOLECULAR IMAGING AND
MOLECULAR RADIOTHERAPY
JOURNAL

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The Journal of Nuclear Medicine

FEATURED ARTICLE

Head-to-Head Comparison of ⁶⁸Ga-PSMA-11 PET/CT and mpMRI with a Histopathology Gold Standard in the Detection, Intraprostatic Localization, and Determination of Local Extension of Primary Prostate Cancer: Results from a Prospective Single-Center Imaging Trial. Ida Sonni et al. See page 847.



FAPI ligands: the promising pharmacokinetics of albumin binder-conjugated fibroblast activation protein inhibitors for cancer therapy. Mengxin Xu et al. See page 952.

Head-to-Head Comparison of ^{68}Ga -PSMA-11 PET/CT and mpMRI with a Histopathology Gold Standard in the Detection, Intraprostatic Localization, and Determination of Local Extension of Primary Prostate Cancer: Results from a Prospective Single-Center Imaging Trial

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The role of prostate-specific membrane antigen (PSMA)-targeted PET in comparison to multiparametric MRI (mpMRI) in the evaluation of intraprostatic cancer foci is not well defined. The aim of our study was to compare the diagnostic performance of ^{68}Ga -PSMA-11 PET/CT (PSMA PET/CT), mpMRI, and PSMA PET/CT + mpMRI using 3 independent masked readers for each modality and with histopathology as the gold standard in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer. **Methods:** Patients with intermediate- or high-risk prostate cancer who underwent PSMA PET/CT as part of a prospective trial (NCT03368547) and mpMRI before radical prostatectomy were included. Each imaging modality was interpreted by 3 independent readers who were unaware of the other modality result. A central majority rule was applied (2:1). Pathologic examination of whole-mount slices was used as the gold standard. Imaging scans and whole-mount slices were interpreted using the same standardized approach on a segment level and a lesion level. A “neighboring” approach was used to define imaging–pathology correlation for the detection of individual prostate cancer foci. Accuracy in determining the location, extraprostatic extension (EPE), and seminal vesicle invasion (SVI) of prostate cancer foci was assessed using receiver-operating-characteristic curve analysis. Interreader agreement was calculated using intraclass correlation coefficient analysis. **Results:** The final analysis included 74 patients (14 [19%] with intermediate risk and 60 [81%] with high risk). The cancer detection rate (lesion-based analysis) was 85%, 83%, and 87% for PSMA PET/CT, mpMRI, and PSMA PET/CT + mpMRI, respectively. The change in AUC was statistically significant between PSMA PET/CT + mpMRI and the 2 imaging modalities alone for delineation of tumor localization (segment-based

analysis) ($P < 0.001$) but not between PSMA PET/CT and mpMRI ($P = 0.093$). mpMRI outperformed PSMA PET/CT in detecting EPE ($P = 0.002$) and SVI ($P = 0.001$). In the segment-level analysis, intraclass correlation coefficient analysis showed moderate reliability among PSMA PET/CT and mpMRI readers using a 5-point Likert scale (range, 0.53–0.64). In the evaluation of T staging, poor reliability was found among PSMA PET/CT readers and poor to moderate reliability was found for mpMRI readers. **Conclusion:** PSMA PET/CT and mpMRI have similar accuracy in the detection and intraprostatic localization of prostate cancer foci. mpMRI performs better in identifying EPE and SVI. For the T-staging evaluation of intermediate to high-risk prostate cancer, mpMRI should still be considered the imaging modality of reference. Whenever available, PSMA PET/MRI or the coregistration or fusion of PSMA PET/CT and mpMRI (PSMA PET/CT + mpMRI) should be used as it improves tumor extent delineation.

Key Words: PSMA PET/CT; prostate cancer; mpMRI; staging; T staging

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Prostate cancer is the most common solid-organ malignancy in men, accounting for over 190,000 new diagnoses and over 33,000 deaths in 2020 (1). Distant extrapelvic staging in patients with unfavorable intermediate- and high-risk disease with cross-sectional imaging and bone scanning is recommended to guide initial therapy (2,3).

Current methods used to locally stage prostate cancer and identify the precise location of foci of disease rely on the results of systematic or targeted biopsies and multiparametric MRI (mpMRI). Although targeted biopsies have considerably improved the identification of clinically significant prostate cancer and even allowed for the tracking of biopsy cores over time, there is still over a 30% chance of missing

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clinically significant prostate cancer in men with multifocal disease (4). Further, in a cohort of men selected as candidates for focal therapy who underwent radical prostatectomy, nearly half had unidentified bilateral disease and would have been inadequately treated (5). Therefore, additional and perhaps complementary methods are needed to better characterize and identify clinically significant prostate cancer foci.

Prostate-specific membrane antigen (PSMA) is a transmembrane cell-surface protein overexpressed in prostate cancer cells relative to most other tissues (6). ^{68}Ga -PSMA-11 PET/CT (PSMA PET/CT) has been shown in prospective studies to be highly sensitive and specific for the identification of biochemically recurrent disease and to improve staging in patients with newly diagnosed disease (7–9). Previous studies comparing PSMA PET and mpMRI in the local staging of prostate cancer had overall discordant results. Although some studies found PSMA PET/CT to be superior to mpMRI (10–12), others showed no significant differences (13,14).

The goal of the current analysis was to compare the diagnostic performance of PSMA PET/CT, mpMRI, and the combination of the two (PSMA PET/CT + mpMRI) in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer, with histopathology as the gold standard, using 3 masked independent readers for each modality.

MATERIALS AND METHODS

Study Design and Patient Population

We report here the results of an exploratory endpoint of a prospective trial conducted at UCLA (NCT03368547). The primary outcome of the trial was to evaluate the diagnostic performance (sensitivity, specificity, positive predictive value, and negative predictive value) of PSMA PET/CT for the detection of regional nodal metastases compared with histopathology at radical prostatectomy in patients with intermediate- to high-risk prostate cancer. The results of the primary endpoint analysis were the foundation of a new-drug application for ^{68}Ga -PSMA-11 (15) and will be reported separately.

For the current study, patients with biopsy-proven intermediate- or high-risk prostate cancer by NCCN (16) and enrolled in the pivotal trial were included in the analysis if they underwent initial staging with both PSMA PET/CT and mpMRI at our institution and subsequently underwent radical prostatectomy. Patients treated with androgen deprivation therapy were excluded from the analysis. The study was done under an investigational-new-drug approval protocol (IND 130649) and was approved by the local institutional review board (approval 16-001684).

mpMRI Image Acquisition

mpMRI was performed on a 3-T MRI system (Magnetom Trio, Skyra, or Verio; Siemens Medical Systems) using a standardized protocol with pelvic external phased-array coils. The mpMRI protocol included conventional multiplanar T2-weighted turbo spin-echo imaging, diffusion-weighted imaging, axial unenhanced T1-weighted imaging, and axial 3-dimensional fast-field echo dynamic contrast-enhanced imaging, as described previously (17). In addition, a small-field-of-view 3-dimensional axial turbo spin-echo T2-weighted sequence was performed using spatial and chemical-shift encoded excitation (SPACE; Siemens Healthcare), as described in detail previously (17,18).

PSMA PET/CT Image Acquisition

PSMA PET/CT images were acquired after intravenous injection of a median of 192.4 MBq of ^{68}Ga -PSMA-11 (interquartile range, 185–203.5 MBq) and a median uptake time of 61.5 min (interquartile range, 58–67 min) using a Biograph 64 or mCT PET/CT scanner (Siemens Medical Systems) (axial field of view, 22.1 cm). ^{68}Ga -PSMA-11

(Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga (HBEDCC)]) was used as the PSMA ligand (19) and was obtained from the Biomedical Cyclotron Facility at UCLA. Oral and intravenous CT contrast media were administered unless contraindicated. A 5-mm slice thickness was used for the CT scan. All PET images acquired from pelvis to vertex were corrected for attenuation, dead time, random events, and scatter. The time per bed position was based on patient weight (20).

Image Analysis

For the purpose of this exploratory endpoint analysis, the PSMA PET/CT and mpMRI were read independently by 3 board-certified nuclear medicine physicians (with 4, 4, and 1 y of experience in interpreting PSMA PET/CT, that is, ~250 scans/y, and 19, 7, and 7 y of experience in interpreting oncologic PET/CT, that is, ~1,000 scans/y) and 3 radiologists (with 5, 5, and 12 y of experience in prostate mpMRI, that is, ~1,000 scans/y) using OsiriX and DynaCAD software, respectively (21).

All readers were aware of the presence of biopsy-proven prostate cancer but not of any other demographic, clinical, pathology, or imaging information. The readers were masked to the PSMA PET/CT and mpMRI clinical reports and to the other readers' findings. A standardized approach was used for imaging interpretation, assessing the presence, location, and size of prostate cancer foci (lesions) within the prostate. The analysis was conducted on an individual-lesion level and on a segment level.

Segment-Level Analysis (Prostate Cancer Localization). The prostate was divided into 12 segments using orthogonal axial planes for PSMA PET/CT and oblique axial planes for mpMRI: base, mid gland, and apex, defined as the upper, middle, and lower thirds, respectively, of the prostate; right/left and anterior/posterior were defined on axial views by a vertical line (sagittal plane) and horizontal line (coronal plane), respectively, passing through the center of the prostate (Fig. 1). The 12 segments used in this analysis represented a compromise between the 41 sectors used in the Prostate Imaging Reporting and Data System (PI-RADS) score and the sextants used for PSMA PET in previous studies (12,22). All PSMA PET/CT and mpMRI readers assigned each segment a score using a 5-point Likert scale (PSMA score, resembling scores using PSMA-RADS version 1.0 (23,24) and PI-RADS version 2.1 (25), respectively) based on the overall likelihood of prostate cancer. Each reader's 5-point scores were further converted into a binary score (1 and 2 = negative for cancer; 3, 4, and 5 = positive for cancer).

Lesion-Level Analysis (Prostate Cancer Detection). A maximum of 3 prostate cancer lesions was listed for each patient and described as the index, secondary, and tertiary lesions. Each reader recorded lesion size and other parameters (i.e., SUV_{max} for PSMA PET/CT and diffusion-weighted imaging PI-RADS score for mpMRI) to aid in the overall interpretation.

T Staging. The presence of bilateral intraprostatic disease, seminal vesicle invasion (SVI [T3b]), and extraprostatic extension (EPE [T3a]) was assessed visually in a binary manner (26).

Majority Rule and Central Reads. One lead investigator collected the imaging and pathology reads and conducted the final analysis. A central majority rule (2:1) was used to obtain the final reads for PSMA PET/CT and mpMRI. On a segment level, lesion level, and T-staging level, positivity for cancer involvement in the individual segment, lesion, or T level was considered present if at least 2 of 3 readers described it as positive for cancer.

PSMA PET/CT + mpMRI. PSMA PET/CT + mpMRI findings were obtained by combining the central majority reads from the 2 imaging modalities. If a segment, lesion, or T-level finding was described as positive on only 1 imaging modality (only on PET or mpMRI), it was automatically considered positive on PSMA PET/CT + mpMRI.

Histopathology Analysis

Whole-mount slices (tissue sections of 5 mm, histologic sections cut at 5 μm) were read by a genitourinary pathologist (with 7 y of whole-mount

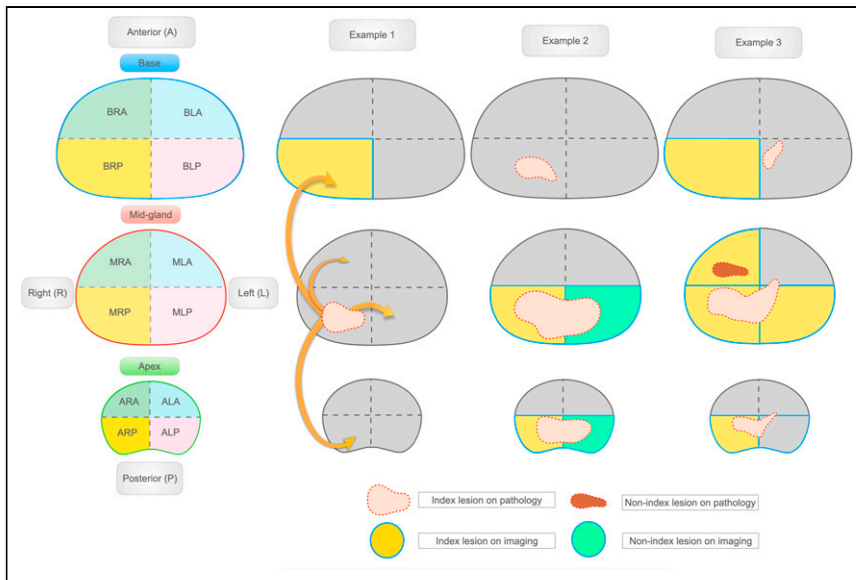


FIGURE 1. Prostate segmentation template and imaging–pathology correspondence for lesion-based analysis. Twelve-segment subdivision of prostate gland was used for standardized reads (left). Examples are shown of imaging–pathology correlation for lesion-level analysis using neighboring approach. Arrows indicate adjacent or neighboring segments. (Example 1) One lesion described on pathology as involving segment MRP, and 1 lesion identified by imaging as involving segment BRP. Imaging–pathology correlation: true-positive finding because BRP and MRP are neighboring segments. (Example 2) One large lesion described on pathology as involving segments ARP, MRP, BRP, ALP, and MLP, and 2 lesions identified by imaging (lesion 1, involving ARP and MRP [yellow segments], and lesion 2, involving ALP and MLP [green segments]). Imaging–pathology correlation: true-positive because one single lesion was described on pathology and correctly identified as cancer by imaging, even though described differently. (Example 3) Two lesions described on pathology (lesion 1, involving ALP, MLP, BLP, ALA, MLA, ARP, and MRP [pink lesion], and lesion 2, involving MRA [red lesion]), and 1 large lesion described by imaging as involving segments ARP, MRP, MLP, BRP, and MRA. Imaging–pathology correlation: 2 true-positive findings because 2 lesions were described on pathology, and both were described as cancer on imaging.

experience) who was masked to all imaging results using the lesion- and segment-level approach. Each lesion was assessed for the presence, location, and size of cancer foci and for the Gleason grade.

Benign prostatic lesions were not considered and were excluded from the detection analysis.

Imaging–Pathology Correlation

To define imaging–pathology correspondence on a lesion level, an adaptation of a previously described approach was used (Fig. 1) (27). This “neighboring” approach did not take into account the number of lesions and allowed the location correspondence to involve the immediately adjacent segments. This approach was used to overcome possible interpretation errors due to misregistration or misalignment deriving from deformation and shrinkage during fixation, commonly happening during whole-mount slice preparation (28), or due to use of different orientations by PSMA PET/CT, mpMRI, and pathologic examination of whole-mount slices (prostatectomy specimen cross section) to define the prostate base, mid-gland, and apical regions.

Statistical Analysis

Patient characteristics and study variables were summarized using mean and SD, median and interquartile range, or frequency and percentage, as appropriate. The diagnostic performance of PSMA PET/CT, mpMRI, and PSMA PET/CT + mpMRI were compared with histopathologic analysis on a lesion level and a segment level. Receiver-operating-characteristic curves and area under the receiver-operating-characteristic curves (AUCs) were obtained along with 95% CIs. AUC CI changes and *P* values were determined using the DeLong test.

Interrater agreement was calculated using the intraclass correlation coefficient (ICC) with the 2-way random-effects model, using absolute-agreement and single-measure options. Statistical analyses were performed using SPSS (version 25; IBM), and *P* values of less than 0.05 were considered statistically significant.

RESULTS

Patient Population

Between January 2017 and November 2019, 398 patients were enrolled in the trial. Seventy-four patients were included in the final analysis of this study (study flow-chart in Fig. 2). The mean time was 43 d (SD, 39.9 d; range, –31 to 123 d) between PSMA PET/CT and mpMRI, 54.1 d (SD, 35.9 d; range, 6–180 d) between PSMA PET/CT and radical prostatectomy, and 100.8 d (SD, 53.4 d; range, 3–288 d) between mpMRI and radical prostatectomy. In 44 of 74 patients (59%), the mpMRI was performed before the biopsy, whereas all PSMA PET/CT scans were obtained after confirmation of a positive biopsy. Patient characteristics are summarized in Table 1.

Prostate Cancer Localization (Segment-Based Analysis)

In total, 425 of 888 segments (48%) were positive for cancer by pathologic examination. PSMA PET/CT, mpMRI, and PSMA PET/CT + mpMRI found cancer (majority reads) in 310 (35%), 314 (35%), and 405 (46%) segments, respectively. The results of

the segment-level analysis and the receiver-operating-characteristic curve analysis per reader and per imaging modality are shown in Figures 3A and 3B. In total, 408 of 888 segments (46%) were described as harboring clinically significant prostate cancer (Gleason score > 3 + 3 = 6). The results of a subanalysis including only clinically significant lesions are shown in Supplemental Figure 1 (supplemental materials are available at <http://jnm.snmjournals.org>).

The AUCs for PSMA PET/CT, mpMRI, and PSMA PET/CT + mpMRI were 0.7 (sensitivity, 0.84; specificity, 0.55), 0.73 (sensitivity, 0.86; specificity, 0.59), and 0.77 (sensitivity, 0.77; specificity, 0.71), respectively. The change in AUC was statistically significant between PSMA PET/CT + mpMRI and the 2 imaging modalities alone (*P* < 0.001) but not between PSMA PET/CT and mpMRI (*P* = 0.093).

The AUCs for readers 1, 2, and 3 were 0.69, 0.69, and 0.66, respectively, using the PSMA score and 0.71, 0.72, and 0.71, respectively, using the PI-RADS score.

ICC analysis showed moderate reliability (29) among PSMA PET/CT and mpMRI readers using the 5-point Likert scale (PSMA PET/CT: reader 1/reader 2, 0.63; reader 1/reader 3, 0.53; and reader 2/reader 3, 0.64) (mpMRI: reader 1/reader 2, 0.61; reader 1/reader 3, 0.55; and reader 2/reader 3, 0.55).

Prostate Cancer Detection (Lesion-Based Analysis)

Pathologic examination of whole-mount slices identified 109 prostate cancer foci (74, 32, and 3 index, secondary, and tertiary lesions, respectively). Using the majority reads, PSMA PET/CT

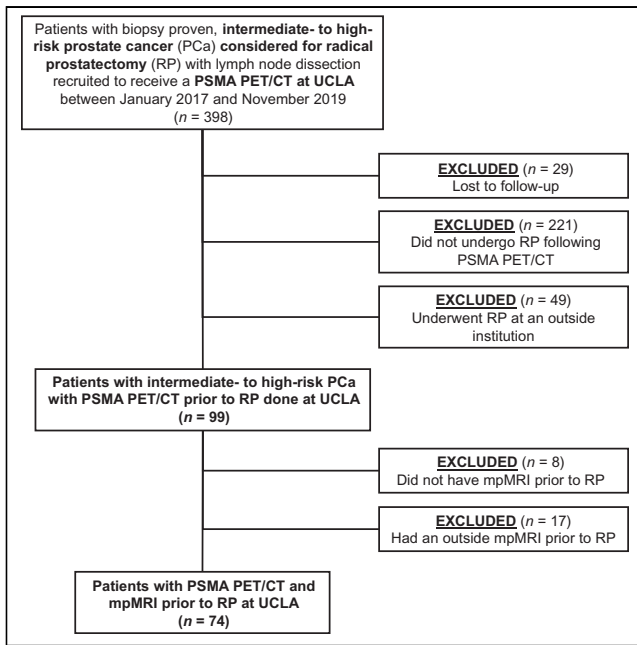


FIGURE 2. Study flowchart.

identified 111 lesions (74, 33, and 4 index, secondary, and tertiary lesions, respectively) and mpMRI identified 91 (74, 16, and 1 index, secondary, and tertiary lesions, respectively). The results of the lesion-level analysis and detection rates for all cancerous lesions are shown in Table 2. Individual readers' results are shown in Supplemental Table 1.

The detection rate was 85%, 83%, and 87% for PSMA PET/CT, mpMRI, and PSMA PET/CT + mpMRI, respectively. PSMA PET/CT identified 4 lesions (1 primary and 3 secondary) missed by mpMRI, whereas mpMRI identified 2 lesions (1 primary and 1 secondary) missed by PSMA PET/CT (Supplemental Table 2). Differences in detection rates between PSMA PET/CT and mpMRI were not statistically significant. The addition of PSMA PET/CT did not provide significant increases in detection rates over mpMRI alone.

Two separate subanalyses excluding small cancerous lesions (≤ 0.5 cm on histopathologic analysis) and lesions with a Gleason score of $3 + 3 = 6$ were conducted.

Twelve of 109 lesions (11%) were graded as having a Gleason score of $3 + 3 = 6$ (10 secondary lesions and 2 tertiary lesions). The overall detection rate excluding these lesions was 95% for PSMA PET/CT + mpMRI (vs. 92% for both PSMA PET/CT and mpMRI alone).

The detection rates for clinically significant lesions are summarized in Table 2.

Five of 109 lesions (5%) measured 0.5 cm or less on histopathologic analysis. Three of the 5 were not detected by either imaging modality, 1 of the 5 was identified by both, and 1 of the 5 was identified by mpMRI and PSMA PET/CT.

Figure 4 and Supplemental Figure 2 show examples of a PSMA PET/CT image, an mpMRI image, and a whole-mount slice from our cohort.

T Staging

Histopathologic examination detected bilateral disease in 37 of 74 patients (50%), SVI in 25 of 74 (34%), and EPE in 43 of 74 (58%). By majority reads, although mpMRI had a higher AUC than PSMA

TABLE 1
Patient Characteristics

Characteristic	Data
No. of patients	74
Median age (y)	65 (IQR, 60–69)
Median PSA (ng/mL)	11.1 (IQR, 7.5–21.5)
Initial PSA (ng/mL)	
<10	29 (39%)
10–20	26 (35%)
>20	19 (26%)
D'Amico risk classification	
Intermediate risk	14 (19%)
High risk	60 (81%)
Presurgical Gleason grade	
3 + 3 = 6	1 (1%)
3 + 4 = 7	14 (20%)
3 + 5 = 8	2 (2%)
4 + 3 = 7	13 (19%)
4 + 4 = 8	24 (34%)
4 + 5 = 9	19 (27%)
5 + 4 = 9	1 (1%)

IQR = interquartile range; PSA = prostate-specific antigen level.

PET/CT for the detection of bilateral disease (0.65 vs. 0.54), this difference was not significantly different (DeLong test, $P = 0.138$) (Fig. 3). mpMRI had a better AUC than PSMA PET/CT for detection of EPE (0.79 vs. 0.59, $P = 0.002$) or SVI (0.84 vs. 0.63, $P = 0.001$). The use of PSMA PET/CT + mpMRI did not provide statistically significant improvements over mpMRI alone.

Poor reliability was found among readers for PSMA PET/CT in the evaluation of bilaterality (ICC, 0.344), EPE (ICC, 0.203), and SVI (ICC, 0.081); moderately strong reliability was found among mpMRI readers for bilaterality (ICC, 0.693) and EPE (ICC, 0.580), and poor reliability was found for SVI (ICC, 0.305).

DISCUSSION

Using the majority reads of 3 masked independent readers for each imaging modality, our single-center study including 74 patients with intermediate- to high-risk prostate cancer found that PSMA PET/CT and mpMRI performed similarly in the detection and intraprostatic localization of primary prostate cancer, whereas mpMRI was superior for determining the T stage. The combined use of PSMA PET/CT and mpMRI improved tumor extent delineation (segment-level analysis) and allowed the identification of multifocal lesions but did not significantly improve the detection rates (lesion-level analysis) of the 2 modalities alone.

Current clinical guidelines (2,30) still recommend the use of cross-sectional imaging (CT or MRI) with bone scanning for extraprostatic distant staging in patients with intermediate- to high-risk prostate cancer. Several studies showed PSMA PET/CT to be superior to conventional imaging in the evaluation of N and M stage (7–9,31–34), but its added value in the definition of

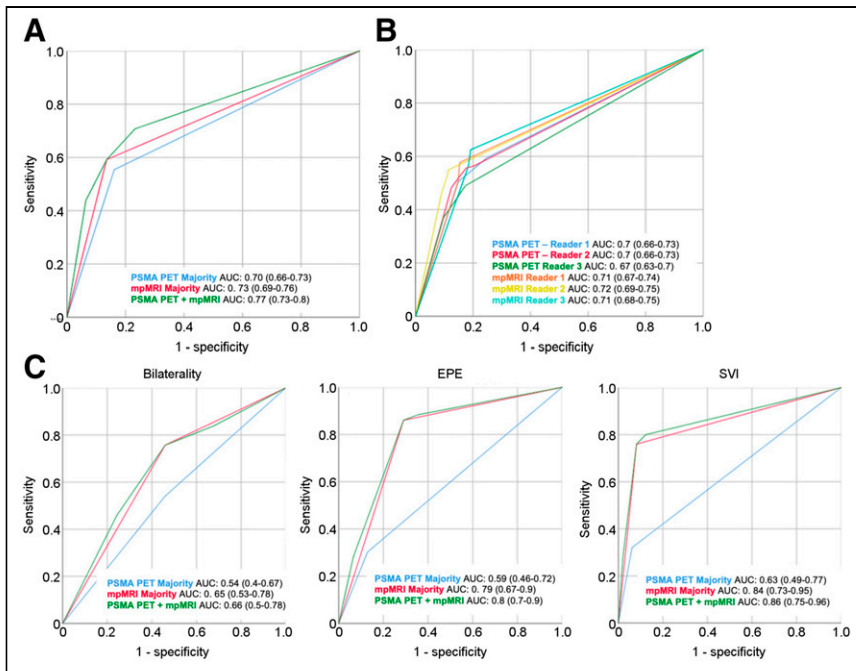


FIGURE 3. Prostate cancer localization (segment-based analysis) and T3 staging. (A and B) Receiver-operating-characteristic curves for segment-level analysis obtained for PSMA PET/CT and mpMRI majority reads (A) and using 1–5 PSMA and PI-RADS score for each individual reader (B). Graphs show change in AUC between PSMA PET/CT and mpMRI (95% CI, -0.01 to 0.07 ; $P = 0.093$), between PSMA PET/CT + mpMRI and PSMA PET/CT (95% CI, 0.05 – 0.1 ; $P < 0.001$), and between PSMA PET/CT + mpMRI and mpMRI (95% CI, 0.03 – 0.06 ; $P < 0.001$). (C) Receiver-operating-characteristic curves for PSMA PET/CT and mpMRI majority reads in evaluation of T staging. Graphs show change in AUC for bilateral disease (0.65 vs. 0.54 , DeLong test, $P = 0.138$), change in AUC for EPE (0.79 vs. 0.59 ; 95% CI, 0.08 – 0.32 ; $P = 0.002$), and change in AUC for SVI (0.84 vs. 0.63 ; 95% CI, 0.09 – 0.33 ; $P = 0.001$).

T stage and in intraprostatic tumor localization is still controversial. The goal of our analysis was to compare the 2 imaging modalities in the definition of local disease and to evaluate whether the combination of the two provides any significant advantage. In this setting, the current literature shows discordant results, mostly due to small cohorts, different study designs, and different approaches in defining the imaging–pathology correlation. Unlike previous studies, the current work included a relatively large cohort of prospectively selected patients and involved a standardized approach to the correlation analysis of image findings and whole-mount pathology findings. An additional analysis on T staging was conducted, as well as a subanalysis on lesions with lower Gleason grades ($3 + 3 = 6$). In our study, PSMA PET/CT allowed the detection of 4 lesions missed by mpMRI (4/109 lesions [4%]) but also misclassified more lesions as prostate cancer (higher number of false-positives) at the expense of the positive predictive value. In a future study, we will conduct an additional analysis specifically looking at lesions negative on both imaging modalities, discordant cases, and the histopathologic features of these tumor foci.

The segment-level analysis for localization of prostate cancer foci did not show significant differences between PSMA PET/CT and mpMRI. Conversely, the addition of PSMA PET/CT to mpMRI significantly increased the number of segments detected, indicating that PSMA PET/CT improves the definition of tumor extent and can be an important aid in guiding the initial therapeutic approach (5). However, to confirm this finding, further investigation is needed.

The results were obtained using a neighboring approach to evaluate imaging–pathology correlation, which was applied to overcome the intrinsic limitation of the lack of registration between imaging and pathology. The use of PSMA PET/CT + mpMRI allowed the detection of 99% of primary lesions and 69% of secondary lesions, with an overall detection rate of 87% (vs. 85% and 83% for PSMA PET/CT and mpMRI alone, respectively) for all lesions, and 95% (vs. 92% for both PSMA PET/CT and mpMRI alone) for clinically significant lesions (Supplemental Table 2). On the basis of the improved performance of the combined PSMA PET/CT + mpMRI information, we recommend that discordant cases in clinical practice be evaluated in consensus between PET/CT and MRI readers or by a multidisciplinary prostate cancer tumor board. A lesion detected on only one of the modalities should be considered suggestive of cancer. Whenever possible, the PSMA PET/CT and mpMRI images should be coregistered using the CT and MRI prostate contours as a reference.

mpMRI performed significantly better than PSMA PET/CT in the definition of T stage, that is, SVI (T3b) and EPE (T3a), but not in the detection of bilateral disease (T2c). This finding is attributable mainly to the poor inter-reader agreement among the 3 PET readers for T staging, probably because of the lack of standardized criteria for T-staging evaluation

by PSMA PET/CT. In contrast, since the correct definition of the locoregional extension of prostate cancer relies strongly on visualization of anatomic detail, the well-established higher soft-tissue contrast, higher spatial resolution, and multiplanar capability of mpMRI represent an advantage over CT and led to good agreement among the 3 MRI readers for T staging. However, interrater reliability was also poor for mpMRI readers in the evaluation of SVI. These results contrast with those of a previously published study involving 54 patients; in that study, PSMA PET/CT showed a higher sensitivity for the definition of EPE but not for SVI (35).

Intraprostatic tumor detection and localization by PSMA PET/CT relies largely on the PSMA PET signal because of the poor tissue contrast of CT. Consequently, lesion localization is highly dependent on the SUV visual scaling threshold used while interpreting the scans. The readers did not receive any specific recommendation on a fixed SUV threshold, as interpretation should be done by adapting the scaling to the background signal. This lack of a recommendation represents a source of interreader variability, but despite this inherent limitation for PSMA PET/CT, the segment-level analysis for localization of prostate cancer foci did not show significant differences from mpMRI.

Several studies showed that the combined use of PSMA PET/CT and mpMRI provides the best diagnostic accuracy overall (10,14). In light of the recent advent of PET/MRI, a growing body of literature is now available using PSMA PET/MRI, which has been shown by several groups to outperform each modality alone (22,28,36–38). However, the limited number of PET/MRI scanners available worldwide

TABLE 2
Prostate Cancer Detection Rates (Lesion-Based Analysis)

Parameter	All lesions			Clinically significant lesions		
	PSMA PET/CT	mpMRI	PSMA PET/CT + mpMRI	PSMA PET/CT	mpMRI	PSMA PET/CT + mpMRI
Index lesion (<i>n</i> = 74)	72 (97%)	72 (97%)	73 (99%)	72 (97%)	72 (97%)	73 (99%)
Secondary lesion (<i>n</i> = 32)	21 (66%)	19 (59%)	22 (69%)	18 (81%)	18 (81%)	19 (86%)
Tertiary lesion (<i>n</i> = 3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Overall (detection rate)	93 (85%)	91 (83%)	95 (87%)	90 (93%)	90 (93%)	92 (95%)
Positive predictive value	97%	100%	—	94%	100%	—

Clinically significant lesions exclude lesions with Gleason score of 3 + 3 = 6. Differences in detection rate between PSMA PET/CT and mpMRI were not statistically significant.

and the associated high costs still limit its widespread use in clinical practice. The well-established superiority of PSMA PET/CT in N and M staging, combined with an enhanced ability to determine T stage and local extension with mpMRI, highlights the complementary role of each imaging modality and underscores the diagnostic potential of PSMA PET/MRI. If available, PSMA PET/MRI should be considered the modality of choice in the initial evaluation of patients with advanced prostate cancer. When a hybrid PET/MRI scanner is not available, the PSMA PET/CT and mpMRI images acquired separately

should be coregistered using a reproducible multimodality DICOM image-fusion tool. If this is not possible, mpMRI remains the imaging modality of reference for the evaluation of T stage.

The main limitations of the study are the lack of coregistration between PSMA PET/CT, mpMRI, and pathology and the absence of the use of a 3-dimensional custom mold (39–41). To compensate for this inaccurate imaging–pathology correlation, we used a neighboring approach. Another limitation is that the interval between mpMRI and radical prostatectomy was not homogeneous, ranging between

3 and 288 d, raising the potential issue of inherent tumor changes over time. Additionally, sources of bias include the lack of negative controls in the cohort, as all imaging readers were aware of the presence of biopsy-proven high- to intermediate-risk prostate cancer, and patient selection, as we cannot rule out the exclusion of patients with a positive mpMRI result and a negative biopsy result from the final cohort. Thus, the PPV should be interpreted with caution. Finally, since we included only patients with intermediate- and high-risk disease, we were not able to address the clinical question of whether PSMA PET/CT can bring a significant added value to mpMRI in the initial staging of a heterogeneous population of patients with prostate cancer, including patients with less aggressive disease.

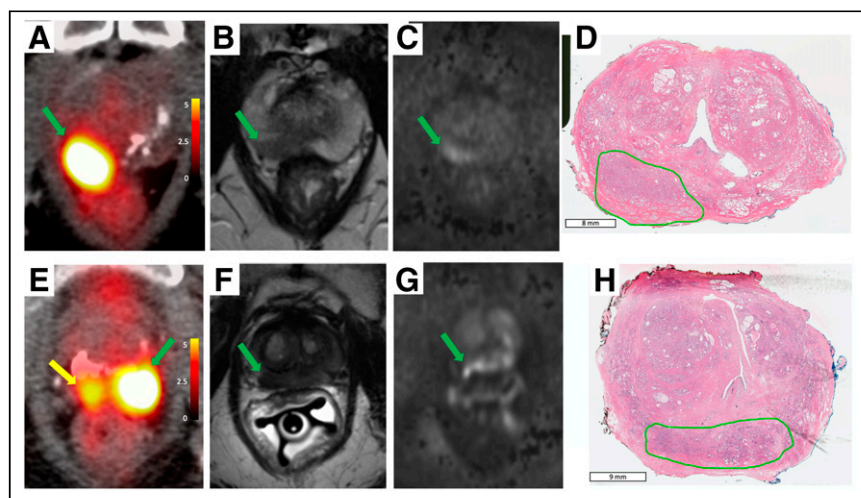


FIGURE 4. Two case examples from our cohort. (A–D) A 68-y-old patient (patient 4) with biopsy-proven prostate cancer with Gleason score of 3 + 4 = 7 and PSA of 8.6 ng/mL at time of PSMA PET/CT. Transverse PSMA PET/CT image (A), T2-weighted MR image (B), and high b-value diffusion-weighted MR image (C) show right-posterior mid-gland lesion (arrows). Whole-mount slice (D) shows 1 lesion, with Gleason score of 4 + 3 = 7, in same segment (contoured in green), and lesion showed EPE. There was good imaging–pathology correspondence (true-positive finding for both imaging modalities). All 6 readers correctly identified and described lesion. (E–H) A 69-y-old patient (patient 5) with biopsy-proven prostate cancer with Gleason score of 3 + 4 = 7 and PSA of 11.4 ng/mL at time of PSMA PET/CT. Transverse PSMA PET/CT image (E) shows 2 foci of increased PSMA uptake in right-posterior apex (yellow arrow) and left-posterior apex (green arrow). PSMA reader 1 correctly described 1 lesion involving left- and right-posterior apex; PSMA readers 2 and 3 described left and right foci as 2 separate lesions. T2-weighted MR image (F) shows hypointense lesion, and diffusion-weighted image (G) shows diffusion restriction in right- and left-posterior apex (arrow). All MRI readers correctly described only 1 lesion. Whole-mount slice (H) shows 1 lesion encompassing both right- and left-posterior apex (contoured in green) with EPE. This is an example of same lesion being described differently by PSMA PET/CT and whole-mount slice (true-positive finding for both imaging modalities).

CONCLUSION

In our study using the majority reads of 3 masked independent readers for each modality, both PSMA PET/CT and mpMRI performed well in the detection and intraprostatic localization of intermediate- to high-risk primary prostate cancer, whereas mpMRI had superior performance in the definition of T stage (T2c, T3). The combined use of PSMA PET/CT and mpMRI improved tumor extent delineation. Our findings highlight the complementarity of the 2 imaging modalities.

DISCLOSURE

Johannes Czernin is a board member of Sofie Biosciences and a founder of Trethera Therapeutics. Jeremie Calais reports prior consulting activities outside the submitted work for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, Janssen, POINT Biopharma, Progenics, Radiomedix, and Telix Pharmaceuticals. He is the recipient of grants from the Prostate Cancer Foundation (2020 Young Investigator Award 20YOUN05), the Society of Nuclear Medicine and Molecular Imaging (2019 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.

KEY POINTS

QUESTION: How does PSMA PET/CT perform in the local evaluation of primary prostate cancer in comparison to mpMRI, and is there an additional value in the combined use of both PSMA PET/CT and MRI in comparison to mpMRI alone?

PERTINENT FINDINGS: The 2 imaging modalities showed similar accuracy in the detection and localization of intraprostatic lesions, whereas mpMRI performed better in the definition of EPE and SVI. The combined use of the two leads to better cancer localization but did not significantly improve detection rates.

IMPLICATIONS FOR PATIENT CARE: In this study, the addition of PSMA PET/CT to mpMRI did not significantly change local staging in patients with intermediate- to high-risk prostate cancer.

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Article #5:

⁶⁸Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA < 1.0ng/ml: Impact on Salvage Radiotherapy Planning (n=270)

PSMA-PET has a profound impact on management of patients with prostate cancer. We observed it quite rapidly after the first few scans and at the Tumor Board. We, as many others, reported on the impact on management of PSMA-PET in various settings (52–58).

Whether better diagnostic efficacy performances and changes in management lead to improved patient outcomes remains to be demonstrated. Clinical trials investigating how Stage migration and new disease stage categories from PSMA-PET (59–62) and powered to show differences on long-term clinical outcomes are warranted.

In the following study, we present a large cohort of patients (n=270) who underwent 68Ga-PSMA-11 PET/CT at a PSA level of less than 1 ng/mL after prior prostatectomy. This cohort of patients is representative of those who are routinely offered SRT in the absence of radiographically visible disease. We mapped the 68Ga-PSMA-11 PET/CT recurrence pattern of early BCR after prostatectomy, evaluated how often SRT based on consensus contouring guidelines failed to cover PSMA-PET detected disease using blinded operators, and assessed the potential impact of 68Ga-PSMA-11 PET/CT on SRT planning for patients with PCa early BCR. We found that PSMA-PET had a major impact on SRT planning in 52 of 270 patients (19%) with early BCR (PSA <1.0 ng/ml) by revealing lesions not covered by the standard radiation fields, including both the prostate bed and pelvic lymph nodes, defined on computed tomography (CT).

We hypothesized that this major impact of PSMA-PET on patient selection and RT planning would translate into better outcomes from PSMA-PET–guided SRT. This provided the rationale to initiate a randomized prospective imaging trial powered for outcome.

The study was published in *The Journal of Nuclear Medicine* on the Cover page as featured article and nominated “Best JNM article of the year 2018”, was highlighted in many other media, and is provided below.

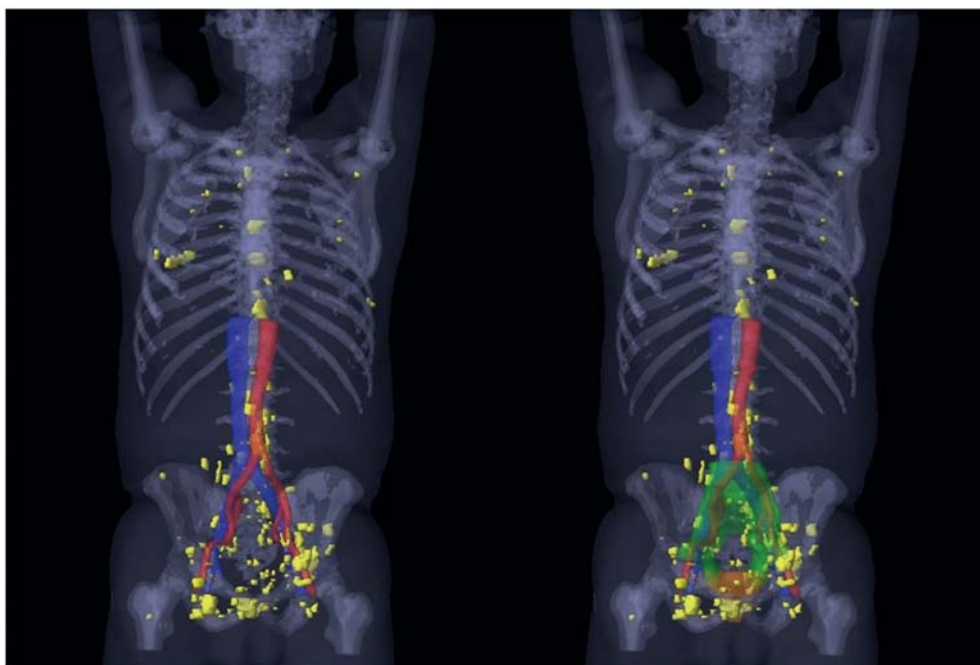
Following this study, we initiated a self-funded randomized phase 3 trial of 193 patients. The trial enrollment has been completed in 2020 and final analysis is planned for 2025. The study protocol and a trial update publication are provided.

This concludes the first part of the manuscript on PSMA-PET imaging.

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FEATURED ARTICLE

⁶⁸Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning. Jeremie Calais et al. See page 230.



Differentiating normal prostate from cancer: Can PET/CT localize PSMA expression? Nadine Woythal et al. See page 238.



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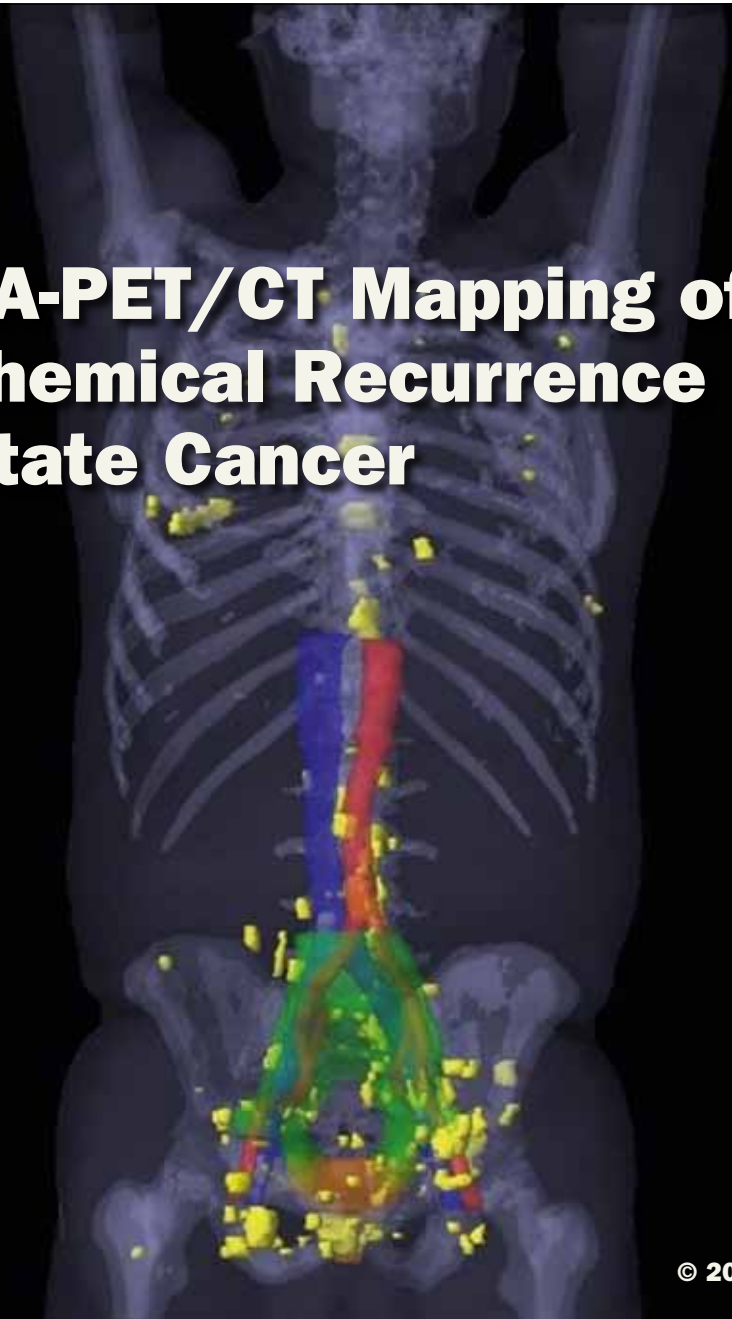


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PSMA-PET/CT Mapping of Biochemical Recurrence Prostate Cancer



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⁶⁸Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning

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See an invited perspective on this article on page 228.

Target volume delineations for prostate cancer (PCa) salvage radiotherapy (SRT) after radical prostatectomy are usually drawn in the absence of visibly recurrent disease. ⁶⁸Ga-labeled prostate-specific membrane antigen (PSMA-11) PET/CT detects recurrent PCa with sensitivity superior to standard-of-care imaging at serum prostate-specific antigen (PSA) values low enough to affect target volume delineations for routine SRT. Our objective was to map the recurrence pattern of PCa early biochemical recurrence (BCR) after radical prostatectomy with ⁶⁸Ga-PSMA-11 PET/CT in patients with serum PSA levels of less than 1 ng/mL, determine how often consensus clinical target volumes (CTVs) based on the Radiation Therapy Oncology Group (RTOG) guidelines cover ⁶⁸Ga-PSMA-11 PET/CT-defined disease, and assess the potential impact of ⁶⁸Ga-PSMA-11 PET/CT on SRT. **Methods:** This was a post hoc analysis of an intention-to-treat population of 270 patients who underwent ⁶⁸Ga-PSMA-11 PET/CT at 4 institutions for BCR after prostatectomy without prior radiotherapy at a PSA level of less than 1 ng/mL. RTOG consensus CTVs that included both the prostate bed and the pelvic lymph nodes were contoured on the CT dataset of the PET/CT image by a radiation oncologist masked to the PET component. ⁶⁸Ga-PSMA-11 PET/CT images were analyzed by a nuclear medicine physician. ⁶⁸Ga-PSMA-11-positive lesions not covered by planning volumes based on the consensus CTVs were considered to have a potential major impact on treatment planning. **Results:** The median PSA level at the time of ⁶⁸Ga-PSMA-11 PET/CT was 0.48 ng/mL (range, 0.03–1 ng/mL). One hundred thirty-two of 270 patients (49%) had a positive ⁶⁸Ga-PSMA-11 PET/CT result. Fifty-two of 270 (19%) had at least one PSMA-11-positive lesion not covered by

the consensus CTVs. Thirty-three of 270 (12%) had extrapelvic PSMA-11-positive lesions, and 19 of 270 (7%) had PSMA-11-positive lesions within the pelvis but not covered by the consensus CTVs. The 2 most common ⁶⁸Ga-PSMA-11-positive lesion locations outside the consensus CTVs were bone (23/52, 44%) and perirectal lymph nodes (16/52, 31%). **Conclusion:** Post hoc analysis of ⁶⁸Ga-PSMA-11 PET/CT implied a major impact on SRT planning in 52 of 270 patients (19%) with PCa early BCR (PSA < 1.0 ng/mL). This finding justifies a randomized imaging trial of SRT with or without ⁶⁸Ga-PSMA-11 PET/CT investigating its potential benefit on clinical outcome.

Key Words: prostate cancer; PSMA; PET/CT; recurrence; salvage radiotherapy

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Prostate cancer (PCa) biochemical recurrence (BCR) takes place in 20%–80% of patients within 10 y after radical prostatectomy, with the risk of failure dependent on National Comprehensive Cancer Network risk group, pathologic features, and genomic classification (1,2). After BCR, salvage radiotherapy (SRT) is the main curative option (3). Overall, SRT offers long-term biochemical control in about 50% of patients (4), depending on pre-SRT prostate-specific antigen (PSA) level (5), radiotherapy dose (6), and risk group (7). For high-risk patients, 5-y BCR after SRT reaches 70% (8,9). Intuitively, SRT is curative only if recurrent disease is completely encompassed by the irradiated volumes. Therefore, accurate estimation of the location of recurrent disease is critical.

In practice, SRT is commonly initiated in patients with serum PSA levels of less than 1 ng/mL, a threshold at which standard-of-care imaging is insensitive for detecting recurrence (10). As such, SRT target volumes are usually drawn in the absence of radiographically visible disease (gross disease). The Radiation Therapy Oncology Group (RTOG) published contouring guidelines for both prostate bed and pelvic lymph node (LN) clinical target

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volumes (CTVs) (areas with potential microscopic occult tumor) based on a consensus panel of experienced genitourinary radiation oncologists (11,12). These consensus CTVs are applied in ongoing clinical trials and guide routine care.

⁶⁸Ga-labeled (Glu-NH-CO-NH-Lys-(Ahx)-[⁶⁸Ga(HBED-CC)]) prostate-specific membrane antigen (PSMA-11) PET/CT is superior to standard-of-care imaging for detecting regional and distant metastatic recurrent PCa at low PSA levels (13–16) and is also highly specific (16) and reproducible (17). Detection rates of about 50% are reported even at PSA levels of less than 0.5 ng/mL (15,16). Therefore, ⁶⁸Ga-PSMA-11 PET/CT has the potential to guide and improve target volume delineations for SRT.

The potential impact of ⁶⁸Ga-PSMA-11 PET/CT on radiotherapy planning has been assessed in several inhomogeneous patient groups with primary and recurrent disease. These studies established that ⁶⁸Ga-PSMA-11 PET/CT can image PCa at low serum PSA values and potentially affect radiotherapy planning. Limitations include inconsistent descriptions of anatomic relapse patterns and the pooling of patients with a wide range of serum PSA values and clinical disease states (18–24).

We present a large cohort of patients who underwent ⁶⁸Ga-PSMA-11 PET/CT at a PSA level of less than 1 ng/mL after prior prostatectomy. This cohort of patients is representative of those who are routinely offered SRT in the absence of radiographically visible disease. We map the ⁶⁸Ga-PSMA-11 PET/CT recurrence pattern of early BCR after prostatectomy, evaluate how often SRT based on consensus contouring guidelines fails to cover PSMA-11–expressing disease, and assess the potential impact of ⁶⁸Ga-PSMA-11 PET/CT on SRT planning for patients with PCa early BCR.

MATERIALS AND METHODS

Patients and Data Management

We first identified 270 consecutive and well-documented patients from databases established at 4 institutions (Technical University of Munich [*n* = 147], University of California at Los Angeles [UCLA, *n* = 47; clinicaltrials.gov identifier NCT02940262, Institutional Review Board approval 16-001095], Ludwig-Maximilians-University of Munich [*n* = 40], and University of Essen [*n* = 36]). All patients underwent radical prostatectomy, had BCR without prior radiotherapy, and underwent ⁶⁸Ga-PSMA-11 PET/CT at a serum PSA level of less than 1 ng/mL between August 2013 and May 2017 to detect the sites of recurrence. All patients gave written consent to undergo the procedures. The clinical data and DICOM files of all patients were anonymized and imported onto a dedicated radiotherapy contouring workstation at UCLA (MIM, version 6.7.5; MIM Software Inc.). The UCLA Institutional Review Board approved this anonymized post hoc retrospective analysis (approval #17-001340), and the requirement to obtain informed consent was waived.

⁶⁸Ga-PSMA-11 PET/CT Image Acquisition

⁶⁸Ga-PSMA-11 PET/CT imaging was performed according to recent guidelines (25). Images were acquired on different PET/CT devices: the Siemens Biograph 128 mCT (*n* = 183, 68%), Siemens Biograph 64 (*n* = 50, 19%), Siemens Biograph 64 mCT (*n* = 24, 9%), or GE Healthcare Discovery 690 (*n* = 13, 5%). The ⁶⁸Ga-PSMA-11 compound was used at all sites (26). The median injected dose was 154 MBq (range, 65–267 MBq). To reduce bladder activity, patients received 20 mg of furosemide at the time of tracer injection if there was no contraindication. The median uptake period was 59 min (range, 37–132 min). A diagnostic CT scan (200–240 mAs, 120 kV) was performed after intravenous injection of contrast agent (if no contraindication existed), followed by the whole-body PET image acquisition (2–4 min/bed position).

Simulation of Consensus SRT Planning

SRT consensus CTVs were contoured on the CT dataset of the PET/CT scan for all 270 patients by an experienced radiation oncologist who was masked to the PET findings. Consensus RTOG contouring guidelines were used (Fig. 1A) (11,12), except that the common iliac nodes were contoured beginning inferior to L4/L5 (rather than L5/S1). Briefly, the prostate bed CTV included the anatomic prostatic fossa and the seminal vesicle remnants. The pelvic nodal CTV included presacral, common iliac, internal iliac, external iliac, and obturator LNs. Although the addition of pelvic LN irradiation in SRT is controversial (27,28) and under investigation (RTOG 0534, NCT00567580), we included pelvic LN coverage along with the prostate bed for all patients to establish a generous estimate of how often SRT based on consensus CTVs fails to cover PSMA-11–expressing recurrent disease.

⁶⁸Ga-PSMA-11 PET/CT Image Analysis

Next, all ⁶⁸Ga-PSMA-11 PET/CT images were analyzed by an experienced nuclear medicine physician according to recent recommendations (25,29): any focal uptake of ⁶⁸Ga-PSMA-11 above the surrounding background level and not associated with physiologic uptake or known pitfalls (30) was considered suggestive of malignancy (Fig. 1B). Distinction between malignant and inflammatory LNs (e.g., reactive or granuloma) was based on degree of PSMA-11 uptake, typically intermediate and low for inflammation, and location, typically perihilar, axillary, or inguinal for inflammatory nodes. On the basis of TNM staging, the following regions were systematically analyzed for recurrence: prostate bed/seminal vesicle remnants (T), pelvic LNs (N) (internal iliac, obturator, external iliac, perirectal, presacral, common iliac), extrapelvic LNs (M1a) (retroperitoneal, inguinal, chest, other), bone (M1b), and other visceral organs (M1c).

⁶⁸Ga-PSMA-11 PET Lesion Contouring

In a third step, ⁶⁸Ga-PSMA-11–positive lesions were contoured on the CT images (Fig. 1C). These contours were subsequently used to define ⁶⁸Ga-PSMA-11–based target volumes. Moreover, we generated a 3-dimensional map of all ⁶⁸Ga-PSMA-11–positive lesion contours across the entire study population on a template patient (Fig. 2). This was achieved by rigid image registration of each patient's CT image to the template patient image. Then, the ⁶⁸Ga-PSMA-11–based contours were transferred to the template patient image through this registration (MIM, version 6.7.5).

Coregistration of Consensus CTVs with ⁶⁸Ga-PSMA-11 PET/CT Images

In a final step, the consensus CTVs were coregistered with the ⁶⁸Ga-PSMA-11 PET/CT images (Fig. 1D). Contours including the PSMA-11–positive lesions were then compared with the consensus CTVs for each patient to assess whether PSMA-11–positive lesions were localized inside (Fig. 3) or outside (Fig. 4) the consensus CTVs. To take into consideration the final planning target volumes, only PSMA-11–positive lesion contours at least 10 mm away from the CTVs were considered inadequately covered. Because many modern centers use CTVs to plan target volume expansions of less than 10 mm, this analysis should yield a generous estimate of how often planning based on consensus CTVs offers adequate coverage. PSMA-11–positive lesions within either the prostate bed or the pelvic LN consensus CTVs were considered covered.

Potential Impact of ⁶⁸Ga-PSMA-11 PET/CT on Radiotherapy Planning

PSMA-11–positive lesions not covered by the consensus CTVs were considered to have a potential major impact on treatment planning. Potential major impact was further subclassified as extension of the CTVs to cover PSMA-11–positive lesions within the pelvis; superior extension of the CTVs to cover paraaortic LNs; addition of

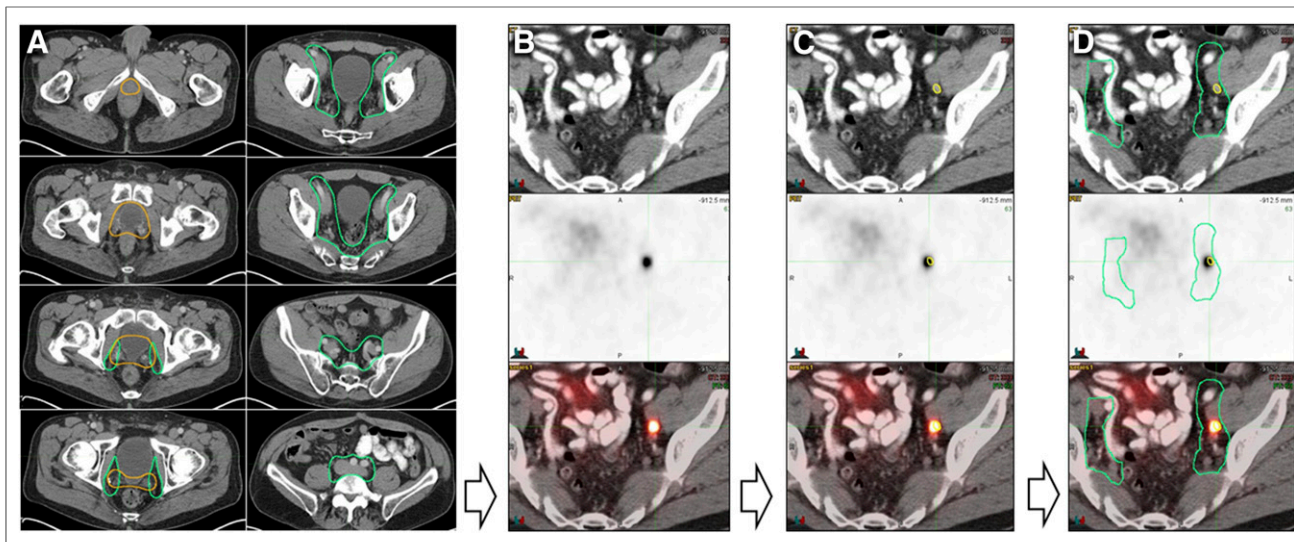


FIGURE 1. Study methodology. (A) Experienced radiation oncologist masked to PET findings contoured RTOG CTVs onto CT dataset of PET/CT scan for all 270 patients (prostate bed CTV in orange and pelvic LN CTV in green). (B) All ^{68}Ga -PSMA-11 PET/CT images were analyzed by an experienced nuclear medicine physician. (C) PSMA-11–positive lesions were contoured in yellow on CT images. (D) Consensus CTVs were coregistered with ^{68}Ga -PSMA-11 PET/CT images and PSMA-11–positive lesion contours (yellow) to assess, for each patient, whether PSMA-11–positive lesions were localized inside or outside consensus CTVs.

metastasis-directed stereotactic body radiation therapy for extrapelvic oligometastatic disease (1–5 extrapelvic sites that are M1a or M1b); or radiotherapy not indicated (futile) because of the presence of visibly polymetastatic (>5 M1a or M1b) or visceral (M1c) metastatic disease. If PSMA-positive lesions were covered by the CTVs, the potential impact of ^{68}Ga -PSMA-11 PET/CT on treatment planning was defined as minor (potential for dose escalation to gross disease (visibly PSMA-11–positive). Negative ^{68}Ga -PSMA-11 PET/CT findings were considered to have no impact on SRT planning.

Statistical Analysis

We performed a post hoc analysis of this intention-to-treat population and simulated the impact of ^{68}Ga -PSMA-11 PET/CT

on SRT planning. Descriptive statistics were used (median, range). The comparisons of clinical and pathologic characteristics between positive and negative ^{68}Ga -PSMA-11 PET/CT patients were conducted using the *t* test along with the Wilcoxon test as a verification for continuous variables and the χ^2 test for categorical variables. The serum PSA level before PET/CT was considered first as continuous variable and converted into categorical-variable—low PSA (0.5–1.0 ng/mL) and very low PSA (<0.5 ng/mL)—groups for comparison. These analyses were conducted in R (31).

RESULTS

Patient Characteristics

Table 1 summarizes the clinical and pathologic characteristics of the 270 patients. In brief, the median age was 68 y (range, 43–90 y), and the median serum PSA level was 0.44 ng/mL (range, 0.03–1 ng/mL). Thirty-three of 270 patients (12.5%) underwent androgen deprivation therapy within 6 mo before the ^{68}Ga -PSMA-11 PET/CT study. Thirty-six of 270 (13.5%) were National Comprehensive Cancer Network–defined intermediate-risk. One hundred sixty-three of 270 (60.5%) were National Comprehensive Cancer Network–defined high-risk, 142 of 270 (52.5%) were pT3, and 54 of 270 (20%) were pN1. Sixty-seven of 270 patients (25%) had positive surgical margins (R1). Overall, the cohort was at high risk for treatment failure after prostatectomy.

^{68}Ga -PSMA-11 PET/CT Findings and Consensus CTVs

Tables 2 and 3 depict the ^{68}Ga -PSMA-11 PET/CT findings. One hundred thirty-two of 270 patients (49%) had a positive ^{68}Ga -PSMA-11 PET/CT result. Fifty-two of 132 patients (39%) had at least one PSMA-11–positive lesion not covered by consensus CTVs: 33 of 132 (25%) had extrapelvic metastases whereas 19 of 132 (14%) had PSMA-11–positive pelvic lesions not covered by consensus CTVs, without extrapelvic metastases. The 3 most common ^{68}Ga -PSMA-11–positive lesion locations outside the consensus CTVs were bone (23/52, 44%), perirectal LNs (16/52, 31%),

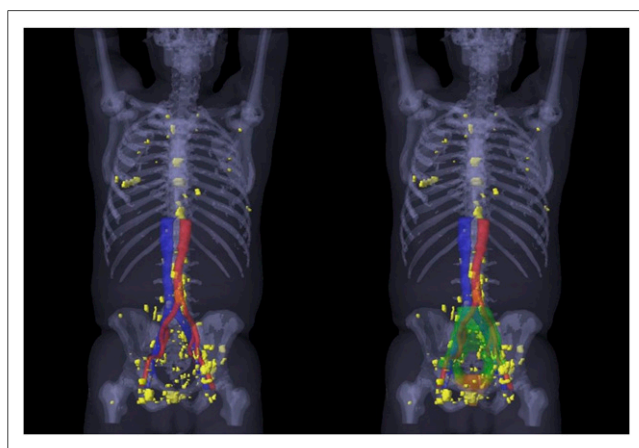


FIGURE 2. A 3-dimensional map of the PSMA-11–positive lesions (yellow) of all 52 patients with recurrence outside consensus CTVs (23 patients with recurrence outside only and 29 patients with recurrence outside and inside consensus CTVs), created by rigid registration of each patient's CT image to template patient's CT image, followed by transfer of each PSMA-11–positive lesion contour to template patient CT image (MIM, version 6.7.5; MIM Software Inc.). On right side, 3-dimensional prostate bed consensus CTV is shown in orange and 3-dimensional pelvic LN consensus CTV in green.

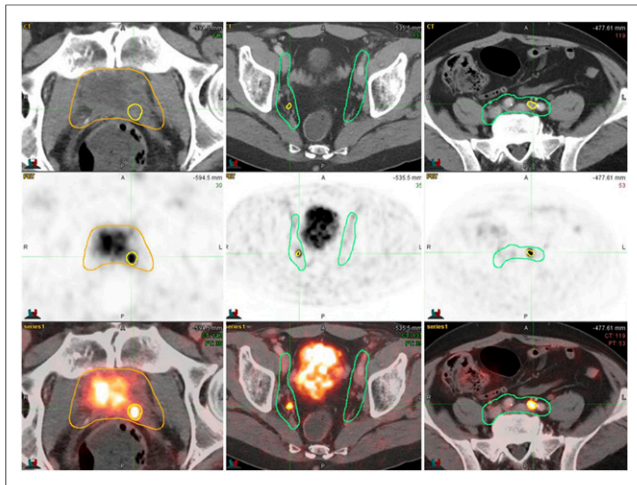


FIGURE 3. PSMA-11–positive lesions (yellow contours) inside prostate bed CTV (gold contours) and nodal CTV (green contours).

and distal external iliac LNs (9/52, 17%). Figure 2 displays a 3-dimensional map of all ^{68}Ga -PSMA-11 PET recurrences outside the consensus CTVs coregistered on a template patient's CT image.

^{68}Ga -PSMA-11 PET/CT Findings and Clinicopathologic Characteristics

The 132 positive ^{68}Ga -PSMA-11 PET/CT patients had significantly higher PSA levels (median, 0.5 vs. 0.36 ng/mL; $P < 0.001$) and shorter times to recurrence (median, 21.3 vs. 30.4 mo; $P = 0.05$) than the 138 negative ones. The detection rate (at least one PSMA-11–positive finding) was significantly higher in patients with a Gleason score of more than 7 than in those with a Gleason score of 7 or less (56/86 [65%] vs. 68/168 [40%]; $P < 0.001$), in

N1 patients than in N0 patients (35/54 [65%] vs. 75/166 [45%]; $P = 0.02$), and in T3 patients than in T2 patients (82/144 [57%] vs. 34/99 [34%]; $P < 0.001$). One hundred fifty-three patients had serum PSA levels of less than 0.5 ng/mL (very low PSA group), and 117 had levels of between 0.5 and 1.0 ng/mL (low PSA group). The detection rate was significantly higher in the low PSA group than in the very low PSA group: (70/117 [60%] vs. 62/153 [40.5%]; $P = 0.003$). The frequency of PSMA-11–positive lesions not covered by the consensus CTVs had a borderline-significant dissimilar pattern in the low and the very low PSA groups (29/117 [25%] vs. 23/153 [15%]; $P = 0.06$).

Verification of PSMA-11–Positive Lesions Outside Consensus CTVs

Lesions not covered by the consensus CTVs were verified in 24 of 52 patients (46%). This was done by biopsy ($n = 1$), surgery ($n = 3$), bone scanning ($n = 1$), MRI ($n = 1$), follow-up imaging (CT or PET/CT) showing progression at the site ($n = 8$), follow-up imaging (CT or PET/CT) showing a response to treatment ($n = 5$), or a decrease in serum PSA after focal treatment (stereotactic body radiation therapy; $n = 5$).

Potential Impact of ^{68}Ga -PSMA-11 PET/CT on SRT Planning

Table 4 summarizes the potential impact of ^{68}Ga -PSMA-11 PET/CT on SRT planning.

Potential Major Impact. Fifty-two patients had at least one PSMA-11–positive lesion not covered by the consensus CTVs (19% of all 270 patients, 39% of 132 PSMA-11–positive patients). SRT based on consensus CTVs would not be curative for these patients. Nineteen patients with pelvic LN metastasis outside the consensus CTVs (7% of all 270 patients, 14% of 132 PSMA-11–positive patients) could have experienced extension of consensus CTVs to cover PSMA-11–expressing disease. Twenty-two of the 33 patients with extrapelvic metastases (67%) were oligometastatic (≤ 5 metastatic sites), potentially eligible for metastasis-directed stereotactic body radiation therapy; 5 of 33 (15%) could

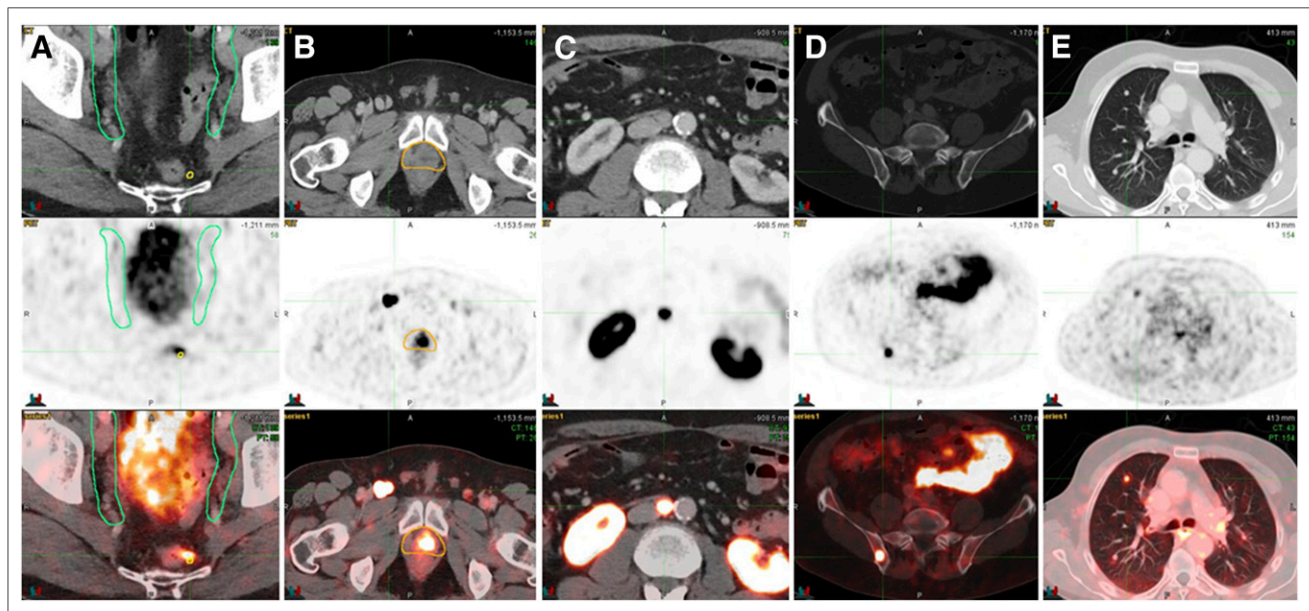


FIGURE 4. Examples of PSMA-11–positive lesions outside consensus CTVs: perirectal LN (A), inguinal LN (B), lumboaortic LN (C), bone (D), and lung (E).

TABLE 1

Clinical and Pathologic Characteristics of the 270 Patients

Characteristic	Data
Age at PET/CT, median (y)	68 (range, 43–90)
Initial PSA level before surgery, median (ng/mL)	8.3 (range, 0.4–200)
10	130 (48%)
≥10 < 20	46 (17%)
≥20	38 (14%)
Unknown	56 (21%)
Gleason score	
≤6	33 (12%)
7	135 (50%)
≥8	86 (32%)
Unknown	16 (6%)
Pathologic primary tumor stage	
pT2	99 (36.5%)
pT3	142 (52.5%)
pT4	2 (0.7%)
Unknown	27 (10%)
Pathologic regional LN stage	
pN0	166 (61.5%)
pN1	54 (20%)
pNx	50 (18.5%)
Positive margin	
R0	152 (56.5%)
R1	67 (25%)
Unknown	51 (19%)
National Comprehensive Cancer Network risk group	
Low	4 (1.5%)
Intermediate	36 (13.5%)
High	163 (60.5%)
N1	54 (20%)
Unknown	13 (5%)
Androgen deprivation therapy within 6 mo before imaging	33 (12.5%)
Time between surgery and PET/CT, median (mo)	25 (range, 2–272)
Last PSA value before PET/CT, median (ng/mL)	0.44 (range, 0.03–1)

have experienced superior extension of the nodal CTVs to encompass the paraaortic LNs, and 6 of 33 (18%) had visceral or diffuse metastatic disease (3 with multiple lung metastasis and 3 with ≥5 metastatic sites) and would be unlikely to benefit from local or metastasis-directed therapy.

Potential Minor Impact. Eighty patients (29.5% of all 270 patients, 61% of 132 PSMA-11–positive patients) had PSMA-11–positive lesions covered by the consensus CTVs and thus could have experienced focal dose escalation, which is often customary for irradiation of areas known to harbor gross disease.

DISCUSSION

The lack of sensitivity of standard-of-care imaging for recurrent PCa combined with a sensitive and specific biomarker of early disease recurrence (PSA) generates a unique challenge for local treatment of PCa BCR: we know there is cancer, but we do not know where it is. There is thus an unmet clinical need to improve target delineation in patients with potentially curable PCa with early BCR.

We report in this post hoc analysis of 270 patients with early BCR after prostatectomy that ⁶⁸Ga-PSMA-11 PET/CT would have had a major impact on 19% of patients imaged (39% of PSMA-11–positive patients) and a minor impact on 30% (61%). Overall, the addition of ⁶⁸Ga-PSMA-11 PET/CT may affect SRT planning in half the patients with a PSA level of less than 1 ng/mL. Prospective clinical trials are necessary to assess the clinical value of a restaging ⁶⁸Ga-PSMA-11 PET/CT study before SRT.

Somewhat encouragingly, although most patients are at high-risk, treatment volumes based on consensus CTVs covered all PSMA-11–positive lesions for 61% of patients with a positive ⁶⁸Ga-PSMA-11 PET/CT result. This frequency is consistent with the historical success rate of SRT. However, consensus CTVs were inadequate to cover all PSMA-11–positive lesions in 39% of patients with a positive ⁶⁸Ga-PSMA-11 PET/CT result.

The detection rate of 49% for PSMA-11–positive lesions in this cohort with BCR after surgery and a low PSA level (<1.0 ng/mL) is consistent with previous reports (15,16). The anatomic distribution of PSMA-11–positive lesions is consistent with previous PET studies using choline and PSMA-11 ligands in the setting of BCR (9,19,24,32–35). The most common nodal regions outside the CTVs in patients in this study were the perirectal (*n* = 16), distal external iliac (*n* = 9), and paraaortic (*n* = 5), which are neither assessed by routine LN dissections at prostatectomy nor targeted by routine SRT. It is unlikely that a uniform expansion of the consensus CTVs to cover these regions would be feasible, given the risks of additional toxicity. Notably, most PSMA-11–positive

TABLE 2
⁶⁸Ga-PSMA-11 PET/CT Patterns of Relapse

Pattern	Number of patients
PSMA-11 PET/CT+	132 (49%)
Prostate bed (T+)	47 (17.5%)
Pelvic LN (N1)	83 (30.5%)
Extrapelvic LN (M1a)	9 (3.5%)
Bone (M1b)	23 (8.5%)
Visceral (M1c)	3 (1%)
PSMA-11 T+ N0 M0	32 (12%)
PSMA-11 T0 N1 M0	59 (22%)
PSMA-11 T+ N1 M0	8 (3%)
PSMA-11 T+ N0 M1	2 (0.7%)
PSMA-11 T0 N0 M1	15 (5.5%)
PSMA-11 T0 N1 M1	11 (4%)
PSMA-11 T+ N1 M1	5 (2%)

Total population = 270. Percentages do not add up to 100 because multiple disease localizations per patient were possible.

TABLE 3

Anatomic Repartition of ⁶⁸Ga-PSMA-11–Positive Findings and Outside Planning Volumes Based on RTOG Consensus CTVs

Site	PSMA-11–positive patients (n)	Outside CTV patients (n)	PSMA-11–positive lesions (n)	Outside CTV lesions (n)	Median size (mm)*	Median SUV _{max} *
Overall	132 (49%)	52 (19.5%)	304	119	6.0 (3.0–23.0)	5.7 (0.5–86.9)
Prostate bed (T+)	47 (17.5%)	1 (0.003%)	52	1	7.0 (4.0–23.0)	6.4 (2.2–86.9)
Pelvic LN (N+)	83 (30.5%)	30 (11%)	174	39	6.0 (3.0–17.0)	5.8 (1.5–69.7)
Internal iliac	27 (10%)	2 (0.7%)	32	2	6.0 (3.0–10.0)	7.3 (2.3–55.0)
External Iliac	38 (14%)	9 (3.5%)	45	9	7.0 (3.5–15.0)	5.9 (1.5–69.7)
Obturator	19 (7%)	2 (0.7%)	24	2	6.0 (4.0–17.0)	3.5 (2.1–17.4)
Perirectal	18 (6.5%)	16 (6%)	25	19	5.0 (4.0–10.0)	5.2 (1.50–57.7)
Presacral	13 (5%)	3 (1%)	22	4	6.0 (4.0–10.0)	7.5 (1.5–45.7)
Common iliac	16 (6%)	2 (0.7%)	26	3	6.0 (3.0–15.0)	5.9 (2.0–33.3)
Extrapelvic LN (M1a)	9 (3.5%)	9 (3.5%)	28	28	8.0 (3.0–12.0)	13.6 (2.7–38.9)
Inguinal	2 (0.7%)	2 (0.7%)	7	7	—	—
Retroperitoneal	6 (2%)	6 (2.2%)	15	15	—	—
Upper diaphragm	2 (0.7%)	2 (0.7%)	6	6	—	—
Bone (M1b)	23 (8.5%)	23 (8.5%)	39	39	—	5.3 (2.7–28.8)
Lung (M1c)	3 (1%)	3 (1%)	11	11	5.0 (4.0–7.0)	1.0 (0.5–2.6)

*Data in parentheses are range.

Percentages do not add up to 100 because multiple disease localizations per patient were possible.

nodes were subcentimeter (median LN short axis: 6 mm [range, 3–17 mm]). Most PSMA-11–positive lesions in the prostate bed were covered. Furthermore, 32 patients (24% of the 132 PSMA-11–positive patients) had PSMA-positive lesions isolated to the prostate bed alone, whereas 67 of 132 patients (51%) had PSMA-11–positive lesions within the pelvis but without distant metastasis. This underscores the potential benefit of including pelvic nodal CTVs, which is currently under investigation in prospective trials (RTOG 0534, NCT00567580).

Importantly, the most common PSMA-11–positive lesion location outside the consensus CTVs was bone (23/52, 44%). No expansion of current CTVs would successfully cover these recurrences. Most M1 patients (67%) in this study were oligometastatic M1a or M1b (1–5 extrapelvic sites). Currently, most patients with M1 PCa receive palliative hormonal therapy as primary treatment.

The use of image-guided, metastasis-directed ablative therapy (such as stereotactic body radiation therapy) to distant lesions is an attractive strategy (35–38) being investigated in prospective trials (NCT01558427, NCT02274779) (39,40). The success of this approach, however, depends on accurate staging. ⁶⁸Ga-PSMA-11 PET/CT is probably the most sensitive imaging modality for selecting patients who might benefit.

The impact of choline PET/CT imaging on SRT planning has been assessed in several retrospective studies (9,32,33,41–45) and has ranged from 13.5% to 81.3%, with a median of 32%. Taken together, these studies found that the addition of choline PET/CT to SRT planning changed the initial plan in 357 of 1,083 patients (33%). However, ⁶⁸Ga-PSMA-11 PET/CT is superior to choline PET/CT, as shown in several studies (13,46–48), with a more favorable tumor-to-background ratio and better sensitivity for

TABLE 4

Potential Impact of ⁶⁸Ga-PSMA-11 PET/CT Imaging on SRT Planning for Early BCR After Primary Prostatectomy

Impact	Data
Major impact on SRT planning—outside RTOG CTV recurrence	52 (19%)
Extension of pelvic consensus CTVs	19 (7%)
Superior extension to cover paraaortic LNs	5 (2%)
Oligometastasis-directed stereotactic body radiation therapy (≤5 M1a or M1b)	22 (9.5%)
Radiotherapy futile because of polymetastatic or visceral disease (>5 M1a, M1b, or M1c)	6 (2.5%)
Minor impact on SRT planning—covered by planning based on consensus CTVs; dose escalation to gross disease (⁶⁸ Ga-PSMA-11–positive disease)	80 (29.5%)
No impact on SRT planning—negative ⁶⁸ Ga-PSMA-11 PET/CT results	138 (51%)

Total population = 270.

lesion detection at low PSA values (<2 ng/mL). Therefore, a higher impact of ⁶⁸Ga-PSMA-11 PET/CT on SRT planning would be expected. Several prior studies did report on the potential impact of ⁶⁸Ga-PSMA-11 PET/CT imaging on radiotherapy planning (18–22,24,35). The impact ranged from 34% to 87%, with a median of 57%. However, these studies had limitations such as inhomogeneous patient groups, with primary and recurrent disease, and a wide range of serum PSA values and clinical disease states (18–24). Therefore, strengths unique to our study include the large number of patients (270), the fact that all patients had BCR after radical prostatectomy without prior radiotherapy, and the fact that all patients had a PSA level of less than 1 ng/mL at the time of ⁶⁸Ga-PSMA-11 PET/CT imaging. This is the most relevant patient cohort to assess the impact of ⁶⁸Ga-PSMA-11 PET/CT on SRT.

This was a post hoc retrospective analysis of a well-controlled patient cohort. The design of this study precludes analysis of the impact of ⁶⁸Ga-PSMA-11 PET/CT on clinical outcomes. To minimize bias, consensus CTVs were drawn with masking of the ⁶⁸Ga-PSMA-11 PET images. Another limitation was the absence of lesion verification in all patients, but lesion confirmation in recurrent patients is frequently not feasible.

CONCLUSION

This multicenter-study post hoc analysis of 270 patients with PCa early BCR (PSA < 1.0 ng/mL) after radical prostatectomy implied a major impact (19%) of ⁶⁸Ga-PSMA-11 PET/CT on SRT. This finding justifies a randomized prospective trial to determine whether ⁶⁸Ga-PSMA-11 PET/CT can improve outcomes in patients with PCa early BCR after radical prostatectomy.

DISCLOSURE

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Article #6:


Randomized prospective phase 3 trial of ⁶⁸Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT] (n=193)

STUDY PROTOCOL

Open Access



Randomized prospective phase III trial of ^{68}Ga -PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]

Jeremie Calais^{1*} , Johannes Czernin^{1*}, Wolfgang P. Fendler^{1,2}, David Elashoff³ and Nicholas G. Nickols^{4,5}

Abstract

Background: Salvage radiotherapy (SRT) for prostate cancer (PCa) recurrence after prostatectomy offers long-term biochemical control in about 50–60% of patients. SRT is commonly initiated in patients with serum PSA levels < 1 ng/mL, a threshold at which standard-of-care imaging is insensitive for detecting recurrence. As such, SRT target volumes are usually drawn in the absence of radiographically visible disease. ^{68}Ga -PSMA-11 (PSMA) PET/CT molecular imaging is highly sensitive and may offer anatomic localization of PCa biochemical recurrence. However, it is unclear if incorporation of PSMA PET/CT imaging into the planning of SRT could improve its likelihood of success. The purpose of this trial is to evaluate the success rate of SRT for recurrence of PCa after prostatectomy with and without planning based on PSMA PET/CT.

Methods: We will randomize 193 patients to proceed with standard SRT (control arm 1, $n = 90$) or undergo a PSMA PET/CT scan (free of charge for patients) prior to SRT planning (investigational arm 2, $n = 103$). The primary endpoint is the success rate of SRT measured as biochemical progression-free survival (BPFS) after initiation of SRT. Biochemical progression is defined by PSA ≥ 0.2 ng/mL and rising. The randomization ratio of 1:1.13 is based on the assumption that approximately 13% of subjects randomized to Arm 2 will not be treated with SRT because of PSMA-positive extra-pelvic metastases. These patients will not be included in the primary endpoint analysis but will still be followed. The choice of treating the prostate bed alone vs prostate bed and pelvic lymph nodes, with or without androgen deprivation therapy (ADT), is selected by the treating radiation oncologist. The radiation oncologist may change the radiation plan depending on the findings of the PSMA PET/CT scan. Any other imaging is allowed for SRT planning in both arms if done per routine care. Patients will be followed until either one of the following conditions occur: 5 years after the date of initiation of randomization, biochemical progression, diagnosis of metastatic disease, initiation of any additional salvage therapy, death.

Discussion: This is the first randomized phase 3 prospective trial designed to determine whether PSMA PET/CT molecular imaging can improve outcomes in patients with PCa early BCR following radical prostatectomy.

Acronym: PSMA-SRT Phase 3 trial.

(Continued on next page)

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(Continued from previous page)

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Keywords: Prostate cancer, PSMA, PET/CT, Randomized phase 3 trial, Salvage radiation therapy**Introduction****Background**

Prostate cancer (PCa) is expected to have an incidence of 161,000 and a mortality of 27,000 in the US in 2017 [1]. Curative treatments for localized PCa include radical prostatectomy or radiotherapy [2]. After failure of local therapy, recurrence is detected by rising serum PSA levels. Biochemical recurrence (BCR) occurs in 20 to 80% of patients within 10 years after radical prostatectomy, with the risk of failure dependent on NCCN risk group, pathologic features, and genomic classification [3, 4]. Locally recurrent disease after radical prostatectomy may be cured by salvage radiation therapy (SRT) [5]. Overall, SRT offers long-term biochemical control in about 50–60% of patients [6, 7], depending on pre-SRT prostate-specific antigen (PSA) [5], RT dose [8] and risk group [9]. Results from RTOG 0534 trial [10], which compared three salvage RT regimens: SRT directed to the prostate bed alone, SRT directed to the prostate bed with 4–6 months of concurrent ADT, and SRT directed to the prostate bed and nodes with 4–6 months of concurrent ADT, was recently presented [11]. Five-year biochemical recurrence free survivals were higher than

expected in all arms at 71.1, 82.7, and 89.1%, respectively. Pre-SRT PSA levels were < 1.0 ng/mL in 90% of patients and only 17% of patients enrolled had a pathologic Gleason Score of 8 or higher. It is likely that these findings will impact routine practice [11]. For high-risk patients, however, 5-year BCR after SRT reaches 70% [6, 12, 13].

Intuitively, SRT is only curative if recurrent disease is completely encompassed by the irradiated volumes. Therefore, accurate localization of recurrent disease is critical. However, standard-of-care imaging modalities are too insensitive to identify recurrence sites in time to guide salvage treatment [14–16]. In practice, SRT is commonly initiated in patients with serum PSA levels < 1 ng/mL, a threshold at which standard-of-care imaging is insensitive for detecting recurrence [15]. As such, SRT target volumes are usually delineated in the absence of radiographically visible disease (gross disease). Based on an expert consensus panel the RTOG (Radiation Therapy Oncology Group) published contouring guidelines for both prostate bed and pelvic lymph node (LN) Clinical Target Volumes (CTV) as these regions often harbor occult tumors not seen on standard-of-care imaging [17, 18]. These consensus

CTV are applied in ongoing trials and guide routine clinical care.

The effectiveness of any local therapy depends on accurate imaging to rule out areas of disease that would remain untreated. The lack of sensitivity of standard-of-care imaging for recurrent PCa combined with a sensitive and specific biomarker of early disease recurrence (serum PSA level) generates a unique challenge for local treatment of PCa BCR: cancer is present, but we do not know where it is. There is thus an unmet clinical need to improve target delineation in patients with potentially curable PCa with early BCR.

⁶⁸Ga-PSMA-11 (PSMA) PET/CT is superior to standard-of-care imaging for detecting regional and distant metastatic recurrent PCa at low PSA levels [19–22], highly specific [22] and reproducible [23]. Detection rates of about 50% are reported even at PSA levels of < 0.5 ng/ml [21, 22] and greater than 95% when PSA > 2 ng/ml [24, 21]. PSMA PET/CT outperformed planar bone scan for detection of osseous metastases in large retrospective analyses [25, 26]. The detection rate of PSMA PET/CT for recurrent PCa exceeds that of choline PET/CT [27, 28], and may exceed that of ¹⁸F-Fluciclovine PET/CT [29].

Therefore PSMA PET/CT has the potential to guide and improve SRT planning in numerous ways [30]. First, PSMA PET/CT defined gross disease within a target volume can be prescribed a higher dose. Second, CTVs can be expanded to encompass areas of disease not seen by current first-line imaging and not normally targeted by consensus CTVs. Third, evidence of metastatic disease indicates that local therapy alone would not offer cure, SRT may be considered futile and abandoned. The potential impact of PSMA PET/CT on SRT planning has been assessed in several studies (Table 1) [30–43].

Taken as a group, the pooled median rate of impact of PSMA PET/CT on SRT planning is 50% (range 17–87%). Our recent multicenter post-hoc analysis of 270 patients with early BCR after prostatectomy showed that PSMA PET/CT would have had a major impact in 19% of patients [38]. Importantly, a major impact was defined as PSMA-positive disease outside planning target volumes expanded from CTVs covering both the prostate bed and pelvic lymph nodes up to L4/L5, which is more expansive than the volumes used in RTOG 0534 [10, 38]. Overall, the addition of PSMA PET/CT would have had an impact on SRT planning in half of patients with a PSA < 1 ng/mL even when using the most generous target volumes. This is the most relevant patient cohort to assess the impact of PSMA PET/CT on SRT.

Few retrospective studies with short-term follow-up reported patient outcome after PSMA PET/CT-based SRT for PCa post-prostatectomy recurrence (Table 2) [44–48]. The mean response rate from these studies is 74% (range 60–83%) after a mean follow-up time of 19 months (range 10.5–29). Interestingly Emmet et al. reported in 99 patients with BCR and PSA 0.05 to 1.0 ng/mL that PSMA PET was independently predictive of treatment response to SRT and stratified men with good response to SRT (negative PSMA (85%) or fossa-confined PSMA (81%)) versus men with poor response to SRT (PSMA N1 (61%) or PSMA M1 (30%)) after a median follow-up of 10.5 months [46].

However, it remains unclear if incorporation of PSMA PET/CT imaging into the planning of SRT could improve its likelihood of success. There is no randomized prospective trial designed to determine whether PSMA PET/CT can improve outcome at 5 years in patients with PCa early BCR following radical prostatectomy. The

Table 1 Studies That Assessed Impact of PSMA PET/CT on SRT Planning

Author	Year	n	PSA (ng/ml) Median (range)	PSMA+	Extrapelvic PSMA+	Any SRT Planning Change	SRT Considered Futile
Shakespeare	2015	18	1.1 (0.017–20.4)	NA	NA	46%	NA
van Leeuwen	2015	70	0.2 (0.05–0.99)	55%	6%	35%	7%
Sterzing	2016	42	2.8 (0.16–113)	60%	NA	61%	NA
Bluemel	2016	45	0.67 (0.10–11.2)	54%	9%	42%	4%
Albisinni	2016	48	2.2 (0.72–6.7)	NA	NA	76%	NA
Schiller	2017	31	0.71 (0.12–14.7)	100%	3%	87%	0%
Henkenberens	2017	39	1.2 (0.3–15.5)	85%	46%	59%	13%
Schmidt-Hegemann	2017	49	0.49 (0.15–6.24)	NA	4%	57%	NA
Habl	2017	83	0.69 (0.09–14.7)	71%	10%	57%	0%
De Bari	2018	12	0.51 (0.10–1.62)	NA	NA	17%	8%
Koerber	2018	71	1.2 (0.03–41.24)	NA	51%	54%	3%
Frenzel	2018	75	0.2 (0.02–653.2)	NA	NA	43%	NA
Farolfi	2018	119	0.32 (0.20–0.50)	35%	21%	30%	18%
Calais	2018	270	0.48 (0.03–1.0)	49%	13%	19%	12%

Table 2 Studies That Assessed Outcome of PSMA PET/CT-based SRT

Author	Year	n	Response rate	Median follow-up (months)
Henkenberens	2017	23	79%	12.4
Zschaeck	2017	20	60%	29
Emmett	2017	99	72%	10.5
Schmidt-Hegemann	2018	129	83%	20
Schmidt-Hegemann	2018	90	78%	23

purpose of this trial is to evaluate the success rate of SRT for recurrence of PCa after prostatectomy with and without planning based on PSMA PET/CT.

Rationale for study design and hypothesis

The overall study design is shown in Fig. 1.

In our recent multicenter post-hoc analysis of 270 patients with early BCR (PSA < 1.0 ng/ml) after prostatectomy we found that 52/270 patients (19%) had at least one lesion detected by PSMA PET/CT which was not covered by the standard radiation fields that covered both the prostate bed and pelvic lymph nodes (RTOG consensus delineations with superior extent extended to L4/L5): extra-pelvic disease was seen in 13% of patients and out-of-field pelvic disease was seen in 7% of patients [38]. SRT delivered based on these volumes would not have generated a durable PSA response. PSMA PET/CT

imaging can improve patient selection for successful SRT by excluding patients with M1 disease where SRT would not be curative (13%) and by improving the coverage of the recurrent lesions by the pelvic radiation fields (7%). Therefore, we hypothesized that the incorporation of PSMA PET/CT to SRT planning will improve 5-year PFS by 20%. Based on available published literature [5–9, 12] 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 [38]. Hence the primary endpoint of the trial is the success rate of SRT. If PSMA PET/CT detects distant metastases, then local salvage with SRT is not a medically indicated therapy because it is not curative. It is therefore not standard-of-care to perform SRT in patients with evidence of distant metastases. The current standard-of-care is to offer SRT to patients who have no evidence of metastatic disease. We acknowledge that patients in the trial who do not undergo PSMA PET/CT may have “hidden/unknown” metastatic disease, but these patients would still receive SRT per routine care. An intention to treat analysis would classify subject who undergo PSMA PET/CT and are found to have distant metastases as failure even without having received treatment. Therefore,

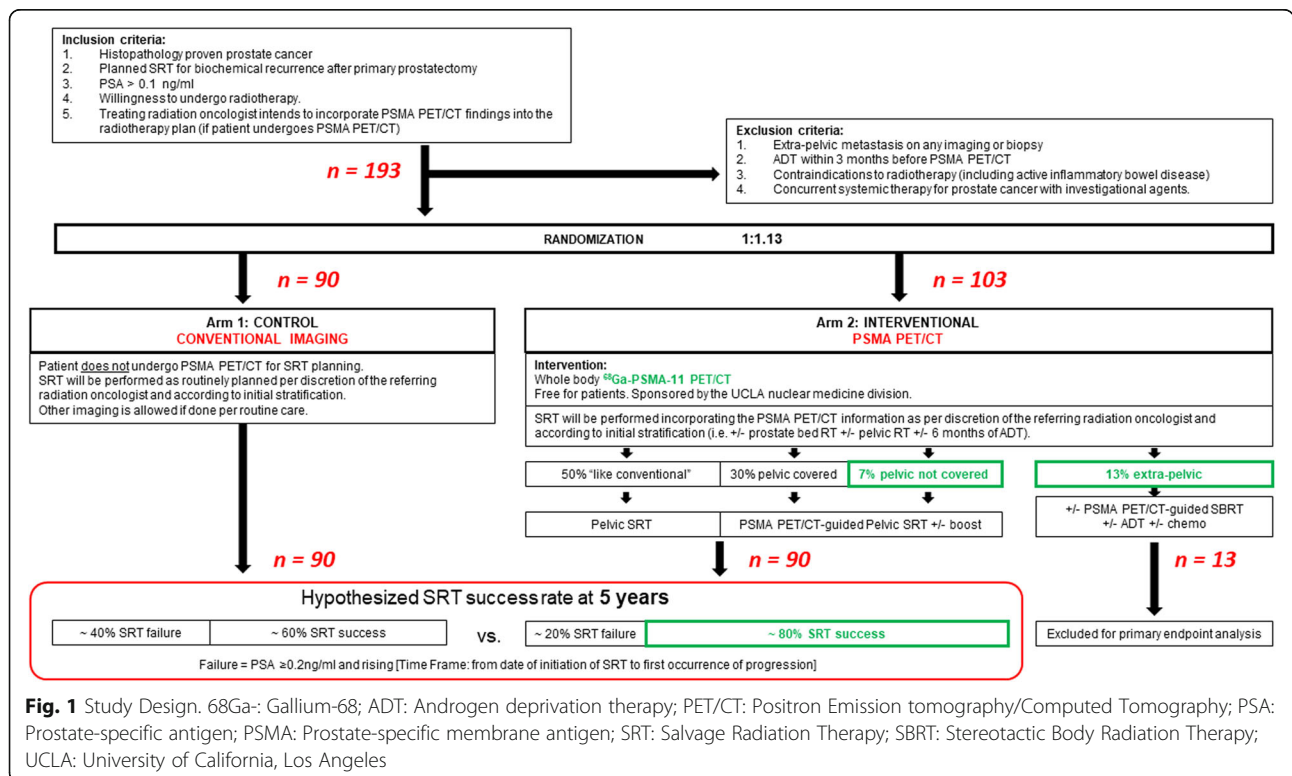


Fig. 1 Study Design. ⁶⁸Ga-: Gallium-68; ADT: Androgen deprivation therapy; PET/CT: Positron Emission tomography/Computed Tomography; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; SRT: Salvage Radiation Therapy; SBRT: Stereotactic Body Radiation Therapy; UCLA: University of California, Los Angeles

the primary endpoint of the trial is the success rate of SRT in patients who actually receive SRT. The question the trial asks is: “*Within patients for whom SRT is appropriate given the imaging results, is the rate of SRT success different between standard-of-care imaging and PSMA PET/CT arms?*”. As such, it would be inappropriate for patients who do not undergo SRT to be included for the primary endpoint. Therefore, patients with PSMA PET/CT showing distant metastases will not be included for the primary endpoint analysis but will still be followed. 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 $n = 90$.

Objective of the trial

To evaluate the success rate of salvage radiation therapy (SRT) for recurrence of PCa after prostatectomy with and without planning based on PSMA PET/CT.

Trial design

Interventional Phase III Randomized Controlled Parallel Assignment Prospective Open Label Clinical Trial.

Allocation Ratio: 1:1.13 ratio

Framework: Superiority

Methods

Study population

Patients with recurrence of PCa after primary radical prostatectomy.

It is anticipated that a total of 193 subjects will be recruited. Such a number is considered appropriate to achieve statistical power for the endpoints of this clinical trial.

Inclusion criteria:

- 1) Histopathology proven PCa
- 2) Planned SRT for recurrence after primary prostatectomy
- 3) PSA ≥ 0.1 ng/ml at time of enrollment
- 4) Willingness to undergo radiotherapy.
- 5) Treating radiation oncologist intends to incorporate PSMA PET/CT findings into the radiotherapy plan if patient undergoes PSMA PET/CT

Exclusion criteria:

- 1) Extra-pelvic metastasis on any imaging or biopsy
- 2) Androgen deprivation therapy (ADT) within 3 months before PSMA PET/CT
- 3) Contraindications to radiotherapy (including active inflammatory bowel disease)
- 4) Concurrent systemic therapy for PCa with investigational agents.

Intervention

Study procedure

Patients allocated to the PSMA SRT arm (arm 2) will undergo one PSMA PET/CT scan at the UCLA Nuclear Medicine clinic before SRT planning.

Investigational PET imaging drug

We will use ^{68}Ga -PSMA-11 (Gallium-68-labeled PSMA-ligand Glu-urea-Lys(Ahx)-HBED-CC) as the PET radio-pharmaceutical. The administered activity is 3–7 mCi i.v.

Source of the study drug

UCLA Biomedical Cyclotron, 780 Westwood Plaza, Los Angeles, CA 90095; Ga-generator generator from Eckert and Ziegler Isotope Products.

PET/CT imaging protocol specific

Oral hydration and voiding are recommended immediately before start of the scan. Oral contrast and IV contrast will be administered if not contraindicated. PET/CT images will be obtained using the Siemens Biograph 64 and mCT scanners and will be acquired in 3D mode at 50–100 min after injection of 3–7 mCi of ^{68}Ga -PSMA-11. Scan coverage will extend from mid-thigh to the vertex, starting from the mid-thighs. A minimum of 3 min per bed position will be used (weight-based protocol) [49]. Attenuation correction of PET emission data is using segmented CT data. PET images are reconstructed using ordered subset expectation maximization (OSEM) with 2 iterations and 8 subsets.

PET/CT imaging analysis

PET/CT Images will be reviewed and analyzed using Siemens Syngo/TrueD and OSIRIX workstations by a board certified nuclear medicine physician and a board certified radiologist experienced in reading PET/CT using recent reporting guidelines (PROMISE criteria, miTNM standardized framework) [50].

PET/CT DICOM images transfer

CD/DVD containing the PSMA PET/CT DICOM images and PET/CT report will be delivered to the treating radiation oncologist.

Salvage radiation therapy management

The treating physician will be asked to describe their general treatment plan prior to randomization. The choice of treating the prostate bed alone vs prostate bed and pelvic lymph nodes, with or without ADT, is at the discretion of the treating physician.

Patients randomized to control arm 1 do not undergo PSMA PET/CT: SRT will be performed as routinely planned per discretion of the treating radiation oncologist in accordance with the initial general treatment plan

whenever possible. Any other imaging is allowed for SRT planning if done per routine care.

Patients randomized to arm 2 will undergo a PSMA PET/CT scan before SRT planning.

- a) If the PSMA PET/CT scan is negative for BCR site identification: SRT will be performed as routinely planned per discretion of the treating radiation oncologist in accordance with the initial general treatment plan whenever possible. The treating physician is encouraged not to de-escalate therapy as a negative PSMA PET/CT does not mean that the patient has no recurrent PCa, rather that it was unable to be detected by the scan (for example, microscopic disease). Thus, if the initial treatment intent was to treat the prostate bed and pelvic nodes, then this should be pursued even in the absence of PSMA-positive nodes.
- b) if the PSMA PET/CT scan is positive for pelvic lesions: SRT can be performed with adapted/extended target volumes to include all pelvic PSMA-positive lesions within the radiation fields. SRT may also be performed with focal dose escalation on the PSMA-positive lesions if feasible. SRT can also be performed as routinely planned in accordance with the initial general treatment plan per discretion of the treating radiation oncologist. Furthermore, a PSMA PET/CT scan showing PSMA-positive disease in one or more pelvic nodes does not exclude the possibility of additional disease in the prostate bed, and vice versa.
- c) If the PSMA PET/CT scan detects PSMA-positive lesions outside the pelvis: Treatment management will be performed as per discretion of the treating radiation oncologist. We assume that approximately 13% of subjects randomized to Arm 2 will have PSMA-positive distant metastases. These patients will not be included in analysis of the primary endpoint, and their actual treatment plan will be determined by the treating radiation oncologist.

Outcome measures

Primary endpoint measure

Success rate of SRT measured as rate of biochemical progression-free survival (BPFS) after initiation of SRT (Time Frame: From date of initiation of SRT until the date of first documented progression or death from any cause, whichever comes first, assessed up to 5 years). Biochemical progression is defined as a serum PSA ≥ 0.2 ng/mL and rising after completion of SRT (second confirmatory value must be rising and separated by ≥ 1 month).

Secondary endpoints measures

- 1) 5-year BPFS rate from date of randomization (Time Frame: 5 years)
- 2) Metastasis free-survival from date of randomization (Time Frame: 5 years). Diagnosis of extra-pelvic metastatic (M1) disease can be obtained by any imaging or biopsy.
- 3) Initiation of additional salvage therapy after completion of SRT measured as rate of additional PCa therapy initiation-free survival (Time Frame: 5 years; from the initiation of SRT until the first documented initiation of any additional PCa treatment).
- 4) Change in initial treatment intent.

Timeline

Screening and enrollment

- 1) Patients seen for consultation in a radiation oncology, urology, or nuclear medicine clinic who are being evaluated for potential SRT will be informed of this clinical study. The decision to participate will be entirely voluntary. All subjects must sign and personally date the IRB approved informed consent form (ICF) after receiving detailed written and verbal information about the reason, the nature and the possible risks of the trial.
- 2) UCLA patients will consent after a thorough discussion between the patient and the consenting UCLA physician.
- 3) All other patients (outside UCLA) will consult over the phone with the UCLA nuclear medicine research team to discuss the study protocol. Signed ICF will be obtained by fax or email.
- 4) To register and enroll a patient, the UCLA nuclear medicine research coordinator will obtain all required medical documentation, signed informed consent and signed Health Information Portability and Accountability Act (HIPAA) authorization form (by fax or email if patient is from outside UCLA).

Randomization and intervention

- 5) Enrolled patients will be randomized to either the control arm (arm 1) or the PSMA SRT arm (arm 2) in a 1:1.13 ratio. The randomization number and assigned arm will be communicated by phone or email to treating physicians and patients 1 day after the enrollment.
- 6) Patients assigned to arm 2 will be scheduled to undergo a PSMA PET/CT scan at UCLA Nuclear Medicine free of charge prior to radiation therapy planning. DICOM images and reports of PSMA

PET/CT scans will be delivered to the treating radiation oncologist.

- 7) SRT will be done per routine care at the treating radiation oncologist institution, and typically takes place over about 2 months. The treating radiation oncologist may change the radiation plan depending on the findings of the PSMA PET/CT scan.

Follow-up

Current standard-of-care includes weekly on treatment visits during radiotherapy followed by follow-up visits with radiation oncologist at least every 3 to 4 months for the first year and every 6 months for the next 5 years.

Total serum PSA measurements are obtained during follow-up visits per standard-of-care. Biochemical progression is defined by PSA \geq 0.2 ng/mL and rising after completion of SRT (second confirmatory value must be rising and separated by \geq 1 month). Additional labs are drawn per the discretion of the treating physician.

Imaging studies are done at the discretion of the treating physicians. Imaging is typically initiated at the time of suspected biochemical or clinical recurrence, and may include CT, MRI, or PET. The treating physician decides if biopsy confirmation is necessary or not.

UCLA Nuclear Medicine Research investigators or their staff will conduct telephone follow-up with enrolled patients at 3–4-month intervals for the first year and then at 6-month intervals. The investigators or staff will ask the patient for their most recent PSA value and the draw date, if and when any additional salvage therapy has been initiated, and if and when any imaging studies suggest radiographic progression. Research investigators or their staff may also conduct telephone or secure email follow-up with the treating physicians to identify changes to the initial general treatment plan (prostate bed alone, prostate bed with ADT, prostate bed and nodes, prostate bed and nodes with ADT). The study team may request more details about the actual radiation treatment plan at the discretion of the patient and the treating physician. Although we acknowledge that toxicity assessments, both patient reported and physician reported, are valuable components of prospective trials, the design of the trial makes rigorous assessments of these difficult.

Study duration

We expect to enroll the 193 patients within 2 years of study initiation. Patients will be followed by UCLA Nuclear medicine (phone calls/ secure emails) until either one of the following conditions occur:

- 1) 5 years after the date of initiation of randomization.
- 2) Biochemical progression.
- 3) Diagnostic of extra-pelvic metastatic disease by any imaging or biopsy.

- 4) Initiation of any additional salvage therapy.
- 5) Death.

Sample size determination

In our a previous study [38], 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 [5–9, 12]. 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 [38]. 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.

Allocation sequence generation, concealment mechanism and implementation

UCLA Department of Medicine Statistics Core (DOM-Stat) will build code to randomly assign patients to control/PSMA groups after the patient eligibility form is filled out in Research Electronic Data Capture (REDCap) [51]. DOMStat will develop reproducible code to randomly generate the allocation sequence. To ensure balance between treatment allocation throughout the study, we will use a blocked randomization of size 6. This block size will be unknown to the nuclear medicine research team and the radiation oncologists when enrolling a patient and the control/PSMA allocation will be masked until after the until after screening/baseline data are

entered and filled out in REDCap (no anticipation of the group assignment possible). All the data management such as the randomization allocation will be performed by UCLA Nuclear Medicine Research Team in the REDCap online database.

This is an open label study. Trial participants, care providers, outcome assessors, and data analysts will be aware of the assignment after enrollment in REDCap is completed. The randomization number and assignment will be communicated 1 day after the registration by phone or email to the treating physician and the patient.

Data collection, management and monitoring

Study database will be developed by DOMStat using REDCap [51], which is supported by the UCLA CTSI program and includes high level data security, access logs, data storage and backup. DOMStat has an extensive computational infrastructure with database and statistical software, desktop computers, and a centralized file server for data storage and backup. The REDCap study database will have validated range checks for data entry fields, branching logic, and rigorous pre-testing to make sure the data are appropriately capture. The UCLA Nuclear Medicine research team will enter all data of each patient into the REDCap database. The UCLA Nuclear Medicine research team will have full access to all interim and final results of the study through the REDCap database and is responsible for the final decision to terminate the trial. There is no planned interim analysis. All the data management will be performed by the UCLA Nuclear Medicine Research Team in the REDCap online database. During the clinical investigation, the UCLA Nuclear Medicine research team will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. All the datasets generated during the current study will be stored and managed on the UCLA REDCap database. All data generated and/or analyzed during this study will be publicly available (own DOI) after completion of the study and the publication of the article of the final analysis of study. The datasets generated and/or analyzed during the trial will not be publicly available before completion of the study but can be available from the corresponding author on reasonable request. Even if the required number of patients to reach statistical power ($n = 193$) is not met, patients already enrolled in the trial will still be followed for 5 years as this data alone would be valuable and unique.

Statistical methods

We will use a log rank test to compare PFS time between the two randomized treatment arms. We assume

that approximately 13% of subjects randomized to Arm 2 will be found to be ineligible for SRT and will not be included for the primary endpoint analysis. Secondary analyses will utilize Cox-proportional hazards regression models. These models will include terms for treatment as well as appropriate clinical/demographic covariates (e.g., ADT, pelvic LN RT, PSA doubling time, Gleason grade, T stage, age, etc.). Residual analyses will be performed to evaluate the proportional hazards assumptions of the Cox model. As a sensitivity analysis, we will also consider survival models that can account for competing risks (ex. death from other causes).

Discussion

⁶⁸Ga-PSMA-11 PET/CT molecular imaging is highly sensitive to detect and localize PCa BCR. However, it is unclear if incorporation of PSMA PET/CT imaging into the planning of SRT could improve its likelihood of success. No randomized prospective trial has been designed to determine whether PSMA PET/CT can improve 5-year outcomes in patients with early BCR after radical prostatectomy. The purpose of this trial is to compare the success rate of SRT in patients with BCR after radical prostatectomy among patients with PSMA PET/CT based SRT planning vs. standard SRT planning.

Potential pitfalls in study design include i) drop-out of patients randomized to the control arm as patients may be able to undergo PSMA PET/CT scans in other institutions; ii) potential FDA approval of PSMA PET imaging probes (Gallium-68-PSMA-11 or Fluor-18-DCFPyL) in the near future which would in essence lead to termination of new enrollment. As PSMA PET/CT imaging may become standard-of-care, randomizing patients to the control arm would no longer be feasible. Therefore, the time period for patient recruitment may be limited (1 to 2 years starting from September 2018). Even if the required number of patients to reach statistical power ($n = 193$) is not met, patients already enrolled in the trial will still be followed for 5 years as this would remain highly valuable and unique data.

Published randomized prospective trials with long-term follow-up demonstrate that the success rate of SRT is enhanced by the addition of concurrent and adjuvant conventional androgen deprivation [6] or first generation antiandrogens [52]. Ongoing trials are now evaluating the role of second-generation systemic therapies that target the Androgen Receptor (NRG GU 006). The magnitude of the impact of adding these systemic therapies to SRT depends on clinicopathologic features including pre-SRT PSA, Gleason Grade, margin status, and genomic classifiers [53]. Moreover, hormonal agents have well known and expected side effects. As such, the expected benefit of adding systemic therapy to SRT may be outweighed by known risks for many patients.

Oligometastatic prostate cancer, variously defined as metastatic disease with between three to five sites of identifiable metastases, is another disease state with rapidly evolving treatment paradigms. STAMPEDE randomized patients with metastatic hormone sensitive prostate cancer to long-term androgen suppression with or without radiotherapy directed to the prostate alone [54]. Pre-planned analyses of patients with limited metastatic disease burden had an improvement in survival [54]. The value of controlling recurrent local disease in patients who have synchronous metastatic prostate cancer is unknown. However, the identification of these patients with modern imaging, such as PSMA PET/CT, will increase. Indeed, we anticipate that 13% of patients randomized to PSMA PET/CT in our trial may fall into this group [38]. The optimal treatment for these patients remains unknown.

This is the first prospective randomized phase 3 trial designed to determine whether a molecular imaging modality, PSMA PET/CT, can improve outcomes after SRT. Like testing the addition of systemic therapies to SRT, testing the addition of PSMA PET/CT to SRT may improve disease control. However, unlike additional systemic therapies, PSMA PET/CT has few if any side effects, minimal risks, and enables better patient selection and disease state identification.

Abbreviations

68Ga: Gallium-68; ADT: Androgen deprivation therapy; BCR: Biochemical recurrence; BPFs: Biochemical progression-free survival; CT: Computed tomography; CTV: Clinical Target Volume; DICOM: Digital imaging and communications in medicine; FDA: Food and Drug Administration; GBq: GigaBecquerel; GCP: Good Clinical Practice; HIPAA: Health Information Portability and Accountability Act; IND: Investigational new drug; IRB: Institutional review board; MBq: MegaBecquerel; mCi: Millicurie; MRI: Magnetic resonance imaging; NCCN: National comprehensive cancer network; NDA: New drug application; PCa: Prostate cancer; PET/CT: Positron emission tomography/computed tomography; PFS: Progression-free survival; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; REDCap: Research Electronic Data Capture; RTOG: Radiation Therapy Oncology Group; SBRT: Stereotactic Body Radiation Therapy; SRT: Salvage Radiation Therapy; UCLA: University of California, Los Angeles; US: United States

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Availability of data and materials

The UCLA Nuclear Medicine research team will have full access to all interim and final results of the study through the REDCap database. There is no planned interim analysis. All data generated and/or analyzed during this

study will be publicly available (own DOI) after completion of the study and the publication of the article of the final analysis of study. The datasets generated and/or analyzed during the trial will not be publicly available before completion of the study but can be available from the corresponding author on reasonable request.

Authors' contributions

All authors read and approved the final manuscript. JCa and NN are the main study designers. JCa is the principal investigator. JCz and NN are the co-principal investigator. WF, JCz, DE participated to the study design. JCz is the IND holder.

Ethics approval and consent to participate

The protocol, the ICF and all forms of participant information related to the study have been reviewed and approved by the UCLA institutional review board (UCLA IRB#18-000484). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. All subjects must sign and personally date the IRB approved ICF after receiving detailed written and verbal information about the reason, the nature and the details of the trial prior to the initiation of any study-related procedures. This will be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice (GCP) and government regulations, including (as applicable) the US Code of Federal Regulations Title 21 CFR 50.20 through 50.27. The subject must be made aware and agree that personal information may be reviewed during an audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available. The UCLA Nuclear Medicine research team will enter all data of each patient into REDCap database. Only the UCLA Nuclear Medicine research team will have access to the REDCap database (protected and encrypted access). Patients will be informed of the extent to which their confidential health information generated from this study may be used for research and publication purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document. ICF and HIPAA form will be given to the patient for review. Consent will be obtained after a clear and thorough discussion between the patient and the consenting physician. If the patient is from outside UCLA, he will have a phone consultation with the UCLA research team in coordination with the treating radiation oncologist to explain and discuss all the above points. Signed ICF and HIPAA form will be obtained by fax or email in this case.

Competing interests

Johannes Czernin is a founder, board member, and holds equity in Sofie biosciences and Trethera Therapeutics. Intellectual property is patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics. No other potential conflict of interest relevant to this article was reported.

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Article #7:

Update from PSMA-SRT Trial NCT03582774: A Randomized Phase 3 Imaging Trial of Prostate-specific Membrane Antigen Positron Emission Tomography for Salvage Radiation Therapy for Prostate Cancer Recurrence Powered for Clinical Outcome (n=193)



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Clinical Studies Update – Prostate Cancer

Update from PSMA-SRT Trial NCT03582774: A Randomized Phase 3 Imaging Trial of Prostate-specific Membrane Antigen Positron Emission Tomography for Salvage Radiation Therapy for Prostate Cancer Recurrence Powered for Clinical Outcome

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Article info

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Salvage radiation therapy (SRT) for prostate cancer (PCa) recurrence after radical prostatectomy (RP) can offer long-term biochemical control in approximately 50–60% of patients [1]. SRT is commonly initiated in patients with serum prostate-specific antigen (PSA) of 0.1–1 ng/ml and recent phase 3 trial data show that early SRT is equivalent to adjuvant RT [2]. However, standard-of-care imaging is insufficiently sensitive for anatomic localization of recurrence. Therefore, SRT target volumes are usually drawn in the absence of radiographically visible disease [3,4].

Prostate-specific membrane antigen (PSMA) is highly overexpressed by PCa cells and represents a relevant target for PCa imaging and therapy. PSMA positron emission tomography (PET) using small radiolabeled ligands is highly

sensitive, even at low PSA levels, and may offer early localization of PCa biochemical recurrence (BCR) [3,5].

In an international multicenter retrospective study, we found that PSMA PET had a major impact on SRT planning in 52 of 270 patients (19%) with early BCR (PSA <1.0 ng/ml) by revealing lesions not covered by the standard radiation fields, including both the prostate bed and pelvic lymph nodes, defined on computed tomography (CT) [6]. We hypothesized that this major impact of PSMA PET on patient selection and RT planning would translate into better outcomes from PSMA PET-guided SRT.

The purpose of the PSMA-SRT trial NCT03582774 is to evaluate the success rate of SRT for post-RP recurrence of PCa with and without planning based on PSMA PET [7]. This

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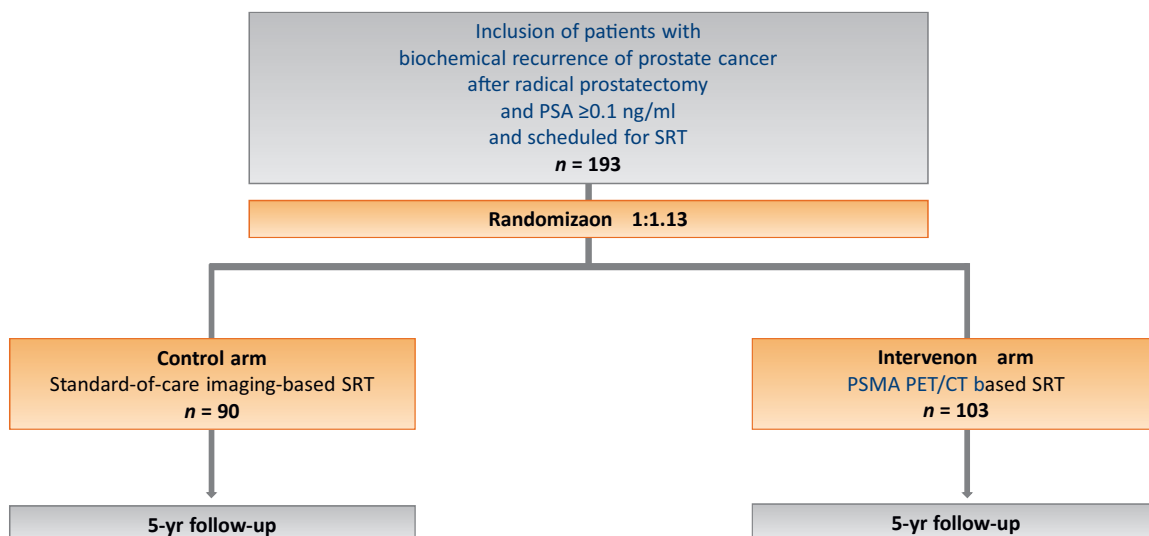


Fig. 1 – Study flowchart.
 CT = computed tomography; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SRT = salvage radiotherapy.

is a multicenter, prospective, randomized, controlled, open-label phase 3 clinical imaging trial conducted at University of California, Los Angeles (lead) and University of California, San Francisco that is powered for clinical outcome at 5 yr. The study is investigator-initiated and self-funded. There is no external funding source.

Patients scheduled for SRT of recurrence after primary RP and with PSA ≥ 0.1 ng/ml at the time of enrollment were eligible (no PSA upper limit). On the basis of our prior study, we hypothesized that PSMA PET would detect extrapelvic M1 disease in 13% of the patients [6]. These patients would probably not undergo SRT and therefore would not be included in the primary endpoint analysis. Indeed, the primary endpoint is the SRT success rate at 5 yr for patients who actually received SRT. We hypothesized that incorporation of PSMA PET in SRT planning will improve 5-yr biochemical progression-free survival (bPFS) by 20%: 60% in the control arm and 80% in the intervention arm at 5 yr. According to the sample size calculation, 90 patients are needed in each group to reach sufficient statistical power. A total sample size of 193 patients is needed assuming that 13 patients randomized to the intervention arm ($n = 103$) would experience extrapelvic disease and would not receive SRT.

The primary endpoint of the trial is the SRT success rate at 5 yr among patients who actually received SRT, measured as bPFS (with biochemical progression defined as PSA ≥ 0.2 ng/ml and rising after completion of SRT). Secondary endpoints include a subgroup analysis of the primary endpoint for patients with baseline PSA ≥ 0.5 ng/ml, metastasis free-survival, and change in the initial treatment intent after randomization.

Enrollment is complete: 193 patients were enrolled from September 6, 2018 to August 17, 2020 (Fig. 1). Seven of the 90 patients in the control arm (9%) dropped out of the study because they underwent PSMA PET at another institution,

while one/103 patients in the intervention arm (1%) dropped out because of COVID-19-related complications. Median PSA at enrollment was 0.32 ng/ml (interquartile range [IQR] 0.17–1.35) in the control arm and 0.22 ng/ml (IQR 0.14–0.50) in the PSMA arm. Patients in the control group were staged using fluciclovine PET (27/83, 33%), computed tomography (30/83, 36%), bone scan (14/83 17%), magnetic resonance imaging (22/83 27%), or fluoro-deoxyglucose PET (one/83 1%), while 28/83 had no imaging (34%; Table 1). In the intervention group, PSMA PET was positive in 38/102 patients (37%): nine/108 (9%) had PCa outside the pelvis (M1), 20/102 (20%) in pelvic nodes with or without concurrent recurrence in the prostate bed, and 13/102 (13%) in the prostate fossa only (Table 2).

In this prospective randomized phase 3 study, PSMA PET localized PCa in more than one-third of patients. PET showed lesions outside the pelvis in 9% of patients in the

Table 1 – Imaging modalities used in the control group (n = 83)

Imaging	Patients, n (%)
Fluciclovine PET only	15 (18.1)
Fluciclovine PET + bone scan	1 (1.2)
Fluciclovine PET + FDG PET	1 (1.2)
Fluciclovine PET + MRI	2 (2.4)
Fluciclovine PET + MRI + bone scan	2 (2.4)
Fluciclovine PET + MRI + CT	5 (6)
Fluciclovine PET + MRI + CT + bone scan	1 (1.2)
Bone scan only	1 (1.2)
Bone scan + MRI + CT	4 (4.8)
CT only	10 (12)
CT + bone scan	5 (6)
CT + MRI	5 (6)
MRI only	3 (3.6)
None	6 (7.2)
N/A	22 (26.5)

CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; N/A = PET = positron emission tomography.

Table 2 – Prostate-specific membrane antigen positron emission tomography findings and staging in the intervention group (n = 102)

Stage	Patients, n (%)
T+	18 (17.6)
N1	20 (19.6)
M1	9 (8.8)
M1a	3 (2.9)
M1b	8 (7.8)
M1c	1 (1)
T0 N0 M0	64 (62.7)
T+ N0 M0	13 (12.7)
T+ N1 M0	12 (11.8)
T0 N1 M0	4 (3.9)
T+ N0 M1	5 (4.9)
T0 N0 M1	3 (2.9)
T0 N1 M1	1 (1)

intervention group. Follow-up is ongoing to assess whether PSMA PET disease localization eventually translates into better patient outcomes.

Conflicts of interest: Jeremie Calais reports prior consulting activities for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, Janssen Pharmaceuticals, Progenics Pharmaceuticals, Radiomedix, and Telix Pharmaceuticals outside the submitted work. Wolfgang P. Fendler is a consultant for Endocyte, Ipsen, and BTG, and has received fees from RadioMedix, Bayer, and Parexel outside the submitted work. Johannes Czernin is a founder and board member of and holds equity in Sofie Biosciences and Trethera Therapeutics, has served on the medical advisory board of Actinium, was a member of the VISION trial steering committee, participated in a clinical trial sponsored by Endocyte, and reports research funding from Endocyte and Ipsen, all outside the submitted work. Thomas A. Hope reports grants from Advanced Accelerator Applications and prior consulting activities for Blue Earth Diagnostics, Curium Pharma, Ipsen, GE Healthcare, and Progenics Pharmaceuticals outside the submitted work. Amar Upadhyaya Kishan reports research funding from ViewRay and personal fees from Varian Medical Systems, ViewRay, and Janssen Pharmaceuticals outside the submitted work. Nicholas George Nickols reports research funding from Janssen, Progenics, and Bayer outside the submitted work. The remaining authors have nothing to disclose.

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Part Two: PSMA Radionuclide Therapy

The first reported clinical use of PSMA Radioligand Therapy was a case report published in 2015 by the Heidelberg team, Germany and nominated as SNMMI Image of the Year in 2015. Similar to PSMA-PET imaging, in view of these very impressive images and positive early experience, the whole nuclear medicine and uro-oncology community had a huge interest to bring and try this new treatment option at their institutions and for their patients.

As described in the PSMA-PET imaging section, we built a clinical research program of PSMA theranostics under the initiative of Johannes Czernin. We used the experience and workforce of our German colleagues (Ken Herrmann, Wolfgang Fendler, Matthias Eiber) to also initiate the first PSMA radionuclide therapy studies. Our collaborator for the IND application of Lu177-PSMA-617 therapy was Ebrahim Delpassand at Excel Diagnostics in Houston, Texas. Together, we initiated the first U.S. prospective trial of 177Lu-PSMA (RESIST-PC, NCT03042312). This was a bi-centric phase 2 study in patients with advanced mCRPC. The study was investigator-initiated and self-funded. Similar to the PSMA-PET initial studies described earlier, there was no external funding for this study. Patients were charged for the drug under Title 21 of the Code of Federal Regulation Section (CFR) 312.8 (49).

In 2017, the worldwide rights to develop and commercialize PSMA-617 were acquired by Endocyte Inc. After the acquisition, the U.S. IND sponsorship was transferred from Ebrahim Delpassand, Excel Diagnostics to Endocyte Inc. during the enrollment phase. As the company initiated the prospective international multicenter registration trial (VISION; NCT03511664), the RESIST-PC trial, subsequently identified as PSMA-617-02, was not consistent with the overall company strategy. The study was closed in 2018 before reaching the target population of 200 patients.

Subsequently in 2018 Novartis acquired Endocyte Inc. to expand its radiopharmaceutical business following the success of the acquisition of Advanced Accelerator Application for Lutathera® (Lu177-DOTATATE). After the sponsorship transfer, site monitoring, pharmacovigilance, and data analysis of the bi-centric trial were supported by Endocyte/Novartis. Later, the safety results of both study sites were used for the regulatory approval of 177Lu-PSMA-617.

Novartis ran the pivotal registration trial (VISION NCT03511664) and successfully obtained FDA approval in 2022 as 177Lu-vipivotide tetraxetan (Pluvicto®) (11,12).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215833s000lbl.pdf

The VISION trial was conducted at 84 sites (52 in North America and 32 in Europe), including UCLA and Excel Diagnostics. Since then, UCLA participated in other industry-sponsored pivotal trials and IIT of PSMA-targeted RNT. More than 200 patients have been treated since 2017 at UCLA. Table 2 lists the clinical studies of PSMA radionuclide therapy conducted at UCLA since 2017.

UCLA IRB #	NCT #	Protocol Short Title
17-000330	NCT03042312	RESIST-PC - Phase 2 Lutetium-177-PSMA-617
18-000693	NCT03511664	VISION - Phase 3 Lutetium-177-PSMA-617
21-005010	NCT04825652	MAP Expanded Access Program Lutetium-177-PSMA-617
20-000369	NCT03939689	ARROW - Phase 2/3 Iodine-131-PSMA-MIP-1095
21-000101	NCT04647526	SPLASH - Phase 3 Lutetium-177-PSMA-I&T
22-000195	NCT04720157	PSMAddition - Phase 3 Lutetium-177-PSMA-617
22-000750	NCT05496959	LUNAR - Phase 2 Lutetium-177-PSMA-I&T + SBRT

Table 2: Clinical studies of PSMA radionuclide therapy conducted at UCLA since 2017

Below are the 2 articles of the RESIST-PC trial published in *The Journal of Nuclear Medicine*.

Due to data ownership conflicts with industry, we were able to analyze the efficacy results of the trial only for the UCLA site. The first paper reports the efficacy results of the UCLA site cohort with more than 2-years of follow-up after end of therapy. The second paper reports the safety results of both study sites that were used for regulatory approval. After the sponsorship transfer, site monitoring, pharmacovigilance, and data analysis were supported by Endocyte/Novartis. Of note, the corresponding author had complete data access and had final responsibility to submit for publication.

Article #8:

Prospective phase 2 trial of PSMA-targeted molecular Radiotherapy with ¹⁷⁷Lu-PSMA-617 for metastatic Castration-resistant Prostate Cancer (RESIST-PC): Efficacy results of the UCLA cohort (n=43)

Prospective phase 2 trial of PSMA-targeted molecular Radiotherapy with ¹⁷⁷Lu-PSMA-617 for metastatic castration-resistant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort

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See an invited perspective on this article on page 1438.

The objective of this study was to determine prospectively the efficacy profile of 2 activity regimens of ¹⁷⁷Lu-PSMA therapy in patients with progressive metastatic castrate-resistant prostate cancer (mCRPC): 6.0 vs. 7.4 GBq. **Methods:** RESIST-PC (NCT03042312) was a prospective multicenter phase 2 trial. Patients with progressive mCRPC after ≥ 1 novel androgen-axis drug, either chemotherapy naïve or postchemotherapy, with sufficient bone marrow reserve, normal kidney function, and sufficient PSMA expression by PSMA PET were eligible. Patients were randomized (1:1) into 2 activity groups (6.0 or 7.4 GBq) and received up to 4 cycles every 8 wk. The primary endpoint was the efficacy of ¹⁷⁷Lu-PSMA measured by the prostate-specific antigen (PSA) response rate (RR) after 2 cycles (≥50% decline from baseline). Secondary endpoints included the PSA RR (≥50% decline) at any time (best response), and overall survival (OS). **Results:** The study was closed at enrollment of 71/200 planned patients because of sponsorship transfer. We report here the efficacy of the University of California Los Angeles cohort results only (*n* = 43). The PSA RRs after 2 cycles and at any time were 11/40 (28%, 95% CI 15–44), 6/13 (46%, 95% CI 19–75), and 5/27 (19%, 95% CI 6–38), and 16/43 (37%, 95% CI 23–53), 7/14 (50%, 95% CI 23–77), and 9/29 (31%, 95% CI 15–51) in the whole cohort, the 6.0-GBq group, and the 7.4-GBq group, respectively (*P* = 0.12 and *P* = 0.31). The median OS was 14.0 mo (95% CI 10.1–17.9), 15.8 (95% CI 11.8–19.4), and 13.5 (95% CI 10.0–17.0) in the whole cohort, the 6.0-GBq group, and the 7.4 GBq group, respectively (*P* = 0.87). OS was longer in patients who experienced a PSA decline ≥ 50% at any time than in those who did not: median, 20.8 versus 10.8 mo (*P* = 0.005). **Conclusion:** In this prospective phase 2 trial of

¹⁷⁷Lu-PSMA for mCRPC, the median OS was 14 mo. Despite the heterogeneous study population and the premature study termination, the efficacy profile of ¹⁷⁷Lu-PSMA appeared to be favorable and comparable with both activity regimens (6.0 vs. 7.4 GBq). Results justify confirmation with real-world data matched-pair analysis and further clinical trials to refine and optimize the ¹⁷⁷Lu-PSMA therapy administration scheme to improve tumor radiation dose delivery and efficacy.

Key Words: metastatic castration-resistant prostate cancer; radionuclide therapy; molecular radiotherapy; prostate-specific membrane antigen; ¹⁷⁷Lu; RESIST-PC; prospective randomized phase 2 trial; theranostics

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The prostate-specific membrane antigen (PSMA) is highly expressed by prostate cancer (PCa) cells and is a relevant target for PCa imaging and therapy. ¹⁷⁷Lu PSMA-617 (¹⁷⁷Lu-PSMA) therapy is an emerging therapeutic option in men with metastatic castrate-resistant PCa (mCRPC). Retrospective studies (1–3) and recent prospective trials from Australia (single-arm LuPSMA trial (4,5), randomized TheraP trial (6)) reported the efficacy and safety of ¹⁷⁷Lu-PSMA in men with mCRPC.

Here we present the first U.S. prospective results of ¹⁷⁷Lu-PSMA (RESIST-PC, NCT03042312). This multicenter prospective phase 2 study investigated the efficacy and safety of ¹⁷⁷Lu-PSMA in patients who were randomized between 2 commonly used activity regimens: 6.0 GBq and 7.4 GBq. We hypothesized that the 2 activities result in comparable antitumor effects and safety profile. This study is the first attempt to compare prospectively 2 activity regimens of ¹⁷⁷Lu-PSMA therapy.

The study was investigator-initiated and self-funded, but the development rights of PSMA-617 were acquired by Endocyte Inc.

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during the enrollment phase and the study was closed before reaching the target population. Therefore, data acquisition and analysis as initially planned was not possible. The safety results of both study sites were used for regulatory approval and will be reported separately. We report here the efficacy results of the University of California Los Angeles (UCLA) single study-site cohort with more than 2 y of follow-up after end of therapy.

MATERIALS AND METHODS

Study Design

RESIST-PC was a prospective, randomized, open-label, multicenter phase 2 study conducted at UCLA (Los Angeles, CA, USA) and Excel Diagnostics Nuclear Oncology Center (Houston, TX, USA). We aimed at assessing the efficacy and safety of 2 ^{177}Lu -PSMA activity regimens in patients with mCRPC. The study was investigator-initiated and conducted under a physician-sponsored investigational new drug (IND#133661) application. There was no external funding for this study. Patients were charged for the drug under Title 21 of the Code of Federal Regulation Section (CFR) 312.8. The UCLA institutional review board approved the study protocol (IRB#17-000330) provided in the supplemental materials (supplemental materials are available at <http://jnm.snmjournals.org>). The study was registered on ClinicalTrials.gov (NCT03042312). Endocyte Inc. licensed the rights to the study drug, initiated a prospective international multicenter trial (VISION; NCT03511664), and closed RESIST-PC at a total enrollment of 71 of the 200 planned patients at both sites (see the “Statistical Analysis” section for rationale of sample size). Here we report the efficacy results of the UCLA cohort only ($n = 43$). The corresponding author had complete data access and had final responsibility to submit for publication.

Patients

Patients ≥ 18 y, who had histologically confirmed PCa, castrate levels of serum testosterone (<0.5 ng/mL), progressive disease (biochemical, radiographic, or clinical), who had received abiraterone or enzalutamide, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2, and had the ability to understand and sign the written informed consent form were eligible. We included patients without prior chemotherapy or with any number of prior chemotherapies if at least 6 wk passed since the last treatment cycle. Patients who had received PSMA-targeted radionuclide therapy were excluded. Pretreatment PSMA PET was required to document sufficient target expression (see the “Procedures” section). Additional inclusion criteria were a sufficient bone marrow reserve (hemoglobin ≥ 9.9 g/dL, platelet count $\geq 100 \times 10^9/\text{L}$, white blood cell count $\geq 2.5 \times 10^9/\text{L}$, and absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$). Patients with diffuse bone involvement by bone scintigraphy (superscan), impaired kidney function (glomerular filtration rate < 40 mL/min, serum creatinine $> 1.5 \times$ upper limit of normal [ULN]), urinary tract obstruction, or marked hydronephrosis), or impaired liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $> 5 \times$ ULN) were excluded. Informed written and verbal consent was obtained from all patients.

Procedures

All patients underwent a screening ^{68}Ga -PSMA-11 PET/CT scan (≤ 3 mo before enrollment) to confirm PSMA expression assessed visually by the local investigators (tumor uptake above the liver background). Patients with PSMA-negative soft-tissue lesions seen on conventional scans (CT, MRI) were excluded (screening failure). Complete blood counts, kidney and liver function, and serum prostate-specific antigen (PSA) levels were measured within 2 wk of treatment initiation.

Patients were randomized (1:1 ratio) to receive either 6.0 or 7.4 GBq of ^{177}Lu -PSMA. Randomization (1:1 ratio) was performed in accordance with Vickers et al. (7) We concealed allocation by creating a

list of random allocations for patients 1 to 200 and stored it at the investigator's site without modification. A clinical research coordinator who was not involved in clinical management assigned the randomized allocation. There was no masking of patients or physicians.

^{177}Lu -PSMA-617 was radiolabeled with carrier-free ^{177}Lu (Radio-Medix, Inc.). The labeled product was produced, tested, released, and delivered under good-manufacturing-practice conditions as a sterile, ready-to-use solution for infusion.

^{177}Lu -PSMA was intravenously applied at 8-wk intervals (± 1 wk) up to a maximum of 4 cycles (cycle 02 at wk 08; cycle 03 at wk 16; cycle 04 at wk 24). Treatment cycles continued until disease progression, severe toxicity occurred, patients withdrew consent, or investigators decided to discontinue treatment.

We performed hematologic and serum assessments at baseline and in 2-wk intervals up to the 12-wk follow-up visit after the last study drug injection. We measured serum PSA levels at baseline and every 6 wk. Subsequent assessments continued at 3-mo intervals until follow-up concluded at 24 mo or on disease progression.

Bone pain intensity was assessed at each cycle using the pain intensity score, a component of the Brief Pain Inventory–Short Form (8): scores ranged from 0 to 10, with lower scores representing lower levels of pain intensity; a change of 2 was required to consider a change relevant (9).

Because of cost considerations (no follow-up imaging was built in the study budget), imaging follow-up was performed by patient and referring oncologist preference. Because of the lack of standardization, effective conclusions could not be assured. The imaging follow-up analysis (methods, radiographic progression-free survival, disease control rate by imaging) is provided in the supplemental materials.

Outcomes

The primary endpoint measure was the PSA response rate (RR) after 2 cycles defined as the proportion of patients with a $\geq 50\%$ decline in serum PSA levels from baseline (10).

Secondary endpoints included the PSA RR ($\geq 50\%$ decline) at any time (best response), biochemical progression-free survival (PSA PFS), pain progression-free survival (pain PFS), and pain RR. A post hoc analysis assessed overall survival (OS). These parameters were defined as the time from first treatment cycle to PSA progression, pain progression, or death from any cause, respectively. We recorded new pain development as a 2-point increase on the pain intensity score without a decrease in opiate use. Patients were included in the pain analysis if they had available baseline assessments and at least 1 follow-up data point 4–6 wk after the last treatment cycle.

All endpoints were analyzed by the local investigators.

Statistical Analysis

On the basis of previous reports (1), we hypothesized that the PSA RR after 2 cycles would range between 38% and 65% for both treatment activities. On the basis of the design of a single-arm phase 2 study in mCRPC (11), we postulated that ^{177}Lu -PSMA would be considered of value for further study if 50% or more patients met the primary endpoint and not worthy if fewer than 40% achieved the primary endpoint. A sample size of 200 patients was required to distinguish between a 40% and a 50% PSA RR with a 78% power (2-sided binomial test with $\alpha 0.05$ and $\beta 0.20$).

We used descriptive statistics including median and interquartile range (IQR) for continuous variables and number and percentage for categorical variables. We present percentage changes in serum PSA levels as a waterfall plot. Kaplan–Meier analysis was used to calculate PSA PFS, pain PFS, and OS by PSA RRs. We used the log-rank test to evaluate the association between treatment arm and patient outcome. The Fisher exact test determined the association between treatment arm and PSA RRs. We tested each endpoint at a 2-sided significance level of 0.05.

In a post hoc analysis, the effect of treatment activity (6.0 vs. 7.4 GBq) on outcome data was adjusted for baseline factors (i.e., ECOG performance score, number of previous chemotherapy lines [0–1 vs. 2], and visceral disease) in multivariate cox/logistic regression models. Hazard ratios/odds ratios and their 95% CIs were derived.

Because of the early study termination, we tested whether the comparison of the 2 activity groups (6.0 vs. 7.4 GBq) would likely have held up in the originally proposed study population of 200 patients with a post hoc conditional power calculation simulation (12). This assumes that the additional patients required to complete the originally planned study cohort exhibit characteristics similar to those of the patients enrolled. The method applies random samples and 1,000 iterations to account for sampling variability. If this calculation yields around a conditional power calculation of 80% (i.e., $P < 0.05$ in 80% of the 1,000 simulations), then the difference in treatment regimen-associated outcomes would be statistically different.

Statistical analyses were performed using SPSS, version 22 (IBM) and STATA, version 15 (StataCorp LLC).

RESULTS

Enrollment and Baseline Characteristics

We enrolled 51 patients with progressive mCRPC between November 2017 and July 2018 (Supplemental Fig. 1). Eight of 51 (16%) patients were excluded after enrollment because of disease progression ($n = 4/8$, 50%), negative PSMA PET ($n = 2/8$, 25%), death ($n = 1/8$, 13%), or screen failure ($n = 1/8$, 13%). Forty-three of 51 (84%) patients received at least 1 cycle of ^{177}Lu -PSMA: 14 of 43 (33%) and 29 of 43 (67%) in the 6.0- and 7.4-GBq groups, respectively.

Baseline characteristics are provided in Table 1. In the overall study population, median baseline PSA levels and doubling times were 27.4 ng/mL (IQR 9.5–115.6) and 1.5 mo (IQR 1.0–2.3), respectively. Twenty-two of 43 patients (51%) had received ≥ 2 chemotherapy regimens, and 35 of 43 (82%) underwent treatment with both abiraterone and enzalutamide before ^{177}Lu -PSMA. Twenty-nine of 43 (67%) patients had > 20 metastasis on PSMA PET.

The cutoff date for follow-up was June 25, 2020. Median follow-up for patients who survived was 24.8 mo (IQR 22.9–28.8).

Efficacy Endpoints

PSA RRs. PSA RR after 2 cycles was available in 40 of 43 patients (93%). Overall PSA RR was 11 of 40 (28%; 95% CI 14.6–43.9) and 16 of 43 (37%; 95% CI 23.0–53.3) after 2 cycles (primary endpoint) and at any time, respectively (Fig. 1; Table 2). There was no difference of PSA RRs between the 2 treatment arms after 2 cycles ($P = 0.12$) or at any time ($P = 0.31$). The median time to best PSA response was 8.9 wk (IQR, 6.9–25.1) in all 43 patients and 28.8 wk (IQR, 15.2–36.2) in the 16 PSA responders.

Biochemical PFS. At the end of follow-up, 2 of 43 patients (5%) were alive without PSA progression. The median PSA PFS was 3.7 mo in the overall study population (95% CI 2.0–5.4). It was 2.9 mo (95% CI 0.0–9.0) and 3.7 mo (95% CI 1.9–5.6) in the 6.0- and the 7.4-GBq groups ($P = 0.25$), respectively (Fig. 2; Table 2; Supplemental Fig. 2).

Bone Pain PFS. The pain RR in evaluable patients was 12 of 18 (67%), 6 of 7 (86%), and 6 of 11 (55%) in the overall study population, the 6.0-GBq group, and the 7.4-GBq group, respectively ($P = 0.31$) (Table 2). Pain PFS was 8.2 mo (95% CI 3.9–12.5), 5.4 mo (95% CI not reached), and 8.2 mo (95% CI 2.3–14.1) in the overall study population, the 6.0-GBq group, and the 7.4-GBq group, respectively ($P = 0.94$) (Supplemental Fig. 3; Table 2).

OS. At the end of follow-up, 12 of 14 (86%) and 25 of 29 (87%) of patients had died in the 6.0- and 7.4-GBq arms, respectively. The median OS of the overall study population was 14.0 mo (95% CI 11.8–19.4). The injected activity was not associated with OS: 15.6 (95% CI 11.8–19.4) versus 13.5 mo (95% CI 10.0–17.0) in the 6.0- and the 7.4-GBq arms ($P = 0.87$), respectively (Fig. 2; Table 2; Supplemental Fig. 2). Patients who experienced a PSA decline $\geq 50\%$ at any time (best response; $n = 16/43$, 37%) had a significantly longer OS than those who did not (27/43, 63%): median: 20.8 versus 10.8 mo; $P = 0.005$ (Fig. 3). However, no significant difference was observed when comparing the OS of patients who had a PSA decline $\geq 50\%$ after 2 cycles only ($n = 11/40$, 28%) with those who did not ($n = 29/40$, 72%): median: 19.1 versus 13.7 mo; $P = 0.46$ (Fig. 3).

After adjusting for baseline factors (ECOG, number of previous chemotherapy regimen [0–1 vs. 2], visceral disease), the treatment activity (6.0 vs. 7.4 GBq) remained not associated with treatment outcomes (P values > 0.05 , multivariate cox/logistic regression models, Supplemental Table 1).

The post hoc conditional power calculation simulation assumed a comparable demographic and disease distribution for 157 simulated patients (to obtain the initially planned population of 200 patients). Randomly sampling (with replacement) 86 patients from the 6.0-GBq cohort and 71 patients from the 7.4-GBq cohort and repeating this process 1,000 times yielded a significant difference ($P < 0.05$) between activity effects on outcome in only 47 of 1,000 simulations (4.7%).

DISCUSSION

This prospective randomized phase 2 study compared two ^{177}Lu -PSMA treatment activity levels in patients with mCRPC who progressed after conventional treatments. PSA RR, PSA PFS, pain RR, and OS did not differ between the 2 activity arms (6.0 vs. 7.4 GBq). This study is, to our knowledge, the first attempt to compare prospectively 2 activity regimens of ^{177}Lu -PSMA therapy. The results are in line with a retrospective study comparing 2 similar treatment activity levels of ^{177}Lu -PSMA (6.0 vs. 7.5 GBq) (13).

The primary efficacy endpoint (i.e., PSA RR after 2 cycles of $\geq 40\%$ in the whole cohort) was not met, possibly because of premature study closure at 36% of the planned enrollment (71/200). This study closure was prompted by the IND sponsorship transfer to Endocyte Inc. and the opening of the phase 3 registration VISION trial (NCT03511664). The current PSA RR is lower than those reported in the Australian prospective phase 2 clinical trials, after 2 cycles (28% vs. 50% in the LuPSMA trial), and at any time point (38% vs. 64% in the LuPSMA trial and 66% in TherAP Trial) (4,6). More rigorous patient selection that included ^{18}F -FDG PET to exclude patients with hyperglycolytic but low PSMA-expressing lesions resulted in improved PSA RR. Dual-tracer PSMA/ ^{18}F -FDG PET phenotyping can improve patient selection to ^{177}Lu -PSMA therapy and this approach should be further implemented in future prospective trials. However, despite different PSA RRs, OS was similar (median: 14.0 vs. 13.7 mo in the LuPSMA trial) (5). Of note, the quality of life improvement previously reported was also observed in our cohort: pain levels improved in 67% of the evaluable patients (4–6). Further studies on patients reported outcomes are warranted.

A comparative metaanalysis suggested that ^{177}Lu -PSMA was less toxic, induced higher PSA RR (mean frequency 44% vs. 22%) and possibly improved OS (median of 14 vs 12 mo; $P = 0.33$) compared with other third-line treatments for mCRPC, such as enzalutamide and cabazitaxel (14). The multicenter prospective randomized

TABLE 1
Characteristics of Study Population at Baseline

Characteristic	Overall (n = 43)	6.0 GBq (n = 14)	7.4 GBq (n = 29)
Age (y)	74 (68–78)	76 (70–79)	72 (65–78)
Time since diagnosis of PCa (y)	7 (4–17)	8 (5–17)	7 (4–15)
Gleason grade group at diagnosis*			
≥4	25 (64%)	9 (69%)	16 (62%)
PSA (ng/mL)	27.4 (9.5–115.6)	31.3 (12.6–160.2)	26.1 (9.5–124.4)
PSA doubling time (mo)	1.5 (1.0–2.3)	1.3 (1.0–1.7)	1.8 (1.0–3.2)
Total alkaline phosphatase (U/l)	87 (67–125)	82 (60–175)	94 (69–117)
Hemoglobin (g/dL)	12.0 (10.9–13.2)	12.1 (11.2–12.9)	11.6 (10.8–13.3)
Platelets (10 ³ /mL)	208 (160–245)	207 (163–356)	208 (158–238)
ECOG performance status			
0	13 (30%)	8 (57%)	5 (17%)
1	21 (49%)	4 (29%)	17 (59%)
2	9 (21%)	2 (14%)	7 (24%)
Pain at baseline (BPI score)			
No pain	21 (49%)	4 (28%)	17 (58%)
Mild (1–4)	11 (26%)	5 (36%)	6 (21%)
Moderate to severe (5–10)	11 (26%)	5 (36%)	6 (21%)
Previous mCRPC systemic treatments			
Chemotherapy regimen lines			
0	11 (26%)	4 (29%)	7 (24%)
1	10 (23%)	4 (29%)	6 (21%)
2	12 (28%)	3 (21%)	9 (31%)
≥3	10 (23%)	3 (7%)	7 (24%)
Abiraterone	41 (95%)	13 (93%)	28 (97%)
Enzalutamide	37 (86%)	13 (93%)	24 (83%)
Abiraterone + enzalutamide	35 (82%)	12 (86%)	23 (79%)
²²³ Ra	14 (33%)	4 (29%)	10 (35%)
Prior lines of mCRPC systemic treatment			
1	4 (9%)	1 (7%)	3 (10%)
≥2	39 (91%)	13 (93%)	26 (90%)
≥3	31 (72%)	10 (71%)	21 (72%)
≥4	25 (58%)	8 (57%)	17 (59%)
Extent of disease on PSMA-PET			
≤20 metastases	14 (33%)	4 (29%)	10 (34%)
2 metastases	29 (67%)	10 (71%)	19 (66%)
Sites of disease on PSMA PET			
Node only (N1 or M1a)	3 (7%)	1 (7%)	2 (7%)
Bone only (M1b)	9 (21%)	3 (21%)	6 (21%)
Node + bone (M1b and [N1 or M1a])	15 (35%)	7 (50%)	8 (28%)
Visceral (M1c with/without any other site) [†]	15 (35%)	3 (21%)	12 (41%)

*Data missing for 4 patients.

[†]Visceral includes lung, liver, rectum, pancreas, peritoneal, brain, and adrenal.

BPI = bone pain index.

Data are median, with IQR in parentheses, or n (%).

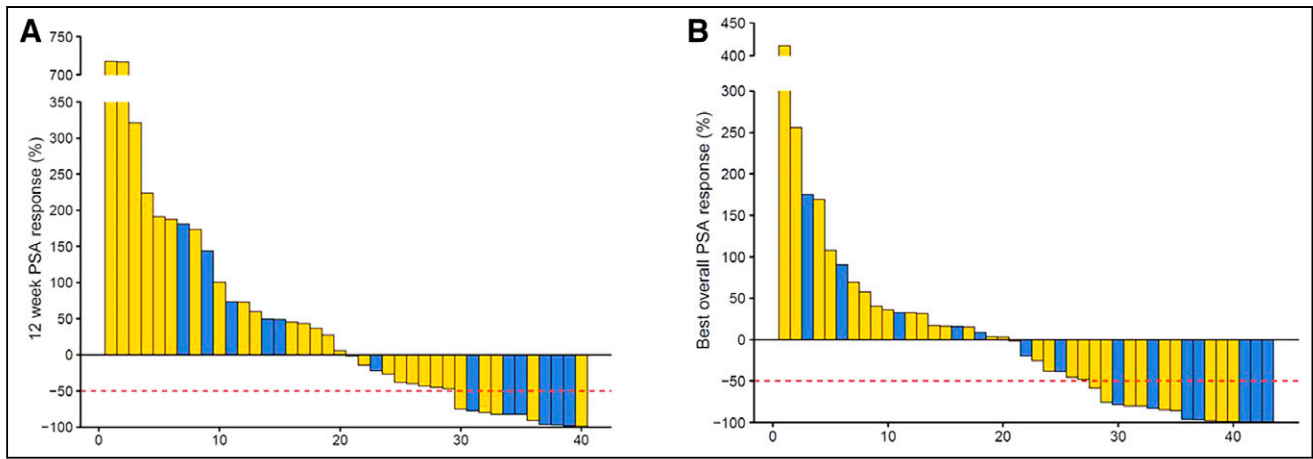


FIGURE 1. Waterfall plots showing PSA changes relative to baseline after 2 cycles of ^{177}Lu -PSMA (A) and any time during treatment (B).

TheraP trial comparing ^{177}Lu -PSMA with cabazitaxel confirmed these findings with higher PSA RR (66% vs. 44%) and less grade 3–4 adverse events (33% vs. 53%) in the ^{177}Lu -PSMA arm (6). Improvement of OS with ^{177}Lu -PSMA will be critical for regulatory approval, and the results of the VISION trial NCT03511664 (best supportive/standard care vs. ^{177}Lu -PSMA + best supportive/standard care) are awaited.

A significant association between best PSA RR and OS was observed, in line with prior reports (3,5), supporting further investigation of PSA RR as an intermediate surrogacy endpoint for OS.

Findings are limited by an early study closure before completing target enrollment (36%). This was beyond the control of the

investigators and resulted in a small sample size. Consequently, the distribution between the 2 treatment groups was also altered (14 vs. 29) as 1:1 randomization was performed centrally for both sites. The premature study termination limits the comparison between the 2 treatment activity groups. However, due to the narrow difference in the 2 tested activities (~20%, 6.0 vs. 7.4 GBq) even the limited data suggest that there is likely no or only small differences in efficacy between these 2 activities. This is consistent with prior reports that found similar response and toxicity rates to comparable levels of injected activity (6.0 vs. 7.5 GBq) (13). To further test whether the current results of the comparison of the 2 activity groups (6.0 GBq vs. 7.4 GBq) in this cohort of 43 patients would likely have

TABLE 2
Primary and Secondary Endpoints Results

Outcome measure	Overall (n = 43)	6.0 GBq (n = 14)	7.4 GBq (n = 29)	Hazard ratio (95% CI)	P
Primary endpoint					
PSA response after 2 cycles					
No. of evaluable patients	40	13	27		
PSA decline \geq 50% after 2 cycles	11 (28%, 95% CI 15–44)	6 (46%, 95% CI 19–75)	5 (19%, 95% CI 6–38)	—	0.12*
Secondary endpoint					
Best PSA response					
No. of evaluable patients	43	14	29		
Best PSA response \geq 50%	16 (37%, 95% CI 23–53)	7 (50%, 95% CI 23–77)	9 (31%, 95% CI 15–51)	—	0.31*
Pain response					
No. of evaluable patients	18	7	11		
Patients with pain improvement (n)	12 (67%)	6 (86%)	6 (55%)	—	0.31*
Pain PFS					
Median (mo)	8.2 (95% CI 3.9–12.5)	5.4 (not reached)	8.2 (95% CI 2.3–14.1)	0.96 (0.35–2.66)	0.94
Post hoc analysis					
OS					
Median (mo)	14.0 (95% CI 10.1–17.9)	15.8 (95% CI 11.8–19.4)	13.5 (95% CI 10.0–17.0)	0.94 (0.46–1.92)	0.87

*P values compare the 6.0- and 7.4-GBq treatment arms using exact Fisher test.

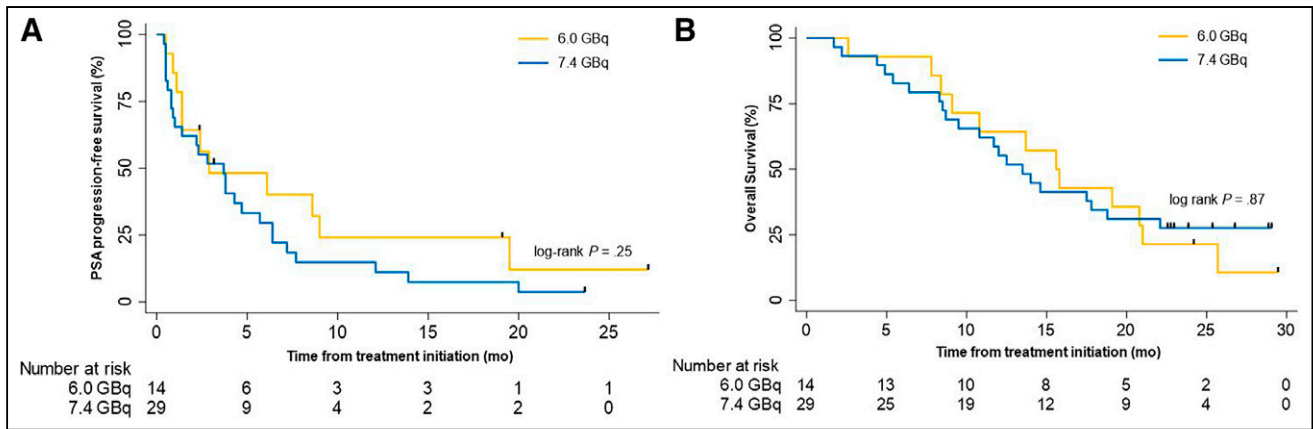


FIGURE 2. Survival Kaplan–Meier curves. Kaplan–Meier curves for PSA PFS (A) and OS (B) by treatment arm. Tick marks indicate censored data. The log-rank test is given with $P < 0.05$ considered significant.

held up in the originally proposed study population of 200 patients, we conducted a post hoc conditional power calculation simulation (12). After 1,000 simulations, only 47 of 1,000 simulations (4.7%) were significant ($P < 0.05$). Further calculation revealed that around 3,400 patients per group (6,800 total) would have been needed to show a significant difference in effectiveness of the 2-activity regimen (conditional power of 80%).

As another limitation, the study population was heterogeneous regarding prior treatment. The study was self-funded and patients were charged for the study drug (cost recovery, Title 21 CFR 312.8). For ethical reasons, the study therefore allowed various prior systemic therapies for inclusion. To correct for heterogeneity in treatment history and baseline characteristics, we conducted a standard covariate adjustment analysis (Supplemental Table 1). After adjusting for baseline factors including ECOG, number of previous chemotherapy regimen (0–1 vs. 2), and presence of visceral disease, the treatment activity was still not associated with treatment outcome. Thus, administered activity (6.0 vs. 7.4 GBq) did not appear to affect treatment outcome.

To reduce out-of-pocket costs, imaging follow-up modalities were selected by patients and referring oncologists. Thus, a variety of imaging modalities (CT, bone scan, MRI, PSMA, choline, fluciclovine, FDG) were used to assess radiographic progression, which

may have increased variance of event data. For instance, PET imaging results in shorter time to progression when compared with conventional anatomic imaging. Because of the lack of standardization, effective conclusions could not be assured. The follow-up imaging analysis is provided in the supplemental material (Supplemental Tables 2 and 3 and Supplemental Fig. 4).

Finally, there was no central blinded review of the screening PSMA PET, and criteria to establish PSMA-target expression were not predefined and left to the discretion of the local investigators. Studies establishing optimal PSMA PET criteria for patient selection and therapy response assessment are warranted.

CONCLUSION

We report here the UCLA study site efficacy results of the prospective phase 2 study RESIST-PC of ^{177}Lu -PSMA for mCRPC after more than 2 y of follow-up. The study closed enrollment before reaching the cohort size because of IND sponsorship transfer to Endocyte Inc. The study population was heterogeneous. PSA RR after 2 cycles and at any time were 28% and 38%. Pain RR was 67%, and the median OS was 14 mo. There was no difference in PSA RR between administration of 6.0 and 7.4 GBq of ^{177}Lu -PSMA. Results justify confirmation with real-world data analysis and further trials to refine and optimize the

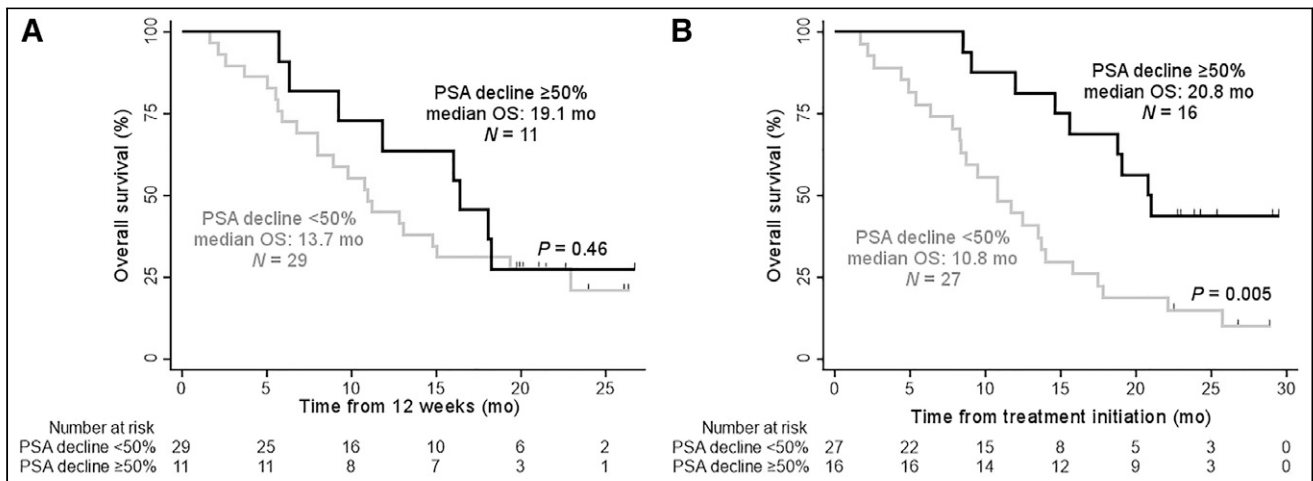


FIGURE 3. Kaplan–Meier curves for OS by PSA response after 2 cycles (A) and at any time (B). Tick marks indicate censored data. The log-rank test is given with $P < 0.05$ considered significant.

¹⁷⁷Lu-PSMA therapy administration scheme to improve tumor radiation dose delivery and efficacy.

DISCLOSURE

Jeremie Calais is the recipient of grants from the Prostate Cancer Foundation (2020 Young Investigator Award, 20YOUN05), the Society of Nuclear Medicine and Molecular imaging (2019 Molecular Imaging Research Grant for Junior Academic Faculty), the Philippe Foundation Inc. (NY, USA), and the ARC Foundation (France) (International Mobility Award SAE20160604150) and reports prior consulting activities outside of the submitted work for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, IBA Radiopharma, Janssen, Progenics, POINT Biopharma, Radiomedix, and Telix Pharmaceuticals. Andrei Gafita was the recipient of the Jonsson Comprehensive Cancer Center Fellowship award and the Dr. Christiaan Schiepers postdoctoral fellowship award. Matthias Eiber was a consultant for ABX, Blue Earth Diagnostics, and Progenics and has patent rights on rhPSMA outside of the submitted work. David Ranganathan is an employee and equity holder of RadioMedix. Ken Herrmann received funding from the German Research Foundation (Deutsche Forschungsgemeinschaft grant HE 5247/4-1) and was a consultant for Advanced Accelerator Applications, Amgen, Bayer, Curium Pharma, GE Healthcare, IPSEN, Janssen Pharmaceuticals, BTG, Sirtex, Novartis, ROTOP, and Bain Capital outside of the submitted work. In addition, Ken Herrmann is a board member of and holds equity in Sofie Biosciences; intellectual property is patented by the University of California and licensed to Sofie Biosciences. Ebrahim Delpassand reports equity ownership at Excel Nuclear Oncology Center and RadioMedix. Wolfgang P. Fendler received financial support from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grants FE1573/1-1/807122 and FE1573/3-1/659216 and DFG Research Training Group 1739); was a consultant for Endocyte and BTG; and received fees from RadioMedix, Bayer, and Parexel outside of the submitted work. Johannes Czernin was supported by the Prostate Cancer Foundation (2019 and 2017 Challenge Award, 19CHAL09, 17CHAL02) and by the Johnson Comprehensive Cancer Center NIH-NCI Cancer Center Support Grant (P30 CA016042) and was a consultant for Endocyte Inc. (VISION trial steering committee), Actinium Pharmaceuticals, and Point Biopharma outside of the submitted work. In addition, Johannes Czernin is a founder and board member of and holds equity in Sofie Biosciences and Trethera Therapeutics; intellectual property is patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics. No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: What is the efficacy profile of 2 activity regimens of ¹⁷⁷Lu-PSMA therapy (6.0 GBq vs. 7.4 GBq) in patients with mCRPC?

PERTINENT FINDINGS: In this prospective randomized phase 2 study that included 43 patients with progressive mCRPC, ¹⁷⁷Lu-PSMA therapy resulted in biochemical response in 38%, and the median OS was 14 mo. There was no difference in efficacy between administration of 6.0 and 7.4 GBq of ¹⁷⁷Lu-PSMA.

IMPLICATIONS FOR PATIENT CARE: ¹⁷⁷Lu-PSMA therapy using and 6.0 and 7.4 GBq is a therapeutic option for patient with mCRPC with a good efficacy.

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Follow-up Imaging analysis

Due to cost considerations (no follow-up imaging was included in the study budget), imaging follow-up was performed by patient and referring oncologist preference. We allowed all imaging modalities including CT, bone scan, MRI, FDG PET/CT, choline PET/CT, Fluciclovine PET/CT and PSMA PET/CT. Thus, a variety of imaging modalities were used to assess radiographic progression which may have increased variance of event data. For instance, PET imaging modalities usually result in a shorter time to progression when compared to conventional anatomic imaging.

Local investigator (JCa) assessed radiographic progression using a combination of RECIST 1.1 for CT and MRI, PCWG3 criteria for bone scans, PERCIST for PET imaging and visual overall assessment.

Endpoints based on imaging follow-up included the radiographic progression-free survival (rPFS) and disease control rate (DCR). These parameters were defined as the time from first treatment cycle to radiographic progression or death from any cause, respectively. We defined disease control rates (DCR) at the end of each cycle as the percentage of patients achieving non progressive disease (PD) (i.e stable disease (SD), partial response (PR) or complete response (CR)). PD more than 12 weeks after cycle #04 was not included in the DCR. Kaplan-Meier analysis was used to calculate rPFS. Log-rank test was used to evaluate the association between treatment arm and patient outcome. Each endpoint was tested at a two-sided significance level of 0.05.

Follow-up imaging was available in 42/43 patients (98%), and progression by imaging as determined by the local investigator occurred in 36/43 of patients (84%). At the end of the follow-up 3/43 patients (70%) were still alive without imaging progression. The imaging modality used for assessment of progression was PSMA PET in 15/43 (35%), CT and bone scan in 10/43 (23%), choline PET in 9/43 (21%), fluciclovine PET in 4/43 (9%), FDG PET in 2/43 (5%) and MRI in 2/43 (5%).

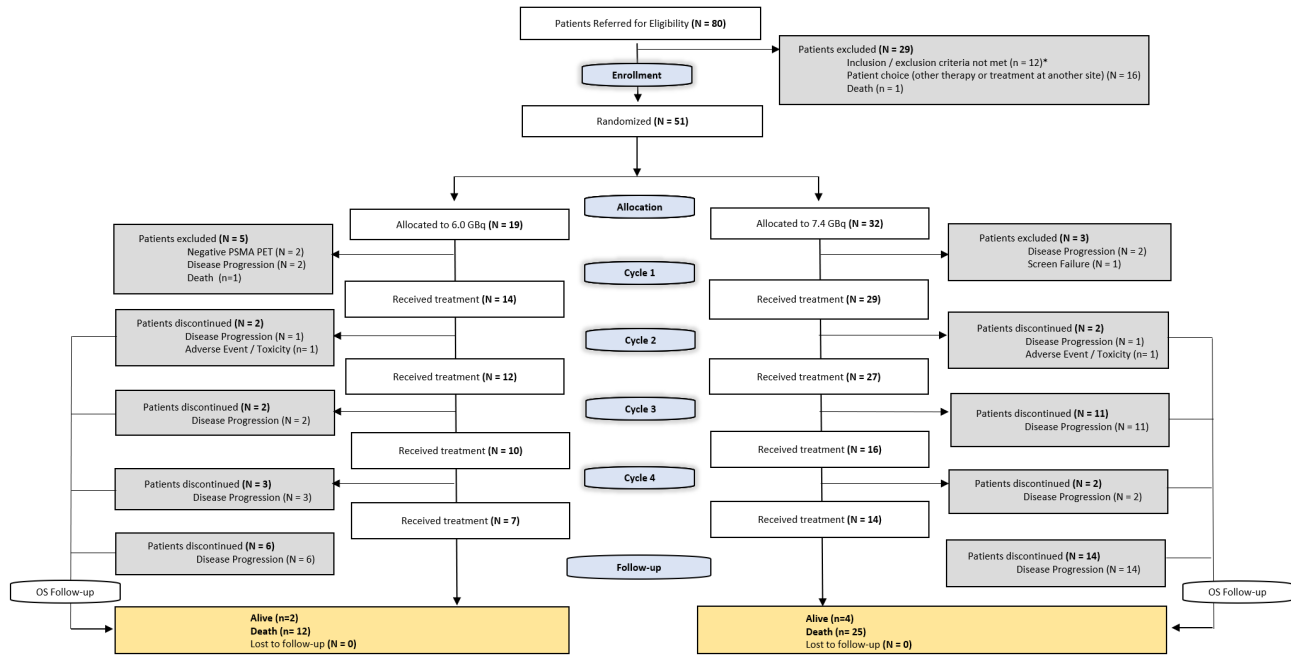
The median rPFS was 4.2 months (95%CI 2.5-5.9), 5.6 months (95%CI 2.6-8.6), 4.2 months (95%CI 2.4-6.0) in the overall study population, the 6.0 GBq and the 7.4 GBq group, respectively ($p=0.51$) (Supplemental Figure 2, Supplemental Figure 4, Supplemental Table 2). The DCR after cycle #02, #03 and #04 was 44%, 30% and 28%, respectively (Supplemental Table 2, Supplemental Table 3).

Supplemental Figure 1

Study CONSORT flowchart.

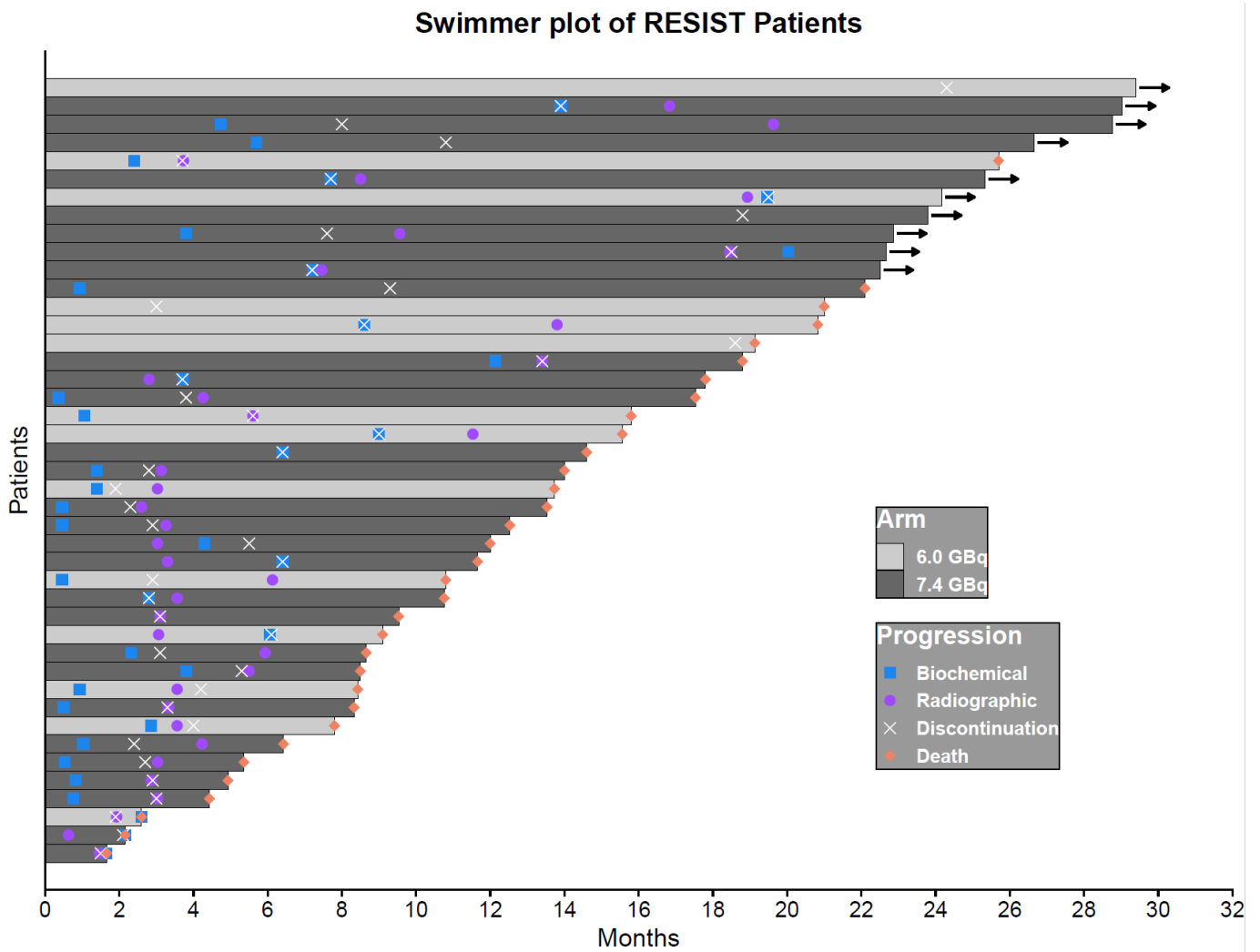
Median follow-up for patients who survived was 24.8 (IQR 22.9-28.8) months.

* details of inc/exc criteria not met: insufficient bone marrow reserve (n=4), no prior abi/enza (n=3), prior Lu-177-PSMA therapy (n=2), ECOG score > 2 (n=1), Kidney obstruction (n=1), Super bone scan (n=1)



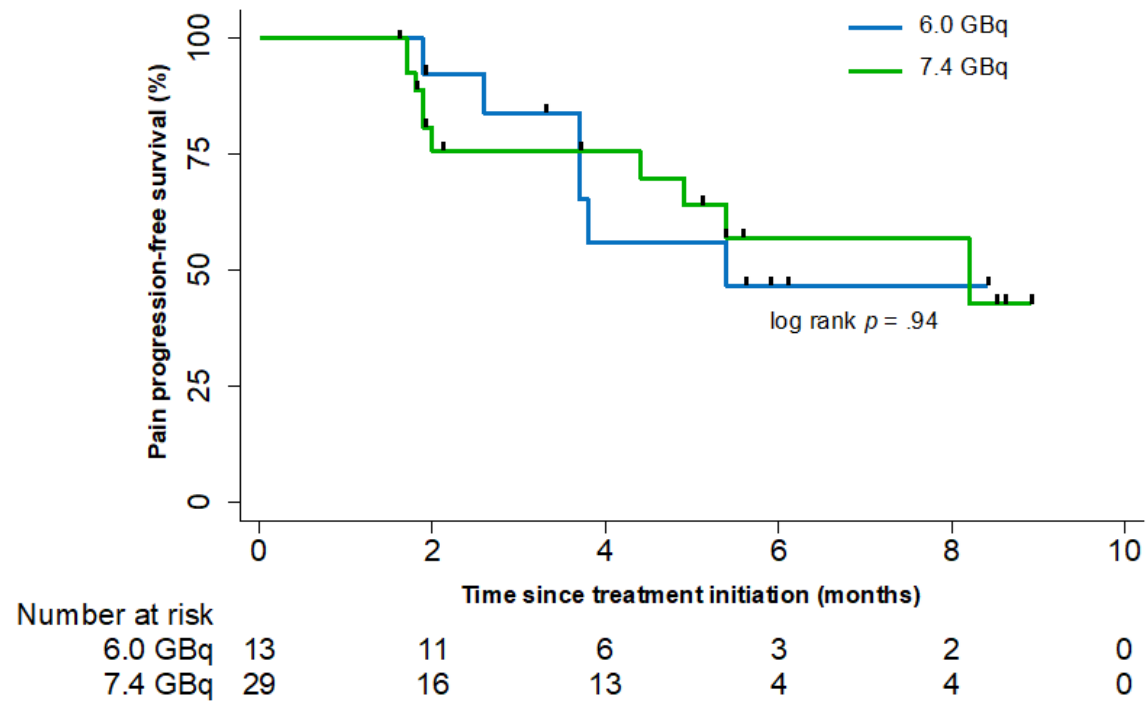
Supplemental Figure 2

Swimmer plot



Supplemental Figure 3

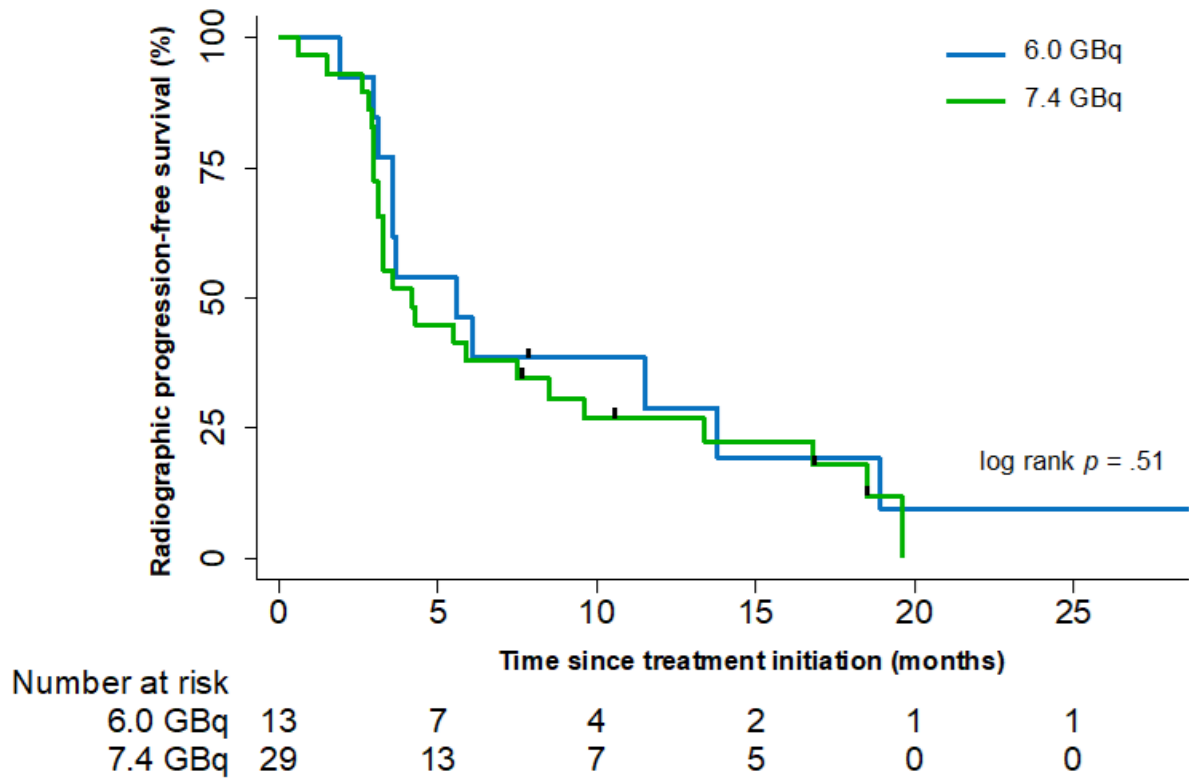
Pain progression-free survival



Kaplan-Meier Curves for radiographic progression-free survival by treatment arm. Tick marks indicate censored data. The log-rank test is given with $p < 0.05$ considered significant.

Supplemental Figure 4

Radiographic progression free survival



Kaplan-Meier Curves for radiographic progression-free survival by treatment arm. Tick marks indicate censored data. The log-rank test is given with $p < 0.05$ considered significant.

Supplemental Table 1.**Multivariate cox / logistic regression models**

	OS	PSA-PFS	Pain-PFS	rPFS	PSA-RR wk*	12 Best RR*	PSA-
Prior Chemotherapy regimen (0-1 vs ≥2)	1.15 (0.55-2.37) p=0.70	1.52 (0.67-3.43) p=0.30	1.99 (0.63-6.26); p=0.23	1.00 (0.40-2.52); p=0.98	0.41 (0.93-1.87); p=0.25	0.67 (0.18-2.46); p=0.67	
ECOG (0-1 vs 2)	1.26 (0.54-2.92); p=0.58	1.31 (0.68-2.53); p=0.41	2.04 (0.69-6.00); p=0.19	1.08 (0.55-2.12); p=0.82	1.06 (0.15-7.20); p=0.94	0.46 (0.08-2.68); p=0.39	
Visceral metastasis (no vs yes)	1.94 (0.94-4.0); p=0.70	2.05 (1.00-4.18); p=0.049	2.08 (0.73-5.92); p=0.17	1.79 (0.87-3.69); p=0.11	0.83 (0.16-4.30); p=0.83	0.56 (0.13-2.33); p=0.43	
Treatment Activity (6.0 vs 7.4 GBq)	0.83 (0.40-1.75); p=0.64	1.40 (0.68-2.88); p=0.35	0.75 (0.25-2.23); p=0.60	1.20 (0.58-2.49); p=0.61	0.27 (0.06-1.25); p=0.095	0.54 (0.14-2.21); p=0.37	

*The effect of treatment dose on outcome data was adjusted for baseline factors in multivariate cox / *logistic regression models. Results are presented in hazard ratio (95%CI) / *odds ratio (95%CI); p value*

Supplemental Table 2:**Imaging Endpoints results**

	Overall (N = 43)	6.0 GBq (N = 14)	7.4 GBq (N = 29)	Hazard Ratio (95%CI)	P value
Radiographic progression-free survival					
Median, months	4.2 (95%CI 2.5-5.9)	5.6 (95%CI 2.6-8.6)	4.2 (95%CI 2.4-6.0)	1.26 (0.61 to 2.58)	.51
Disease control rate (DCR) by imaging					
After cycle #02	19 (44%)	6 (43%)	13 (45%)		
After cycle #03	13 (30%)	4 (29%)	9 (31%)		
After cycle #04	12 (28%)	4 (29%)	8 (28%)		

Abbreviations: CI, confidence interval; PSA, prostate specific antigen; P values compare the 6.0 and 7.4 GBq treatment arms using exact Fisher.

Supplemental Table 3:**Disease control rates after each cycle.**

		C1	C2	C3	C4
Overall study cohort n=43	SD/PR/CR	19 (44%)	19 (44%)	13 (30%)	12 (28%)
	PD	3 (7%)	18 (42%)	4 (9%)	2 (5%)
	N/A	21 (49%)	6 (14%)	26 (60%)	29 (67%)
Arm 6.0 GBq n=14	SD/PR/CR	6 (43%)	6 (43%)	4 (29%)	4 (29%)
	PD	1 (7%)	5 (36%)	2 (14%)	0 (0%)
	N/A	7 (50%)	3 (21%)	8 (57%)	10 (71%)
Arm 7.4 GBq n=29	SD/PR/CR	13 (45%)	13 (45%)	9 (31%)	8 (28%)
	PD	2 (7%)	13 (45%)	2 (7%)	2 (7%)
	N/A	14 (48%)	3 (10%)	18 (62%)	19 (66%)

The disease control rate (DCR) at the end of each cycle was defined as the number and percentage of patients achieving stable disease (SD), partial response (PR) or complete response (CR). PD: progressive disease.

Article #9:

Safety of PSMA-targeted molecular radioligand therapy with ¹⁷⁷Lu-PSMA-617: results from the prospective multicenter phase 2 trial RESIST-PC NCT03042312 (n=64)

Safety of PSMA-Targeted Molecular Radioligand Therapy with ¹⁷⁷Lu-PSMA-617: Results from the Prospective Multicenter Phase 2 Trial RESIST-PC (NCT03042312)

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The purpose of this analysis was to report the safety evaluation of ¹⁷⁷Lu-PSMA-617 derived from the cohort of 64 patients exposed to ¹⁷⁷Lu-PSMA-617 in the RESIST-PC trial NCT03042312. **Methods:** RESIST-PC was a prospective multicenter phase 2 trial. Patients with progressive metastatic castration-resistant prostate cancer after ≥ 1 novel androgen-axis drug, either chemotherapy naïve or postchemotherapy, with sufficient bone marrow reserve, normal kidney function, sufficient PSMA expression by PSMA PET, and no PSMA-negative soft-tissue lesions were eligible. Patients were randomized (1:1) into 2 activity groups (6.0 or 7.4 GBq per cycle) and received up to 4 cycles every 8 wk. The primary safety endpoint was assessed by collecting and grading adverse events using the Common Terminology Criteria for Adverse Events. Patients were followed until disease progression, death, serious or intolerable adverse events, study termination by sponsor, patient withdrawal, lost to follow-up, or 24 mo after the first cycle. **Results:** The study was closed at enrollment of 71 of 200 planned patients because of sponsorship transfer. A total of 64 (90.1%) patients received at least 1 cycle of ¹⁷⁷Lu-PSMA-617: 28 (36%) in arm 1 (6.0 GBq) and 41 (64%) in arm 2 (7.4 GBq). There were 10 (43.5%), 19 (46.5%), and 29 (45.3%) patients who completed 4 cycles of ¹⁷⁷Lu-PSMA-617 in the 6.0-GBq arm, 7.4-GBq arm, and overall, respectively. The most common treatment-emergent adverse events (TEAEs) of any grade in the 6.0-GBq arm, the 7.4-GBq arm and overall, were dry mouth (47.8%; 63.4%; 57.8%, respectively), fatigue (56.5%; 51.2%; 53.1%, respectively), nausea (52.2%; 43.9%; 46.9%, respectively), and diarrhea (13.0%; 31.7%; 25.0%, respectively). Frequencies of all other TEAEs were comparable among the 2 groups (within 10% difference). Serious possibly drug-related TEAEs were reported for 5 (7.8%) patients overall (none were considered as probably or definitely related to treatment): 1 subdural hematoma grade 4, 1 anemia grade 3, 1 thrombocytopenia grade 4, 1 gastrointestinal hemorrhage grade 3, and 1 acute kidney injury grade 3. There were no clinically significant changes in vital signs in electrocardiograms in the 2 treatment groups. No trend to creatinine increase or increasing frequency of shifts from

normal to abnormal over time for any hematologic parameter was noted. **Conclusion:** ¹⁷⁷Lu-PSMA-617 was safe and well-tolerated at 6.0 and 7.4 GBq per cycle given at 8-wk intervals with side effects easily managed with standard medical support. With established safety, further clinical trials applying individualized dosimetry and testing different ¹⁷⁷Lu-PSMA-617 administration schemes (activity levels, time intervals) are needed to optimize tumor dose delivery and treatment efficacy.

Key Words: metastatic castration-resistant prostate cancer; radionuclide therapy; molecular radiotherapy; prostate-specific membrane antigen; ¹⁷⁷Lu, RESIST-PC; prospective randomized phase 2 trial; theranostics; safety

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Targeted molecular radioligand therapy (RLT) offers the possibility to treat cancer lesions in a specific and tumor-selective manner by targeting cell surface proteins expressed on malignant cells. RLT targeting somatostatin receptor using ¹⁷⁷Lu-DOTA-TATE gained regulatory approval in 2018 in patients with metastatic neuroendocrine tumors based on the results on an industry-sponsored randomized phase 3 trial (*J*) and is now an established therapy. The prostate-specific membrane antigen (PSMA) is a target for prostate cancer (PCa) therapy because it is highly expressed in PCa (2). PSMA-617 is a small molecule that clears rapidly from plasma and binds with high affinity to the extracellular domain of PSMA (3). It can be labeled with lutetium-177 (¹⁷⁷Lu) for RLT. β-particles emitted from ¹⁷⁷Lu have a short-range of approximately 1 mm, enabling delivery of high doses of radiation to tumors while minimizing damage to surrounding normal tissues.

The RESIST-PC trial was designed in 2017 to assess the efficacy and safety of ¹⁷⁷Lu-PSMA-617 using 2 commonly used activity regimens (6.0 and 7.4 GBq per cycle) in patients with progressive metastatic castration-resistant prostate cancer (mCRPC). The administration scheme of ¹⁷⁷Lu-PSMA-617 (amount of injected peptide or ligand [nmol], amount of injected activity [GBq – mCi], time interval between each cycle or fractionation, number of

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cycles) derives mostly from prior empiric compassionate use of ^{177}Lu -PSMA-617 in Germany (4–6) and prospective trials using other established molecular radionuclide therapy agents (^{177}Lu -DOTATATE, ^{223}Ra , ^{90}Y -ibritumomab-tiuxetan) (1,7,8). The selected 8-wk interval between treatment cycles was based on established hematologic safety considerations (blood count Nadir at 3–6 wk after molecular radionuclide therapy administration) reported in the above-mentioned randomized prospective phase 3 trials (1,7,8). The 6.0- and 7.4-GBq activity regimens were chosen based on dosimetry data (9,10) and the NETTER-1 trial experience (1).

RESIST-PC was an investigator-initiated trial (IIT) but was switched to a sponsored study after the acquisition of the development rights of PSMA-617 by Endocyte (see the “Materials and Methods” section) and subsequently closed before reaching the target enrollment in 2018. Because of the early study termination and limited data availability, the efficacy endpoints were not analyzed as initially planned. The efficacy outcome results of the University of California Los Angeles (UCLA) study cohort were published separately (11). Here we report the safety evaluation of the study drug derived from the multicenter prospective cohort of 64 patients exposed to ^{177}Lu -PSMA-617.

MATERIALS AND METHODS

Study Design

RESIST-PC was a prospective, randomized, open-label, multicenter phase 2 study conducted at University of California Los Angeles (UCLA; Los Angeles, CA) and Excel Diagnostics Nuclear Oncology Center (Houston, TX). The primary objective of the study was to assess the efficacy and safety of 2 ^{177}Lu -PSMA-617 activity regimens (6.0 GBq and 7.4 GBq per cycle) in patients with mCRPC. It was initially an IIT cosponsored by the principal investigators under a U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) application. The study was approved by the UCLA institutional review board (IRB# 17-000330) and registered on ClinicalTrials.gov (NCT03042312). After the acquisition of the worldwide rights to develop and commercialize PSMA-617 in 2017, the U.S. IND sponsorship was transferred to Endocyte. As the company initiated the prospective international multicenter registration trial (VISION; NCT03511664), the RESIST-PC trial, subsequently identified as PSMA-617-02, was not consistent with the overall company strategy. Thus, the study was closed before all 200 planned patients were enrolled in 2018. Here we report the safety evaluation in the patients exposed to the study drug ($n = 64$).

Patients

Patients with progressive mCRPC after abiraterone or enzalutamide, chemotherapy-naïve or chemotherapy-treated (regardless the number of prior chemotherapy regimens) were eligible. Patients who had received PSMA-targeted radionuclide therapy were excluded. Pretreatment PSMA PET was required for eligibility (see the “Procedures” section below). Sufficient bone marrow reserve (hemoglobin ≥ 9.9 g/dL, platelet count $\geq 100 \times 10^9/\text{L}$, white blood cell count [WBC] $\geq 2.5 \times 10^9/\text{L}$, and absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$) and Eastern Cooperative Oncology Group Performance Score of 0–2 were required inclusion criteria. Patients with diffuse bone involvement by bone scintigraphy (superscan), impaired kidney function (glomerular filtration rate [GFR] < 40 mL/min, serum creatinine $> 1.5 \times$ upper limit of normal [ULN], urinary tract obstruction or marked hydronephrosis), or impaired liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $> 5 \times$ ULN) were excluded.

Patients were referred specifically to this trial and continued care with their treating medical oncologist or urologist in close coordination with the study site investigators. They traveled to the trial sites per protocol.

Patients were prescreened based on their prostate cancer history before initial consultation visit. Informed written and oral consent was obtained from all patients during the initial consultation visit.

Procedures

Screening PSMA PET. PSMA PET performed within 3 mo before randomization was required for eligibility. Local study-site investigators visually determined sufficient target expression (majority of lesions with uptake equal to or above liver uptake) and absence of PSMA-negative lesions visible on anatomic imaging modalities (CT, MRI). No semi-quantitative thresholds were applied. OsiriX software (Pixmeo) was used for visual assessment (12).

Randomization. Patients were randomized (1:1 ratio) to receive either 6.0 ($\pm 10\%$, arm 1) or 7.4 GBq ($\pm 10\%$, arm 2) of ^{177}Lu -PSMA-617 per treatment cycle. Randomization (1:1 ratio) was performed in accordance with Vickers et al. (13). Randomization was not stratified for any variable. A list of random allocations for patients 1 to 200 was created, concealed, and stored at the investigator’s site without modification. A clinical research coordinator who was not involved in clinical management assigned the randomized allocation. There was no blinding of patients or physicians.

Treatment Intervention. ^{177}Lu -PSMA-617 was radiolabeled with carrier-free ^{177}Lu (RadioMedix, Inc.). The labeled product was produced, tested, released, and delivered under good-manufacturing-practice conditions as a sterile, ready-to-use solution for infusion. ^{177}Lu -PSMA-617 was intravenously applied over approximately 15–30 min using an infusion pump at 8 ± 1 wk intervals up to a maximum of 4 cycles. Salivary glands were cooled using icepacks (started 30 min before injection of ^{177}Lu -PSMA-617 and maintained for 4 h after injection). Treatment cycles continued until disease progression, severe toxicity occurred (see the “Safety Assessments” section below), patient withdrawal, or per investigator decision. Patients were permitted to receive concurrent radiotherapy or other non-chemotherapy treatments.

Safety Assessments. Physical examination, vital signs, and 12-lead electrocardiogram were performed at each site visit. Laboratory tests (comprehensive metabolic panel [CMP], estimated GFR [eGFR], complete blood count [CBC]) were performed at baseline (within 72 h of the first treatment dose) and every 2 wk (± 3 d) after the first dose of study medication, continued until 12 wk after the last dose, and every 3 mo ($\pm 1 \times$ wk) thereafter until discontinuation from the study. The CBC, eGFR, and CMP within 2 wk of each subsequent treatment cycle were used to assess the eligibility for the corresponding treatment cycle. Telephone follow-up was performed 7 ± 3 d after each treatment cycle, and for the follow-up phase in 3 ± 1 mo intervals until study termination.

Serious AEs (SAEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, whereas AEs were described by severity (i.e., mild, moderate, severe) by the local investigators. Severity was used to describe the intensity of a specific event, which can be of relatively minor medical significance (such as a grade 3 headache). SAE is based on patient/event outcome or action criteria and was used for events that posed a threat to the patient’s life or ability to function. Seriousness (not intensity/severity) serves as a guide for defining regulatory reporting obligations.

In the case of occurrence of grade 3–4 SAEs or severe AEs, treatment administration was suspended until resolution (defined as CTCAE grade ≤ 2) up to 12 wk after the last cycle. Patients were discontinued from the study in the case of grade 4 hematologic SAE during > 3 wk, grade 3 renal SAE during > 3 wk, or any other grade 3–4 SAEs during > 12 wk.

In the case of a patient experiencing the same event more than once, the maximum toxicity grade was presented. Multiple occurrences of the same AEs occurring in 1 individual were counted only once. The local investigators assessed whether AEs were study drug-related as follows: not, unlikely, possibly, probably or definitely related. A treatment-emergent adverse event (TEAE) was defined as an AE that was not

present before the first dose of ^{177}Lu -PSMA-617 but appeared after treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment was a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period was defined as the period from the date of initiation of randomized treatment up to 30 d after date of last administration of study treatment or the day before the initiation of subsequent anticancer treatment, whichever occurred first.

Kidney dosimetry was required by the FDA to be performed in the initial versions of the study protocol with a discontinuation rule using a maximum threshold dose to the kidneys of 23 Gy. Dosimetry data obtained after the first cycle for the first 20 patients (16 from UCLA and 4 from Excel Diagnostics) were analyzed. The estimated cumulated radiation dose after 4 cycles did not exceed the permitted renal dose of 23 Gy in any patient, demonstrating overall favorable renal dosimetry. Thus, dosimetry was no longer required per protocol (protocol PSMA-617-02 amendment 4, June 2018). Final dosimetry analysis will be reported separately.

Study Duration

Patients were followed until disease progression, death, serious or intolerable AE (that in the opinion of the investigator required the patient's discontinuation), study termination by sponsor, patient withdrawal, lost to follow-up, or 24 mo after the first treatment cycle.

Data Management and Quality

Designated investigator staff entered the data into an electronic data/electronic Case Report Form (OpenClinica eDC). The contract research organization responsible for site monitoring was Pharmtrace. PrimeVigilance was responsible for the pharmacovigilance safety database once Endocyte became the sponsor for this study.

Statistical Analysis

The primary endpoints were the efficacy and the safety of ^{177}Lu -PSMA-617. Safety was assessed by collecting and grading AEs using the CTCAE, version 4.0. Efficacy (assessed by baseline to 12-wk decline in tumor marker level [prostate-specific antigen, PSA \geq 50%] (14)) is not reported here due to premature study termination after only 71 of 200 patients enrolled. As the power of the predefined test could not be ensured, no formal statistical test for overall response \geq 50% was performed. The actual sample size was insufficient to perform the analyses that would allow for appropriate evaluation of effectiveness. Therefore, no statistical test for comparing the 2 groups was performed. No interim analysis was planned. Missing data were not replaced. We used descriptive statistics including mean, SD, median and interquartile range (Q1–Q3), and range (minimum–maximum) for continuous variables, and number and percentage for categorical variables. Data were analyzed using SAS, version 9.4 (SAS Institute Inc.).

Role of the Funding Source

RESIST-PC was initially an investigator-sponsored trial. Patients were charged for the drug under Title 21 of the Code of Federal Regulation Section (CFR) 312.8. After the sponsorship transfer, site monitoring, pharmacovigilance, and data analysis was supported by Endocyte/Novartis. The corresponding author had complete data access and had final responsibility to submit for publication.

RESULTS

Patient Enrollment

Between July 5, 2017, and June 22, 2018, a total of 71 patients (51 at UCLA and 20 at Houston) signed informed consent and were randomized (ITT population): 28/71 (39%) in arm 1 (6.0 GBq) and 43/71 (61%) in arm 2 (7.4 GBq). There were 7/71 patients (9.9%)

randomized but not treated: 2 with PSMA-negative liver lesions (screen failure), 2 were too weak for treatment, 1 with low platelets ($34 \times 10^9/\text{L}$), 1 withdrew consent, and 1 died. A total of 64/71 (90.1%) patients received at least 1 cycle of ^{177}Lu -PSMA-617 (safety population): 23/64 (36%) in arm 1 (6.0 GBq) and 41/64 (64%) in arm 2 (7.4 GBq). The last visit of the last subject was on January 15, 2020, and the study completion date was January 8, 2021. Seven of 71 (9.9%) deaths were reported during the study from enrollment through the 24-mo follow-up: 4 of 28 (14.3%) and 3 of 43 (7.0%) in the 6.0-GBq and 7.4-GBq treatment arms, respectively (patient disposition [ITT population] in Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>).

Protocol Deviations

Fifty seven/71 subjects (80.3%) experienced protocol deviations (Supplemental Table 2). Most of these included procedures done outside the protocol required timing. In 40 of 71 (56.3%) patients, the pretherapy baseline PSA was performed after the randomization and was not included for analysis.

Baseline Characteristics and Prostate Cancer Treatment History (ITT Population, $n = 71$)

The demographic and baseline disease characteristics were comparable across the 2 treatment groups and are presented in Table 1. Fifty-four/71 (80.6%) patients had a PSA doubling time \leq 6 mo. Fifty-eight/71 (81.7%) patients underwent at least 1 round of chemotherapy for PCa before study enrollment. Fifty-seven/71 (80.3%) patients underwent at least 1 prior taxane regimen; 54/71 (76.1%) patients had docetaxel and 26/71 (36.6%) had cabazitaxel therapy. Sixty-seven/71 (94.4%) patients were treated with abiraterone and 55/71 (77.5%) patients with enzalutamide.

Screening PSMA PET Findings (ITT Population, $n = 71$)

A summary of the screening PSMA PET staging of the ITT population is provided in Supplemental Table 3. Three patients did not undergo the screening PSMA PET scan because of poor clinical status/disease progression (withdrawal). PSMA PET was performed using ^{68}Ga -PSMA-11 in 66 of 68 (97%) and ^{18}F -DCFPyL in 2 of 68 (3%) patients. Two patients were excluded from the study because of PSMA-negative liver lesions (screen failure). Overall, 4 of 68 patients (6%) had nodal disease only (N1 or M1a), 62 of 68 (91%) had bone disease (M1b), and 25 of 68 (37%) had visceral metastasis.

Treatment Exposure (Safety Population, $n = 64$)

There were 10/23 (43.5%), 19/41 (46.5%), and 29/64 (45.3%) patients who completed 4 cycles of ^{177}Lu -PSMA-617 in the 6.0-GBq arm, 7.4-GBq arm, and overall, respectively (Table 2). The mean \pm SD cumulative activity was 16.9 ± 7.6 , 21.4 ± 8 , and 19.8 ± 8.1 GBq in the 6.0-GBq arm, 7.4 GBq, arm and overall, respectively (Table 2).

There were 13/23 (56.5%), 27/41 (65.9%), and 40/64 (62.5%) patients with at least 1 other concurrent systemic therapy for mCRPC during the study (Table 3): hormonal therapy in 12/23 (52.2%), 25/41 (61%), 37/64 (57.8%); abiraterone in 3/23 (13%), 5/41 (12.2%), 8/64 (12.5%); enzalutamide in 2/23 (8.7%), 7/41 (17.7%), 9/64 (14.1%); and other in 10/23 (43.5%), 16/41 (39%), 26/64 (40.6%) in the 6.0-GBq arm, 7.4-GBq arm, and overall, respectively. Two patients received concurrent radiotherapy: 1 bone lesion (6.0-GBq arm 1) and 1 local recurrence (7.4-GBq arm 2).

TABLE 1
Baseline Characteristics (ITT Population)

Characteristic	6.0 GBq arm (<i>n</i> = 28)	7.4 GBq arm (<i>n</i> = 43)	Overall (<i>n</i> = 71)
Age (y)			
Mean (SD)	72.1 (8.39)	69.1 (8.62)	70.3 (8.60)
Minimum; maximum	55; 95	54; 84	54; 95
<65 y (<i>n</i>)	4 (14.3%)	13 (30.2%)	17 (23.9%)
≥65 y (<i>n</i>)	24 (85.7%)	30 (69.8%)	54 (76.1%)
Race/ethnicity (<i>n</i>)			
Asian	1 (3.6%)	1 (2.3%)	2 (2.8%)
Black/African American	0	1 (2.3%)	1 (1.4%)
Hispanic/Latino	0	1 (2.3%)	1 (1.4%)
White	26 (92.9%)	40 (93.0%)	66 (92.9%)
Other	1 (3.6%)	0	1 (1.4%)
Time since initial prostate cancer diagnosis (y)			
Mean (SD)	8.06 (7.323)	8.06 (7.152)	8.06 (7.156)
Minimum; maximum	0.7; 27.2	0.3; 25.9	0.3; 27.2
Initial Gleason score, categorized (<i>n</i>)			
4–7	7 (25.0%)	13 (30.2%)	20 (28.2%)
8–10	20 (71.4%)	26 (60.5%)	46 (64.8%)
Unknown	1 (3.6%)	4 (9.3%)	5 (7.0%)
Baseline PSA doubling time (mo)			
<i>n</i>	26	41	67
Mean (SD)	4.35 (7.131)	3.89 (3.977)	4.07 (5.376)
Median	1.91	2.46	2.07
Q1; Q3	1.18; 3.38	1.41; 4.90	1.22; 4.90
Minimum; maximum	0.0; 31.4	0.0; 20.7	0.0; 31.4
≤6 (<i>n</i>)	21 (80.8%)	33 (80.5%)	54 (80.6%)
>6 (<i>n</i>)	5 (19.2%)	8 (19.5%)	13 (19.4%)
Baseline PSA (ug/L)			
<i>n</i>	12	19	31
Mean (SD)	208.86 (391.804)	287.92 (830.231)	257.32 (686.578)
Median	46.03	19.34	23.66
Q1; Q3	11.28; 99.35	5.34; 68.00	5.59; 93.20
Minimum; maximum	0.6; 1166.0	1.9; 3499.0	0.6; 3499.0
Number of prior chemotherapies per patient			
<i>n</i>	22 (78.6%)	36 (83.7%)	58 (81.7%)
Median	2.0	2.0	2.0
Q1; Q3	1.0; 3.0	1.0; 3.0	1.0; 3.0
Minimum; maximum	1; 7	1; 5	1; 7
Type of prior chemotherapies per patient (<i>n</i>)			
Cabazitaxel	9 (32.1%)	17 (39.5%)	26 (36.6%)
Docetaxel	21 (75.0%)	33 (76.7%)	54 (76.1%)
Other	9 (32.1%)	18 (41.9%)	27 (38.0%)
Type of other prior systemic treatment (<i>n</i>)			
Abiraterone	26 (92.9%)	41 (95.3%)	67 (94.4%)
Enzalutamide	21 (75.0%)	34 (79.1%)	55 (77.5%)
Hormonal therapy	22 (78.6%)	39 (90.7%)	61 (85.9%)
Standard ADT	19 (67.9%)	22 (51.2%)	41 (57.7%)
²²³ Ra	5 (17.9%)	14 (32.6%)	19 (26.8%)
Other	20 (71.4%)	31 (72.1%)	51 (71.8%)

TABLE 2
Randomized Treatment Exposure, Summary of Cycles (Safety Population)

	6.0 GBq (n = 23)	7.4 GBq (n = 41)	Overall (n = 64)
Duration of study treatment (mo)			
Mean (SD)	3.49 (2.37)	3.66 (2.01)	3.60 (2.13)
Median	3.71	3.71	3.71
Q1; Q3	1.87; 5.75	1.87; 5.55	1.87; 5.55
Minimum; maximum	0.0; 6.3	0.0; 7.7	0.0; 7.7
Number of cycles started by patient			
Mean (SD)	2.8 (1.23)	3.0 (1.07)	2.9 (1.12)
Median	3.0	3.0	3.0
Q1; Q3	2.0; 4.0	2.0; 4.0	2.0; 4.0
Minimum; maximum	1; 4	1; 4	1; 4
Number of cycles started by patient categories (n)			
1 cycle	5 (21.7%)	3 (7.3%)	8 (12.5%)
2 cycles	4 (17.4%)	15 (36.6%)	19 (29.7%)
3 cycles	4 (17.4%)	4 (9.8%)	8 (12.5%)
4 cycles	10 (43.5%)	19 (46.3%)	29 (45.3%)
Dose per cycle (GBq/cycle)			
Mean (SD)	5.909 (0.2953)	7.245 (0.5241)	6.765 (0.7891)
Median	6.031	7.363	7.111
Q1; Q3	5.696 ; 6.142	7.134 ; 7.486	6.048 ; 7.410
Minimum; maximum	5.07 ; 6.31	4.91 ; 7.84	4.91 ; 7.84
Cumulative dose (GBq)			
Mean (SD)	16.913 (7.6668)	21.404 (8.0335)	19.790 (8.1376)
Median	18.583	22.287	19.917
Q1; Q3	11.392; 24.169	14.711; 29.454	14.297; 28.394
Minimum; maximum	5.07; 24.91	6.92; 30.59	5.07; 30.59

Results given as xx (xx.x) where xx = number of patients, (xx.x) = percentage of patients.

Duration of study treatment (months) = (treatment end date – treatment start date + 1)/30.4375.

Safety Evaluation (Safety Population, n = 64)

A summary overview of TEAEs that occurred in the study is presented in Supplemental Table 4. Main TEAEs are described in Table 4. In general, incidence of any AE was comparable between the groups: 22/23 (95.7%), 39/41 (95.1%), and 61/64 (95.3%) in the 6.0-GBq group, the 7.4-GBq group, and overall, respectively. The most frequently occurring TEAEs were dry mouth, fatigue, and nausea: 37/64 (57.8%), 34/64 (53.1%), and 30/64 (46.9%), respectively (Table 4). Notably, none of these events was reported to be severe, except 1 event of nausea in the 7.4-GBq treatment group (but did not require tube feeding, parenteral nutrition, or hospitalization). Dry mouth (47.8% vs. 63.4%) and diarrhea (13.0% vs. 31.7%) occurred more frequently in the 7.4-GBq group than in the 6.0 GBq group. Frequencies of all other TEAEs were comparable among the 2 groups (within 10% difference). There were no differences in AEs between patients aged ≥ 65 y (n = 48) and patients aged < 65 y (n = 16).

Anemia, thrombocytopenia, and leukopenia were reported overall in 8/64 (12.5%), 1/64 (1.6%), and 1/64 (1.6%), respectively. Mild decreases in mean white blood cell count, red blood cell count, and platelets (all components) were observed during treatment.

However, during follow-up, the mean values tended to increase again. This was observed for the overall patient population, with no relevant differences between the groups. No trend to creatinine increase was observed during the study. There were 4 patients with grade 3 AST or ALT levels above the reference ranges that were primarily explained by liver metastases and were not considered to be related to the study treatment. Alkaline phosphatase (ALP) mean values over time during treatment had no substantial change, but individual patients had variable increase or decrease of ALP that was compatible with the disease. These overall laboratory findings for the patient population showed no relevant differences between the groups. The data must be interpreted with caution due to the small number of patients with available information at some of the time points.

There were no clinically significant changes in vital signs (systolic blood pressure [mm Hg], diastolic blood pressure [mm Hg], heart rate [bpm], temperature [°C], and respiratory rate [breaths per min]). There were no clinically significant abnormalities reported of electrocardiogram interpretations.

TEAEs leading to the reduction of $^{177}\text{Lu-PSMA-617}$ were reported for 2/41 (4.9%) patients in the 7.4-GBq arm; both events

TABLE 3
Concurrent Therapies (Population: Safety Population)

	6.0 GBq (n = 23)	7.4 GBq (n = 41)	Overall (n = 64)
Number of patients with at least 1 other treatment	13 (56.5)	27 (65.9)	40 (62.5)
Type of other treatments			
Abiraterone	3 (13.0)	5 (12.2)	8 (12.5)
Enzalutamide	2 (8.7)	7 (17.1)	9 (14.1)
Hormonal therapy	12 (52.2)	25 (61.0)	37 (57.8)
Other	10 (43.5)	16 (39.0)	26 (40.6)
Standard ADT	1 (4.3)	2 (4.9)	3 (4.7)
Bone metastasis RT	1 (4.3)	0	1 (1.6)
Prostate local recurrence RT	0	1 (2.4)	1 (1.6)
Number of other treatments			
n	13	27	40
Mean (SD)	2.8 (1.42)	2.4 (1.39)	2.5 (1.40)
Median	2.0	2.0	2.0
Q1; Q3	2.0; 3.0	1.0; 3.0	1.5; 3.0
Minimum; maximum	1; 6	1; 6	1; 6

Results given as xx (xx.x) where xx = number of patients, (xx.x) = percentage of patients. Data in parentheses are percentages, unless otherwise indicated.

ADT = Androgen deprivation therapy; RT = radiation therapy.

were anemia. The only TEAE that led to the discontinuation of ¹⁷⁷Lu-PSMA-617 was abdominal pain (grade 3 severity) reported in 1 patient in the 7.4-GBq group who had diffuse liver metastases and only received 1 cycle (unlikely related to treatment).

Serious drug-related TEAEs were reported for 5/64 (7.8%) patients overall: 1/23 (4.3%) in the 6.0-GBq group; and 4/41 (9.8%) in the 7.4-GBq group (Table 5). None was considered as *probably* or *definitely* related to treatment by the investigators, and all were reported as *possibly* related to treatment.

There was 1 acute kidney injury reported (grade 3 severity) in the 7.4-GBq arm. The nephrologist concluded that the creatinine elevation was likely related to concomitant medication with meloxicam. However, it could not be excluded that additional renal toxicity was caused by ¹⁷⁷Lu-PSMA-617. The investigator considered the acute kidney injury as possibly related to the treatment.

Of the 7 deaths reported, there was 1 death in the 7.4-GBq group determined to be possibly related to treatment due to hemotoxicity and gastrointestinal hemorrhage (72 d after last dose, grade 3 severity) and 1 death (94 d after last dose) in the 6.0-GBq group determined to be possibly related to treatment due to a subdural hematoma. Four deaths were reported as unrelated adverse events (death > 30 d after last dose of ¹⁷⁷Lu-PSMA-617, brain metastasis (n = 3), liver metastasis (n = 1)), and 1 death occurred in a patient before he received his first dose of ¹⁷⁷Lu-PSMA-617.

No patients developed myelodysplasia during the follow-up period.

DISCUSSION

This randomized phase 2 study compared 2 ¹⁷⁷Lu-PSMA-617 treatment activity levels in 64 patients with mCRPC who progressed after conventional therapies. ¹⁷⁷Lu-PSMA-617 was well tolerated

irrespective of the activity regimen (6.0 vs. 7.4 GBq per cycle, in average 3 cycles per patient), in line with a prior retrospective study comparing similar activity levels (15). The most frequently occurring TEAEs were dry mouth, fatigue, and nausea in 57.8%, 53.1%, and 46.9% of the population, respectively. None of these events was reported to be severe. Serious TEAEs classified as possibly drug-related occurred in only 7.8% patients overall. The safety profile of ¹⁷⁷Lu-PSMA-617 in this study was as anticipated based on the mechanism of action and is generally consistent with previous ¹⁷⁷Lu-PSMA-617 experiences as documented in literature in similar populations of patients with mCRPC. The low toxicity profile of ¹⁷⁷Lu-PSMA-617 is attributed to the high binding affinity to the PSMA target protein and rapid renal excretion, limiting toxicity to nontarget organs.

Because ¹⁷⁷Lu-PSMA-617 is predominantly excreted by the kidneys, potential nephrotoxicity represents the main safety concern. In our cohort, the renal safety profile was excellent, with only 1 of 64 (1.5%) acute kidney injury recorded (grade 3) that was reversible and very likely related to concomitant medication. This is in line with prior reports. In an Australian retrospective cohort study reporting renal outcomes of ¹⁷⁷Lu-PSMA-617 therapy (mean cumulative activity 18.86 ± 6.7 GBq) after 8 mo of median follow-up, only 5 of 110 (4.5%) patients experienced grades 1–2 nephrotoxicity, with the main risk factor being prior chronic kidney disease (relative risk 4.2) (16). In the retrospective German multicenter study, grade 1–2 renal failure was reported in 12% (5). In the phase 2 LuPSMA trial, grade 1–2 renal toxicity was reported in 10% (17). In the TheraP trial, grade 1–2 creatinine increase occurred in 4 of 98 (4%), and 1 (1%) grade 3 acute kidney injury was reported (18). In the VISION trial, renal AEs of any grade were observed in 46 of 529 (9%) and of grade 3–5 in 18 of 529 (3.4%) (19).

TABLE 4

Main Treatment-Emergent Adverse Events (More Than 5% of Patients in Either Treatment Arm, and Blood and Kidney Laboratory Tests) (Safety Population)

Adverse event	6.0 GBq (n = 23)		7.4 GBq (n = 41)		Overall (n = 64)	
	All severity (n)	Severe (n)	All severity (n)	Severe (n)	All severity (n)	Severe (n)
Any event	22 (95.7)	2 (8.7)	39 (95.1)	7 (17.1)	61 (95.3)	9 (14.1)
Dry mouth	11 (47.8)	0	26 (63.4)	0	37 (57.8)	0
Fatigue	13 (56.5)	0	21 (51.2)	0	34 (53.1)	0
Nausea	12 (52.2)	0	18 (43.9)	1 (2.4)	30 (46.9)	1 (1.6)
Diarrhea	3 (13.0)	0	13 (31.7)	0	16 (25.0)	0
Constipation	6 (26.1)	0	9 (22.0)	0	15 (23.4)	0
Vomiting	4 (17.4)	0	8 (19.5)	1 (2.4)	12 (18.8)	1 (1.6)
Taste disorder	4 (17.4)	0	7 (17.1)	0	11 (17.2)	0
Pain	3 (13.0)	0	6 (14.6)	1 (2.4)	9 (14.0)	1 (1.6)
Decreased appetite	1 (4.3)	0	5 (12.2)	0	6 (9.4)	0
Arthralgia	3 (13.0)	0	2 (4.9)	0	5 (7.8)	0
Hemorrhage/hematoma	1 (4.3)	1 (4.3)	3 (7.3)	1 (2.4)	4 (6.3)	2 (3.1)
Infection	1 (4.3)	0	3 (7.3)	1 (2.4)	4 (6.3)	1 (1.6)
Headache	2 (8.7)	0	2 (4.9)	0	4 (6.3)	0
Dry eye	1 (4.3)	0	3 (7.3)	0	4 (6.3)	0
Back pain	2 (8.7)	0	1 (2.4)	0	3 (4.7)	0
Dyspnea	0	0	3 (7.3)	1 (2.4)	3 (4.7)	1 (1.6)
Key laboratory tests events						
Anemia	4 (17.4)	0	4 (9.8)	1 (2.4)	8 (12.5)	1 (1.6)
Thrombocytopenia	0	0	1 (2.4)	1 (2.4)	1 (1.6)	1 (1.6)
Leukopenia	0	0	1 (2.4)	0	1 (1.6)	0
Lymphopenia	0	0	1 (2.4)	0	1 (1.6)	0
Acute kidney injury	0	0	1 (2.4)	1 (2.4)	1 (1.6)	1 (1.6)
GFR decreased	1 (4.3)	0	0	0	1 (1.6)	0

Results given as xx (xx.x) where xx = number of patients with AEs, (xx.x) = percentage of patients. Every patient was counted a single time for each applicable specific AE. All AE tables are coded using MedDRA, version 22.1. Preferred terms are sorted in descending frequency of 'All severity' column, as reported in the 'Overall' column. Data in parentheses are percentages, unless otherwise indicated.

Bone marrow toxicity was rare, reversible, and manageable. Two patients delayed their subsequent cycle because of anemia. Thrombocytopenia and leukopenia were each reported only in 1 patient (1.6%). Hemorrhage/hematoma and infections were both reported in 4 patients (6.3%). The relationship to study drug in this population of advanced mCRPC patients with multiple bone metastasis at risk of having impaired bone marrow function from the disease is uncertain. Of note, the incidence of hematologic side effects in our study is slightly lower than that reported in the retrospective German multicenter study (grade 3–4 anemia 10%, thrombocytopenia 4%, leukopenia 3%)(5), the phase 2 LuPSMA trial (grade 3–4 anemia 10%, thrombocytopenia 10%, neutropenia 6%)(17), the TheraP trial (grade 3–4 anemia 8%, thrombocytopenia 11%, leukopenia 1%)(18), and the VISION trial (grade 3–4 anemia 13%, thrombocytopenia 8%, leukopenia 3%)(19). One reason may be that bone marrow may have been involved less frequently or less extensively in our cohort.

Because of the high uptake of PSMA radioligands in the salivary glands, xerostomia is a known side effect of ¹⁷⁷Lu-PSMA-617. Dry

mouth occurred in 63.4% in the 7.4-GBq arm and 47.8% in the 6.0-GBq arm (57.8% overall) but was never graded as severe or irreversible, in line with the phase 2 LuPSMA trial (mean injected activity 7.5 GBq, grade 1–2 xerostomia in 66%, no grade 3–4)(17), the TheraP trial (injected activity 8.5 GBq, grade 1–2 xerostomia in 60%, no grade 3–4)(18), and the VISION trial (injected activity 7.4 GBq, grade 1–2 xerostomia in 39%, no grade 3–4)(19). Early reports underestimated this side effect (8% in the retrospective German multicenter study, mean injected activity 5.9 GBq) probably because of the absence of systematic data collection (5). Other symptoms such as taste disorder/dysgeusia (17% in our cohort, 12% in TheraP) or decreased appetite (9% in our cohort, 21% in VISION) are likely related to the salivary gland toxicity. Of note, we performed cooling of the salivary glands at the time of ¹⁷⁷Lu-PSMA-617 administration but without any tangible effect, as previously described (20,21).

Frequent, non-life-threatening but unpleasant side effects are important to know to adequately inform and, when possible, pre-medicate patients. Early reports significantly underestimated

TABLE 5
Serious Drug-Related TEAEs (Safety Population)

System organ class, preferred term	6.0 GBq (n = 23)	7.4 GBq (n = 41)	Overall (n = 64)
Any Serious Drug Related TEAE	1 (4.3)	4 (9.8)	5 (7.8)
Blood and lymphatic system disorders			
Anemia (grade 3, possibly related)	0	1 (2.4)	1 (1.6)
Thrombocytopenia (grade 4, possibly related)	0	1 (2.4)	1 (1.6)
Gastrointestinal disorders			
Gastrointestinal hemorrhage (grade 3, possibly related)	0	1 (2.4)	1 (1.6)
General disorders			
Death (grade 5, possibly related)	0	1 (2.4)	1 (1.6)
Injury complications			
Subdural hematoma (grade 4 possibly related)	1 (4.3)	0	1 (1.6)
Renal and urinary disorders			
Acute kidney injury (grade 3, possibly related)	0	1 (2.4)	1 (1.6)
Respiratory, thoracic and mediastinal disorders			
Pleural effusion (grade 3, possibly related)	0	1 (2.4)	1 (1.6)

Results given as xx (xx.x) where xx = number of patients with serious, drug-related TEAEs, (xx.x) = percentage of patients. Every patient was counted a single time for each applicable specific serious, drug-related AE with highest severity. A patient with multiple serious, drug-related TEAEs within a system organ class (SOC) was counted a single time for that SOC with the highest severity. None of the Serious drug-related TEAEs were considered as probably or definitely related to treatment by the investigators and all were reported as possibly related to treatment. Data in parentheses are percentages.

important side effects: the retrospective German multicenter study reported mild/moderate nausea in 6% and no intestinal transit disorder (5). Nausea and vomiting occurred in 46.9% (1.6% severe) and 18.8% (1.6% severe) of our study population, respectively. These numbers are in line with the phase 2 LuPSMA trial (nausea 48% and vomiting 22%) (17), the TheraP trial (nausea 41% and vomiting 13%) (18), and the VISION trial (nausea 35% and vomiting 19%) (19). Premedication with antiemetic medication (ondansetron or equivalent) is recommended and side effects usually do not last more than 24–48 h. Finally, diarrhea was reported in 31.7% of the 7.4-GBq arm and 13.0% of the 6.0-GBq arm (25% overall) and constipation in 23.4% overall. For comparisons, diarrhea was reported in 19.4 and 18.9% and constipation in 38% and 20.2% in the *TheraP* and *VISION* trials, respectively (18,19).

Overall, ¹⁷⁷Lu-PSMA-617 administered at 6.0 and 7.4 GBq per cycle and 8-wk interval appears to be better tolerated than available chemotherapy options which are associated with potentially life-threatening complications. Grade ≥ 3 neutropenia occurred in 45% of patients receiving cabazitaxel in the CARD trial and was reported in 32% to 47% of mCRPC patients receiving docetaxel (22–24). In the randomized TheraP trial that prospectively compared 98 patients receiving ¹⁷⁷Lu-PSMA-617 with 85 patients receiving cabazitaxel for progressing mCRPC, the toxicity profile was more favorable for ¹⁷⁷Lu-PSMA-617 than for cabazitaxel, with fewer grade 3–4 AEs (33% vs. 53%), except thrombopenia (11% vs. 0%). Of note, severe neutropenia and diarrhea occurred 3 times less: 4% versus 13% and 19% versus 56%, respectively.

The amount of injected activity (GBq – mCi) has been tailored to meet the dose limits used in external-beam radiation therapy (25). However, these dose limits are potentially overly conservative due to the low dose rate exposure from molecular radionuclide therapy compared with high dose rate of external-beam radiation. Higher

activity regimen were safely administered in the German compassionate-use studies (up to 9.7 GBq [range 2–9.7 GBq]) (5) and the Australian clinical trials (up to 8.7 GBq per [range 4.4–8.7 GBq]) (18,26,27). Of note, in the phase I dose-escalation study NCT03042468, up to 22.2 GBq per cycle was safely administered with promising early efficacy and tolerability signals (28).

Due to IND sponsorship transfer to Endocyte Inc. and the early study closure before completion of the target enrollment (36%), the study findings are limited by the smaller sample size than the initially planned 200 patients. Thus, efficacy endpoints could not be analyzed as the power of the predefined test was insufficient for reliable statistical analysis. Consequently, the distribution between the 2 treatment groups was also altered (i.e., 40% patients assigned to the 6.0-GBq group and 60% assigned to the 7.4-GBq group) and the actual sample size cannot ensure formal statistical testing for comparing the 2 groups. However, due to the small difference in the 2 tested activities (~20%, 6.0 vs. 7.4 GBq) even the limited data suggest that there are likely no or only small differences in toxicity between these 2 activities. This is consistent with prior reports that found similar toxicity rates for comparable levels of injected activity (6.0 vs. 7.5 GBq) (15). The prematurely terminated randomization also makes it impossible to completely exclude differences in baseline characteristics or other possible confounders.

As another limitation, the study population was heterogeneous regarding prior treatments. Because the study was self-funded and patients were charged for the study drug (cost recovery, Title 21 CFR 312.8), the common denominator for inclusion was mCRPC disease. This reflects the clinical reality of a multitude of treatment options in advanced prostate cancer. Thus clinical selection for ¹⁷⁷Lu-PSMA-617 may be independent of prior treatments.

In addition, because patients were recruited from all across the United States, strict adherence to protocols was difficult to achieve.

Patients were seen at the study site most frequently for treatment only. They were managed by their off-site medical oncologist or urologist who often scheduled study procedures locally when possible. The required protocol procedures were completed locally when possible by treating physicians or, alternatively, completed locally at the trial site when patients were seen for treatments. Therefore, rigid adherence to predefined schedules was frequently not feasible. All study procedures falling outside the predefined protocol time windows (before randomization) were not considered for the analysis. This affected mostly the serum PSA measurements for the efficacy endpoint. It is deemed that protocol deviations did not have an impact on the safety results of this study but the data must be interpreted with caution due to the small number of patients with available data at some of the time points.

Finally, AEs were defined as occurring during the treatment period for only up to 30 d after the last cycle of ^{177}Lu -PSMA-617, which precludes assessments of any potential longer term toxicity.

CONCLUSION

In the prospective phase 2 multicenter trial RESIST-PC, 2 activity levels of ^{177}Lu -PSMA-617 were safely administered to 64 patients. There were no efficacy conclusions in this study due to early study termination. Overall, ^{177}Lu -PSMA-617 administered at up to 4 cycles at 8-wk intervals was safe and well tolerated at 6.0 and 7.4 GBq per cycle. Side effects were easily managed with standard medical support.

With established safety, further clinical trials applying individualized dosimetry and testing different ^{177}Lu -PSMA-617 administration schemes (activity levels, time intervals) are needed to optimize tumor dose delivery and treatment efficacy.

DISCLOSURE

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KEY POINTS

QUESTION: What is the safety profile of 2 activity regimens of ^{177}Lu -PSMA-617 therapy in patients with mCRPC?

PERTINENT FINDINGS: In this prospective multicenter randomized phase 2 study that included 64 patients with progressive mCRPC, 2 activity regimens of ^{177}Lu -PSMA-617 therapy (6.0 and 7.4 GBq per cycle) were well tolerated. There was no difference in toxicity between administration of 6.0 and 7.4 GBq of ^{177}Lu -PSMA-617 per treatment cycle.

IMPLICATIONS FOR PATIENT CARE: ^{177}Lu -PSMA-617 therapy is a therapeutic option for patients with mCRPC with a good safety profile.

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SUPPLEMENTAL TABLES:

Supplemental Table 1 Patient Disposition (ITT Population)

	6.0 GBq N = 28 n (%)	7.4 GBq N = 43 n (%)	Overall N = 71 n (%)
Patients who discontinued from ¹⁷⁷ Lu-PSMA-617	23 (82.1)	41 (95.3)	64 (90.1)
Reason for discontinuation from ¹⁷⁷Lu-PSMA-617			
Completion of 4 RLT cycles	10 (35.7)	19 (44.2)	29 (40.8)
Patient withdrawal	6 (21.4)	6 (14.0)	12 (16.9)
PSA/radiographic progression at ≥ 12 weeks	7 (25.0)	16 (37.2)	23 (32.4)
Patients who completed the study	18 (64.3)	31 (72.1)	49 (69.0)
Reason for study completion			
Completed	1 (3.6)	0	1 (1.4)
Death	3 (10.7)	2 (4.7)	5 (7.0)
Progressive disease	14 (50.0)	29 (67.4)	43 (60.6)
Patients who early discontinued from the study	10 (35.7)	12 (27.9)	22 (31.0)
Reason for early discontinuation from the study			
Administrative reason	1 (3.6)	1 (2.3)	2 (2.8)
Adverse event	0	1 (2.3)	1 (1.4)
Lost to follow-up	1 (3.6)	3 (7.0)	4 (5.6)
Occurrence of condition*	4 (14.3)	2 (4.7)	6 (8.5)
Patient withdrawal	4 (14.3)	5 (11.6)	9 (12.7)
Total number of deaths	4 (14.3)	3 (7.0)	7 (9.9)

*Any occurrence of conditions that prevented the patient's participation in the study.
 AE = Adverse event; RLT = Radioligand therapy.

Supplemental Table 2 : Summary of Protocol Deviations (ITT Population)

Protocol Deviation Category	6.0 GBq (N=28)		7.4 GBq (N=43)		Overall (N=71)	
	n (%) [m]		n (%) [m]		n (%) [m]	
	Any	Important	Any	Important	Any	Important
Patient with at least one protocol deviation	19 (67.9) [95]	9 (32.1) [13]	38 (88.4) [249]	22 (51.2) [32]	57 (80.3) [344]	31 (43.7) [45]
Procedure Violation	17 (60.7) [93]	8 (28.6) [12]	38 (88.4) [239]	20 (46.5) [29]	55 (77.5) [332]	28 (39.4) [41]
Drug Dosing	1 (3.6) [1]	0	5 (11.6) [7]	0	6 (8.5) [8]	0
Informed Consent Procedure	1 (3.6) [1]	1 (3.6) [1]	2 (4.7) [2]	2 (4.7) [2]	3 (4.2) [3]	3 (4.2) [3]
Inc-/Exclusion Criteria	0	0	1 (2.3) [1]	1 (2.3) [1]	1 (1.4) [1]	1 (1.4) [1]

n is the number of subjects, [m] is the number of protocol deviations

Supplemental Table 3: Screening PSMA PET/CT findings

T+= Prostate fossa lesion(s) ; N1 = pelvic LN lesion(s); M1a = extra-pelvic LN lesions(s); M1b = bone lesion(s); M1c (visceral lesion(s)).

	6.0 GBq Arm		7.4 GBq Arm		Overall	
	n=26	%	n=42	%	n=68	%
T+	7	26.92%	9	21.43%	16	23.53%
N1	9	34.62%	17	40.48%	26	38.24%
M1a	16	61.54%	23	54.76%	39	57.35%
<i>Abdominal</i>	9	56.25%	17	73.91%	26	66.67%
<i>Upper-Diaphragm</i>	14	87.50%	23	100.00%	37	94.87%
<i>Inguinal</i>	3	18.75%	2	8.70%	5	12.82%
M1b	25	96.15%	37	88.10%	62	91.18%
< 5	3	12.00%	5	13.51%	8	12.90%
> 5	16	64.00%	22	59.46%	38	61.29%
<i>Diffuse</i>	6	24.00%	10	27.03%	16	25.81%
M1c	9	34.62%	16	38.10%	25	36.76%
<i>Liver</i>	2	22.22%	11	68.75%	13	52.00%
<i>Lung</i>	3	33.33%	5	31.25%	8	32.00%
<i>Adrenal</i>	2	22.22%	2	12.50%	4	16.00%
<i>Brain</i>	1	11.11%	1	6.25%	2	8.00%
<i>Colon</i>	1	11.11%	1	6.25%	2	8.00%
<i>Muscle</i>	0	0.00%	2	12.50%	2	8.00%
<i>Penis</i>	0	0.00%	1	6.25%	1	4.00%
<i>Pancreas</i>	0	0.00%	1	6.25%	1	4.00%
<i>Bladder</i>	1	11.11%	0	0.00%	1	4.00%
<i>Peritoneum</i>	1	11.11%	0	0.00%	1	4.00%
N1/M1a (LN only)	1	3.85%	3	7.14%	4	5.88%
M1b (bone only)	7	26.92%	12	28.57%	19	27.94%
M1c (visceral only)	0	0.00%	0	0.00%	0	0.00%
N1/M1a M1b (LN + bone)	9	34.62%	11	26.19%	20	29.41%
N1/M1a M1c (LN + visceral)	0	0.00%	2	4.76%	2	2.94%
M1b M1c (bone + visceral)	1	3.85%	3	7.14%	4	5.88%
N1/M1a M1b M1c (LN + bone + visceral)	8	30.77%	11	26.19%	19	27.94%

Supplemental Table 4: Summary Table of Treatment Emergent Adverse Events – Safety Population

	6.0 GBq N = 23 n (%)	7.4 GBq N = 41 n (%)	Overall N = 64 n (%)
Patients with at least one TEAE	22 (95.7)	39 (95.1)	61 (95.3)
Patients with at least one serious TEAE	4 (17.4)	8 (19.5)	12 (18.8)
Patients with at least one drug-related TEAE	20 (87.0)	37 (90.2)	57 (89.1)
Patients with at least one serious drug-related TEAE	1 (4.3)	4 (9.8)	5 (7.8)
Patients having a TEAE leading to reduction of ¹⁷⁷ Lu-PSMA-617	0	2 (4.9)	2 (3.1)
Patients having a TEAE leading to discontinuation of ¹⁷⁷ Lu-PSMA-617	0	1 (2.4)	1 (1.6)
TEAE leading to death	2 (8.7)	1 (2.4)	3 (4.7)

Results given as xx (xx.x) where xx = number of patients with adverse events, (xx.x) = percentage of patients. TEAE = is considered study drug-related if relatedness is recorded as possible, probably, definite, or when the value is missing.

The phase 3, multicenter VISION trial confirmed the results of the earlier studies, reporting a significant improvement in patients undergoing ¹⁷⁷Lu-PSMA-617 plus standard-of-care compared to standard-of-care alone in overall survival (median, 15.3 vs. 11.3 months) and radiographic progression-free survival (median 8.7 vs. 3.4 months), and PSA response were also improved with ¹⁷⁷Lu-PSMA-617 (64; 73). Additionally, it could be shown that ¹⁷⁷Lu-PSMA-617 delayed time to worsening of pain and health-related quality of life (74).

Following the VISION trial positive results, Lu¹⁷⁷-PSMA-617 was approved by the FDA for the treatment of patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215833s000lbl.pdf

Patients should be selected with an approved PSMA-PET imaging agent. Lesions should be considered positive if PSMA-PET tracer uptake is greater than normal liver (as assessed visually) and negative if less than or equal to normal liver. Patients should be considered eligible for lutetium Lu-177 vipivotide tetraxetan therapy if at least one tumor lesion is positive and all lesions on anatomical imaging larger in short axis than size criteria are also positive [size criteria: organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm]. Patients should be considered ineligible for lutetium Lu-177 vipivotide tetraxetan therapy if all lesions are negative or any one lesion larger than size criteria is negative.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215841s000lbl.pdf

In the VISION trial the screen failure rate using these criteria was 12.6 %: 126/1003 were excluded by PSMA-PET for a total of 831 patients finally included. People questioned whether PSMA-PET screening is really necessary.

As a nuclear medicine physician and theranostics specialist, I believe in individualized medicine and precision medicine: the right treatment to the right patient. You treat what you see. You see what you treat. PET molecular imaging provides a remarkable whole-body molecular target expression assessment. Following the concerns mentioned above against pretreatment assessments of target expression with PET, we conducted a multicenter retrospective study to assess the outcome of patients with metastatic castration-resistant prostate cancer treated with Lu¹⁷⁷-PSMA who would have been a screen failure (SF) in the VISION trial based on PSMA-PET/CT criteria. The study showed that VISION-PET screen failure patients had worse outcomes than the VISION-PET eligible patients.

The study was published in *the Journal of Nuclear Medicine* as provided below.

Article #10:

Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with ¹⁷⁷Lu-PSMA therapy: a multicenter retrospective analysis (n=301)

Outcome of Patients with PSMA PET/CT Screen Failure by VISION Criteria and Treated with ^{177}Lu -PSMA Therapy: A Multicenter Retrospective Analysis

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See an invited perspective on this article on page 1482.

The aim of the study was to assess the outcome of patients with metastatic castration-resistant prostate cancer treated with ^{177}Lu -prostate-specific membrane antigen (PSMA) who would have been a screen failure (SF) in the VISION trial based on PSMA PET/CT criteria.

Methods: We conducted a retrospective multicenter cohort study on 301 patients with metastatic castration-resistant prostate cancer treated with ^{177}Lu -PSMA. The patients were classified into eligible (VISION-PET-E) and SF (VISION-PET-SF) groups on the basis of the baseline PSMA PET/CT results. Prostate-specific antigen (PSA) response rates, PSA progression-free survival, and overall survival were compared. **Results:** Of 301 patients, 272 (90.4%) and 29 (9.6%) were VISION-PET-E and VISION-PET-SF, respectively. The VISION-PET-SF patients had a worse rate of $\geq 50\%$ PSA decline (21% vs. 50%, $P = 0.005$) and PSA progression-free survival (2.1 vs. 4.1 mo, $P = 0.023$) and tended to have a shorter overall survival (9.6 vs. 14.2 mo, $P = 0.16$) than the VISION-PET-E patients. **Conclusion:** The VISION-PET-SF patients had worse outcomes than the VISION-PET-E patients. Our cohort did not include preexcluded patients (10%–15%) by local site assessments. Thus, 20%–25% of the patients may be SFs in unselected populations. Refinements in patient selection for ^{177}Lu -PSMA are needed to optimize outcomes.

Key Words: metastatic castration-resistant prostate cancer; radionuclide therapy; PSMA PET; ^{177}Lu ; VISION trial

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Men with metastatic castration-resistant prostate cancer have few alternative therapeutic options when the disease progresses after androgen-deprivation therapy, androgen receptor signaling inhibitors, and chemotherapy. Recently, the VISION trial, an international open-label, randomized phase 3 trial showed that prostate-specific membrane antigen (PSMA)-targeted molecular radionuclide therapy (MRT) with ^{177}Lu -PSMA can improve the outcome of patients with advanced metastatic castration-resistant prostate cancer. In this trial, 831 patients with metastatic castration-resistant prostate cancer previously treated with androgen receptor signaling inhibitor and

taxane regimens were randomized in a 2:1 ratio to ^{177}Lu -PSMA (7.4 GBq every 6 wk \times 6 cycles) plus the best standard of care ($n = 551$) or the standard of care alone ($n = 280$). The trial met both primary endpoints of overall survival (OS) and radiographic progression-free survival (PFS). The median OS was 15.3 mo in the ^{177}Lu -PSMA arm versus 11.3 mo in the standard-of-care-alone arm, resulting in a 38% reduction in the risk of death. The radiographic PFS was 8.7 versus 3.4 mo, respectively (1).

The VISION trial used PSMA PET/CT to select patients for inclusion. The screen failure (SF) rate was “only” 12.6% (126/1,003) (1), and some have argued that the trial could have been positive even in an unselected population (2). Eligibility by PSMA PET/CT results was determined by the sponsor’s central readers (criteria initially not disclosed). The VISION PET selection criteria were released publicly at the American Society of Clinical Oncology 2021 meeting (3). It remains unknown whether the VISION PET criteria were appropriate to screen for and identify patients who will not benefit from ^{177}Lu -PSMA. Here, we exploited a database established retrospectively from multiple institutions to evaluate the outcome of patients treated with ^{177}Lu -PSMA who would have been a SF by VISION PET criteria.

MATERIALS AND METHODS

We conducted a retrospective cohort study in our institutional database of patients treated with at least 1 cycle of ^{177}Lu -PSMA between November 2017 and July 2021 ($n = 74$) and a multicenter dataset published previously ($n = 230$) (4). Patients were treated under compassionate use, an expanded access program, or clinical trials (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>). All patients underwent a baseline ^{68}Ga -PSMA-11 PET/CT scan before receiving ^{177}Lu -PSMA therapy. The eligibility criteria and institutional treatment protocols are described in Supplemental Tables 1 and 2. The presence of PSMA-positive disease by PET was not consistently predefined and was determined by the local clinical investigators at each institution.

One reader dually board-certified in radiology and nuclear medicine, and masked to the patient outcomes, reviewed the baseline PSMA PET/CT scan of each patient to apply the VISION PET criteria and determine eligible (VISION-PET-E) versus SF (VISION-PET-SF) patients. Patients were classified as VISION-PET-E if they had at least 1 PSMA-positive and no PSMA-negative metastatic lesions. The presence of PSMA-positive lesions was defined as PSMA uptake greater than uptake by liver parenchyma (3). The patients were classified as VISION-PET-SF if the baseline scan showed either of the following: absence of a metastatic lesion with uptake greater than in the liver background (i.e., low PSMA expression) or the presence of at least 1 metastatic lesion measurable by CT (≥ 1 cm for bone lesions with a soft-tissue component [M1b] or solid/visceral organ

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FIGURE 1. Baseline PSMA PET maximum-intensity projection of patient with metastatic castration-resistant prostate cancer categorized as VISION-PET-SF because of low PSMA expression (i.e., no PSMA-positive [$>$ liver] metastatic lesion). SUV_{max} of liver and highest-uptake lesion were 9.6 and 6.4, respectively.

lesions [M1c], ≥ 2.5 cm for lymph node lesions [N1-M1a]) with uptake less than or equal to that in the liver background (i.e., PSMA-negative lesions) (1). Typical PSMA PET/CT images of low PSMA expression and PSMA-negative lesions are shown in Figures 1 and 2, respectively.

Outcome measures included prostate-specific antigen (PSA) response rates ($\geq 50\%$ PSA decline or any decline), PSA PFS, and OS. Kaplan–Meier curves with log-rank testing and Cox regression analysis were used to compare survival outcomes. The Fisher exact test and logistic regression analysis were used for categorical variable comparisons. The UCLA institutional review board waived written informed consent requirements because of the retrospective design of the analysis (waivers 19-000896 and 21-001565).

RESULTS

Overall, 3 of 304 (1.0%) men were lost to follow-up ($n = 2$) or had missing DICOM CT images ($n = 1$) and were excluded. Among 301 men, 272 (90.4%) and 29 (9.6%) were classified as VISION-PET-E and VISION-PET-SF, respectively. Cohort characteristics are provided in Table 1. The VISION-PET-SF patients had more visceral metastasis than VISION-PET-E patients (58.6% vs. 25.4%, $P < 0.001$). The median number of cycles was lower for VISION-PET-SF patients than for VISION-PET-E patients (2 cycles [interquartile range, 2–3] vs. 3 [interquartile range, 2–4], $P = 0.010$).

In the VISION-PET-SF group, 8 (2.7%) and 21 (7.0%) of 301 men were deemed to have low-PSMA-expressing or PSMA-negative lesions, respectively (summary images of these 29 patients are provided in Supplemental Figs. 1–29). The PSMA-negative lesions were in lymph nodes ($n = 7$), bone ($n = 1$), and visceral organs (liver, $n = 4$; lung, $n = 5$; pleura, $n = 2$; brain, $n = 1$; and muscle, $n = 1$).

Our cohort of VISION-PET-E patients was fairly comparable to the cohort included in the VISION trial (analysis set used for imaging-based PFS, Supplemental Table 3) (1). However, the treatment history differed. All VISION patients had been treated with a regimen of androgen receptor signaling inhibitor and taxane. In contrast, 94.5% and 80.1% of the current cohort underwent androgen receptor signaling inhibitor therapy and chemotherapy before MRT, respectively. Nevertheless, the PSA response and OS were comparable between the 2 cohorts ($\geq 50\%$ PSA decline, 50.3% vs. 46.0%; any PSA decline, 71.3% vs. 71.5%; OS, 14.2 mo vs. 14.6 mo).

The median follow-up time was 22.5 mo (interquartile range, 12.5–29.2 mo; range, 2.1–62.3 mo). The outcomes of the VISION-PET-E and VISION-PET-SF patients are shown in Table 2. The VISION-PET-SF patients had a significantly worse rate of $\geq 50\%$ PSA decline, any PSA decline, and median PSA PFS than the VISION-PET-E patients. Although not statistically significant, median OS was 4.6 mo shorter in the VISION-PET-SF patients (Fig. 3).

In the VISION-PET-SF patients, the patients with PSMA-negative lesions ($n = 21$) had a shorter OS than those with low PSMA expression ($n = 8$) (Supplemental Table 4). However, there was no statistical difference in $\geq 50\%$ PSA decline, any PSA decline, and median PSA PFS between the patients with PSMA-negative lesions and those with low PSMA expression (Fig. 4).

DISCUSSION

The VISION trial used PSMA PET as a biomarker to select patients for ^{177}Lu -PSMA therapy. The VISION-PET-SF rate was “only” 12.6% (126/1,003) (1). Therefore, some have argued that the trial could have been positive even in an unselected population (2).

Here, we report that the VISION-PET-SF patients had worse outcomes than the

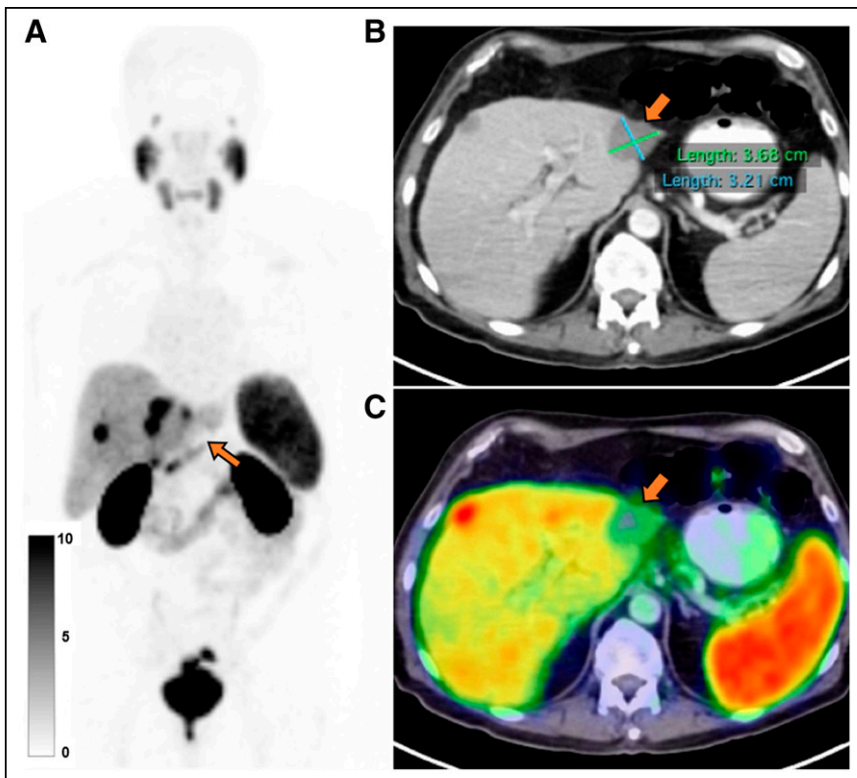


FIGURE 2. Baseline PSMA PET maximum-intensity projection (A), CT image (B), and PSMA PET/CT image (C) of patient with metastatic castration-resistant prostate cancer categorized as VISION-PET-SF because of PSMA-negative lesion (i.e., PSMA-negative metastatic lesion: liver metastasis ≥ 1.0 cm, uptake \leq liver). One liver metastasis (arrow) showed lower uptake (SUV_{max} , 4.1) than liver parenchyma (SUV_{max} , 6.3).

TABLE 1
Patient Characteristics

Characteristic	VISION-PET-E	VISION-PET-SF	P
<i>n</i>	272	29	
Median age (y)	72 (range, 66–76)	73 (range, 65–76)	0.91
Median PSA (ng/mL)	116.6 (interquartile range, 28.4–340.0)	74.0 (interquartile range, 17.5–198.3)	0.069
Treatment history			
Previous docetaxel	218 (80.1%)	25 (86.2%)	0.62
Second-line chemotherapy	95 (34.9%)	8 (27.6%)	0.54
Androgen receptor signaling inhibitor	257 (94.5%)	27 (93.1%)	0.67
Extent of disease on PSMA PET/CT			
Number of metastases ≥ 20	194 (71.3%)	16 (55.2%)	0.089
Number of metastases < 20	78 (28.7%)	13 (44.8%)	
Sites of disease on PSMA PET/CT			
Node only (N1 or M1a)	21 (7.7%)	1 (3.4%)	0.71
Bone only (M1b)	60 (22.1%)	3 (10.3%)	0.23
Node + bone (M1b and [N1 or M1a])	122 (44.9%)	8 (27.6%)	0.08
Viscera (any M1c)	69 (25.4%)	17 (58.6%)	<0.001
Number of cycles of ¹⁷⁷ Lu-PSMA received			
1	38 (14.0%)	5 (17.2%)	0.065
2	68 (25.0%)	13 (44.8%)	
3	37 (13.6%)	5 (17.2%)	
4	91 (33.5%)	5 (17.2%)	
>4	38 (13.9%)	1 (3.4%)	
Median injected activity per cycle (GBq)	7.4 (interquartile range, 5.7–8.9)	7.4 (interquartile range, 6.0–8.5)	0.30

TABLE 2
Outcomes of VISION-PET-E and VISION-PET-SF Patients

Outcome	VISION-PET-E	VISION-PET-SF	P
<i>n</i>	272	29	
≥50% PSA decline			
<i>n</i>	131 (50.3%)	6 (20.7%)	0.005
Odds ratio	1	0.28 (95%CI, 0.11–0.71)	0.007
Any PSA decline			
<i>n</i>	194 (71.3%)	12 (41.4%)	0.003
Odds ratio	1	0.28 (95%CI, 0.13–0.62)	<0.001
PSA PFS			
Median months	4.9 (95%CI, 4.0–5.8)	2.1 (95%CI, 1.4–3.3)	0.023
Hazard ratio	1	1.6 (95%CI, 1.1–2.5)	0.025
OS			
Median months	14.2 (95%CI, 12.6–15.9)	9.6 (95%CI, 4.7–14.0)	0.16
Hazard ratio	1	1.4 (95%CI, 0.89–2.3)	0.16

VISION-PET-E patients in response to ¹⁷⁷Lu-PSMA therapy. We retrospectively identified a VISION-PET-SF rate of 9.6% in a cohort of 301 patients who were nevertheless deemed VISION-PET-E and treated with PSMA MRT on the basis of local assessments. Eligibility for treatment was determined by the local clinical investigators at each institution. The VISION PET criteria were released in June 2021 and were not available at the time of initial treatment. There are 2 main explanations for why patients with SF criteria by VISION PET criteria were still treated with ¹⁷⁷Lu-PSMA. First, VISION-PET-SF patients with PSMA-negative lesions also had PSMA-positive lesions. The local investigators may have considered that these PSMA-positive lesions were sufficiently suggestive of a treatment response. Second, in VISION-PET-SF patients with low PSMA expression, the local investigators may have considered the PSMA expression PET signal uptake as not sufficiently low to exclude patients from treatment, as there was no consistently pre-defined threshold to characterize PSMA positivity.

Our cohort did not include patients who were excluded upfront from PSMA MRT by the local clinical investigators. The local SF rate was estimated at around 10%–15% by contributing sites. Thus, SF numbers in our cohort are underestimated and can range from 20% to 25% in unselected populations. Including these patients in the analysis would further enhance the observed outcome differences.

Absent or low target expression limits the response to PSMA-targeted therapies (5,6). However, the key driving parameter of patient outcome seems to be the presence of PSMA-negative lesions that

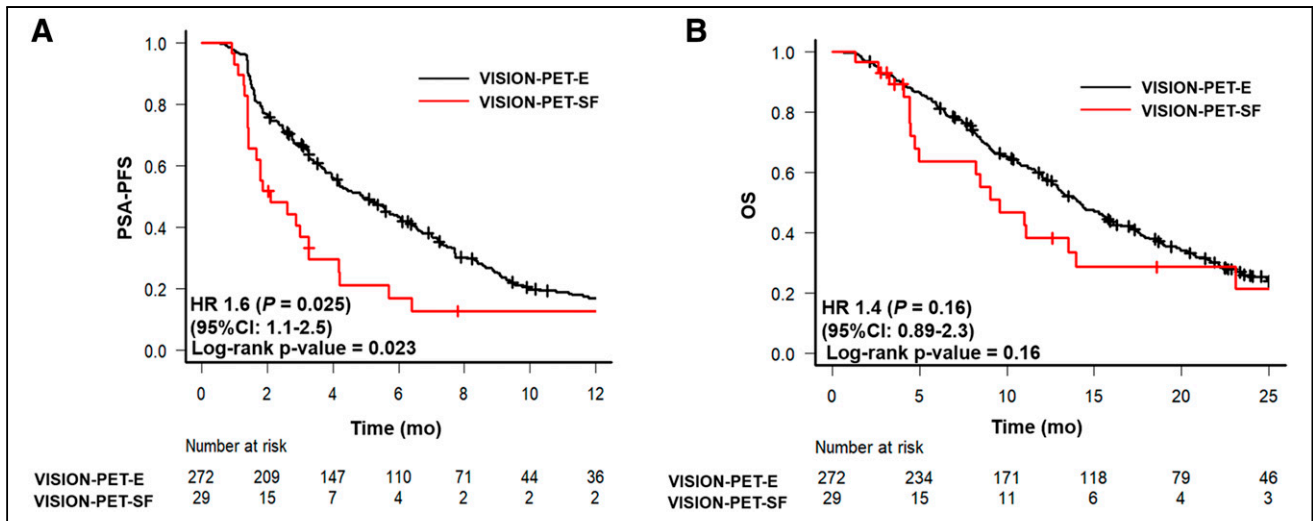


FIGURE 3. Kaplan–Meier curves of PSA PFS (A) and OS (B) comparing VISION-PET-E and VISION-PET-SF patients. HR = hazard ratio.

respond poorly to PSMA-targeted MRT and drive the prognosis of the patient (7,8). These lesions can be better identified with ^{18}F -FDG PET than with conventional imaging, as illustrated by the higher PSA response rates and PSA PFS observed in the Australian trials that used ^{18}F -FDG PET in addition to PSMA PET for patient selection (9).

Our results highlight the importance of using baseline PSMA PET/CT to identify patients unlikely to respond to PSMA-targeted therapies and stratify them toward other treatment options. However, the best management of patient with PSMA-negative lesions or with low-PSMA-expressing disease is unknown. Combination with stereotactic body radiation therapy to the largest or most glycolytic (i.e., aggressive) or non-PSMA-expressing lesions together with PSMA-targeted MRT may be one effective synergistic therapeutic approach. Use of this approach alternatively or in combination with other non-PSMA-targeted systemic therapies may be required.

Refinements in patient selection for PSMA MRT are needed to optimize patient outcomes. More comprehensive phenotyping via PET imaging may provide the road map to such refinements. Not characterizing target expression before PSMA-targeted treatment

appears now nonethical, as a predictive whole-body imaging biomarker for response to PSMA-targeted therapies is available.

CONCLUSION

Patients with low or no PSMA-expressing lesions as assessed by PSMA PET/CT have a poor response profile to ^{177}Lu -PSMA therapy. Refinements in patient selection for ^{177}Lu -PSMA are needed to optimize patient outcomes.

DISCLOSURE

Jeremie Calais reports prior consulting activities outside the submitted work for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, Janssen, IBA RadioPharma, POINT Biopharma, Progenics, Radiomedix, and Telix Pharmaceuticals. Johannes Czernin is a founder and holds equity in Sofie Biosciences and Trethera Therapeutics. Intellectual property is class 99-patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics. Johannes Czernin was a consultant for Endocyte Inc. (VISION trial steering

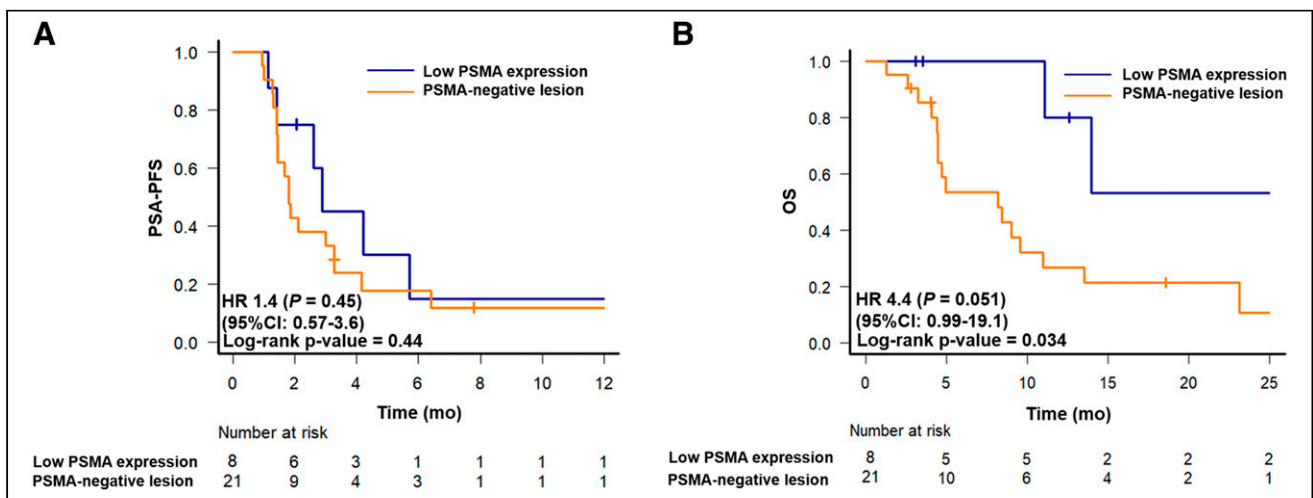


FIGURE 4. Kaplan–Meier curves of PSA PFS (A) and OS (B) comparing patients with low PSMA expression and PSMA-negative lesion. HR = hazard ratio.

committee), Actinium Pharmaceuticals, and Point Biopharma outside the submitted work. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

(We acknowledge the following individuals for their assistance with the creation of the multicenter study dataset, none of whom were compensated for their contributions and all of whom agreed to have us include their names here: Matthias Eiber (Technical University Munich), Michael Hofman (Peter MacCallum Cancer Center Melbourne), Ken Herrmann and Wolfgang Fendler (University Hospital Essen), Clemens Kratochwil and Uwe Haberkorn (University Hospital Heidelberg), and Ebrahim Delpassand (Excel Diagnostic Center Houston).

KEY POINTS

QUESTION: What is the outcome of patients who would have been VISION-PET-SF and who were still treated with ¹⁷⁷Lu-PSMA therapy?

PERTINENT FINDINGS: The patients who were VISION-PET-SF showed worse outcomes after ¹⁷⁷Lu-PSMA therapy than those who were VISION-PET-E.

IMPLICATIONS FOR PATIENT CARE: Pretherapy PSMA PET/CT is a biomarker of target expression that helps to predict patient response to ¹⁷⁷Lu-PSMA therapy. Refinements in patient selection for ¹⁷⁷Lu-PSMA are needed to optimize patient outcomes.

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Article #11:

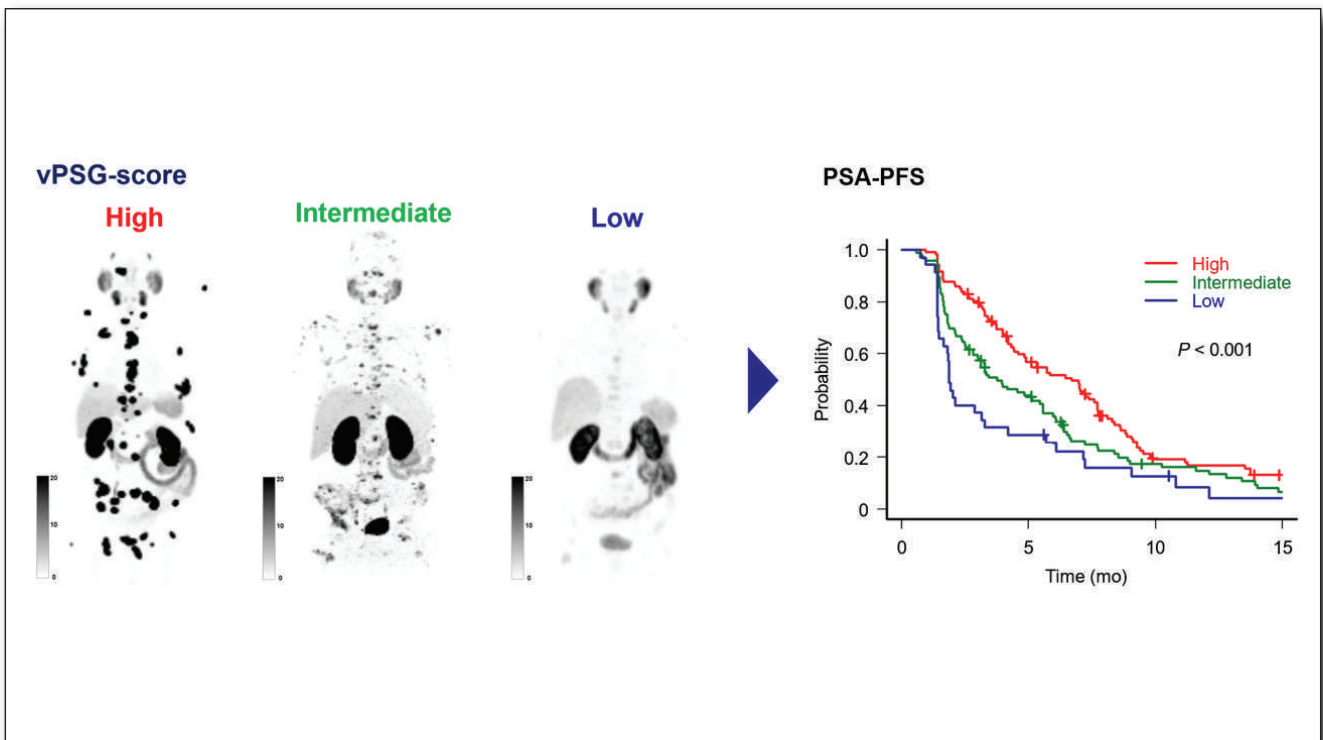
PSMA-PET Tumor-to-Salivary Gland Ratio to Predict Response to ^{177}Lu -PSMA Radioligand Therapy: An International Multicenter Retrospective Study (n=237)

However further refinements in patient selection for ^{177}Lu -PSMA are needed to optimize outcomes as patients do not respond uniformly. We attempted to refine the PET selection criteria using the 3D-MIP of the PSMA-PET and the salivary glands as reference organs instead of the liver. We created the PSMA-PET Tumor-to-Salivary Gland Ratio (PSG-score) and asked 10 blinded independent readers to apply it on 237 patients (visually). Patients with high expression classified visually by the PSG-score showed a significantly better PSA response and OS after ^{177}Lu -PSMA. This study proposes a PSG-score derived from pretherapeutic ^{68}Ga -PSMA-11 PET as a novel predictive and prognostic biomarker for response to ^{177}Lu -PSMA therapy. After further clinical validation, this score, together with other cross-sectional or metabolic imaging, may improve patient selection.

The study was published in *the Journal of Nuclear Medicine* on the Cover Page as featured article of the month and is provided below.

**FEATURED
ARTICLE**

PSMA PET Tumor-to-Salivary Gland Ratio to Predict Response to [¹⁷⁷Lu]PSMA Radioligand Therapy: An International Multicenter Retrospective Study. Masatoshi Hotta et al. See page 1024.



Enhancing NET treatment: Can combined PRRT and immune checkpoint inhibition improve response in neuroendocrine tumors? Shadi Esfahani et al. See page 1056.

PSMA PET Tumor-to-Salivary Gland Ratio to Predict Response to [¹⁷⁷Lu]PSMA Radioligand Therapy: An International Multicenter Retrospective Study

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Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy can improve the outcome of patients with advanced metastatic castration-resistant prostate cancer, but patients do not respond uniformly. We hypothesized that using the salivary glands as a reference organ can enable selective patient stratification. We aimed to establish a PSMA PET tumor-to-salivary gland ratio (PSG score) to predict outcomes after [¹⁷⁷Lu]PSMA. **Methods:** In total, 237 men with metastatic castration-resistant prostate cancer treated with [¹⁷⁷Lu]PSMA were included. A quantitative PSG (qPSG) score (SUV_{mean} ratio of whole-body tumor to parotid glands) was semiautomatically calculated on baseline [⁶⁸Ga]PSMA-11 PET images. Patients were divided into 3 groups: high (qPSG > 1.5), intermediate (qPSG = 0.5–1.5), and low (qPSG < 0.5) scores. Ten readers interpreted the 3-dimensional maximum-intensity-projection baseline [⁶⁸Ga]PSMA-11 PET images and classified patients into 3 groups based on visual PSG (vPSG) score: high (most of the lesions showed higher uptake than the parotid glands) intermediate (neither low nor high), and low (most of the lesions showed lower uptake than the parotid glands). Outcome data included a more than 50% prostate-specific antigen decline, prostate-specific antigen (PSA) progression-free survival, and overall survival (OS). **Results:** Of the 237 patients, the numbers in the high, intermediate, and low groups were 56 (23.6%), 163 (68.8%), and 18 (7.6%), respectively, for qPSG score and 106 (44.7%), 96 (40.5%), and 35 (14.8%), respectively, for vPSG score. The interreader reproducibility of the vPSG score was substantial (Fleiss weighted κ , 0.68). The more than 50% prostate-specific antigen decline was better in patients with a higher PSG score (high vs. intermediate vs. low, 69.6% vs. 38.7% vs. 16.7%, respectively, for qPSG [$P < 0.001$] and 63.2% vs 33.3% vs 16.1%, respectively, for vPSG [$P < 0.001$]). The median PSA progression-free survival of the high, intermediate, and low groups by qPSG score was 7.2, 4.0, and 1.9 mo ($P < 0.001$), respectively, by qPSG score and 6.7, 3.8, and 1.9 mo ($P < 0.001$),

respectively, by vPSG score. The median OS of the high, intermediate, and low groups was 15.0, 11.2, and 13.9 mo ($P = 0.017$), respectively, by qPSG score and 14.3, 9.6, and 12.9 mo ($P = 0.018$), respectively, by vPSG score. **Conclusion:** The PSG score was prognostic for PSA response and OS after [¹⁷⁷Lu]PSMA. The visual PSG score assessed on 3-dimensional maximum-intensity-projection PET images yielded substantial reproducibility and comparable prognostic value to the quantitative score.

Key Words: PSMA PET; [¹⁷⁷Lu]PSMA; radioligand therapy; visual criteria; parotid glands

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Patients with advanced metastatic castration-resistant prostate cancer (mCRPC) do not respond uniformly to [¹⁷⁷Lu]prostate-specific membrane antigen (PSMA) (1,2). Thus, identification of patients who will likely benefit from PSMA-targeted radioligand therapy remains an unmet clinical need.

High PSMA expression as assessed by PET and whole-body (WB) tumor SUV_{mean} is associated with better outcomes (3–7). PSMA PET should be used to select patients on the basis of tumor PSMA expression (8). However, the inclusion criteria based on baseline PSMA PET vary among major clinical trials and therapy centers across the world (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>) (1,2,6,9–17). The VISION trial applied qualitative (i.e., tumor uptake > liver uptake, assessed visually) thresholds (18). These criteria are relevant in identifying patients with absence of or low [⁶⁸Ga]PSMA-11 expression, and 13% (126/1003) of patients were screening failures (1). Men with screening failure according to the VISION PET criteria had worse short-term outcomes than those who were eligible (19). However, even after selection of patients by VISION PET criteria, many patients do not respond favorably to [¹⁷⁷Lu]PSMA, suggesting the need for further refinements of PSMA PET and other screening parameters.

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TABLE 1
Visual PSMA PET vPSG Score

PSMA expression	Finding of MIP image
High	Most of lesions show higher uptake than parotid glands
Intermediate	Neither low nor high
Low	Most of lesions show lower uptake than parotid glands

When assessing PSMA expression, 3 anteroposterior MIP images adjusted to 0–10, 0–20, and 0–30 SUV window range should be used. “Most of lesions” refers to 80% of extent (total area) of lesion (not number). If parotid glands show heterogeneous uptake, area showing lower uptake should be used as reference. When more than half of parotid glands are out of scan range, patient should not be evaluated with these criteria.

When measured quantitatively, [⁶⁸Ga]PSMA-11 uptake in the parotid glands exceeds liver uptake 2- to 3-fold (median SUV_{max} for liver vs. parotids, 9.7 vs. 21.3 (20)), which is close to the criteria used in the TheraP trial (lesion SUV_{max}, 20) (2). We hypothesized that use of the parotid glands rather than the liver as a reference organ would improve patient stratification for [¹⁷⁷Lu]PSMA. The aim of this study was to test a quantitative and visual PSMA PET tumor-to-salivary gland ratio (PSG score) to predict outcomes after [¹⁷⁷Lu]PSMA in a cohort of patients with mCRPC established retrospectively from multiple institutions.

MATERIALS AND METHODS

Study Design

This was a retrospective multicenter study using a published dataset ($n = 270$) (4,19). Images were visually analyzed by 10 masked central, independent readers. The informed consent requirement was waived by the UCLA institutional review board (waiver 19-000896).

Patients

Patients received [¹⁷⁷Lu]PSMA-617 or [¹⁷⁷Lu]PSMA-I&T between December 10, 2014, and July 19, 2019, in phase 2 clinical trials (NCT03042312 and ACTRN12615000912583) or via compassionate-use access programs (Supplemental Table 2). The [⁶⁸Ga]PSMA-11 PET/CT protocol is provided in the supplemental Materials and Methods (20) and in Supplemental Table 3. Treatment details are provided in the supplemental Materials and Methods (21–23). Patients were excluded from the current analysis if more than 50% of the parotid glands was outside the PET field of view (as described in the eligibility criteria in Supplemental Table 4).

Image Analysis

Quantitative PSG (qPSG) Score. We first assessed the WB tumor burden quantitatively using the [⁶⁸Ga]PSMA-11 PET qPSG score. Parotid glands and WB tumors were segmented semiautomatically on baseline [⁶⁸Ga]PSMA-11 PET images using qPSMA software (24). Output parameters included WB SUV_{mean}, the SUV_{max} of the lesion with the highest uptake (H-lesion), WB PSMA tumor volume, and bilateral parotid gland SUV_{mean}.

The ratio of WB tumor to parotid gland SUV_{mean} (qPSG = mean tumor WB SUV/mean parotid gland SUV_{mean}) was calculated. Patients were divided into 3 groups according to qPSG score: high (>1.5), intermediate (0.5–1.5), and low (<0.5). In addition, patients were grouped as high SUV versus low SUV to compare SUV-based criteria (2,6) with PSG scores (supplemental Materials and Methods).

Visual PSG (vPSG) Score. In a second step, we assessed the reproducibility and prognostic value of visual criteria using the parotid glands as an organ of reference (vPSG score). All readers were board-certified nuclear medicine physicians with more than 2 y of experience in PSMA PET interpretation. To assess whether the reader experience in treating patients with [¹⁷⁷Lu]PSMA therapy influences image scoring, both readers with extensive experience (>50 treatments; 5 readers) and readers with limited experience (≤50 treatments; 5 readers) were selected (Supplemental Table 5).

Three-dimensional maximum-intensity-projection (MIP) baseline [⁶⁸Ga]PSMA-11 PET images adjusted to 3 different SUV window ranges (0–10, 0–20, and 0–30) were generated by a single lead investigator not involved in image analysis. Each reader was provided with the images (portable document format). Readers were asked to classify the patients into 3 groups (i.e., high, intermediate, and low) according to the vPSG score as described in Table 1. Representative images of each group are shown in Figure 1.

At more than 2 wk after the first reads, 50 cases were randomly selected for rereading to determine intrareader agreement. One lead investigator conducted the final analysis. A central majority rule (6 vs. 4) was applied in cases of disagreement to obtain the final reads. If disagreement persisted on intermediate versus high or on low versus intermediate (e.g., 5 vs. 5), the cases were classified as high or low, respectively, avoiding the intermediate category.

Clinical Outcomes

The clinical outcomes included a more than 50% prostate-specific antigen (PSA) decline (PSA50), PSA progression-free survival (PFS), and overall survival (OS). PSA50 was defined by a PSA decline of more than 50% compared with baseline at any time during the treatment (best response). PSA PFS was defined as the time from treatment initiation to PSA progression or death from any cause, as per the criteria of Prostate Cancer Clinical Trials Working Group 3 (25). OS was defined as time from treatment initiation to death of any cause.

Statistical Analysis

The R software package was used for statistical analysis. Two-tailed P values of less than 0.05 were considered significant. Clinical characteristics were compared among PSMA expression groups using the Mann–Whitney U and Fisher exact tests for continuous and

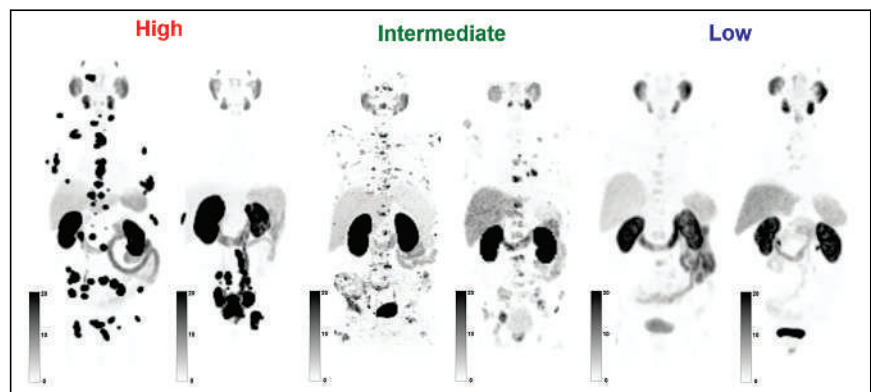


FIGURE 1. Representative MIP images of 6 patients classified as having high, intermediate, and low vPSG scores (MIP SUV range, 0–20).

categorical variables. The proportion of patients who had a PSA50 was assessed by the Fisher exact test, and the odds ratio from logistic regression was calculated. Kaplan–Meier analysis with the log-rank test and Cox hazard ratio regression was performed to evaluate survival outcomes. Multivariate Cox and logistic regression analyses were performed to test the PSG scores and previously reported prognostic factors for [¹⁷⁷Lu]PSMA (4). Intra- and interreader agreement was evaluated by weighted Fleiss κ -coefficients. Agreement between vPSG score (majority rule) and qPSG score was assessed by weighted Cohen κ -coefficients.

RESULTS

Patients

Between April 23, 2019, and January 13, 2020, 414 patients were retrospectively screened, and 177 men were excluded as specified in Supplemental Figure 1. Thus, 237 men were included in the final analysis. Seventy-five and 162 men were treated with [¹⁷⁷Lu]PSMA-617 and [¹⁷⁷Lu]PSMA-I&T, respectively. Table 2 depicts the clinical characteristics of the cohort. The median follow-up time was 21.2 mo (interquartile range, 14.1–30.6 mo).

PSG Score

Of the 237 patients, the numbers in the high-, intermediate-, and low-PSG groups were 56 (23.6%), 163 (68.8%), and 18 (7.6%), respectively, by qPSG score and 106 (44.7%), 96 (40.5%), and 35 (14.8%), respectively, by vPSG score (majority rule) (Supplemental Tables 6 and 7 show the clinical and PSMA PET characteristics of each qPSG and vPSG score group). There was no difference between the baseline clinical characteristics of any groups, except for the lower proportion of patients with prior docetaxel treatment in the low-qPSG group. The number of patients with PSMA PET nodal metastasis (N1) was lowest in the low groups both by qPSG score (33.3%) and by vPSG score (20.0%) ($P < 0.001$). The number of distant metastases (≥ 20) was lower in the low group (45.7%) than the intermediate (75.0%) and high (76.4%) groups by vPSG score ($P = 0.001$). WB tumor SUV_{mean} and PSMA tumor volume were highest in the high group, followed by the intermediate and low group, both by qPSG score and by vPSG score.

PSG Score and Clinical Outcome

Clinical outcomes for each of the 3 groups by vPSG and qPSG scores are summarized in Table 3. Comparisons between PSA PFS and OS in patients with a nonhigh PSG score (intermediate + low) versus a high PSG score (2 groups) are provided in Supplemental Figures 2 and 3, respectively. The PSA50, PSA PFS, and OS obtained by PSG scores and SUV-based criteria (high SUV vs. low SUV) are compared in the supplemental Materials and Methods.

PSA Response. A higher PSA50 was observed in the groups with a high PSG score than in those with an intermediate or low PSG score ($P < 0.001$) (PSA50 odds ratios for qPSG and vPSG scores are shown in Supplemental Tables 8 and 9). Both qPSG score and vPSG score were independent predictors of PSA50. Moreover, PSA50 in patients with a high PSG score was significantly better than in those with an H-lesion SUV_{max} of at least 20 (supplemental Materials and Methods).

PSA PFS. PSA PFS was longest in the groups with a high qPSG or vPSG score (Fig. 2). The corresponding hazard ratios are shown in Supplemental Tables 10 and 11, respectively.

OS. The longest OS was in the groups with a high qPSG or vPSG score (Fig. 3). The hazard ratios of the high groups were lower than those of the intermediate groups but were not significantly different from the low groups in univariate and multivariate analyses (Supplemental Tables 12 and 13). There was no difference

TABLE 2
Patient Characteristics and Clinical Outcome

Characteristic	Data
Total patients	237
Age (y)	72 (IQR, 66, 76)
PSA (ng/mL)	116.3 (IQR, 34.2, 388.1)
Initial NCCN risk group	
Low risk	9 (3.8%)
Intermediate risk	42 (17.7%)
High risk	92 (38.8%)
Metastatic	94 (39.7%)
Treatment history	
Previous docetaxel	190 (80.2%)
Second-line chemotherapy	86 (36.3%)
Androgen receptor signaling inhibitor	225 (94.9%)
Extent of disease on PSMA PET/CT	
Number of metastases ≥ 20	169 (71.3%)
Number of metastases < 20	68 (28.7%)
Sites of disease on PSMA PET/CT	
Pelvic nodal metastasis (N1)	113 (47.7%)
Distant nodal metastasis (M1a)	156 (65.8%)
Bone metastasis (M1b)	218 (92.0%)
Other organ metastasis (M1c)	72 (30.4%)
Cycles of [¹⁷⁷ Lu]PSMA received	
1	37 (15.6%)
2	64 (27.0%)
3	34 (14.3%)
4	78 (32.9%)
>4	24 (10.1%)
Injected activity per cycle (GBq)	7.4 (IQR, 7.4, 7.4)
OS (mo)	12.6 (95% CI, 11.0–14.2)
OS events	195 (82.3%)
PSA progression-free survival (mo)	4.6 (95% CI, 3.7–5.6)
PSA progression-free survival events	210 (88.6%)
PSA decline $\geq 50\%$	105 (44.3%)

IQR = interquartile range; NCCN = National Comprehensive Cancer Network.

Qualitative data are number; continuous data are median.

in OS between patients with an H-lesion SUV_{max} of at least 20 and those with an H-lesion SUV_{max} of less than 20. In contrast, OS was longer in patients with a WB SUV_{mean} of at least 10 than in those with a WB SUV_{mean} of less than 10. OS did not significantly differ between patients with a high PSG score and patients with a WB SUV_{mean} of at least 10 (Supplemental Fig. 3).

TABLE 3
Outcomes of qPSG Score and vPSG Score for High, Intermediate, and Low Patients

Outcome	High	Intermediate	Low	P
qPSG score				
PSA decline \geq 50% (<i>n</i>)	39/56 (69.6%)	63/163 (38.7%)	3/18 (16.7%)	<0.001
PSA PFS	7.2 (4.9–8.3)	4.0 (3.3–5.4)	1.9 (1.4–4.2)	<0.001
OS	15.0 (12.0–19.0)	11.2 (9.1–13.1)	13.9 (8.0–30.6)	0.017
vPSG score				
PSA decline \geq 50% (<i>n</i>)	67/106 (63.2%)	32/96 (33.3%)	6/35 (17.1%)	<0.001
PSA PFS	6.7 (4.6–7.7)	3.8 (2.8–5.6)	1.9 (1.5–3.1)	<0.001
OS	14.3 (12.0–17.8)	9.6 (8.0–12.9)	12.9 (9.0–18.8)	0.018

Survival data are median, in months, followed by 95% CI in parentheses.

Agreement

Agreement between qPSG and vPSG scores was moderate (weighted Cohen κ , 0.60; 95% CI, 0.52–0.68). Complete agreement between qPSG and vPSG scores was seen in 160 (67.5%) of the 237 patients.

The inter- and intrareader reproducibility of the vPSG score for all readers (*n* = 10) showed substantial agreement (Fleiss weighted κ , 0.68; 95% CI, 0.63–0.73) or almost perfect agreement (Cohen weighted κ [mean], 0.83 ± 0.06), respectively (supplemental Materials and Methods). Agreement among readers with and without prior ^{177}Lu -PSMA experience is shown in Supplemental Table 14 and Supplemental Figure 4.

DISCUSSION

Quantitative (qPSG) and visual (vPSG) PET-derived scores for tumor ^{68}Ga PSMA-11 expression relative to parotid gland uptake predicted the PSA response and PSA PFS to ^{177}Lu PSMA of patients with mCRPC. The 3-dimensional MIP image-based vPSG score was substantially reproducible and did not require extensive experience with ^{177}Lu PSMA.

In the VISION study, the liver was used as the reference organ, and 87.4% of patients were eligible after ^{68}Ga PSMA-11 PET screening (1). PSMA tumor uptake equal to or greater than liver uptake appears to be the minimum target expression requirement for response to ^{177}Lu PSMA. The ^{68}Ga PSMA-11 uptake of the parotid

gland is 2–3 times higher than that of the liver (20). Therefore, use of the parotid gland as a reference organ would make the criteria more stringent and specific.

Only MIP images were used for visual analysis. MIP images display WB tumor PSMA expression and disease extent in a single image. However, vPSG score should be used in combination with cross-sectional image analysis to determine the presence of PSMA-negative lesions (1,18,19). The greatest value of the PSG score may be in its use to exclude patients less likely to benefit from ^{177}Lu PSMA—those with a low PSG score. Also, when available, ^{18}F FDG PET/CT may complement the PSG score and potentially improve prognostication. The presence of ^{18}F FDG-positive/PSMA-negative lesions was associated with poor response to ^{177}Lu PSMA (9,26–28). We propose that patients with a low PSG score be deprioritized from ^{177}Lu PSMA. PSMA PET-based exclusion criteria for ^{177}Lu PSMA may encompass patients with PSMA-negative lesions by CT or by FDG, patients with lesion uptake below liver uptake, and patients with a low vPSG score.

Three different SUV-scale windows were used for interpreting MIP images. A MIP image with a narrow window (SUV, 0–10) is useful to observe the distribution of lesions with low PSMA expression, and MIP images with a wider window (SUVs, 0–20 and 0–30) are helpful to compare lesion uptake with parotid gland uptake. Using MIP images enables rapid and reproducible evaluations, which can facilitate clinical implementation.

Agreement between qPSG score and vPSG score (majority rule) was moderate, because vPSG score is based on the extent (>80%) of lesions with uptake greater than that of the parotid gland, whereas qPSG score is independent of disease extent (based on SUV ratio only). Despite the methodologic difference, the outcomes of each group by qPSG and vPSG score were similar, suggesting that both criteria are valuable. qPSG score enables higher reproducibility as it is obtained semiautomatically; however, segmentation software is necessary.

Recently developed nomograms to predict outcome after ^{177}Lu PSMA require WB SUV_{mean} as a parameter (4). A classification using a WB SUV_{mean} of at least

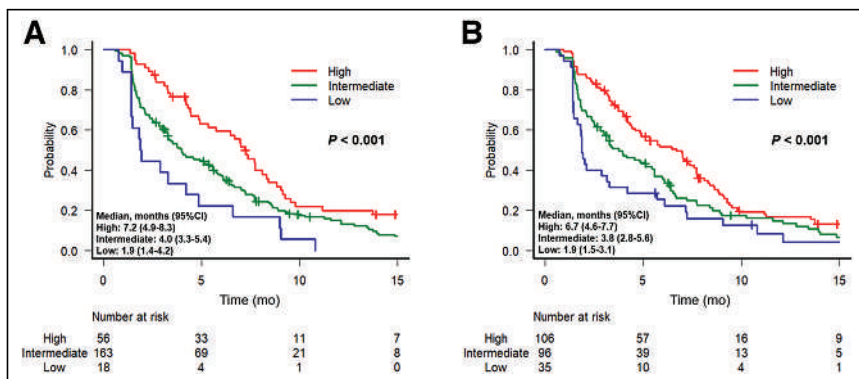


FIGURE 2. Kaplan-Meier curves for PSA PFS comparing groups with high, intermediate, and low PSMA expression classified by qPSG score (A) and vPSG score (B).

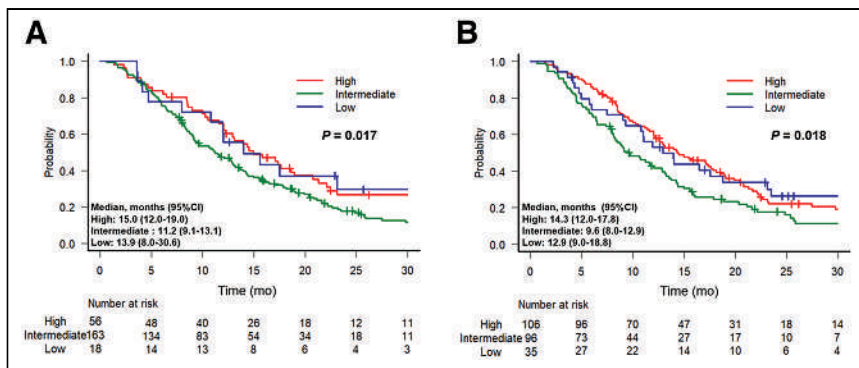


FIGURE 3. Kaplan-Meier curves for OS comparing groups with high, intermediate, and low PSMA expression classified by qPSG score (A) and vPSG score (B).

10 identified treatment responders in the VISION and TheraP cohorts (6). In our cohort, both qPSG score and vPSG score had similar prognostic value to a WB SUV_{mean} of at least 10. The qPSG score is based on an SUV ratio (WB tumor to parotid glands) rather than a fixed SUV threshold to reduce some inherent variability in SUV measurements across patients, scanners, and reconstruction algorithms (29). The need for tumor segmentation software precludes current clinical use of quantitative parameters such as WB tumor volume/SUV_{mean}. There are multiple WB segmentation tools under clinical development (24,30–33), but none are yet validated and widely available.

We propose a simple visual score to derive prognostic information from the screening 3-dimensional MIP [⁶⁸Ga]PSMA-11 PET images. In contrast, a binary SUV_{max} classification (H-lesion SUV_{max} ≥ 20 vs. < 20) was not prognostic of patient OS, because H-lesion SUV_{max} does not account for disease heterogeneity, a key determinant of treatment response to [¹⁷⁷Lu]PSMA (3,12). The 3-dimensional MIP-based vPSG score can be implemented quickly and at no cost in the clinic after further validation. Integration of the vPSG score in the [¹⁷⁷Lu]PSMA nomogram approach (4) may improve its accuracy and further support clinical adoption.

We divided patients into 3 rather than 2 groups. The rationale was to capture, in the intermediate group, patients with heterogeneous PSMA expression. This grouping predicted PSA responses well. However, the group with an intermediate PSG score tended to show worse OS than the group with a low PSG score. Possible explanations include the small population, partial-volume effects, less advanced disease stage, and lower tumor burden in the low group. As such, the 3-group PSG score is more suitable as a biomarker for PSA response than for OS.

Limitations of this study include the lack of independent PSG score validation and the retrospective design. Moreover, the cohort did not include patients who were excluded from [¹⁷⁷Lu]PSMA by the local treating sites. Thus, patients with low PSMA expression may be underrepresented. Also, the PSG score was tested only with [⁶⁸Ga]PSMA-11 PET, and its efficacy with other PSMA-targeted PET tracers (e.g., [¹⁸F]DCFPyL) is unknown. Considering similar normal-organ and tumor biodistribution patterns between [⁶⁸Ga]PSMA-11 and [¹⁸F]DCFPyL (34), we anticipate that the PSG score may be applicable to [¹⁸F]DCFPyL PET as well. Nevertheless, confirmatory studies have yet to be conducted. Finally, our criteria focus on only PSMA expression. Although high PSMA expression

increases the likelihood of sufficient delivery of radiopharmaceutical to tumor, various factors (e.g., administered and absorbed dose, genomic DNA repair mechanism, radiosensitivity, and other biologic tumor characteristics) are associated with radioreistance (35). More comprehensive inclusion criteria may be necessary to refine patient selection.

CONCLUSION

This study proposes a PSG score derived from pretherapeutic [⁶⁸Ga]PSMA-11 PET as a novel predictive and prognostic biomarker for response to [¹⁷⁷Lu]PSMA. After further clinical validation, this score, together

with other cross-sectional or metabolic imaging, may improve patient selection.

DISCLOSURE

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

KEY POINTS

QUESTION: Can the PSMA PET criteria using salivary glands as a reference organ (i.e., PSG score) optimize stratification of patients with mCRPC based on the response to [¹⁷⁷Lu]PSMA?

PERTINENT FINDINGS: WB tumor uptake was compared with salivary gland uptake visually and quantitatively on baseline [⁶⁸Ga]PSMA-11 PET images, and patients were classified into groups with high, intermediate, and low PSMA expression. Patients with high expression classified visually and by qPSG score showed a significantly better PSA response and OS after [¹⁷⁷Lu]PSMA.

IMPLICATIONS FOR PATIENT CARE: The PSG score can be a valuable biomarker for response to [¹⁷⁷Lu]PSMA and may assist in individual clinical decision making and future clinical trial design.

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SUPPLEMENTAL DATA

[68Ga]PSMA-11 PET/CT imaging protocol

Baseline [68Ga]PSMA-11 PET/CT scan was performed a median 24 ([IQR: 15-37]) days before the administration of the first cycle of [177Lu]PSMA. Patients received a median of 162 ([IQR]: 116-200) MBq [68Ga]PSMA-11 intravenously, and PET/CT scanning was started after a median of 60 (IQR: 54-67) minutes post-injection. PET/CT images were acquired from the mid-thigh to the base of the skull. All scans were corrected for decay, scatter, and random coincidences. CT images were used for attenuation correction as well as image fusion. All images were acquired following the [68Ga]PSMA-11 PET joint EANM/SNMMI procedure guideline to ensure reproducibility (20). The PET/CT scanners and applied reconstruction parameters of each center are summarized in Supplemental Table 3.

[177Lu]PSMA treatment protocol

Patients were treated either under compassionate use programs or in Phase II clinical trials (NCT03042312, ACTRN12615000912583). For patients treated under compassionate access programs, [177Lu] PSMA-617 and [177Lu]PSMA I&T were offered as surrogate therapy in accordance with the updated Declaration of Helsinki, paragraph-37 “Unproven Interventions in Clinical Practice,” and in accordance with The German Medicinal Products Act, AMG §13 2b, including priority of all approved treatments (in the absence of contraindications) and confirmation of the indication by the nuclear medicine physician, urologist and oncologist.

[177Lu]PSMA-I&T was synthesized locally in the Pharmaceutical Radiochemistry Department from Technical University Munich as reported previously (21). [177Lu]PSMA-617 was radiolabeled with carrier-free [177Lu] (9,22,23). The labelled product was produced, tested, and released under Good Manufacturing Practice (GMP) conditions as a sterile and ready to use solution for infusion. [177Lu]PSMA

was administered intravenously. Oral hydration or administration of sodium chloride (500-1000 ml) was performed. 30 minutes prior to the administration of [177Lu]PSMA, an ice pack was applied to the region of the salivary glands and kept in place for 4 hours to reduce the xerostomia risk. [177Lu]PSMA was administered by slow intravenous injection of 6.0–8.5 GBq at 6-8 weekly intervals. All patients underwent a screening [68Ga]PSMA-11 PET/CT within 10 weeks of treatment. Clinical and laboratory assessments were done within 24 hours before each drug injection.

Image analysis

Quantitative analysis. To compare the prognostic performance of PSG-scores with a previously published SUV based criteria, we measured 1) the whole-body-tumor SUV_{mean} using qPSMA software and 2) the SUV_{max} of the lesion with the highest [68Ga]PSMA-11 uptake (H-lesion).

Patients were then separated into two groups (low vs. high SUV) with the following cut-off SUVs: 10 for WB-SUV_{mean} (i.e., high: WB-SUV_{mean} \geq 10, non-high: WB-SUV_{mean} $<$ 10) (12) and 20 for the H-lesion SUV_{max} (i.e., high: H-lesion SUV_{max} \geq 20, non-high: H-lesion SUV_{max} $<$ 20) (2).

High PSG vs. non-high PSG. In addition to the 3-group analysis of the PSG-scores, we performed a 2-group analysis by combining the intermediate *PSG*- and low *PSG-score* groups into non-high *PSG-score* group (i.e., high *PSG* vs. non-high *PSG* (intermediate + low)).

High vs. non-high

The number of the patients in high and non-high groups were 56 (23.6%) and 181 (76.4%) for qPSG-score, 106 (44.7%) and 131 (55.3%) for vPSG-score, 74 (31.2%) and 163 (68.8%) for WB-SUV_{mean} \geq 10 classification, and 201 (84.8%) and 36 (15.2%) for the H-lesion SUV_{max} \geq 20 classification, respectively.

PSA50. A greater PSA response rate was seen in the high groups than non-high groups with PSG-scores and SUV criteria (high vs. non-high (%): [qPSG] 69.6 vs. 30.4, $p < 0.001$; [vPSG] 63.2 vs. 36.8, $p < 0.001$; [WB-SUV_{mean} \geq 10] 66.2 vs. 34.4 $p < 0.001$; [H-lesion SUV_{max} \geq 20] 51.2 vs. 48.8, $p = 0.001$). The PSA50 of the high qPSG- and high vPSG-score groups were significantly greater than in the group with H-lesion SUV_{max} \geq 20 (qPSG vs. H-lesion SUV_{max}: $p = 0.006$, vPSG vs. H-lesion SUV_{max}: $p = 0.017$).

PSA-PFS. The median PSA-PFS was higher in the high groups than non-high groups with PSG-scores and SUV criteria (median months: [qPSG] 7.2 vs. 3.7, $p = 0.003$; [vPSG] 6.7 vs. 3.3, $p < 0.001$, [WB-SUV_{mean} \geq 10] 7.0 vs. 3.4, $p = 0.001$, [H-lesion SUV_{max} \geq 20] 4.9 vs. 2.4, $p = 0.001$) (Supplemental Figure 2). PSA-PFS tended to be longer in the high qPSG- and high vPSG-score groups than in the group with H-lesion SUV_{max} \geq 20, but not statistically significant (qPSG vs. H-lesion SUV_{max}: $p = 0.084$, vPSG vs. H-lesion SUV_{max}: $p = 0.20$).

OS. The median OS was higher in the high PSG-score group and in patients with WB-SUV_{mean} \geq 10, but not in the high H-lesion SUV_{max} group (median months: [qPSG] 15.0 vs. 11.7, $p = 0.013$; [vPSG] 14.3 vs. 11.0, $p = 0.038$; [WB-SUV_{mean} \geq 10] 17.1 vs. 11.0; [H-lesion SUV_{max} \geq 20] 15.0 vs. 14.0, $p = 0.91$) (Supplemental Figure 3). Although the median OS of patients with WB-SUV_{mean} \geq 10 was slightly longer than the one in patients with high PSG-scores, there was no significant difference (qPSG vs. WB-SUV_{mean}: $p = 0.89$, vPSG vs. WB-SUV_{mean} \geq 10: $p = 0.26$).

Agreement between readers

Perfect agreement between all readers was obtained in 61/237 (25.8%) patients. Equal (i.e., 5 vs. 5) votes were seen in 13/237 (5.5%) patients, of which 10 were “intermediate vs. high” and 3 were “low vs. intermediate”. These were classified into the high and low group, respectively.

Readers with and without [177Lu]PSMA experience

The Fleiss’ weighted Kappa values of the experienced and non-experienced readers (n=5) were 0.71 (95%CI: 0.65-0.76) and 0.71 (95%CI: 0.65-0.76), respectively. The experienced reader classified more patients in the high and low PSG-score groups, whereas non-experienced readers classified more in the intermediate PSG-score group ($p < 0.001$). The predictive value of the vPSG-scores of the experienced and non-experienced readers were not significantly different for PSA-PFS, PSA50 (Supplemental Table 14 and Supplemental Figure 4).

Supplemental Table 1: Summary or the reported imaging criteria for PSMA-targeted radioligand therapy

Study	Study design	Used image	PET criteria	No. of patients	Outcomes
Sartor et al. (VISION) (1)	Prospective (phase III)	[68Ga]PSMA-11 PET/CT	PSMA uptake (> liver) in one or more metastatic lesions of any size in any organ system No PSMA negative (\leq liver) lesions in any lymph node (≥ 2.5 cm), solid-organ (≥ 1.0 cm), and bone lesion (≥ 1.0 cm)	Total: n = 1003 Eligible: n = 877 (87.4%) not-Eligible: n = 126 (12.6%)	median PFS: 8.7 m median OS: 15.3 m PSA50: 46%
Hofman et al. (TheraP) (2)	Prospective (phase II)	[68Ga]PSMA-11 PET/CT and [18F]FDG PET/CT	PSMA-positive (SUVmax ≥ 20) disease at a site of disease & SUVmax > 10 at all other measurable sites of metastatic disease No metastatic disease with discordant [18F] FDG-positive and PSMA-negative findings	Total: n = 291 Eligible: n = 211 (72.5%) not-Eligible: n = 80 (27.5%)	median PFS: 5.1 m PSA50: 66%
Hofman et al. (LuPSMA) (9)	Prospective (phase II)	[68Ga]PSMA-11 PET/CT and [18F]FDG PET/CT	PSMA-positive (SUVmax \geq Liver SUV x 1.5) disease at a site of metastatic disease No metastatic disease with discordant [18F] FDG-positive and PSMA-negative findings	Total: n = 43 Eligible: n = 36 (83.7%) not-Eligible: n = 7 (16.2%)	median PFS: 7.6 m median OS: 13.5 m PSA50: 57%
Calais et al. (RESIST-PC) (10, 11)	Prospective (phase II)	[68Ga]PSMA-11 PET/CT	Majority of lesions with uptake equal to or above liver uptake (visual analysis) Absence of PSMA-negative lesions visible on anatomic imaging modalities (CT, MRI).	Total: n = 51 Eligible: n = 43 (84.3%) not-Eligible: n = 8 (15.7%)	median PFS: 3.7 m median OS: 14.0 m PSA50: 37%
Buteau et al. (6)	Retrospective (TheraP cohort)	[68Ga]PSMA-11 PET/CT	PSMA whole-body-tumor SUVmean: SUVmean ≥ 10 (High) SUVmean < 10 (Low)	Total: n = 99 SUVmean ≥ 10 : n = 35 (35.4%) SUVmean < 10: n = 64 (64.6%)	PSA50: SUVmean ≥ 10 : 91% SUVmean < 10: 52%
Vlachostergios et al. (12)	Retrospective	Planar/SPECT ([111In]PSMA-J591 or [177Lu]PSMA-J591 or [177Lu]PSMA-617) or [68Ga]PSMA-11 PET/CT	[Planar/SPECT] Three lesions with the highest uptake: Low (“no uptake” or “weakly positive”), High (“definitely positive” or “equal intensity to liver” or “greater uptake than liver”) [PET] Average SUVmax of the five lesions with the highest uptake: Low (< liver SUVmean), High (\geq liver SUVmean)	Total: n = 215 High: n = 160 (74.4%) Low: n = 55 (25.6%)	PSA50: (High) 26% (Low) 7%
Seifert et al. (3)	Retrospective	[68Ga]PSMA-11 PET/CT	High: average SUVmax of all metastases (PSMAaverage) > 14.3 and lowest PSMA expressing metastasis (PSMAmin) > 10.2 Intermediate: PSMAaverage > 14.3 and PSMAmin ≤ 10.2 Low: PSMAaverage ≤ 14.3 and PSMAmin ≤ 10.2	Total: n = 85 High: n = 16 (18.8%) Intermediate: n = 49 (57.6%) Low: n = 20 (23.5%)	median OS: (High) 21.3 m (Intermediate) 11.4 m (Low) 5.3 m
Rathke et al. (13)	Retrospective	[177Lu]PSMA-617 planner	(Visual analysis) Intense: Tumor uptake > salivary glands Heterogeneous: liver \leq Tumor uptake \leq salivary glands Faint: Tumor uptake < liver	Total: n = 100 Intense: n = 50 (50.0%) Heterogeneous: n = 31 (31.0%) Low: n = 19 (19.0%)	Odds ratio for PSA50: (Intense) 18.0 (Heterogeneous) 2.7
Derlin et al. (14)	Retrospective	[177Lu]PSMA-617 planner	(Visual analysis) High: Tumor uptake > salivary glands Low: Tumor uptake \leq salivary glands	Total: n = 50 High: n = 30 (60%) Low: n = 20 (40%)	median PFS: (High) not reached (Low) 90 days

Ongoing trials

Sartor et al. (PSMAfore) (15)	Prospective (phase III)	[68Ga]PSMA-11 PET/CT	PSMA positive determined by the sponsor's central reader	Total: n = 450 (estimated)	Primary endpoint: rPFS
Chi et al. (SPLASH) (16)	Prospective (phase III)	[68Ga]PSMA-11 or [18F]DCFPyL PET/CT	For patients with measurable disease (per RECIST 1.1 criteria) <ul style="list-style-type: none"> - SUVmax \geq 15 at one site of disease, and - SUVmax > 10 at all measurable disease sites For those without measurable disease, at least 1 positive lesion SUVmax > 10 must be evident	Total: n = 415 (estimated)	Primary: rPFS
Yu et al. (ARROW) (17)	Prospective (phase II)	[18F]DCFPyL PET/CT	Significant PSMA uptake, defined as 18F-DCFPyL SUVmax > 1 x liver SUVmean in all prostate cancer lesions, except as noted below: <ul style="list-style-type: none"> - PSMA negative soft tissue lesion(s) < 1.0 cm short axis - PSMA negative lymph node lesion(s) < 1.5 cm short axis - PSMA negative bone lesions(s) with a soft tissue component < 1.0 cm short axis or without a soft tissue component of any size. 	Total: n = 120 (estimated)	Primary: PSA50

PSMA: prostate-specific membrane antigen., PFS: progression-free survival, OS: overall survival, m: months, rPFS: radiographic progression-free survival, PSA: prostate-specific antigen, PSA50: PSA decline of \geq 50%

Supplemental Table 2. Site description and institutional treatment protocol

Center	No. patients	Principal Investigator/ responsible physician	Regulatory Pathway	Radiopharmaceutical	Intervals	Activity (GBq)
TUM	n = 75	M. Eiber	Compassionate use*	[177Lu]PSMA-I&T	6-8wk	7.4
PMCC	n = 50	M. Hofman	Clinical Trial	[177Lu]PSMA-617	6wk	6.0-8.5
UCLA	n = 43	J. Calais	Clinical Trial	[177Lu]PSMA-617	8wk	6.0-7.4
UKH	n = 30	C. Kratochwil	Compassionate use*	[177Lu]PSMA-617	8wk	6.0-8.5
UKE	n = 19	WP. Fendler	Compassionate use*	[177Lu]PSMA-617	8wk	7.4
EDNOC	n = 20	E. Delpassand	Clinical Trial	[177Lu]PSMA-617	8wk	6.0-7.4

TUM: Technical University Munich, PMCC: Peter MacCallum Center Melbourne, UCLA: University of California, Los Angeles, UKH: University Hospital Heidelberg, UKE: University Hospital Essen, EDNOC: Excel Diagnostics Nuclear Oncology Center

* Compassionate use employing the administration of non-approved drugs complying with the German Medicinal Products Act, AMG §13 2b, and the responsible regulatory bodies.

Supplemental Table 3. PET/CT systems and reconstruction parameters

Center	PET/CT scanner	Matrix size	Reconstruction (iterations, subsets)	Pixel size (mm)
TUM	Siemens, Biograph mCT	200x200	PSF-TOF (3, 21)	4.06x4.06
PMCC	GE, Discovery 710	192x192	VPFXS	2.9x2.9
UCLA	Siemens, Biograph 64	200x200	OSEM (2, 24)	4.06x4.06
UKH	Siemens, Biograph mCT	200x200	PSF-TOF (2, 21)	4.06x4.06
UKE	Siemens, Biograph mCT	200x200	PSF-TOF (3, 21)	4.06x4.06
EDNOC	Siemens, Biograph 16	168x168	OSEM (2, 24)	4.06x4.06

TUM: Technical University Munich, PMCC: Peter MacCallum Center Melbourne, UCLA: University of California, Los Angeles, UKH: University Hospital Heidelberg, UKE: University Hospital Essen, EDNOC: Excel Diagnostics Nuclear Oncology Center, PSF: point spread function, TOF: time of flight, OSEM: ordered subset expectation maximization

Supplemental Table 4. Eligibility criteria

Eligibility criteria to receive [177Lu]PSMA radioligand therapy assessed by local investigators

- Histopathological confirmed adenocarcinoma of the prostate
- Confirmed metastatic castration-resistant prostate cancer (testosterone levels below 50 ng/dL)
- Failure of standard treatments, including taxane-based chemotherapy (docetaxel, cabazitaxel) and androgen-signaling- targeted inhibitor (abiraterone, enzalutamide, or both), unless patients were unsuitable or refused these standard treatment regimens
- Progressive disease by prostate-specific antigen according to Prostate Cancer Working Group 3 criteria or radiographic progression according to RECIST 1.1
- Eastern Cooperative Oncology Group performance status score of 2 or lower
- Life expectancy greater than 3 months (6 months for TUM)
- Hemoglobin concentration greater than 90 g/L
- Platelet count greater than $75 \times 10^9/L$
- Neutrophil count greater than $1.5 \times 10^9/L$
- PSMA-avid lesions on the screening PSMA-targeted PET

Inclusion criteria for the international multicenter analysis

- [177Lu]PSMA administered activity of 6.0-8.5 GBq
- Treatment initiation between October 1, 2014 and December 1, 2018
- Available screening 68Ga-PSMA11 PET/CT within ten weeks of treatment
- Available baseline laboratory data within 24 hours of treatment
- Available survival outcome data (overall survival, PSA progression-free survival)

PSA: prostate-specific antigen, PSMA: prostate-specific membrane antigen, RECIST: response evaluation criteria in solid tumors

Supplemental Table 5. Background and experience with [177Lu]PSMA of the readers

Reader	Institution	Specialty	[177Lu]PSMA experience (number of patients treated)
M Benz	Los Angeles, USA	NM + RAD	≤ 50 cases
I Burger	Zurich, Switzerland	NM + RAD	≤ 50 cases
M Eiber	Munich, Germany	NM + RAD	> 50 cases
L Emmett	Sydney, Australia	NM	> 50 cases
A Farolfi	Bologna, Italy	NM	≤ 50 cases
W Fendler	Essen, Germany	NM	> 50 cases
M Hofman	Melbourne, Australia	NM	> 50 cases
T Hope	San Francisco, USA	NM + RAD	≤ 50 cases
C Kratochwil	Heidelberg, Germany	NM	> 50 cases
I Sonni	Los Angeles, USA	NM	≤ 50 cases

NM: nuclear medicine, RAD: radiology, PSMA:

Supplemental Table 6: Patient Characteristics Stratified by qPSG-score

	High	Intermediate	Low	p-value
No.	56	163	18	
Age (years), median [IQR]	72 [66, 75]	71 [66, 76]	72 [66, 76]	0.96
PSA (ng/ml), median [IQR]	185.7 [64.8, 766.7]	100.5 [27.9, 333.3]	112.1 [30.0, 259.5]	0.062
Treatment history				
Previous docetaxel	46 (82.1%)	134 (82.2%)	10 (55.6%)	0.024
Second-line chemotherapy	24 (42.9%)	55 (33.7%)	7 (38.9%)	0.46
Androgen receptor signaling agent	52 (92.9%)	156 (95.7%)	17 (94.4%)	0.70
Extent of disease on PSMA-PET/CT				
Number of metastases \geq 20	39 (69.6%)	120 (73.6%)	10 (55.6%)	0.26
Sites of disease on PSMA-PET/CT				
Pelvic nodal metastasis (N1)	40 (71.4%)	67 (41.1%)	6 (33.3%)	< 0.001
Distant nodal metastasis (M1a)	41 (73.2%)	106 (65.0%)	9 (50.0%)	0.18
Bone metastasis (M1b)	48 (85.7%)	153 (93.9%)	17 (94.4%)	0.14
Other organ metastasis (M1c)	15 (26.8%)	54 (33.1%)	3 (16.7%)	0.28
Liver metastasis	7 (12.5%)	27 (16.6%)	2 (11.1%)	0.68
Non-liver visceral metastasis	8 (14.3%)	27 (16.6%)	1 (5.6%)	0.46
PSMA PET parameters				
WB Tumor SUVmean, median [IQR]	11.8 [9.7, 16.4]	7.9 [6.5, 9.5]	5.4 [4.0, 6.4]	< 0.001
PSMA tumor volume (mL), median [IQR]	1447.5 [380.0, 2776.5]	684.0 [183.5, 1370.6]	236.5 [106.9, 342.5]	< 0.001

PSA: prostate-specific antigen, IQR: interquartile range, PSMA: prostate-specific membrane antigen.

Supplemental Table 7. Patient Characteristics Stratified by vPSG-scores

	High	Intermediate	Low	p-value
No.	106	96	35	
Age (years), median [IQR]	71 [64, 75]	72 [67, 77]	71 [65, 75]	0.32
PSA (ng/ml), median [IQR]	126.2 [58.4, 443.7]	119.3 [26.3, 416.1]	88.1 [22.0, 164.2]	0.14
Treatment history				
Previous docetaxel	85 (80.2%)	81 (84.4%)	24 (68.6%)	0.18
Second-line chemotherapy	43 (40.6%)	34 (35.4%)	9 (25.7%)	0.13
Androgen receptor signaling agent	101 (95.3%)	92 (95.8%)	32 (91.4%)	0.58
Extent of disease on PSMA-PET/CT				
Number of metastases \geq 20	81 (76.4%)	72 (75.0%)	16 (45.7%)	0.001
Sites of disease on PSMA-PET/CT				
Pelvic nodal metastasis (N1)	62 (58.5%)	44 (45.8%)	7 (20.0%)	< 0.001
Distant nodal metastasis (M1a)	76 (71.7%)	62 (64.6%)	18 (51.4%)	0.086
Bone metastasis (M1b)	97 (91.5%)	90 (93.8%)	31 (88.6%)	0.61
Other organ metastasis (M1c)	29 (27.4%)	32 (33.3%)	11 (31.4%)	0.65
Liver metastasis	14 (13.2%)	16 (16.7%)	6 (17.1%)	0.65
Non-liver visceral metastasis	15 (14.2%)	16 (16.7%)	5 (14.3%)	0.87
PSMA PET parameters				
WB Tumor SUVmean, median [IQR]	11.1 [9.3, 14.3]	7.2 [6.5, 8.6]	5.2 [4.4, 6.2]	< 0.001
PSMA tumor volume (mL), median [IQR]	1035.5 [403.0, 2211.6]	688.0 [229.5, 1297.0]	121.0 [36.0, 405.6]	< 0.001

PSA: prostate-specific antigen, IQR: interquartile range, PSMA: prostate-specific membrane antigen.

Supplemental Table 8. Odds ratios of the univariate and multivariate analyses for PSA50 comparing the 3 groups (high vs. intermediate vs. low) for qPSG-score.

	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
qPSG		< 0.001		0.001
[High]	(reference)		(reference)	
[Intermediate]	0.28 (0.14-0.53)	< 0.001	0.36 (0.17-0.74)	0.006
[Low]	0.09 (0.02-0.34)	< 0.001	0.07 (0.02-0.33)	< 0.001
Previous docetaxel	0.46 (0.24-0.89)	0.020	0.34 (0.16-0.72)	0.005
Number of metastases \geq 20	1.01 (0.57-1.78)	0.97	1.27 (0.57-2.83)	0.56
Pelvic nodal metastasis (N1)	2.13 (1.27-3.59)	0.004	2.24 (1.17-4.30)	0.015
Distant nodal metastasis (M1a)	0.85 (0.50-1.46)	0.56	0.52 (0.27-1.03)	0.060
Bone metastasis (M1b)	0.55 (0.21-1.42)	0.22	0.60 (0.17-2.08)	0.42
Liver metastasis	0.43 (0.20-0.94)	0.034	0.42 (0.18-0.98)	0.044
PSMA tumor volume (mL)	1.00 (1.00-1.00)	0.093	1.00 (1.00-1.00)	0.33

Supplemental Table 9. Odds ratios of the univariate and multivariate analyses for PSA50 comparing the 3 groups (high vs. intermediate vs. low) in vPSG-score.

	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
vPSG		< 0.001		0.001
[High]	(reference)		(reference)	
[Intermediate]	0.29 (0.16-0.52)	< 0.001	0.32 (0.17-0.59)	< 0.001
[Low]	0.12 (0.05-0.32)	< 0.001	0.11 (0.04-0.34)	< 0.001
Previous docetaxel	0.46 (0.24-0.89)	0.020	0.38 (0.17-0.82)	0.013
Number of metastases \geq 20	1.01 (0.57-1.78)	0.97	1.09 (0.48-2.48)	0.84
Pelvic nodal metastasis (N1)	2.13 (1.27-3.59)	0.004	2.14 (1.12-4.12)	0.022
Distant nodal metastasis (M1a)	0.85 (0.50-1.46)	0.56	0.49 (0.25-0.98)	0.043
Bone metastasis (M1b)	0.55 (0.21-1.42)	0.22	0.48 (0.13-1.73)	0.26
Liver metastasis	0.43 (0.20-0.94)	0.034	0.45 (0.19-1.05)	0.063
PSMA tumor volume (mL)	1.00 (1.00-1.00)	0.093	1.00 (1.00-1.00)	0.38

Supplemental Table 10. Hazard ratios for PSA-PFS comparing the 3 groups (high vs. intermediate vs. low) in qPSG-score.

	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
qPSG		< 0.001		0.003
[High]	(reference)		(reference)	
[Intermediate]	1.54 (1.11-2.14)	0.010	1.44 (1.01-2.06)	0.046
[Low]	2.71 (1.57-4.69)	< 0.001	2.95 (1.64-5.32)	< 0.001
Previous docetaxel	1.40 (0.99-1.98)	0.059	1.20 (0.83-1.73)	0.33
Number of metastases \geq 20	1.37 (1-1.86)	0.050	0.88 (0.60-1.28)	0.49
Pelvic nodal metastasis (N1)	0.69 (0.52-0.9)	0.007	0.68 (0.50-0.94)	0.019
Distant nodal metastasis (M1a)	1.11 (0.84-1.49)	0.46	1.45 (1.04-2.04)	0.030
Bone metastasis (M1b)	2.43 (1.39-4.23)	0.0018	2.03 (1.07-3.85)	0.031
Liver metastasis	2.10 (1.43-3.08)	< 0.001	2.17 (1.46-3.21)	< 0.001
PSMA tumor volume (mL)	1.00 (1.00-1.00)	0.36	1.00 (1.00-1.00)	0.58

Supplemental Table 11. Hazard ratios for PSA-PFS comparing the 3 groups (high vs. intermediate vs. low) in vPSG-score.

	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
vPSG		0.001		0.009
[High]	(reference)		(reference)	
[Intermediate]	1.46 (1.09-1.97)	0.012	1.46 (1.07-1.99)	0.018
[Low]	2.00 (1.34-2.99)	< 0.001	2.30 (1.47-3.60)	< 0.001
Previous docetaxel	1.40 (0.99-1.98)	0.059	1.27 (0.87-1.84)	0.22
Number of metastases \geq 20	1.37 (1-1.86)	0.05	0.87 (0.59-1.27)	0.47
Pelvic nodal metastasis (N1)	0.69 (0.52-0.9)	0.007	0.73 (0.53-1.00)	0.052
Distant nodal metastasis (M1a)	1.11 (0.84-1.49)	0.46	1.38 (1.00-1.92)	0.052
Bone metastasis (M1b)	2.43 (1.39-4.23)	0.0018	2.25 (1.19-4.26)	0.013
Liver metastasis	2.10 (1.43-3.08)	< 0.001	2.14 (1.44-3.18)	< 0.001
PSMA tumor volume (mL)	1.00 (1.00-1.00)	0.36	1.00 (1.00-1.00)	0.43

Supplemental Table 12. Hazard ratios for OS comparing the 3 groups (high vs. intermediate vs. low) in qPSG-score.

	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
qPSG		0.018		0.001
[High]	(reference)		(reference)	
[Intermediate]	1.60 (1.13-2.27)	0.008	2.04 (1.39-3.00)	< 0.001
[Low]	1.08 (0.58-2.02)	0.81	1.78 (0.91-3.48)	0.091
Previous docetaxel	1.75 (1.21-2.54)	0.003	1.50 (1.02-2.21)	0.039
Number of metastases \geq 20	1.66 (1.2-2.3)	0.002	1.10 (0.74-1.65)	0.63
Pelvic nodal metastasis (N1)	1.02 (0.77-1.35)	0.91	0.94 (0.68-1.31)	0.73
Distant nodal metastasis (M1a)	1.46 (1.07-1.98)	0.016	1.52 (1.07-2.17)	0.02
Bone metastasis (M1b)	1.98 (1.13-3.49)	0.018	1.35 (0.70-2.60)	0.37
Liver metastasis	2.04 (1.39-3)	< 0.001	2.04 (1.37-3.02)	< 0.001
PSMA tumor volume (mL)	1.00 (1.00-1.00)	< 0.001	1.00 (1.00-1.00)	< 0.001

Supplemental Table 13. Hazard ratios for OS comparing the 3 groups (high vs. intermediate vs. low) in vPSG-score.

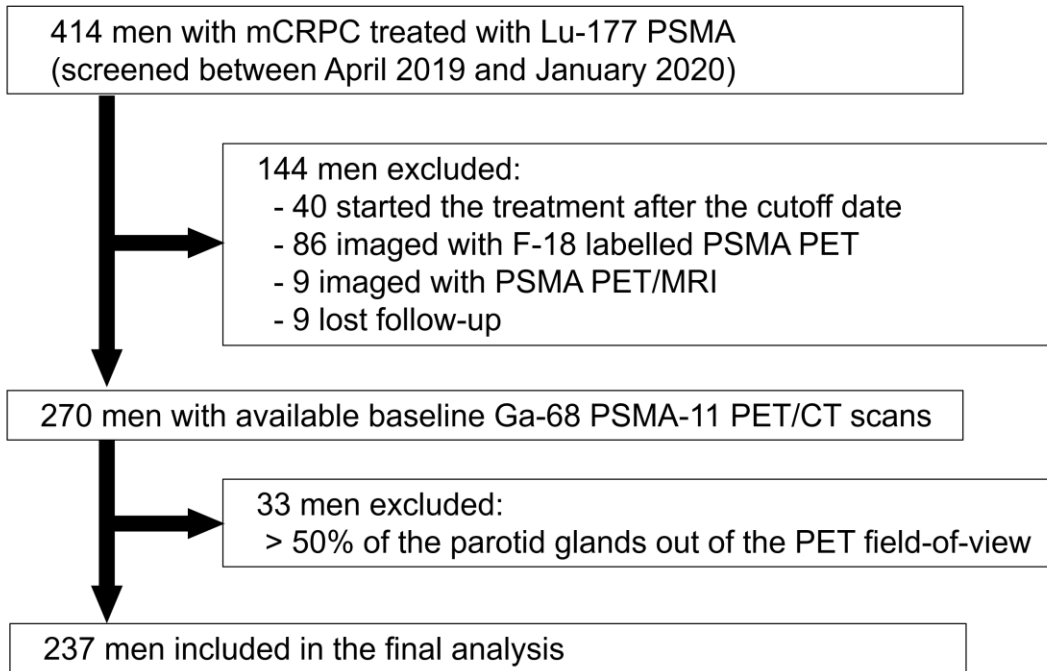
	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
vPSG		0.019		0.003
[High]	(reference)		(reference)	
[Intermediate]	1.51 (1.12-2.05)	0.0077	1.73 (1.26-2.38)	0.00072
[Low]	1.01 (0.65-1.57)	0.97	1.40 (0.86-2.28)	0.18
Previous docetaxel	1.75 (1.21-2.54)	0.003	1.41 (0.96-2.07)	0.083
Number of metastases \geq 20	1.66 (1.2-2.3)	0.002	1.11 (0.74-1.67)	0.61
Pelvic nodal metastasis (N1)	1.02 (0.77-1.35)	0.91	0.89 (0.63-1.24)	0.48
Distant nodal metastasis (M1a)	1.46 (1.07-1.98)	0.016	1.53 (1.08-2.18)	0.018
Bone metastasis (M1b)	1.98 (1.13-3.49)	0.018	1.57 (0.82-3.00)	0.18
Liver metastasis	2.04 (1.39-3)	< 0.001	2.03 (1.37-3.02)	< 0.001
PSMA tumor volume (mL)	1.00 (1.00-1.00)	< 0.001	1.00 (1.00-1.00)	< 0.001

Supplemental Table 14. Clinical outcomes of the vPSG-score high, intermediate, and low groups assessed by the readers with and without [177Lu]PSMA experience

	[177Lu]PSMA experience (> 50)			p-value
	High	Intermediate	Low	
No. (%)	120 (50.6%)	73 (30.8%)	44 (18.6%)	
PSA decline ≥ 50% (%)	71 (59.2%)	27 (37.0%)	7 (15.9%)	< 0.001
Any PSA decline (%)	95 (79.2%)	48 (65.8%)	18 (40.9%)	< 0.001
PSA-PFS median months (95%CI)	5.7 (4.4-7.3)	3.8 (2.8-5.6)	2.0 (1.4-4.2)	0.003
OS median months (95%CI)	13.9 (12.0-17.3)	9.0 (6.5-12.9)	12.9 (9.0-17.5)	0.034
	[177Lu]PSMA experience (≤ 50)			p-value
	High	Intermediate	Low	
No. (%)	83 (35.0%)	131 (55.2%)	23 (9.7%)	
PSA decline ≥ 50% (%)	55 (66.3%)	47 (35.9%)	3 (13.0%)	< 0.001
Any PSA decline (%)	71 (85.5%)	82 (62.6%)	8 (34.8%)	< 0.001
PSA-PFS median months (95%CI)	7.0 (5.3-7.7)	3.7 (2.8-5.1)	1.9 (1.5-3.1)	0.003
OS median months (95%CI)	14.4 (12.0-18.1)	10.5 (8.5-13.0)	14.0 (10.8-30.6)	0.077

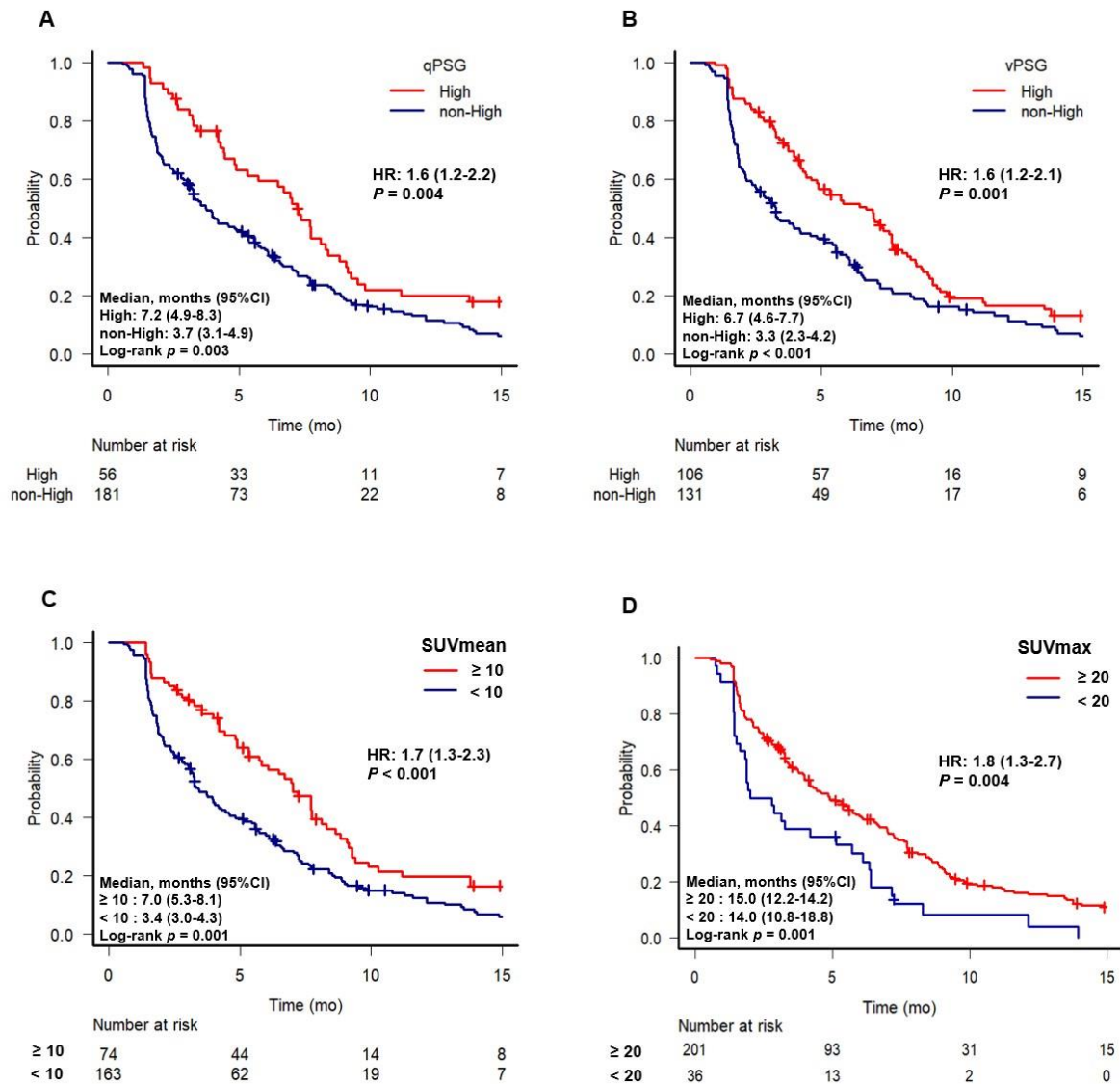
PSA: prostate-specific antigen, PSMA: prostate-specific membrane antigen, PFS: progression-free survival, OS: overall survival

Supplemental Figure 1.



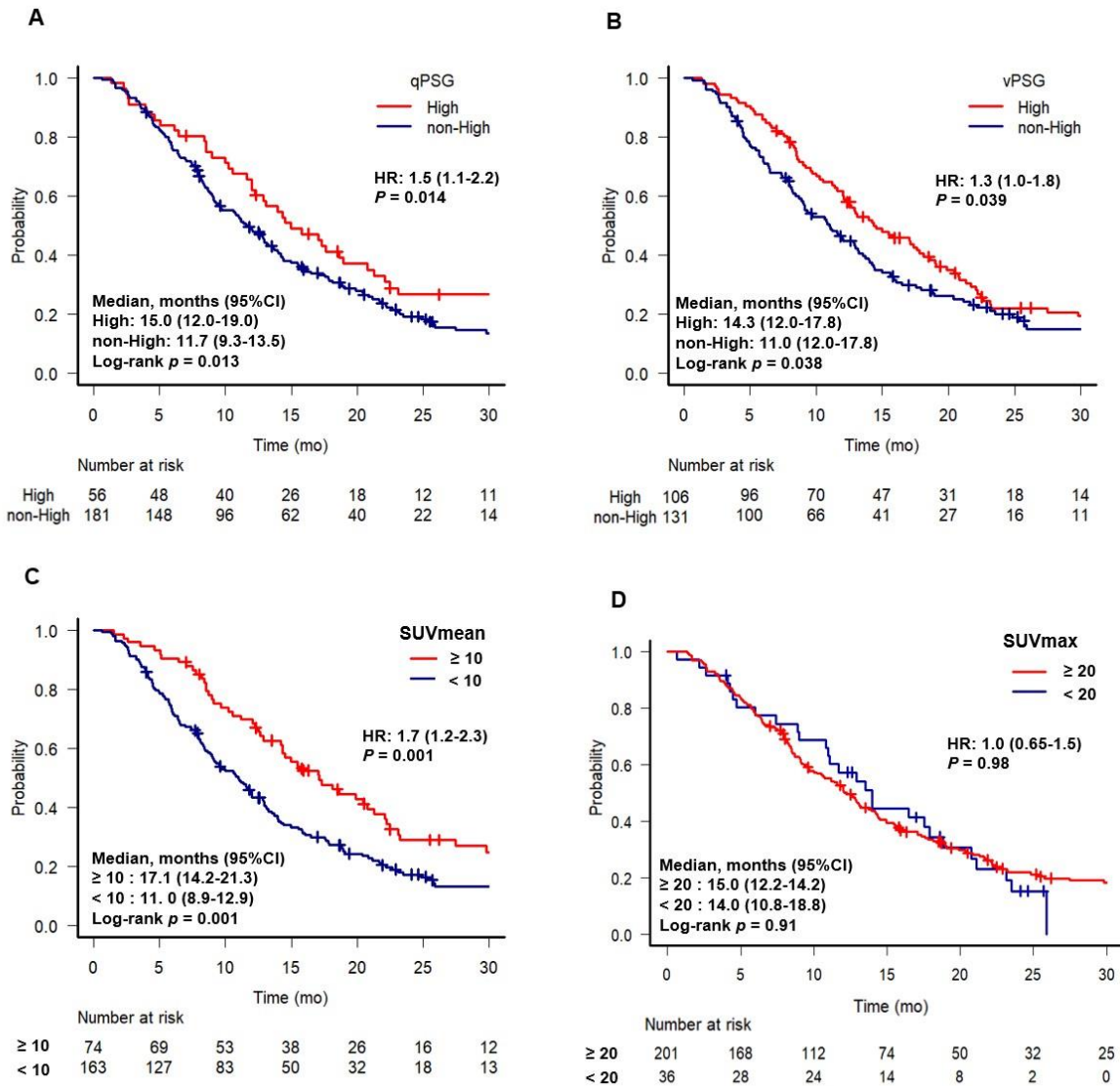
Supplemental Figure 1. Patients selection

Supplemental Figure 2.



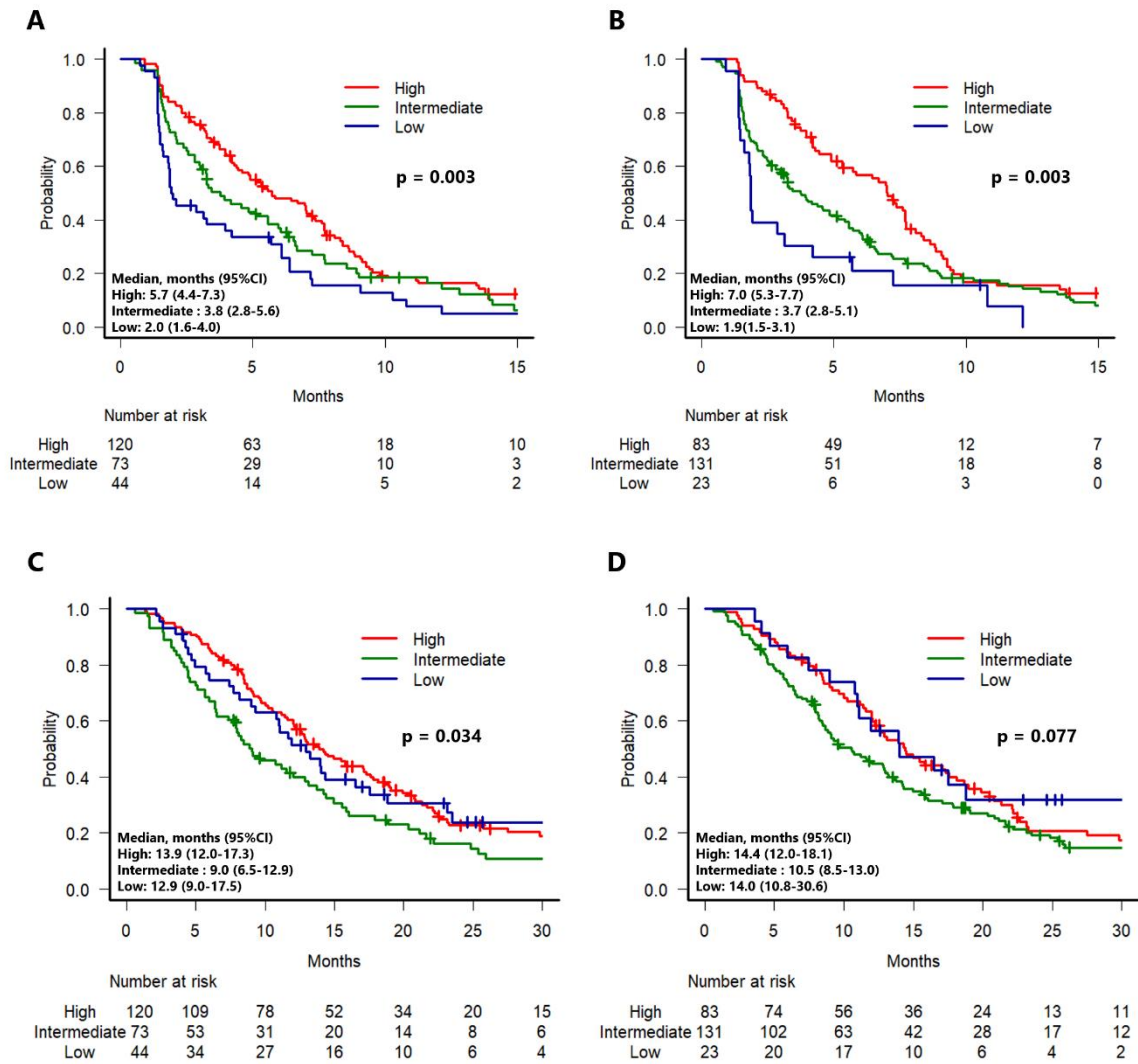
Supplemental Figure 2. Kaplan-Meier curves of PSA-PFS comparing the “high vs. non-high” groups by the (A) qPSG-score (B) vPSG-score, (C) whole-body-tumor SUVmean ≥ 10 , and (D) the highest [Ga68]PSMA-11 uptake lesion (H-lesion) SUVmax ≥ 20 .

Supplemental Figure 3.



Supplemental Figure 3. Kaplan-Meier curves of OS comparing the “high vs. non-high” groups by the (A) qPSG-score (B) vPSG-score, (C) whole-body-tumor SUVmean ≥ 10 , and (D) the highest [Ga68] PSMA-11 uptake lesion (H-lesion) SUVmax ≥ 20 .

Supplemental Figure 4.



Supplemental Figure 4. Kaplan-Meier curves comparing between high, intermediate, and low groups graded by vPSG-score (A, B) PSA-PFS of each group classified by the readers with (A) and without (B) [177Lu]PSMA experience (> 50 cases). (C, D) OS of each group classified by the readers with (C) and without (D) [177Lu]PSMA experience (> 50 cases).

Article #12:

Nomograms to predict outcomes after ^{177}Lu -PSMA therapy in patients with metastatic castration-resistant prostate cancer: an international multicenter retrospective study (n=270)

The treatment options for mCRPC have greatly expanded in the past decade with novel agents, and multiple drugs are currently available for mCRPC. Identification of patient candidates most likely to benefit from a certain therapy represents an unmet need in the therapeutic landscape of advanced prostate cancer. In the next study, we aimed to develop nomograms to predict outcomes in patients with mCRPC who are candidates for ¹⁷⁷Lu-PSMA. We hypothesized that a combination of baseline PSMA-PET-derived and clinical parameters can aid clinical decision making and selection of candidates for this therapy. An international database containing data from men with late stage mCRPC treated with ¹⁷⁷Lu-PSMA at six institutions in Germany, the USA, and Australia was established. Using both clinical trial and real-world data, a collaborative group of clinical experts and biostatisticians developed prognostic models for outcomes after ¹⁷⁷Lu-PSMA, which, to our knowledge, are the first such models. Previously identified variables in early-stage mCRPC were reinforced, and additional variables derived from ⁶⁸Ga-PSMA-11 PET/CT were identified with novel interactions between covariates. To enable immediate clinical implementation on a large scale, an online risk calculator was developed and is available online (<https://www.uclahealth.org/nuc/nomograms>). These models can be further tested and updated as new clinical trial data become available.

The study was published in *The Lancet Oncology* as provided below.

Nomograms to predict outcomes after ^{177}Lu -PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study



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Summary

Background Lutetium-177 (^{177}Lu) prostate-specific membrane antigen (^{177}Lu -PSMA) is a novel targeted treatment for patients with metastatic castration-resistant prostate cancer (mCRPC). Predictors of outcomes after ^{177}Lu -PSMA to enhance its clinical implementation are yet to be identified. We aimed to develop nomograms to predict outcomes after ^{177}Lu -PSMA in patients with mCRPC.

Methods In this multicentre, retrospective study, we screened patients with mCRPC who had received ^{177}Lu -PSMA between Dec 10, 2014, and July 19, 2019, as part of the previous phase 2 trials (NCT03042312, ACTRN12615000912583) or compassionate access programmes at six hospitals and academic centres in Germany, the USA, and Australia. Eligible patients had received intravenous 6.0–8.5 GBq ^{177}Lu -PSMA once every 6–8 weeks, for a maximum of four to six cycles, and had available baseline [^{68}Ga]Ga-PSMA-11 PET/CT scan, clinical data, and survival outcomes. Putative predictors included 18 pretherapeutic clinicopathological and [^{68}Ga]Ga-PSMA-11 PET/CT variables. Data were collected locally and centralised. Primary outcomes for the nomograms were overall survival and prostate-specific antigen (PSA)-progression-free survival. Nomograms for each outcome were computed from Cox regression models with LASSO penalty for variable selection. Model performance was measured by examining discrimination (Harrell's C-index), calibration (calibration plots), and utility (patient stratification into low-risk vs high-risk groups). Models were validated internally using bootstrapping and externally by calculating their performance on a validation cohort.

Findings Between April 23, 2019, and Jan 13, 2020, 414 patients were screened; 270 (65%) of whom were eligible and were divided into development (n=196) and validation (n=74) cohorts. The median duration of follow-up was 21.5 months (IQR 13.3–30.7). Predictors included in the nomograms were time since initial diagnosis of prostate cancer, chemotherapy status, baseline haemoglobin concentration, and [^{68}Ga]Ga-PSMA-11 PET/CT parameters (molecular imaging TNM classification and tumour burden). The C-index of the overall survival model was 0.71 (95% CI 0.69–0.73). Similar C-indices were achieved at internal validation (0.71 [0.69–0.73]) and external validation (0.72 [0.68–0.76]). The C-index of the PSA-progression-free survival model was 0.70 (95% CI 0.68–0.72). Similar C-indices were achieved at internal validation (0.70 [0.68–0.72]) and external validation (0.71 [0.68–0.74]). Both models were adequately calibrated and their predictions correlated with the observed outcome. Compared with high-risk patients, low-risk patients had significantly longer overall survival in the validation cohort (24.9 months [95% CI 16.8–27.3] vs 7.4 months [4.0–10.8]; $p < 0.0001$) and PSA-progression-free survival (6.6 months [6.0–7.1] vs 2.5 months [1.2–3.8]; $p = 0.022$).

Interpretation These externally validated nomograms that are predictive of outcomes after ^{177}Lu -PSMA in patients with mCRPC might help in clinical trial design and individual clinical decision making, particularly at institutions where ^{177}Lu -PSMA is introduced as a novel therapeutic option.

Funding Prostate Cancer Foundation.

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Introduction

Lutetium-177 (^{177}Lu) prostate-specific membrane antigen (^{177}Lu -PSMA) is a radiolabelled small-molecule inhibitor that binds with high affinity to prostate-specific membrane antigen (PSMA) and delivers β particle radiation. Several phase 2 studies and larger multicentre retrospective

analyses have established the antitumour activity and favourable safety profile of ^{177}Lu -PSMA in men with metastatic castration-resistant prostate cancer (mCRPC).^{1,2} The TheraP trial³ showed superior prostate-specific antigen (PSA) responses and progression-free survival in patients who received [^{177}Lu]Lu-PSMA-617 compared with

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<https://www.uclahealth.org/nuc/nomograms>

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published in English from database inception to April 23, 2019, with the terms “LuPSMA”, “prognosis”, “nomogram”, “PSMA”, and “mCRPC”. Our search yielded identification of five prognostic models that were developed using data from patients who were in an early stage of metastatic castration-resistant prostate cancer (mCRPC) and had received first-line or second-line treatments. We found no prognostic models described for late-stage mCRPC for patients treated with lutetium-177 (¹⁷⁷Lu) prostate-specific membrane antigen (¹⁷⁷Lu-PSMA).

Added value of this study

An international database containing data from men with late-stage mCRPC treated with ¹⁷⁷Lu-PSMA at six institutions in Germany, the USA, and Australia was established. Using both clinical trial and real-world data, a collaborative group of clinical

experts and biostatisticians developed prognostic models for outcomes after ¹⁷⁷Lu-PSMA, which, to our knowledge, are the first such models. Previously identified variables in early-stage mCRPC were reinforced, and additional variables derived from [⁶⁸Ga]Ga-PSMA-11 PET/CT were identified with novel interactions between covariates. To enable immediate clinical implementation on a large scale, an online risk calculator was developed and is available online.

Implications of all the available evidence

Our nomograms for outcomes after ¹⁷⁷Lu-PSMA in late-stage mCRPC could help in trial design and provide guidance for clinicians. Robust and accurate risk assessment might aid physician decision making regarding treatment plans and clinical trial patient stratification. These models can be updated as new clinical trial data become available.

patients who received cabazitaxel. In the phase 3 VISION trial,⁴ [¹⁷⁷Lu]Lu-PSMA-617 improved overall survival and imaging-based progression-free survival when added to standard of care in patients with mCRPC. Since the first prospective signals of its efficacy,¹ the number of clinical trials of ¹⁷⁷Lu-PSMA and compassionate use of the treatment are expanding rapidly. Hence, there is growing need for predictors of outcomes after ¹⁷⁷Lu-PSMA to support clinical implementation of this novel therapy and rationale design for the next generation of ¹⁷⁷Lu-PSMA trials. The armamentarium for mCRPC has greatly expanded in the past decade with novel agents, and more than seven drugs are currently available for mCRPC.⁵ Identification of patient candidates most likely to benefit from a certain therapy represents an unmet need in the therapeutic landscape of advanced prostate cancer.

PSMA ligands are also used for diagnostic purposes using whole-body PET imaging (PSMA-PET).⁶ Candidates for ¹⁷⁷Lu-PSMA are typically screened with a PSMA-PET scan to verify sufficient PSMA expression of tumour lesions. Guiding treatment decisions with PSMA-specific vectors such as findings from the entry PSMA-PET might lead to better treatment outcomes. Considerable efforts have been dedicated to understanding tumour heterogeneity and developing prognostic nomograms in men with mCRPC who receive first-line or second-line treatments.^{7,8} However, there are still no models that adequately assess the prognosis for patients who are later in the mCRPC course and are candidates for ¹⁷⁷Lu-PSMA therapy.

We aimed to develop nomograms to predict outcomes in patients with mCRPC who are candidates for ¹⁷⁷Lu-PSMA. We hypothesised that a combination of baseline PSMA-PET-derived and clinical parameters can improve evidence-based selection of candidates for this therapy

and aid clinical decision making and subsequent implementation in clinical trials.

Methods

Study design and participants

We did a multicentre, retrospective study. Nomograms for predicting outcomes after ¹⁷⁷Lu-PSMA treatment were developed and validated using data from six hospitals and academic institutions in Germany, the USA, and Australia (appendix p 5).

We screened patients who had received [¹⁷⁷Lu]Lu-PSMA-617 or [¹⁷⁷Lu]Lu-PSMA-I&T between Dec 10, 2014, and July 19, 2019, as part of the previous phase 2 clinical trials (NCT03042312, ACTRN12615000912583) or compassionate use access programmes at the participating sites. Eligible patients had been treated with ¹⁷⁷Lu-PSMA administered by intravenous injection of 6.0–8.5 GBq once every 6–8 weeks, for a maximum of four to six cycles in absence of progression or severe toxicity according to the treating physician. Eligible patients had available baseline [⁶⁸Ga]Ga-PSMA-11 PET/CT scan, clinical data, and survival outcomes (appendix p 5). We excluded patients who received ¹⁸F-labelled PSMA-PET at baseline.

We followed a prospectively defined protocol (appendix), which was approved by the institutional review board of the University of California Los Angeles (number 19-000896). The requirement to obtain informed consent for inclusion in this analysis was waived by the institutional review board.

Procedures

We divided the study dataset into development and validation cohorts (approximately 2:1) and followed predefined criteria to ensure comparability between the cohorts. Each cohort had an equal number of institutions,

See Online for appendix

included patients enrolled in both clinical trials and compassionate access programmes, and included patients treated in different countries. 26 pretherapeutic parameters were collected (appendix p 6); these included information about demographics, initial diagnosis of prostate cancer, treatment history, baseline clinical status, baseline laboratory tests, and baseline [^{68}Ga]Ga-PSMA-11 PET/CT tumour characteristics. 18 (69%) of 26 collected parameters were tested in the models as putative predictors for outcome after ^{177}Lu -PSMA. A number of 18 putative predictors allowed for nine to ten events per predictor for the primary outcomes in the training cohort, which satisfied the recommended minimal number of events per predictor.⁹ The putative predictors were chosen based on previous work that showed their potential prognostic value in mCRPC, and based on the investigators clinical experience with ^{177}Lu -PSMA.^{2,10–13}

Clinical laboratory assessments were done within 24 h before each cycle. Screening [^{68}Ga]Ga-PSMA-11 PET/CT was done within 10 weeks of treatment initiation. Treatment and imaging protocols are detailed in the appendix (pp 1, 8). [^{68}Ga]Ga-PSMA-11 PET/CT scans were analysed centrally by a nuclear medicine physician (AG). [^{68}Ga]Ga-PSMA-11 PET/CT tumour characteristics included the pattern of spread by molecular imaging TNM classification system,¹⁴ calculated using a semi-automatic tool (ePROMISE version 1.0), and quantitative whole-body tumour burden assessment using a semi-automatic software (qPSMA version 1.0).¹⁵ Output parameters from qPSMA tested in the models were number of metastatic lesions and tumour average standardised uptake value (SUV_{mean}) as a surrogate measure of tumour PSMA target expression (PSMA-PET SUV correlates significantly with tumour PSMA expression measured by immunohistochemistry).¹⁶

Outcomes

The primary outcomes for the nomograms were overall survival and PSA-progression-free survival. The secondary outcome was PSA decline of 50% or more (PSA50) from baseline at any time during treatment. Overall survival was defined as the time from treatment initiation to death from any cause; PSA-progression-free survival was defined as the time from treatment initiation to PSA progression or death from any cause.¹⁷ PSA progression, according to Prostate Cancer Clinical Trials Working Group 3 criteria, was defined as a 25% or greater increase in PSA and at least 2 ng/mL above the nadir.¹⁷ The first reported PSA progression was confirmed by repeated PSA measurements at least 3 weeks later whenever possible, or by unequivocal tumour progression as measured by imaging, clinical assessment, or both. PSA-progression-free survival was chosen as an endpoint instead of radiographical progression-free survival because inconsistent timepoints and different imaging modalities were used for radiological assessment across

the cohorts. By contrast, PSA concentrations were measured uniformly across the study centres in each treatment cycle.

Statistical analysis

The sample size was derived on the basis of the available data and no power calculation for sample size was done upfront. Descriptive statistics were reported as frequencies and proportions for categorical variables, and median (IQR) or mean (SD) for continuous variables. The median (95% CI) overall survival and PSA-progression-free survival were estimated using the Kaplan-Meier method. Patients who did not have survival data available were not included in the final analysis. The proportion of patients who had a PSA50 was recorded. Differences in overall survival and PSA-progression-free survival between the development and validation cohorts were determined using the log-rank test. The distribution of putative variables between the development and validation cohorts was compared using the Wilcoxon Mann-Whitney test (for continuous variables) or exact Fisher test (for categorical variables).

Model building followed a prospectively defined plan. A penalised Cox's proportional hazards model using the adaptive least absolute shrinkage and selection operator (LASSO) was used.¹⁸ Cox regression analyses were applied to estimate the hazard ratios (HRs) or odds ratios and their 95% CIs or p values. Prediction accuracy of overall survival and PSA-progression-free survival models was evaluated using two methods. First, the discrimination was measured by the Harrell's concordance index

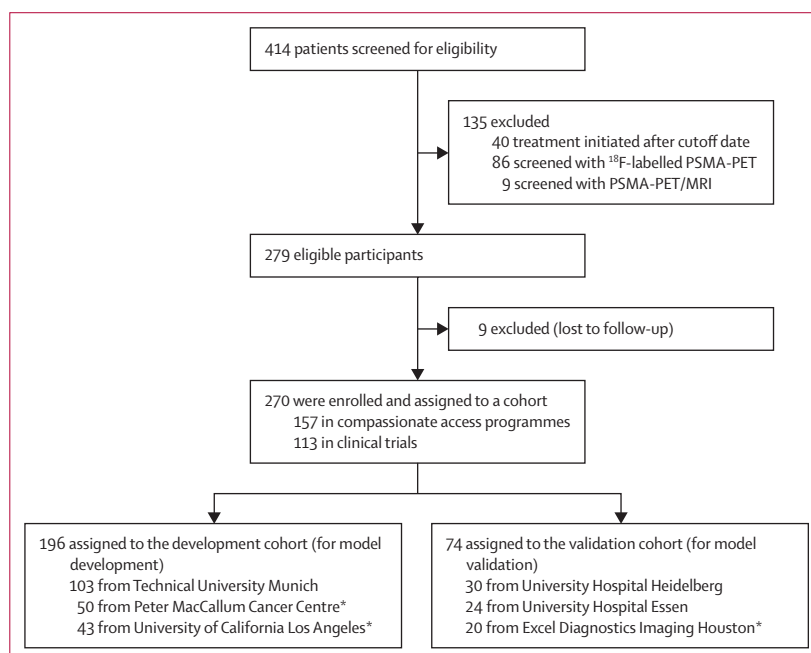


Figure 1: Study profile

<https://publikacije.stat.gov.rs/G2021/Pdf/G20211180.pdf>. *Patients enrolled in phase 2 clinical trials (NCT03042312, ACTRN12615000912583).

	Development cohort (n=196)	Validation cohort (n=74)	p value*
Median age, years	72 (67-76)	70 (65-76)	0.17
Median time since initial diagnosis, years	7 (4-12)	6 (4-12)	0.21
Initial NCCN risk group			0.41
Low risk	7 (4%)	4 (5%)	..
Intermediate risk	39 (20%)	9 (12%)	..
High risk	76 (39%)	29 (39%)	..
Metastatic	74 (38%)	32 (43%)	..
Treatment history			
Previous docetaxel	160 (82%)	59 (80%)	0.72
Second-line chemotherapy	66 (34%)	26 (35%)	0.88
Androgen receptor signalling inhibitor	189 (96%)	68 (92%)	0.19
Baseline clinical status			
ECOG performance status ≥2	23 (12%)	17 (23%)	0.033
ECOG performance status <2	173 (88%)	57 (77%)	..
Symptomatic disease	140 (71%)	38 (51%)	0.0024
Asymptomatic disease	56 (29%)	36 (49%)	..
Baseline laboratory tests			
Alkaline phosphatase ≥ULN	76 (39%)	37 (50%)	0.099
Alkaline phosphatase <ULN	120 (61%)	37 (50%)	..
Median PSA, ng/mL	117 (30-391)	135 (62-387)	0.61
Median haemoglobin, g/dL	11.3 (10.2-12.6)	10.8 (9.3-12.9)	0.14
PSMA-PET tumour characteristics			
Number of metastases (≥20)	147 (75%)	55 (74%)	1.00
Number of metastases (<20)	49 (25%)	19 (26%)	..
SUV _{mean}	8.6 (6.7-10.8)	7.9 (6.5-10.7)	0.22
Pelvic nodal involvement (N1)	96 (49%)	36 (49%)	1.00
Distant nodal involvement (M1a)	129 (66%)	50 (68%)	0.88
Bone involvement (M1b)	179 (91%)	68 (92%)	1.00
Liver involvement	30 (15%)	11 (15%)	1.00
Superscan appearance	29 (15%)	5 (7%)	0.099
Primary endpoint: overall survival, months			
Median (95% CI)	13.0 (11.4-14.6)	12.9 (9.2-16.5)	0.32†
Events	170 (87%)	55 (74%)	0.0077
Primary endpoint: PSA-progression-free survival, months			
Median (95% CI)	4.4 (3.4-5.4)	3.9 (2.3-5.5)	0.15†
Events	180 (92%)	65 (88%)	0.34
Secondary endpoint: PSA decline ≥50%	89 (45%)	32 (43%)	0.81

Data are median (IQR) or n (%) unless otherwise stated. N, M1a, and M1b refer to molecular imaging TNM classifications. NCCN=National Comprehensive Cancer Network. ECOG=Eastern Cooperative Oncology Group. ULN=upper limit of normal. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. SUV_{mean}=mean standardised uptake value. *p values compare the patient characteristics and outcome events in the development and validation cohorts using Wilcoxon Mann-Whitney test or exact Fisher test depending on whether the variable is continuous or categorical. †Log-rank test.

Table 1: Participant characteristics and treatment outcomes

(C-index) and its 95% CI. Second, models' calibration was evaluated by calibration plots predicting the probability of death at 12 and 18 months and PSA progression at 3 and 6 months versus observed probability. These timepoints were chosen on the basis of the observed median overall survival and PSA-progression-free survival. One nomogram was computed from each model and individual risk scores were obtained by applying the nomograms on the

development cohort. An optimal cutoff point for the risk score for each model was computed to stratify patients into low-risk or high-risk groups. The optimal cutoff was determined using log-rank statistics to provide the largest discrepancy in overall survival and PSA-progression-free survival between the risk groups (*cutp* function; *SurvMisc* package in R).

Model validation was done in two steps. First, we did an internal validation using a bootstrap resampling process to provide an unbiased estimate of model performance (*validate.cph* package in R), as the C-index. The original development cohort was resampled to obtain a dataset of the same size. Second, to assess external validity, prediction accuracy of overall survival and PSA-progression-free-survival models was determined on the validation cohort by computing the C-indices and calibration plots. The nomograms were applied to the validation cohort to obtain the individual risk scores. The optimal cutoff obtained in the development cohort was used to stratify patients in the validation cohort into low-risk or high-risk groups. Clinical utility of the nomograms was evaluated by using the log-rank test to determine if the survival distributions differed between the low-risk and high-risk groups. Two-sided p values of less than 0.05 were considered significant. For the PSA50 model, a penalised logistic regression model using the adaptive least absolute shrinkage and selection operator (LASSO) penalty was considered. Model discrimination was determined using the area under the curve and its 95% CI, and calibration was evaluated by predicting the probability of achieving PSA50. To evaluate the model's accuracy, the cutoff point of a sensitivity of 90% or greater (independent of the specificity) in the development cohort was determined. A specificity of 90% or greater was rationalised as offering sufficient confidence in using the nomogram in a clinical environment to identify non-responders. The utility of the model was assessed by computing the sensitivity, specificity, positive predictive value, and negative predictive value based on the cutoff in the development and validation cohorts (appendix pp 2-3). Study data were curated using REDCap data capture tools.¹⁹ All statistical analyses were done using R version 3.6.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 23, 2019, and Jan 13, 2020, 414 patients were retrospectively screened; 270 (65%) of whom met the eligibility criteria and were divided into development (n=196; datasets from Technical University Munich, Peter MacCallum Cancer Center, and University of California Los Angeles) and independent validation (n=74; datasets from Heidelberg University Hospital, University Hospital Essen, and Excel Diagnostics Imaging Houston)

cohorts (figure 1). 144 (35%) of 414 patients were excluded: 40 (10%) started treatment after the cutoff date (Dec 1, 2018), 86 (21%) were imaged with ^{18}F -labelled PSMA-PET, nine (2%) were imaged with PSMA-PET/MRI, and nine (2%) were lost to follow-up. 113 (42%) of 270 patients were enrolled in clinical trials, whereas 157 (58%) received ^{177}Lu -PSMA as part of compassionate access programmes. ^{177}Lu -PSMA was administered for a median of 3 cycles (IQR 2–4) per patient. The median number of previous mCRPC systemic treatments was 3 (IQR 2–4). 257 (95%) of 270 patients had received second-generation antiandrogens, and 219 (81%) had previously been treated with chemotherapy. Baseline characteristics and outcome data were well balanced between the two cohorts except for Eastern Cooperative Oncology Group (ECOG) performance status and symptomatic status (table 1). The median duration of follow-up was 21.5 months (IQR 13.3–30.7). 225 (83%) of 270 patients had died by the last follow-up and 245 (91%) experienced PSA progression. The median overall survival and PSA-progression-free survival were similar between the development and validation cohorts (table 1).

The estimated 12-month overall survival was 54% (95% CI 48–60) and the estimated 18-month overall survival was 34% (29–40). Predictors selected in the overall survival model were time since diagnosis of prostate cancer, chemotherapy status, baseline haemoglobin concentration, bone involvement status, liver involvement status, number of metastatic lesions, and tumour SUV_{mean} (table 2, appendix p 7). On the calibration plots, the model's predicted probabilities were close to the observed probabilities, but deviated slightly at 12 months when higher probabilities were predicted (figure 2). The C-index of the overall survival model was 0.71 (95% CI 0.69–0.73). Similar C-indices were achieved at internal validation (0.71 [0.69–0.73]) and external validation (0.72 [0.68–0.76]). The nomogram built based on the overall survival model is shown in figure 2C.

The estimated 3-month PSA-progression-free survival was 64% (95% CI 58–70) and the estimated 6-month PSA-progression-free survival was 38% (32–43). Predictors selected in the PSA-progression-free survival model were time since diagnosis of prostate cancer, chemotherapy status, pelvic nodal status, bone involvement status, liver involvement status, and tumour SUV_{mean} (table 2, appendix p 7). On the calibration plots, the model's predicted probabilities were close to the observed probabilities, but deviated slightly (figure 3). The C-index of the PSA-progression-free survival model was 0.70 (95% CI 0.68–0.72). Similar C-indices were achieved at internal validation (0.70 [0.68–0.72]) and external validation (0.71 [0.68–0.74]). The nomogram built based on the PSA-progression-free survival model is shown in figure 3C.

Patients in the development cohort, validation cohort, and complete set were stratified into two risk groups

	Definition	Estimate HR or OR (95% CI)	p value
Overall survival			
Time since diagnosis	Continuous, years	0.92 (0.89–0.95)	<0.0001
Chemotherapy status	Previous chemotherapy vs no chemotherapy	1.53 (1.01–2.37)	0.044
Baseline haemoglobin	Continuous, g/dL	0.85 (0.77–0.95)	0.0035
Number of metastases	≥20 vs <20	1.66 (1.12–2.44)	0.0031
Tumour SUV _{mean}	Continuous, no unit	0.94 (0.90–0.98)	0.0078
Bone involvement	M1b vs no M1b	1.10 (0.57–2.13)	0.77
Liver involvement	Liver metastases vs no liver metastases	2.11 (1.38–3.23)	<0.0001
PSA-progression-free survival			
Time since diagnosis	Continuous, years	0.94 (0.92–0.97)	0.00012
Chemotherapy status	Previous chemotherapy vs no chemotherapy	1.55 (1.03–2.34)	0.028
Tumour SUV _{mean}	Continuous, no unit	0.92 (0.88–0.96)	0.00052
Pelvic nodal involvement	N1 vs N0	0.70 (0.51–0.97)	0.035
Bone involvement	M1b vs no M1b	1.93 (1.07–3.52)	0.032
Liver involvement	Liver metastases vs no liver metastases	2.59 (1.69–3.95)	<0.0001
PSA decline ≥50%			
Chemotherapy status	Previous chemotherapy vs no chemotherapy	0.32 (0.13–0.77)	0.012
Tumour SUV _{mean}	Continuous, no unit	2.88 (1.80–4.62)	<0.0001
Pelvic nodal involvement	N1 vs N0	1.87 (0.96–3.62)	0.062
Liver involvement	Liver metastases vs no liver metastases	0.29 (0.11–0.81)	0.018
Estimates are hazard ratios for the overall survival and PSA-progression-free survival analyses, and odds ratios for the PSA decline of 50% or greater analysis. HR=hazard ratio. OR=odds ratio. SUV=standardised uptake value. PSA=prostate-specific antigen.			
Table 2: Multivariate analysis of predictors selected by LASSO regression procedure in the development cohort			

(high risk vs low risk) using the calculated optimal cutoff for the risk scores (197 points for overall survival nomogram and 178 points for PSA-progression-free survival nomogram). Median overall survival for low-risk patients versus high-risk patients was 19.1 months (95% CI 17.1–21.1) versus 8.4 months (7.4–9.4; $p<0.0001$; figure 4A) in the development cohort, 24.9 months (16.8–27.3) versus 7.4 months (4.0–10.8; $p<0.0001$; figure 4B) in the validation cohort, and 19.9 months (17.5–22.3) versus 8.2 months (7.2–9.1; $p<0.0001$; figure 4C) in the complete set. Median PSA-progression-free survival during ^{177}Lu -PSMA for low-risk patients versus high-risk patients was 9.4 months (95% CI 6.6–12.1) versus 3.3 months (2.9–3.7; $p<0.0001$; figure 4D) in the development cohort, 6.6 months (6.0–7.1) versus 2.5 months (1.2–3.8; $p=0.022$; figure 4E) in the validation cohort, and 8.8 months (7.3–10.3) versus 3.3 months (2.8–3.7; $p<0.0001$; figure 4F) in the complete set.

Results of the PSA50 model are shown in table 2 and the appendix (pp 3, 9). The area under the curve of the PSA50 model in the validation cohort was 0.78 (95% CI 0.68–0.88). Using a cutoff of 41 points, the sensitivity for patient stratification into responders or non-responders in the validation cohort was 94%, the specificity was 38%, the positive predictive value was 54%, and the negative predictive value was 89%.

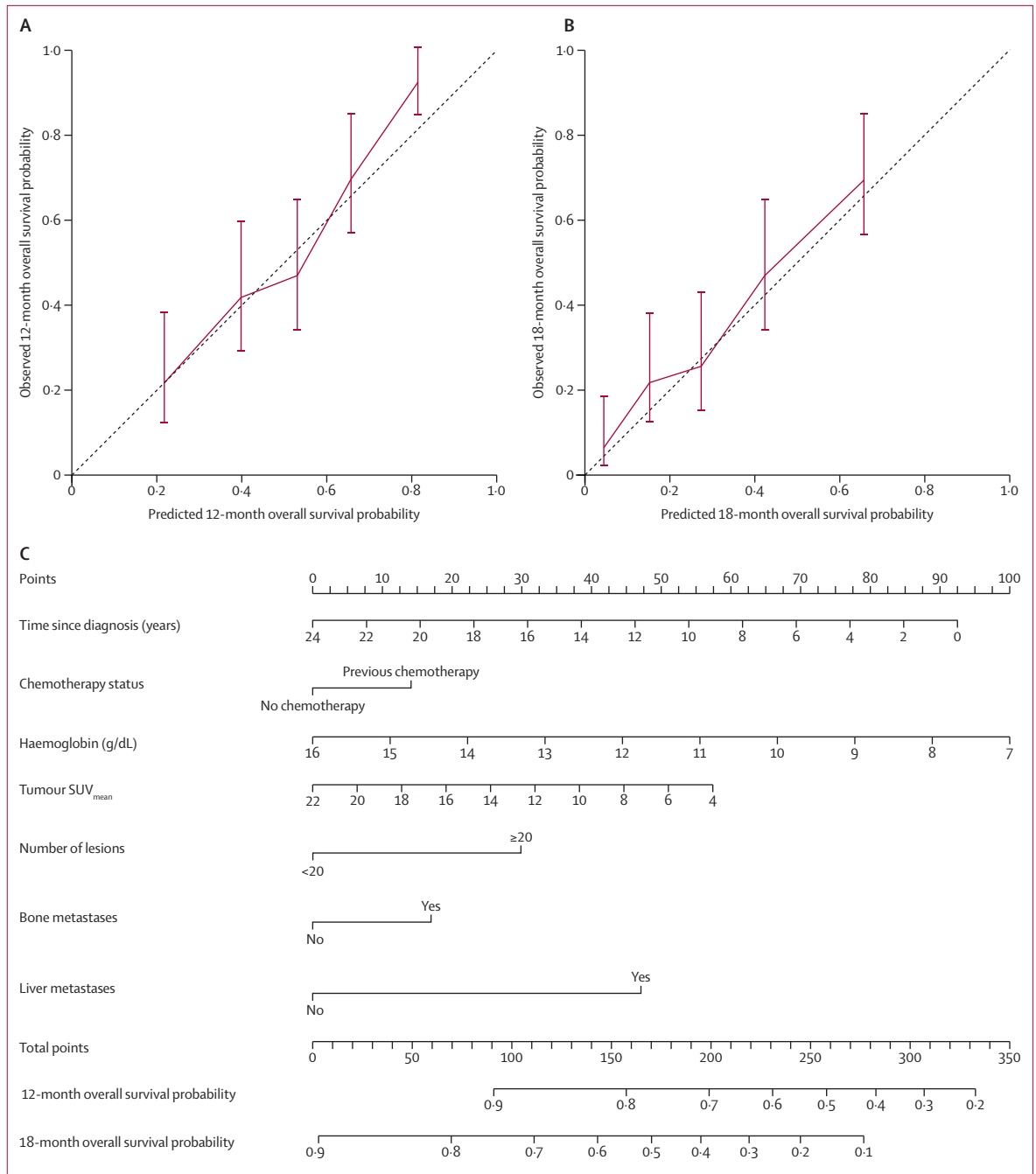


Figure 2: Overall survival probabilities

Calibration plots of overall survival probabilities at 12 months (A) and 18 months (B). Nomogram-predicted overall survival is plotted on the x-axis, with observed overall survival on the y-axis. Dashed lines along the diagonal line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (C) Nomogram for predicting probability of overall survival at 12 months and 18 months. The presence or absence of each clinical characteristic indicates a certain number of points. Number of points for each clinical characteristic is on the top row. For each characteristic, absence is assigned 0 points. The presence of characteristics is associated with a number of points generated using the nomogram function, SvyNom package in R based on the results of LASSO analysis. The points for each characteristic are summed together to generate a total-points score. The total points correspond to respective 12-month and 18-month overall survival probabilities. SUV=standardised uptake value.

Discussion

Our nomograms for overall survival, PSA-progression-free survival, and PSA50 combine traditional clinical

prognostic variables (ie, time since diagnosis, history of chemotherapy, and haemoglobin levels) and incorporate several novel prognostic variables that are relevant in this

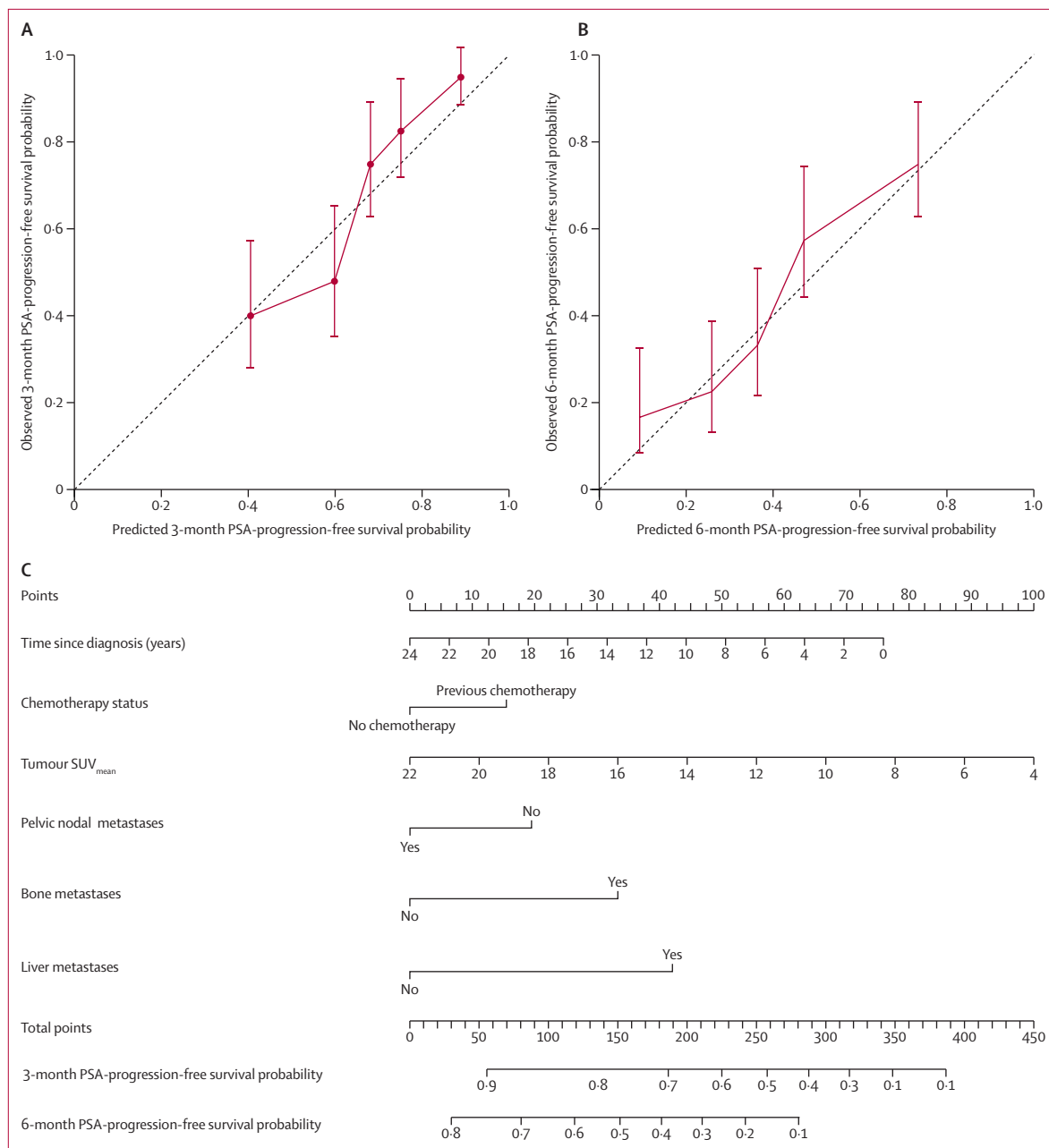


Figure 3: PSA-progression-free survival probabilities

Calibration plots of PSA-progression-free survival probabilities at 3 months (A) and 6 months (B). Nomogram-predicted PSA-progression-free survival is plotted on the x-axis, with observed PSA-progression-free survival on the y-axis. Dashed lines along the diagonal line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (C) Nomogram for predicting probability of PSA-progression-free survival at 3 months and 6 months. The presence or absence of each clinical characteristic indicates a certain number of points. Number of points for each clinical characteristic is on the top row. For each characteristic, absence is assigned 0 points. The presence of characteristics is associated with a number of points generated using the nomogram function, *SvyNom* package in R based on the results of LASSO analysis. The points for each characteristic are summed together to generate a total-points score. The total points correspond to respective 3-month and 6-month PSA-progression-free survival probabilities. PSA=prostate-specific antigen. SUV=standardised uptake value.

patient population: tumour PSMA expression, number of PSMA-positive metastatic lesions, and disease site based on molecular imaging TNM classification system.¹⁴ Tumour PSMA expression correlates with prostate cancer

aggressiveness and poor outcomes,²⁰ but higher PSMA expression leads to improved delivery of ¹⁷⁷Lu-PSMA to the tumour targets. Current and colleagues²¹ showed that higher PSMA expression results in higher deposition

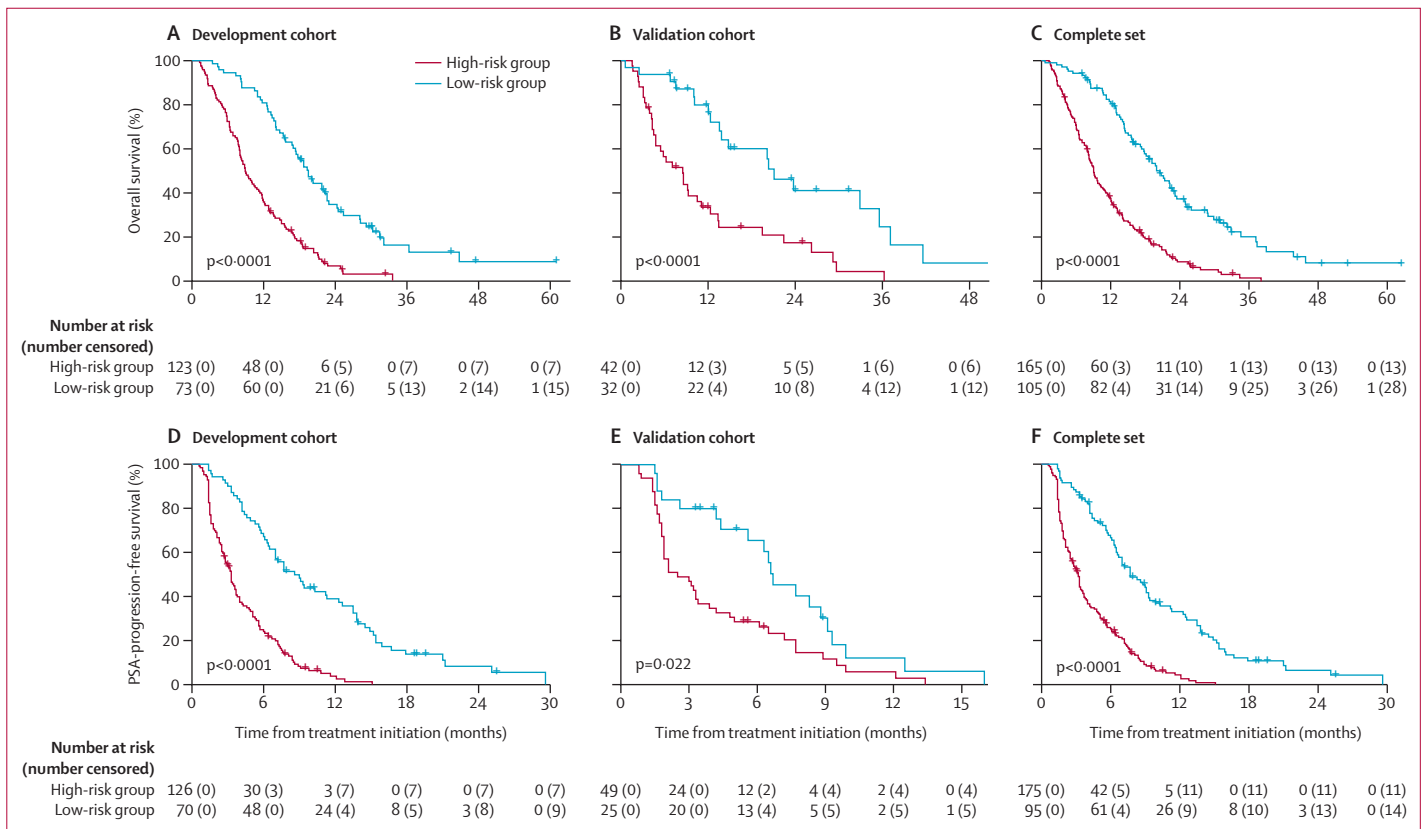


Figure 4: Survival curves by risk groups
 Overall survival curves for the development cohort (A), validation cohort (B), and complete set (C), stratified into low-risk and high-risk groups by optimal cutoff point. PSA-progression-free survival curves for the development cohort (D), validation cohort (E), and complete set (F), stratified into low-risk and high-risk groups by optimal cutoff point. PSA=prostate-specific antigen.

dose of ¹⁷⁷Lu-PSMA and consequent higher levels of DNA damage in mouse models. Our nomograms support preclinical findings and suggest that high levels of tumour PSMA expression is a requisite for favourable outcome following ¹⁷⁷Lu-PSMA (higher PSMA expression is associated with longer overall survival and PSA-progression-free survival, and greater likelihood of PSA 50% decline). As observed clinically and previously reported,²² our nomograms show that bone disease is less likely to be adequately controlled with ¹⁷⁷Lu-PSMA (patients with bone metastases have shorter overall survival and PSA-progression-free survival, and are less likely to have PSA 50% decline than patients without bone metastases). Several factors might be responsible for the resistance mechanism of bone metastases from prostate cancer: tumour microenvironment (bone lesions have a higher net growth rate compared with soft-tissue lesions²³ and can contain prosurvival factors absent in other organs²⁴) and lower target expression (lower tumour uptake in bone vs lymph nodes²⁵). By contrast with chemotherapy status, previous use of androgen receptor signalling inhibitors was not associated with outcome of our models. This finding might be related to low statistical power, as 95% of the patients in this study had received abiraterone or enzalutamide before ¹⁷⁷Lu-PSMA.

This study has several advantages compared with studies that previously identified prognostic markers for ¹⁷⁷Lu-PSMA.^{2,12,26} Our analysis included a larger multicentric population, and modelled 18 clinicopathological and imaging variables simultaneously using regression models with LASSO penalty for variable selection. Unlike other statistical modelling methods, the LASSO procedure uses shrinkage property, which results in more stable variable selection. Additionally, the identification of predictive factors does not rely on statistical significance. Other strengths of this study include external validation of the findings and the use of both clinical trial and real-world data. Previous studies showed that baseline characteristics of mCRPC trial populations differ from real-world populations, leading to differential treatment and survival.²⁷ Although building nomograms on the basis of data from phase 3 trials is meritorious, the validity of these trial-tailored models in clinical practice requires further validation in a real-world population. As such, we specifically sought to build and validate the nomograms by use of both non-trial and prospective trial data. By contrast with previous prognostic models for mCRPC that were built using data from first-line or second-line mCRPC treatments,^{7,8} we included patients who were later in their disease

course, often having exhausted most standard treatment regimens. Clinical prognostic markers previously identified in early stages of mCRPC were also selected in our final models, which validates their importance even in late-stage disease.⁸ Nomograms using PSMA-PET imaging were developed previously to predict the probability of a positive scan or upstaging in patients with early disease stage, but not for outcome of patients with mCRPC.^{28,29} Lastly, our models meet the acceptance criteria of the American Joint Committee on Cancer for inclusion of risk models for individualised prognosis in the practice of precision medicine.³⁰

This study has important clinical implications. Following the positive results of the phase 3 VISION trial,^{4,31} approval of [¹⁷⁷Lu]Lu-PSMA-617 is imminent. There is currently little evidence on patient selection for ¹⁷⁷Lu-PSMA therapy and no standardised criteria have been developed to date. Our predictive models for outcomes following ¹⁷⁷Lu-PSMA could therefore play an important role in further optimisation of trial design and individual care. These prognostic tools could aid clinical decision making, particularly at institutions where this therapy is introduced as a novel therapeutic option. To enable implementation of the nomograms in the clinical environment, we integrated our findings into an interactive risk calculator, which provides automatic prediction of patient outcomes. Nevertheless, the nomograms should not displace the well informed clinical judgment of physicians, but should instead be utilised as a complementary tool for treatment plan decision making or during discussions with patients. The nomograms can be used for patient selection in clinical trials on the basis of their predicted outcome, and randomisation can be stratified using the high-risk and low-risk grouping. The required sample size of therapy trials is calculated on the basis of the estimated percentage of treatment responders, and a higher number of non-responders requires a larger sample size. Being able to enrich trial participation with patients who are most likely to respond will result in smaller sample size, and thus reduce costs and time, and reduce the risk of exposing patients to an ineffective drug. Notably, 89% of the patients classified by our PSA50 model as non-responders did not have a PSA response, which shows the model's usefulness in identifying patients who are likely to be PSA non-responders with ¹⁷⁷Lu-PSMA.

Applicability of the current models includes patients with mCRPC who progressed on (or are unfit to receive) chemotherapy and androgen receptor signalling inhibitor agents, and have received a screening [⁶⁸Ga]Ga-PSMA-11 PET. This patient population is representative of the VISION patient cohort. Ongoing trials investigating ¹⁷⁷Lu-PSMA in the chemotherapy-naïve mCRPC setting (NCT04663997, NCT04419402) or the metastatic hormone-sensitive setting (NCT04343885,³² NCT04443062) might lead to expansion of ¹⁷⁷Lu-PSMA use with respective nomogram updates in the future. Patients enrolled in this study were treated with ¹⁷⁷Lu-labelled PSMA-617 or

PSMA-I&T. These different compounds share similar biodistribution and tumour uptake,³³ which supports the use of our models in candidates for radionuclide therapy scheduled to receive either [¹⁷⁷Lu]-PSMA-617 or [¹⁷⁷Lu]Lu-PSMA-I&T. [⁶⁸Ga]Ga-PSMA-11 PET is currently established for screening candidates for ¹⁷⁷Lu-PSMA, but ¹⁸F-labelled PSMA ligands are expected to be increasingly used. Despite no reported differences in detection rates, ¹⁸F-labelled PSMA ligands have higher tumour uptake than [⁶⁸Ga]Ga-PSMA-11.³⁴ The application of our nomograms in patients who received ¹⁸F-labelled PSMA-PET could lead to an overestimation of prognosis in our models, therefore, increasing use of ¹⁸F-labelled PSMA ligands for screening candidates for ¹⁷⁷Lu-PSMA might necessitate adaptations of the nomograms in the future.

The major limitations of this study are the absence of a prospective validation of the models and the small size of the validation cohort. Although the recommended number of at least ten events per predictor variable was followed,⁹ validation of the models in larger patient populations is warranted. The C-indices of the models when applied to the development and validation cohorts were similar, which provides evidence against overfitting the data. The prognostic discrimination (C-index: 0.72 for the overall survival model and 0.71 for the PSA-progression-free survival model) of the models were in the range of previously developed nomograms for mCRPC;^{7,8} however, the performance was not ideal. Addition of further parameters on a larger patient population might increase the prognostic discrimination. Using multicentric data collected across several countries increased the generalisability of the model, but it also increased the risk of selection bias. Also, previously identified risk factors in mCRPC, such as lactate dehydrogenase or albumin, were not available or were not collected systematically and consequently not tested in the models. Similarly, 2-[¹⁸F]FDG-PET was available only in a minority of patients in this study and thus could not be tested in the models. Dual-tracer PET imaging with [⁶⁸Ga]Ga-PSMA-11 and 2-[¹⁸F]FDG-PET can improve patient selection for ¹⁷⁷Lu-PSMA therapy;²⁶ however, several steps are required to establish 2-[¹⁸F]FDG-PET as a screening tool for ¹⁷⁷Lu-PSMA in practice (ie, confirmation of its prognostic value in a multicentre setting, standardisation of image interpretation, inclusion in drug label and guidelines, and insurance coverage). Lastly, we could not include genomic data, which was shown in a case series to be responsible for non-response to PSMA-targeted treatment despite high PSMA expression,³⁵ although this has not yet been validated in a large patient population. Cancer-specific survival has well known advantages as an endpoint over overall survival, but is often difficult to evaluate in this population with old age and multiple comorbidities. Future models should consider cancer-specific survival as an endpoint whenever reliable data is available. Re-staging PSMA-PET was not homogeneously implemented among centres for treatment response evaluation and was not

For the interactive risk calculator see <https://www.uclahealth.org/nuc/nomograms>

included in the progression-free survival analysis. The role of PSMA-PET for response evaluation is being investigated in a separate study.

In conclusion, three nomograms to predict overall survival, PSA-progression-free survival, and PSA50 in men with mCRPC receiving ^{177}Lu -PSMA radionuclide treatment were developed and externally validated. Our findings validate PSMA-PET companion imaging as a gatekeeper for patient selection and as a quantitative prognostic biomarker. Our nomograms, integrated in an online risk calculator, can assist in clinical trial design and individual clinical decision making. These models can be further tested and updated as new clinical trial data become available.

Contributors

AG, ME, WPF, JCa, JcZ, MSH, and CK were involved in the conception, design, or planning of the study. JcZ, ME, WPF, KH, JCa, CK, UH, ESD, CD'A, and DE provided resources and administrative support. AG, HW, MW, HR, RE, WRA, AR, PT, WPF, JCa, and RT collected the data. AG, TRG, and WRA analysed the data. AG, TRG, and WRA accessed and verified the underlying data. TRG and AG did the statistical analyses. AZ developed the software application. AG, ME, and WPF wrote the first draft of the manuscript with contribution from all authors. AG, ME, WPF, JCa, MSH, BH, SS, MBR, and RT critically reviewed or revised the manuscript for important intellectual content. All authors reviewed the interim drafts and the final version of the manuscript, and agree with its content and submission. AG had final responsibility for the decision to submit this manuscript for publication.

Declaration of interests

JCa reports previous consulting activities for Curium Pharma, GE Healthcare, Janssen Pharmaceuticals, and Point Biopharma, outside of the submitted work. BH reports personal fees from ABX, Bayer, Lightpoint Medical, Janssen, Bristol-Myers Squibb, and Astellas and travel fees from AstraZeneca, Janssen, and Astellas, outside of the submitted work. KH reports personal fees from Bayer, SIRTEX, Adacap, Curium, Endocyte, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Novartis, Y-mAbs, Bain Capital, and MBM Capital; personal fees and non-financial support from Sofie Biosciences; non-financial support from ABX; and grants and personal fees from BTG, outside of the submitted work. JcZ is a founder, board member, and holds equity in Sofie Biosciences and Trethera Therapeutics (intellectual property is patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics); and was a consultant for Endocyte (VISION trial steering committee), Actinium Pharmaceuticals, and Point Biopharma, outside of the submitted work. MSH reports personal fees from Janssen (lecture honorarium), Mundipharma (lecture honorarium), Astellas (lecture honorarium), AstraZeneca (lecture honorarium), and MSD (advisory forum); and research support from Endocyte, AAA, and Novartis, outside of the submitted work. WPF has been a consultant for Endocyte and BTG, and has received fees from RadioMedix and Bayer, outside of the submitted work. ME reports previous consulting activities for Blue Earth Diagnostics, Progenics Pharmaceuticals, and Point Biopharma, and a patent application for rhPSMA, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Deidentified participant data will be made available to researchers conditionally upon receipt of an approved study proposal along with evidence of approval of the proposal by an accredited ethics committee. Methodologically sound proposals for any purpose will be considered by the study committee. Proposals should be made by email to the corresponding author. To gain access, data requesters will need to sign a data access agreement.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gafita A, Calais j, Grogan TR, et al. Nomograms to predict outcomes after ^{177}Lu -PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. *Lancet Oncol* 2021; published online July 8. [http://dx.doi.org/10.1016/S1470-2045\(21\)00274-6](http://dx.doi.org/10.1016/S1470-2045(21)00274-6).

METHODS

LuPSMA Treatment Protocol

The name of the principal investigator responsible for each participating site and the number of patients recruited from each site are provided in Table A1 (p 5). Patients were treated either under a compassionate use protocol or in Phase II clinical trials (NCT03042312, ACTRN12615000912583). For patients treated under compassionate access programs, ¹⁷⁷Lu-PSMA-617 was offered as surrogate therapy in accordance with the updated Declaration of Helsinki, paragraph-37 “Unproven Interventions in Clinical Practice,” and in accordance with The German Medicinal Products of all approved treatments (without contraindications) and confirmation of the indication by both a nuclear medicine physician and an expert in urology or oncology.

Synthesis and radiolabeling of ¹⁷⁷Lu-PSMA-I&T was performed locally in the Pharmaceutical Radiochemistry Department from Technical University Munich as reported previously (1). ¹⁷⁷Lu-PSMA-617 was radiolabeled with carrier-free [¹⁷⁷Lu] Lutetium-177 (2-4). The labelled product was produced, tested, and released under Good Manufacturing Practice (GMP) conditions as a sterile and ready to use solution for infusion. LuPSMA was administered by intravenous injection. Oral hydration or administration of 500-1000 ml NaCL was performed. At three institutions, cold ice pack in the region of salivary glands was applied to minimize dry mouth: start 30 minutes prior to administration of the ¹⁷⁷Lu-PSMA-617 and continued for 4 hours (Table A8, p 8).

¹⁷⁷Lu-PSMA was administered by slow intravenous injection of 6.0 - 8.5 GBq of LuPSMA at 6 - 8 weekly intervals. Treatment was continued up to a maximum of 4 or 6 cycles in patients with absence of progression and lack of severe toxicity according to the treating physician. All patients underwent a screening [⁶⁸Ga]Ga-PSMA-11 PET/CT within ten weeks of treatment. Hematological measurements and clinical laboratory assessments were done within 24 hours before each drug injection. Institutional treatment protocols are summarized in Table A8. All treatments were performed in accordance with international procedure guidelines for radionuclide therapy with LuPSMA (5).

⁶⁸Ga-PSMA-11 PET/CT Imaging Protocol

Patients received an average±SD of 160±4 MBq ⁶⁸Ga-PSMA-HBED-CC (PSMA-11) via complete intravenous injection. Image acquisition was started after an average±SD of 62±1 minutes post-injection. Static, whole-body images were used (mid thighs to skull vertex). All scans were corrected for decay, scatter, and random coincidences. Photon attenuation was performed using CT. Images were

acquired using GE Discovery 710 (n=50), Siemens Biograph mCT (n=127), Siemens Biograph 64 (n=43) and Siemens Biograph 16 (n=20) scanners. All images were obtained in accordance with the ⁶⁸Ga-PSMA11-PET joint EANM/SNMMI guideline, ensuring harmonized quantification (21). Standard, vendor-provided image reconstructions were used. The applied reconstruction parameters are summarized in appendix Table A9 (p 8).

Data Collection and Analyses

Twenty-six pre-therapeutic parameters were collected (Table A3, p 6). 18 (69%) of 26 parameters were tested in the models as putative predictors for outcome after LuPSMA to satisfy the recommended minimal number of events per predictor (≥ 10)(6). Eight (31%) of 26 parameters were chosen to not be included in the models due to: missing values in large number of patients (lactate dehydrogenase; n=63), redundancy based on investigators clinical experience with LuPSMA and considering the results of univariate analyses (white blood cells, platelets levels, sequencing of previous drugs), and multicollinearity (SUV_{mean} with SUV_{max} , tumor volume with number of metastatic lesions, and number of previous systemic mCRPC treatments with previous docetaxel, second-line chemotherapy, and androgen receptor signaling inhibitors). SUV_{mean} was chosen over SUV_{max} because it provides a better representation of tumor expression and accounts for tumor heterogeneity. The number of metastatic lesions was chosen over PSMA-positive tumor volume because it showed higher associations with outcome data. Previous docetaxel, second-line chemotherapy, and androgen receptor signaling inhibitors were chosen over the number of previous systemic mCRPC treatments based on the results of univariate cox regression analyses and because they provide more granularity on treatment history.

Statistical Analysis

To build the PSA50 model, a penalized logistic regression model using the adaptive least absolute shrinkage and selection operator (lasso) penalty was used. The accuracy of the model was evaluated using two methods. First, model's discrimination was determined using the area under the curve (AUC) and its 95% confidence interval (CI) derived from the receiver operator characteristic (ROC) curve. Second, the calibration of the model was evaluated by comparing the predicting the probability of achieving PSA50. The model was applied on the development cohort to obtain the individual nomogram-based risk score. An optimal cutoff point for the risk score which provided a sensitivity $\geq 90\%$ for prediction of PSA50 was

calculated. A specificity $\geq 90\%$ was rationalized as offering sufficient confidence in using the nomogram in a clinical environment to identify non-responders.

Model validation was performed in two steps. Firstly, we carried out internal validation using bootstrapping to obtain an unbiased estimate of model performance. The original development cohort was resampled to obtain a dataset of the same size. Secondly, to assess external validity, the final model was applied on the independent validation cohort to obtain the individual nomogram-based risk score. The performance of the model on the validation cohort was assessed by computing the AUC and by applying the optimal cutoff obtained in the development cohort to stratify patients into responders vs. non-responders group. The predicted vs observed PSA50 response rates in responders and non-responder group were compared. The utility of the model was assessed by computing the sensitivity, specificity, positive, and the negative predictive value based on the cutoff in the development and validation cohorts.

RESULTS

PSA50 Model

Overall, 121 (45%) of 270 (95% CI 39%–51%) patients achieved a maximum PSA reduction $\geq 50\%$ from baseline. The lasso logistic analysis included in the final model of PSA50 the following variables: the chemotherapy status, tumor PSMA expression, pelvic nodal status, and liver involvement status (Figure A1, p 9). The AUC in the development and validation cohort were 0.77 (95% CI 0.71–0.83) and 0.78 (95% CI 0.68–0.88), respectively. The bias corrected AUC was 0.78 (95% CI 0.69–0.87). The sensitivity, specificity, positive predicted value, and negative predicted value was 92%, 36%, 54%, and 85% in the development cohort, respectively, and 94%, 38%, 54%, and 89% in the validation cohort. A cutoff of 41 points provided a sensitivity $\geq 90\%$ in the development cohort and was used to stratify patients from the validation cohort into responders vs. non-responders.

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Table A1. Site Description			
No. Pts.	Center	Principal Investigator	Cohort
N = 103	Technical University Munich	Dr. Eiber	Development
N = 50	Peter MacCallum Center Melbourne	Dr. Hofman	Development
N = 43	University of California, Los Angeles	Dr. Calais	Development
N = 30	University Hospital Heidelberg	Dr. Kratochwil	Validation
N = 24	University Hospital Essen	Dr. Fendler	Validation
N = 20	Excel Diagnostics Nuclear Oncology Center	Dr. Delpassand	Validation

Table A2. Eligibility criteria to receive LuPSMA and for enrollment in the international multicenter study.
<p>Eligibility criteria to receive LuPSMA</p> <ul style="list-style-type: none"> • Histopathological confirmed adenocarcinoma of the prostate • Confirmed metastatic castration-resistant prostate cancer (testosterone levels below 50 ng/dL) • Failure of standard treatments, including taxane-based chemotherapy (docetaxel, cabazitaxel) and androgen-signaling-targeted inhibitor (abiraterone, enzalutamide, or both), unless patients were unsuitable or refused these standard treatment regimens • Progressive disease by prostate-specific antigen according to Prostate Cancer Working Group 3 criteria or radiographic progression according to RECIST 1·1 • Eastern Cooperative Oncology Group performance status score of 2 or lower • Life expectancy greater than 3 months • Hemoglobin concentration greater than 90 g/L • Platelet count greater than $75 \times 10^9/L$ • Neutrophil count greater than $1.5 \times 10^9/L$ • PSMA-avid lesions on the screening PSMA-targeted PET
<p>Inclusion criteria for the international multicenter analysis:</p> <ul style="list-style-type: none"> • LuPSMA administered activity of 6·0 - 8·5 GBq • Treatment initiation between October 1, 2014 and December 1, 2018 • Available screening ^{68}Ga-PSMA11 PET/CT within ten weeks of treatment • Available baseline laboratory data within 24 hours of treatment • Available survival outcome data (Overall survival, PSA progression-free survival)

Table A3. Parameters collected		
	Parameters	Definition
Demographics	Age	Continuous, years
Initial Staging	Time since PC diagnosis	Continuous, years
	Metastatic status*	M1 vs. M0
	NCCN risk group	Low-risk vs. Intermediate-risk vs. High-risk vs. Metastatic disease
	Prostatectomy*	Yes vs. No
Treatment History	Docetaxel status	Docetaxel-naïve vs. Post-docetaxel
	Second-line chemotherapy	Yes vs. No
	Androgen receptor signaling inhibitors	Yes vs. No
	No. of previous mCRPC systemic treatments*	Continuous, no unit
Clinical Status	Drug sequencing*	Docetaxel + ARSI vs. ARSI + Docetaxel
	ECOG performance status	0-1 vs. 2
Laboratory Tests	Symptomatic status	Asymptomatic vs. Symptomatic*
	White blood cells*	Continuous, 10 ⁹ /L
	Platelets*	Continuous, 10 ⁹ /L
	Hemoglobin levels	Continuous, g/dl
	Alkaline phosphatase levels	<ULN vs. ≥ULN
	PSA levels	Continuous, ng/ml
PSMA PET/CT	Lactate dehydrogenase*	Continuous, U/L
	Tumor volume*	Continuous, ml
	Number of metastatic lesions	≥20 vs. < 20
	Tumor expression by SUVmean	Continuous, no unit
	Pelvic node (N) involvement	No pelvic nodes vs. Pelvic nodes
	Distant node (M1a) involvement	No distant nodes vs. Distant nodes
	Skeleton (M1b) involvement	No bone metastases vs. Bone metastases
	Liver (M1c) involvement	No liver metastases vs. Liver metastases
‘Superscan’ appearance	No ‘Superscan’ vs. ‘Superscan’	
<p>NOTE: N, M1a, and M1b refer to miTNM classification system. Abbreviations: PC, prostate cancer; NCCN, National Comprehensive Cancer Network; ARSI, androgen receptor signaling inhibitors; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen. *Not included in the models as putative predictor</p>		

Table A5. Equation for overall survival risk score calculation		
$Risk\ score = -0.043TDT + 0.141Docetaxel - 0.125Hemoglobin - 0.035SUVmean + 0.336Mets + 0.191Bone_mets + 0.530Liver_mets$		
Prognostic variable	Value used in equation	
Time since diagnosis to treatment ^a	Years	
Previous Docetaxel	No = 0	Yes = 1
Hemoglobin ^a	Baseline, g/dL	
Number of metastases	< 20	>20
Bone metastases	No = 0	Yes = 1
Liver metastases	No = 0	Yes = 1
Abbreviations: TDT, time from diagnosis to treatment; Mets, number of metastases. ^a Continuous variable.		

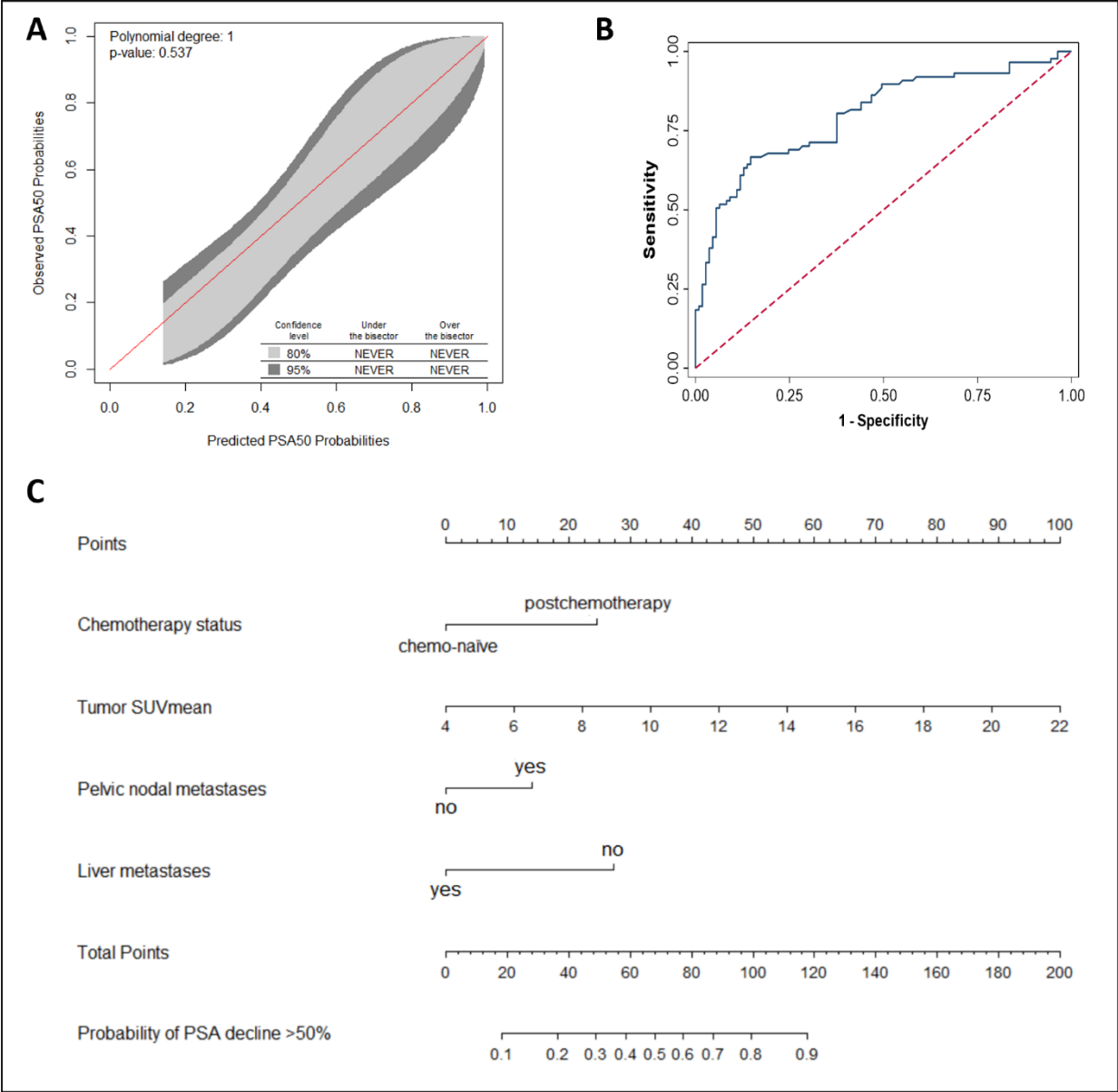
Table A6. Equation for PSA progression-free survival risk score calculation		
$Risk\ score = -0.029TDT + 0.144Docetaxel - 0.051SUVmean - 0.181PNM + 0.311Bone_mets + 0.392Liver_mets$		
Prognostic variable	Value used in equation	
Time since diagnosis to treatment ^a	Years	
Previous Docetaxel	No = 0	Yes = 1
Tumor SUVmean ^a	Baseline, no unit	
Pelvic nodes metastases	No = 0	Yes = 1
Bone metastases	No = 0	Yes = 1
Liver metastases	No = 0	Yes = 1
Abbreviations: TDT, time from diagnosis to treatment; PNM, pelvic node metastases. ^a Continuous variable.		

Table A7. Equation for PSA decline ≥50% risk score calculation		
$Risk\ score = -1.427 - 0.518Docetaxel + 0.174SUV + 0.264PNM - 0.503Liver_mets$		
Prognostic variable	Value used in equation	
Previous Docetaxel	No = 0	Yes = 1
Tumor SUVmean ^a	Baseline, no unit	
Pelvic nodes metastases	No = 0	Yes = 1
Liver metastases	No = 0	Yes = 1
Abbreviations: PNM, pelvic node metastases. ^a Continuous variable.		

Table A8. Overview of the institutional treatment protocol.							
No. Pts.	Center	Regimen	Tracer	Intervals	Activity (GBq)	Administration	Salivary gland protection
N=103	TUM	Compassionate use	¹⁷⁷ Lu-PSMA-I&T	6-8 wk	7.4	i.v. injection	Single patients
N=50	PMCC	Clinical Trial	¹⁷⁷ Lu-PSMA-617	6 wk	6.0 – 8.5	i.v. injection	No
N=43	UCLA	Clinical Trial	¹⁷⁷ Lu-PSMA-617	8 wk	6.0 – 7.4	i.v. injection	Ice pack
N=30	UKH	Compassionate use	¹⁷⁷ Lu-PSMA-617	8 wk	6 – 8.5	i.v. injection	Single patients
N=24	UKE	Compassionate use	¹⁷⁷ Lu-PSMA-617	8 wk	7.4	i.v. injection	No
N=20	EDNOC	Clinical Trial	¹⁷⁷ Lu-PSMA-617	8 wk	6.0 – 7.4	i.v. injection	Ice pack

Table A9. Overview of the applied reconstruction parameters.								
No. Pts.	Center	PET/CT system	Tracer	Matrix Size	Recon- struction algorithm	Point- Spread- Functions	Pixel size (mm)	EANM/SNMMI Guideline
N=103	TUM	Siemens, Biograph mCT	⁶⁸ Ga-PSMA	200x200	PSF-TOF (3i, 21s)	Yes	4.06x4.06	Yes
N=50	PMCC	General Electric, Discovery 710	⁶⁸ Ga-PSMA	192x192	VPFXS	Yes	2.9x2.9	Yes
N=43	UCLA	Siemens, Biograph 64	⁶⁸ Ga-PSMA	200x200	OSEM3D (2i, 24s)	No	4.06x4.06	Yes
N=30	UKH	Siemens, Biograph mCT	⁶⁸ Ga-PSMA	200x200	PSF-TOF (2i, 21s)	Yes	4.06x4.06	Yes
N=24	UKE	Siemens, Biograph mCT	⁶⁸ Ga-PSMA	200x200	PSF-TOF (3i, 21s)	Yes	4.06x4.06	Yes
N=20	EDNOC	Siemens, Biograph 16	⁶⁸ Ga-PSMA	168x168	OSEM3D (2i, 24s)	No	4.06x4.06	Yes

Figure A1. PSA decline $\geq 50\%$ (PSA50). (A) Calibration plot of PSA50. Nomogram-predicted PSA50 is plotted on the x-axis, with observed PSA50 on the y-axis. Dashed lines along the 45-degree line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (B) The receiver-operating characteristic (ROC) curve for the risk score of PSA50. (C) Nomogram for predicting probability of PSA50. The presence or absence of each clinical characteristic indicates a certain number of points. Number of points for each clinical characteristic is on the top row. For each characteristic, the absence is assigned zero points. The presence of characteristics is associated with number of points. The points for each characteristic are summed together to generate a total-points score. The total points correspond to respective PSA50 probabilities.



**Predictive value of baseline image-derived and clinical parameters for the outcome to
¹⁷⁷Lu-PSMA radioligand therapy: an international multicenter retrospective study**

Protocol Acronym: LuPSMA Prognostic Model

UCLA IRB#: 19-000896

Version 1

Date: 4-23-2019

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TABLE OF CONTENTS

1. STUDY SYNOPSIS.....	11
2. BACKGROUND AND RATIONALE....	12
3. STUDY ENDPOINTS... ..	12
2.1. Co-primary Endpoints.	12
2.2. Secondary Endpoints.....	12
4. DATA COLLECTION.....	12
3.1. Participating Sites	12
3.2. Eligibility Criteria	13
3.2.1. Inclusion Criteria.....	13
3.2.2. Exclusion Criteria	13
3.3. Database Establishment	13
5. DATA ANALYSIS.....	13
4.1. Image Analysis.....	13
4.2. Model Building	14
6. STUDY APPROVAL.	15
7. FOUNDING SOURCE.....	15
8. REFERENCES... ..	16
9. CASE REPORT FORM	17

1. STUDY SYNOPSIS

Title:	Predictive value of baseline image-derived and clinical parameters for the outcome to ¹⁷⁷ Lu-PSMA radioligand therapy: an international multicenter retrospective study
Study Description:	This is an international, multicenter, retrospective study in men with metastatic castration-resistant prostate cancer who were treated with ¹⁷⁷ Lu-PSMA radioligand therapy. LuPSMA is a novel therapeutic option which showed high PSA response rates, low toxicity, and symptomatic improvements in men with mCRPC who progressed after standard treatments. However, up to 50% of patients do not respond to LuPSMA. The aim of the study is to develop prognostic models (nomograms) for outcome after LuPSMA using baseline clinicopathologic and PSMA-PET derived parameters.
Primary Endpoint:	Overall Survival and PSA Progression-free survival
Secondary Endpoint:	PSA decline ≥50% at any time during treatment
Study Population:	<p>Estimated sample size: 250</p> <p><i>Inclusion criteria:</i></p> <ol style="list-style-type: none"> 1. mCRPC patients who were treated with 6.0 – 8.5 GBq ¹⁷⁷Lu-PSMA 2. ⁶⁸Ga-PSMA11 PET/CT performed within 12 weeks of treatment initiation 3. Clinical and biochemical information available within 8 weeks of treatment initiation 4. Outcome data available <p><i>Exclusion criteria:</i></p> <ol style="list-style-type: none"> 1. Patients who received ¹⁸F-PSMA PET at baseline
Study Design:	International, multi-center, retrospective study.
Description of Sites:	Data will be collected locally at each participating site (UCLA, Technical University Munich, Peter MacCallum Cancer Center, University Hospital Essen, University Hospital Heidelberg and Excel Diagnostics). Anonymized data will be centralized at UCLA. All analyses will be conducted at UCLA Nuclear Medicine.
Study Duration:	Estimated study duration until completion of model development is 18 months

2. BACKGROUND AND RATIONALE

In metastatic prostate cancer, progression from a hormone-sensitive state to castration-resistance marks a transition to the lethal phenotype of the disease. Despite recent innovations for the treatment of metastatic castration-resistant prostate cancer (mCRPC), more than 250,000 men are still dying from prostate cancer each year [1]. Therefore, the development of new effective therapeutic options is urgently needed. Prostate-specific membrane antigen (PSMA) is a cell surface glycoprotein overexpressed on prostate cancer cells [2]. High affinity small molecule PSMA ligands enable whole-body tumor-specific imaging (^{68}Ga -PSMA11 positron emission tomography/computer tomography; PSMA PET/CT) and systemic targeted therapy (^{177}Lu -PSMA617 radionuclide therapy; LuPSMA) [3]. LuPSMA showed high PSA response rates, low toxicity, and symptomatic improvements in men with mCRPC who progressed after standard treatments [4, 5]. These positive results have led to an ongoing randomized phase 3 study (VISION trial), which aims at drug approval. However, up to 50% of patients do not respond to LuPSMA [4, 6]. The mechanisms underlying response vs. resistance to LuPSMA are poorly understood. This gap in knowledge represents a key barrier to the development of more effective therapeutic approaches in advanced prostate cancer. It has been postulated that low tumor PSMA expression contributes to resistance to LuPSMA. Baseline clinical prognostic markers (e.g. presence of visceral metastases, high prostate-specific antigen levels) for poor survival following LuPSMA treatment were identified [5, 7]. Based on these findings, we hypothesize that clinical parameters, laboratory test values, and PSMA PET/CT derived tumor burden parameters can be used to stratify patients into likely LuPSMA responders vs. non-responders.

3. STUDY ENDPOINTS

3.1. The **co-primary endpoints** of the analysis are:

- Overall Survival (OS), defined as the time from treatment initiation to death
- PSA Progression-free survival (PSA-PFS), defined as the time from treatment initiation to PSA progression or death, whichever occurs first.

3.2. The **secondary endpoint** is PSA response ($\geq 50\%$ decline)

4. DATA COLLECTION

4.1. Participating Sites

- University of California Los Angeles
- Technical University Munich
- Peter MacCallum Cancer Center Melbourne
- University Hospital Essen
- University Hospital Heidelberg
- Excel Diagnostic Center Houston

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

5. mCRPC patients who were treated with 6.0 – 8.5 GBq ¹⁷⁷Lu-PSMA
6. ⁶⁸Ga-PSMA11 PET/CT performed within 12 weeks of treatment initiation
7. Clinical and biochemical information available within 8 weeks of treatment initiation
8. Survival data available

4.2.2. Exclusion Criteria

- Patients who received ¹⁸F-PSMA PET at baseline

4.3. Database Establishment

To generate data, we initiated a bi-centric phase 2 clinical trial of LuPSMA in mCRPC patients in 2017 (NCT03042312, IND#133661). Eligible patients underwent a baseline ⁶⁸Ga-PSMA-11 PET/CT study to confirm PSMA expression, as well as blood tests for complete blood count, metabolic panel and serum PSA levels. Outcome data of the phase 2 trial will be used as a foundation for the international database. To increase the number of patients and count for heterogeneity among different patient populations, we will additionally include men who were treated with LuPSMA at four institutions across Europe and Australia. To ensure homogeneity, European and Australian collaborators will build their datasets from patients using same inclusion criteria and treatment protocols. Research electronic data capture (REDCap) tools will be used to collect and manage the data (11). A REDCap project template that defines eligibility criteria and clinicopathologic parameters to be included in the database was created at UCLA (Appendix) and will be provided to the collaborating sites. In this way we will facilitate a standardized methodology for centralizing clinical data. Anonymized PSMA PET/CT datasets will be provided by each participating site. The international database will be stored in a central repository at UCLA. Overall, we anticipate a number of approximately 250 patients eligible for this study.

5. DATA ANALYSIS

5.1. Image analysis

The principal investigator will perform centrally tumor segmentation on PSMA-PET using the semi-automatic qPSMA software (TUM, Munich). Tumor PSMA expression will be assessed non-invasively by PET standardized uptake values (SUVmean and SUVmax). Total PSMA-positive tumor volume will also be extracted (**Fig. 1a**). The extent of disease will be categorized by an image-based TNM system [8] (**Fig. 1b**).

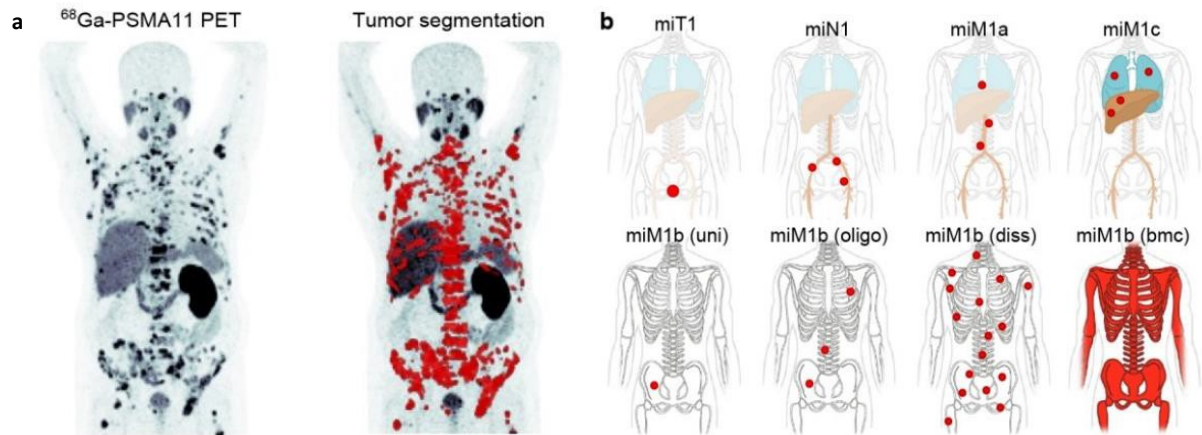


Fig. 1 | Analysis of baseline ^{68}Ga -PSMA-11 PET/CT patterns.

(a) Software based segmentation of ^{68}Ga -PSMA11 PET/CT to obtain total tumor burden delineated in red. (b) Molecular imaging TNM system to categorize patients by extent of disease into prognostic groups. Diseased regions are shown in red. Abbreviations: mi = molecular imaging; uni = unifocal; oligo = oligometastatic; diss = disseminated; bmc = bone marrow carcinomatosis.

5.2. Model Building

We will use cox and logistic regression models to construct multivariable predictive models based on pre-treatment ^{68}Ga -PSMA-11 PET scan results, laboratory values and clinical data. A summary of parameters that will be included in the model is given in **Figure 2**. Three separate models will be constructed, one for each endpoint: OS, PSA-PFS, and PSA response. For each model we will use best subsets selection to identify the optimal combination of factors for inclusion into the model. We will evaluate the performance of the model by using model-based risk scores to obtain the Harrell's concordance index (c-index). Model's calibration will be evaluated using the calibration plots by comparing the predicted vs. observed probability of death or PSA progression at different timepoints. Using the split-sample method, a training set ($\approx n=170$) and a validation set ($\approx n=80$) will be separated with a ratio of 2:1 [9]. The models will be fit in the training set; the models will then be applied to the subjects in the validation set to compute model-based risk scores (predicted probabilities). Based on these scores we will compute the c-index for each model. The utility of the model will be evaluated by creating a two-group risk model. The patients in the validation cohort will be stratified into low- and high-risk groups using the medians of the nomogram-derived risk scores. The log-rank test statistic will be used to determine whether the survival distributions between the two risk groups are significantly different. A nomogram will be created as an individualized graphical representation of each prognostic model. A desktop- and web-based risk calculator will be developed on the basis of our prognostic models to enable their implementation in clinical trial design or practice.

DEMOGRAPHICS	1. Age (continuous or by elderly)
INITIAL STAGING	2. Time since prostate cancer diagnosis (continuous) 3. Metastatic status at prostate cancer diagnosis (1: M1 / 0: M0) 4. NCCN risk group (1: low / 2: intermediate / 3: high risk / 4: metastatic) 5. Prostatectomy (1: yes / 0: no)
mCRPC HISTORY	6. No. of previous systemic treatments (continuous or by median) 7. Previous chemotherapy (1: yes / 0: no) 8. Previous second-line chemotherapy (1: yes/ 0: no) 9. Previous androgen receptor signaling inhibitors (1: yes/ 0: no) 10. Drug sequencing (1: taxanes + ARSI / 0: ARSI + taxanes)
BASELINE BIOCHEMICAL	11. Prostate-specific antigen (continuous) 12. Hemoglobin (continuous or by anemia) 13. White blood cells (continuous) 14. Platelets (continuous) 15. Lactate dehydrogenase (continuous) 16. Alkaline phosphatase (1: >ULN / 0: < ULN)
BASELINE CLINICS	17. Symptomatic disease (1: yes / 0: no) 18. ECOG Performance Status (1: 0-1 / 2: 2)
BASELINE IMAGING	19. PSMA-avid tumor volume (continuous or by median) 20. Number of lesions per PSMA PET (>20; 1: yes / 0: no) 21. SUVmean (continuous or by median) 22. SUVmax (continuous or by median) 23. N status (1: positive/ 0: negative) 24. M1a status (1: positive/ 0: negative) 25. M1b status (1: positive/ 0: negative) 26. M1c Liver status (1: positive/ 0: negative)

Fig. 2 | Summary of parameters for the prognostic model.

NCCN = National Comprehensive Cancer Network; mCRPC = metastatic castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group;

6. APPROVAL

6.1. Institutional Review of Protocol

The protocol and all forms of participant information related to the study will be reviewed and approved by UCLA IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Principal Investigators will disseminate the protocol amendment information to all participating investigators.

7. FUNDING SOURCE

This is an investigator-initiated study supported with institutional funding (Discretionary department funds) and by Prostate Cancer Foundation (Grant number: 17CHAL02). The study is and will be initiated, planned, conducted, analyzed and published by the academic investigators.

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Article #13:

Predictors and Real-World Use of Prostate-Specific Radioligand Therapy: PSMA and Beyond.

Despite the positive results of the VISION trial, up to 30% of patients have inherent resistance to PSMA-based radionuclide therapy, and acquired resistance is inevitable in all patients. Hence, strategies to increase the efficacy of PSMA-based radionuclide therapy have been under clinical investigation.

Further refinements in patient selection for ¹⁷⁷Lu-PSMA are needed to optimize outcomes as patients do not respond uniformly. Standardized criteria for PSMA-PET/CT selection and addition of FDG PET/CT as a screening procedure may increase therapeutic responses in more selectively treated patients. Predictive factors for outcome after ¹⁷⁷Lu-PSMA RNT were identified and incorporated in nomograms to assist during the patient selection process and should be tested.

Resistance mechanisms to PSMA-based RNT include low or heterogeneous tumor PSMA receptor expression, failure to deliver a lethal dose of radiation to metastatic sites, tumor microenvironment, and tumor biologic radioresistance.

Combining PSMA-based RNT with potentially synergistic agents (e.g., immune checkpoint inhibitors, PARP inhibitors, antiandrogens, CDK-4/6 inhibitor, taxanes) or using PSMA-based RNT with alpha-emitters may improve therapeutic responses. Biologic targets other than PSMA are currently being investigated for potential theranostic applications in prostate cancer.

In this article is provided a review of the potential improvements for Lu177-PSMA therapy and areas of future research.

This paper concludes this manuscript for PhD by Accreditation of Prior Learning.

Predictors and Real-World Use of Prostate-Specific Radioligand Therapy: PSMA and Beyond

Andrei Gafita, MD¹; Charles Marcus, MD²; Louise Kostos, MBBS³; David M. Schuster, MD²; Jeremie Calais, MD¹; and Michael S. Hofman, MBBS^{4,5}

OVERVIEW

PSMA is a transmembrane protein that is markedly overexpressed in prostate cancer, making it an excellent target for imaging and treating patients with prostate cancer. Several small molecule inhibitors and antibodies of PSMA have been radiolabeled for use as therapeutic agents and are currently under clinical investigation. PSMA-based radionuclide therapy is a promising therapeutic option for men with metastatic prostate cancer. The phase II TheraP study demonstrated superior efficacy, lower side effects, and improved patient-reported outcomes compared with cabazitaxel. The phase III VISION study demonstrated that radionuclide therapy with β -emitter ¹⁷⁷Lu-PSMA-617 can prolong survival and improve quality of life when offered in addition to standard-of-care therapy in men with PSMA-positive metastatic castration-resistant prostate cancer whose disease had progressed with conventional treatments. Nevertheless, up to 30% of patients have inherent resistance to PSMA-based radionuclide therapy, and acquired resistance is inevitable. Hence, strategies to increase the efficacy of PSMA-based radionuclide therapy have been under clinical investigation. These include better patient selection; increased radiation damage delivery via dosimetry-based administered dose or use of α -emitters instead of β -emitters; or using combinatorial approaches to overcome radioresistance mechanisms (innate or acquired), such as with novel hormonal agents, PARP inhibitors, or immunotherapy.

PSMA is a type 2 membrane glycoprotein that is expressed selectively by prostate cells, with expression level increasing dramatically in malignant prostatic tissue.¹ Because of its properties, PSMA has emerged as an attractive target for theranostics in prostate cancer.² In the past decade, numerous imaging and therapeutic radiopharmaceuticals targeting PSMA have been developed and investigated in clinical trials.^{3–8} PSMA-based radionuclide therapy (RNT) is a promising therapeutic option for men with metastatic prostate cancer.⁵ PSMA radioligands are internalized after binding to the target, enabling delivery of radiation directly into the malignant cells.

The β -emitting radioisotope ¹⁷⁷Lu conjugated with small molecule PSMA-617 (¹⁷⁷Lu-PSMA-617) is the PSMA-based RNT currently furthest along in clinical development. The VISION study, an international, open-label, randomized phase III trial, demonstrated that ¹⁷⁷Lu-PSMA-617 can prolong survival and improve quality of life when offered in addition to standard care in men with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed with taxanes and novel anti-androgens.⁵ In this trial, 831 patients were randomly assigned in a 2:1 ratio to ¹⁷⁷Lu-PSMA-617 (7.4 GBq

every 6 weeks for six cycles; 551 patients) plus best standard of care or standard of care alone (280 patients). The trial met both primary endpoints of overall survival (OS) and radiographic progression-free survival (PFS). The median OS was 15.3 months in the ¹⁷⁷Lu-PSMA-617 arm versus 11.3 months in the standard of care–alone arm, resulting in a 38% reduction in the risk of death. The median radiographic PFS was 8.7 versus 3.4 months, respectively. Another randomized trial (TheraP) showed that ¹⁷⁷Lu PSMA-617 led to higher prostate-specific antigen (PSA) response rates (66% vs. 37%), superior PFS (HR, 0.63), and fewer grade 3 or 4 adverse effects compared with cabazitaxel in men with mCRPC whose disease progressed after docetaxel.⁹

The U.S. Food and Drug Administration recently approved ¹⁷⁷Lu-PSMA-617 for men with PSMA-positive mCRPC previously treated with androgen receptor–targeted agents and taxane-based chemotherapy.¹⁰ Nevertheless, a subset of patients has inherent resistance to PSMA-based RNT (approximately 30% in VISION⁵ and 17% in TheraP⁹), and acquired resistance is inevitable. Hence, strategies to increase the efficacy of PSMA-based RNT have been under clinical investigation. These include better patient selection; increased

Author affiliations and support information (if applicable) appear at the end of this article.

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PRACTICAL APPLICATIONS

- Standardized criteria in PSMA PET/CT for patient selection for ^{177}Lu -PSMA radionuclide therapy (RNT) have been established, but further refinement to enhance therapeutic responses is warranted.
- Prognostic factors for outcome after ^{177}Lu -PSMA RNT were identified and included in nomograms to assist during the patient selection process.
- Contributing factors of resistance to PSMA-based RNT include heterogeneity of tumor PSMA expression, failure to deliver a lethal dose of radiation to metastatic sites, tumor microenvironment, and tumor biological radioresistance.
- Combining PSMA-based RNT with potentially synergistic agents (e.g., immune checkpoint inhibitors, PARP inhibitors, antiandrogens, CDK-4/6 inhibitor) or RNT with α -emitters may improve therapeutic responses.
- Biological targets other than PSMA showed potential for theranostic applications in prostate cancer and are currently being investigated.

radiation damage delivery via dosimetry-based administered dose or use of α -emitters instead of β -emitters; or use of combinatorial approaches to overcome radioresistance mechanisms (innate or acquired), such as with novel hormonal agents, PARP inhibitors, or immunotherapy. In this article, we provide an overview of the currently available and forthcoming PSMA-based RNT and discuss approaches aimed at improving the efficacy and safety of PSMA-based RNT.

MODELS TO PROGNOSTICATE OUTCOME AFTER PSMA-BASED RNT IN PROSTATE CANCER

Clinical Parameters Prognostic for Outcome After PSMA-Based RNT

Information gained from initial diagnosis of prostate cancer, treatment history, baseline clinical status, and laboratory values are evaluated during the screening process for PSMA-based RNT. The prognostic value of clinical parameters for outcome after PSMA-based RNT has been assessed in multiple retrospective studies.¹¹ Longer time from diagnosis of prostate cancer to initiation of ^{177}Lu -PSMA RNT was found to have a positive impact on OS and PFS.¹²⁻¹⁴ The impact of exposure to previous systemic treatments on outcome after PSMA-based RNT has been addressed in several studies. Prior treatment with

radium-223 and androgen receptor signaling inhibitors was found not to be associated with short- or long-term outcome after ^{177}Lu -PSMA RNT.^{11,15-20} In contrast, two studies reported that prior treatment with second-line taxane-based chemotherapy is associated with worse OS.^{15,16} These data, however, are subject to substantial lead-time bias. The clinical status of the patient is of importance during the screening process for PSMA-based RNT. Commonly, those with acceptable performance status are eligible for the treatment.⁵ A higher Eastern Cooperative Oncology Group score (≥ 2) and need for pain medication at treatment initiation were found to be associated with worse outcome after ^{177}Lu -PSMA RNT.^{13,16,17,21,22} Furthermore, sufficient bone marrow reserve is an important inclusion criterion among candidates for PSMA-based RNT.⁵ Bone marrow impairment may be caused by bone marrow replacement with tumor cells or exposure to prior treatments, such as chemotherapy or radiation. Patients with diffuse bone marrow involvement or “superscan” appearance on a screening bone scan were excluded from the VISION study because of lack of safety data in such patients at the time of study design.⁵ However, a report found later that ^{177}Lu -PSMA RNT is efficacious at acceptable toxicity levels in patients with diffuse bone marrow involvement, suggesting that these patients could still benefit from PSMA-based RNT.²³ Lower concentrations of hemoglobin at treatment initiation were found to be associated with shorter OS after ^{177}Lu -PSMA RNT.^{12,14,22,24} The impact of baseline tumor markers was evaluated in multiple retrospective analyses. Higher concentrations of serum PSA were prognostic of worse OS but were not associated with PFS or PSA responses.^{13,14,25,26} Higher concentrations of lactate dehydrogenase and alkaline phosphatase were also found to have a negative impact on patient prognosis.^{22,25-27} The prognostic value of neuroendocrine tumor markers such as chromogranin A and pro-gastrin-releasing peptide was also investigated; however, no correlation with OS or tumor response was found.^{25,28} Like with other mCRPC treatments, serum markers mirroring liver involvement have been found to be correlated with OS after ^{177}Lu -PSMA RNT,^{21,22,29} and visualization of liver metastases on imaging (M1c) is associated with worse outcome after ^{177}Lu -PSMA RNT.^{12-16,22,24,26} The impact of other image-derived features on treatment outcome are discussed in the following sections.

PSMA-PET as a Gatekeeper for PSMA-Targeted RNT

As part of the theranostic approach, candidates for PSMA-based RNT are routinely screened with PSMA-targeted PET/CT to evaluate the presence of PSMA-positive lesions. The VISION trial used PSMA PET/CT to select patients for inclusion. Patients eligible on the basis of PET had PSMA-positive metastatic lesions (defined as tumor maximum standardized uptake value greater than liver standardized uptake

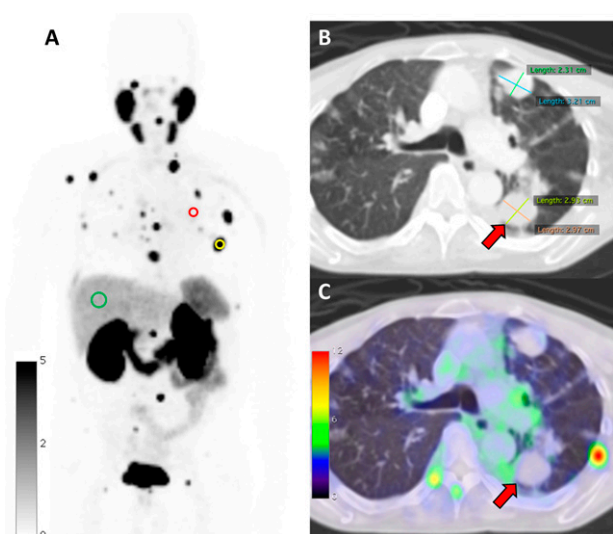


FIGURE 1. Patient Selection for PSMA-Based Radionuclide Therapy Using ^{68}Ga -PSMA-11 PET/CT

Left rib lesion (yellow circle) with PSMA uptake higher than liver uptake (green circle) (tumor maximum standardized uptake value [SUV_{max}], 17.4; greater than liver SUV_{max} , 4.2) and on PSMA PET imaging (A). This lesion is classified as “PSMA-positive” by VISION PET criteria. Left lung mass measurable by CT images according to RECIST 1.1 criteria (2.93 × 2.97 cm) (red arrows) (B,C) with PSMA uptake (red circle) lower than liver uptake (tumor SUV_{max} , 1.6; less than liver SUV_{max} , 4.2). This lesion is classified as “PSMA-negative” by VISION PET criteria.

Images courtesy of Masatoshi Hotta, University of California, Los Angeles.

value) and no PSMA-negative lesion measurable by CT (Fig. 1). The rationale of the VISION criteria for PSMA PET images was presented recently.³⁰ The liver was chosen as a reference organ to assess tumor PSMA positivity based on Deauville criteria from fluorodeoxyglucose (FDG)-PET for lymphoma,³¹ whereas the definition of PSMA-negative lesions was based on RECIST 1.1 criteria.³² The screen failure rate was “only” 13% (126 of 1,003), and some have argued that the trial could have been positive even in an unselected population.³³ A retrospective study analyzed a multicenter dataset of 301 patients treated with ^{177}Lu -PSMA to identify patients who would have been screen failures by the VISION PET criteria and were nevertheless treated on the basis of local assessment.³⁴ Twenty-nine (10%) of 301 patients with VISION PET screen failure criteria were identified, among whom 8 (3%) of 301 had low PSMA expression and 21 (7%) of 301 had PSMA-negative lesions. These patients had notably lower PSA response rates (21% vs. 50%) and shorter PSA PFS (median, 2.1 vs. 4.1 months) than patients who met the VISION PET criteria (272 [90.4%] of 301).³⁴ Similarly, several phase I/II trials of PSMA-based radioimmunotherapy (J591 Ab) performed PSMA-targeted imaging at baseline but did not use images

for patient selection.^{7,35–38} A post hoc analysis of these studies demonstrated that high PSMA uptake on baseline imaging was associated with higher rates of PSA response $\geq 50\%$.³⁹

Quantitative Parameters Versus Visual Criteria for Patient Selection for PSMA-Based RNT

The impact of whole-body tumor burden parameters derived from baseline PET images on outcome after PSMA-based RNT has been investigated in multiple retrospective studies and prospectively in the TheraP trial.^{12,27,40–43} The predictive value of PSMA-PET whole-body tumor parameters as a quantitative imaging biomarker for treatment response to ^{177}Lu -PSMA-617 was further established in a planned analysis of the randomized TheraP trial.⁴⁴ Higher PSMA tumor uptake (whole-body tumor mean standardized uptake value ≥ 10) on screening ^{68}Ga -PSMA-11 PET/CT was associated with higher odds of achieving a PSA response $\geq 50\%$ in the ^{177}Lu -PSMA-617 group compared with the cabazitaxel group (odds ratio, 12.2 vs. 2.2). Patients with very high PSMA expression randomly assigned to ^{177}Lu -PSMA-617 had a 91% response rate. The TheraP trial only included patients with high PSMA expression, and, accordingly, the group with lower PSMA expression still had a high response rate (52%). Nevertheless, calculation of whole-body tumor burden parameters requires tumor segmentation of patients with heavily metastasized disease, which is manually laborious. To enable quantitative assessment of total disease burden during treatment, different vendors are currently developing software tools, but none has been clinically validated.^{40,45–47} Hence, the quantification of whole-body tumor volume is not performed in clinical routine outside of research-focused academic centers. Given the recent U.S. Food and Drug Administration approval of ^{177}Lu -PSMA-617, optimal standardized criteria for patient selection for PSMA-targeted RNT represents an urgent clinical need. Visual criteria and standardized uptake value measurement of individual lesions seem feasible for clinical use in the near future. PROMISE criteria proposed a visual score for grading PSMA tumor expression on PET images relative to liver and parotid glands as reference organs.⁴⁸ Currently, only the liver PSMA uptake has been used as an organ of reference for screening patients for PSMA-targeted RNT.^{5,49} The feasibility of using parotid glands as an organ of reference for patient selection for PSMA-targeted RNT was investigated in a multicenter retrospective study.³⁴ Patients with higher whole-body tumor PSMA uptake than salivary gland uptake assessed visually achieved higher rates of PSA response (63% vs. 33% vs. 17%) and longer median PSA PFS (6.7 vs. 3.8 vs. 1.9 months) than those with intermediate and lower uptake. Overall, PSMA PET is a predictive whole-body imaging biomarker for response to

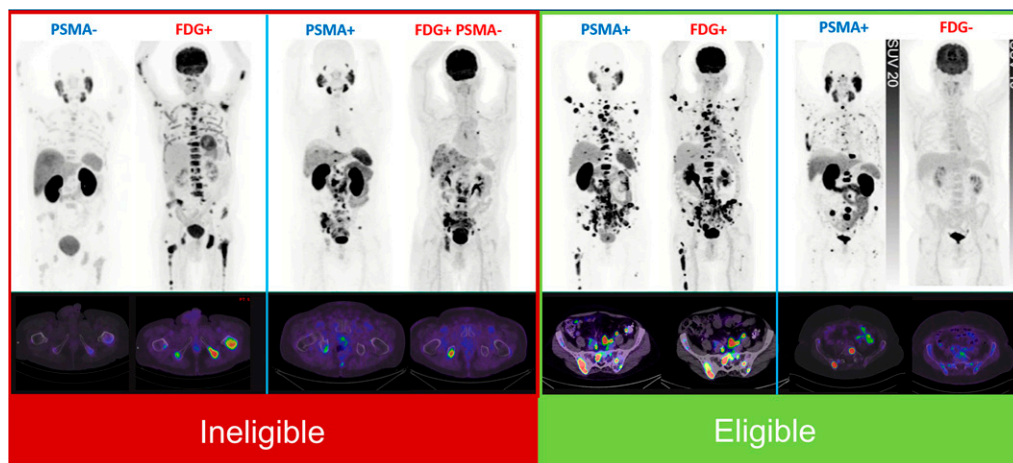


FIGURE 2. Patient Selection for PSMA-Based Radionuclide Therapy Using Dual-Tracer ^{18}F -Fluorodeoxyglucose and ^{68}Ga -PSMA-11 PET/CT Screening Procedure

Images courtesy of Prof. Michael S. Hofman, Peter MacCallum Cancer Center, Australia.

PSMA-targeted therapies in prostate cancer. Inclusion versus exclusion criteria based on baseline PSMA PET/CT imaging may be further refined.⁵⁰

Statistical Prognostic Models for Outcome After PSMA-Based RNT

An international multicenter study centralized retrospectively collected data of 270 patients treated with ^{177}Lu -PSMA RNT at six centers to develop predictive models (nomograms) for treatment outcome.¹² A penalized Cox proportional hazards model using the adaptive least absolute shrinkage and selection operator was used to develop three models to predict three outcomes: OS, PSA PFS, and PSA response. Baseline PSMA PET/CT parameters were analyzed in combination with clinical and laboratory parameters, and 18 variables were tested for associations with outcome data. Shorter time since diagnosis, previous treatment with taxanes, lower hemoglobin concentrations, lower whole-body tumor PSMA expression assessed by mean standardized uptake value, lower number of PSMA-positive tumor lesions (<20), and absence of bone (M1b) and liver (M1c) metastases were associated with longer OS (model C-index = 0.72). Similarly, shorter time since diagnosis, previous treatment with taxanes, higher whole-body tumor PSMA expression assessed by mean standardized uptake value, pelvic nodal disease (N1), and absence of bone (M1b) and liver (M1c) metastases were associated with longer PSA PFS (model C-index = 0.71). Previous treatment with taxanes, lower whole-body tumor PSMA expression assessed by mean standardized uptake value, no pelvic nodal involvement (NO), and presence of liver metastases (M1c) were associated with lower PSA response rates (model area under the curve = 0.78). Based on these nomograms, an online risk calculator was

developed and is available online at <https://uclahealth.org/nuc/nomograms>. Importantly, these prognostic nomograms were developed on the basis of data from a single-arm retrospective study. Their predictive value is yet to be evaluated using data from randomized clinical trials.

Promising Biomarkers for PSMA-Based RNT

^{18}F -FDG-PET/CT Absent or low target expression limits the response to PSMA-targeted therapies. However, one key driving parameter of patient outcome seems to be the presence of PSMA-negative lesions that can be identified with ^{18}F -FDG-PET. Two Australian landmark studies of PSMA-targeted RNT with ^{177}Lu -PSMA-617 screened patients with dual-tracer ^{68}Ga -PSMA-11 and ^{18}F -FDG-PET/CT.^{9,49} Eligibility criteria included high PSMA tumor uptake at metastatic site(s) and no discordant disease (FDG-positive lesion with no or low PSMA uptake; Fig. 2). The screen failure rates based on these combined FDG/PSMA PET images were 21% in the LuPSMA trial and 28% in the TheraP trial, which is higher than the PSMA PET-only screen failure rate of the VISION trial (13%). The PSA response rates of the LuPSMA and TheraP trials were higher than in the VISION trial (64% vs. 66% vs. 46%), likely attributed to superior patient selection by FDG-PET/CT. The prognostic value of FDG-positive tumor volume as a quantitative imaging biomarker for outcome after ^{177}Lu -PSMA-617 was established in further analyses of these trials: High FDG-positive whole-body tumor volume is prognostic of worse outcome independent of treatment (cabazitaxel or ^{177}Lu -PSMA-617).^{27,44} Previous studies demonstrated that patients with $\text{FDG}^+/\text{PSMA}^-$ discordant disease who were excluded from receiving ^{177}Lu -PSMA-617 had a notably worse OS than patients who were deemed eligible by dual FDG/PSMA PET/CT.^{51,52} One

retrospective study showed that patients with discordant FDG⁺/PSMA⁻ lesions who were still treated with ¹⁷⁷Lu-PSMA-617 had shorter OS than those without discordant disease (median OS, 6 vs. 16 months).⁵³ However, there are many unresolved issues that surround whether adding ¹⁸F-FDG-PET in the clinical setting as a screening procedure for candidates with mCRPC for PSMA-based RNT is advantageous (two different imaging procedures on two separate days, dual-readout standardized results format, insurance coverage).⁵⁴

RESISTANCE MECHANISMS AND COMBINATORIAL APPROACHES TO ENHANCE PSMA-BASED RADIONUCLIDE RESPONSES

RNT Principles

RNT requires radionuclides to be conjugated to carrier molecules for targeted delivery to tumor cells. Some RNT agents, such as radium-223-dichloride or ¹³¹I are directly delivered to the targets without a carrier molecule.⁵⁵ Prostate cancer RNT can be achieved with different radionuclides emitting decay products.

β -Particles (50-2300 keV) have the lowest linear energy transfer (0.2 keV/mm) and cause mainly single-strand DNA breaks. Because of their longer range (0.05–12 mm), β -particles travel to nearby cells (crossfire). This can be an advantage in large heterogeneous tumors but may also harm adjacent normal tissue. α -Particles (two-proton and two-neutron naked helium nucleus) have high energy (5–9 MeV) with shorter range (40–100 μ m) and the highest linear energy transfer (80 keV/mm), causing double-stranded DNA breaks and chromosomal damage independent of cell cycle and oxygenation status. This is best for small tumors or micrometastases because adjacent normal cells are spared as long as the cells themselves are not targeted by the radionuclide.^{56–58} Compared with β -particles, the equivalent radiation dose deposited in both microscopic and measurable disease is much higher when administered at a much lower administered dose.⁵⁸ Auger electrons emitted during electron capture of certain radiotracers have very low energy and moderate linear energy transfer (4–26 keV/mm) with the shortest range (2–500 nm) and must be delivered at or near the nucleus, limiting their effect to single cells.⁵⁹

Tumoricidal effects of RNT are also attributed to radiation-induced bystander effect, which is an off-target therapeutic effect on neighboring tumor cells that are not directly exposed to ionizing radiation, possibly because of complex cell signaling. An abscopal effect also may occur in distant tumor cells through a systemic immunologic response, which may also be associated with α -therapy.⁶⁰

Mechanisms of Resistance

The durability of responses for PSMA-based RNT is often short-lived, even in patients with initial responses. The mechanisms of how tumors develop resistance to PSMA-

based RNT are currently not well understood. A summary of the potential mechanisms of resistance to PSMA-based RNT is provided in Fig. 3.

Insufficient radiation dose delivery The mean whole-body tumor-absorbed radiation dose was reported to be substantially higher in responders to ¹⁷⁷Lu-PSMA than in nonresponders (median, 14.1 Gy vs. 9.6 Gy).⁶¹ The PSMA-targeting radiopharmaceutical accumulates at the tumor sites and delivers radiation that induces DNA strand breaks and causes cell death. ¹⁷⁷Lu is a β -particle emitter with a maximum soft-tissue penetration of 1.5 mm. β -Particulate emission leads mainly to single-stranded DNA breaks, and higher absorbed doses are often needed to induce double-stranded DNA breaks.^{62,63} A lack of tumor PSMA expression leads to insufficient radiopharmaceutical delivery and therefore insufficient radiation dose delivery. This is directly visualizable on PET imaging in the form of low PSMA uptake at all sites or tumor heterogeneity with areas of PSMA-negative and -positive disease.^{64,65} Neuroendocrine differentiation, which can occur in advanced prostate cancer, particularly after prolonged androgen deprivation, also suppresses PSMA expression.^{66–68} The failure to deliver a lethal dose of radiation to micrometastatic sites may also contribute to treatment resistance. Because of their travel path length, β -particles deliver high absorbed radiation to macrotumors but a lower absorbed dose to small metastatic cell clusters.^{69,70} The most frequent progression pattern after treatment with ¹⁷⁷Lu-PSMA is diffuse marrow infiltration, which may be due to small-volume disease receiving an inadequate radiation dose.⁹

Given that the therapeutic failure of ¹⁷⁷Lu-PSMA appears to be linked in many cases to the progression of micrometastatic disease, the shorter path length of other radionuclides may overcome this.^{58,71,72} α -Particles or Auger electrons differ from β -particles in terms of energy, tissue range, linear energy transfer, and the number of DNA hits required to exert a cytotoxic effect.^{73,74} In contrast to β -particles, the traversal of a single α -particle or Auger electron (if close enough to the nucleus) is enough to induce cytotoxic double-stranded DNA breaks.^{58,62,75}

Tumor microenvironment The distribution of metastatic disease also impacts response to treatment. Nodal metastases have demonstrated more significant responses than have osseous metastases to PSMA-based RNT.⁷⁶ Hepatic metastases are associated with poor response to ¹⁷⁷Lu-PSMA and inferior survival outcomes, regardless of PSMA expression.⁷⁷ Liver metastases that develop after PSMA-based RNT frequently have low PSMA expression and high metabolic activity.^{27,78} Pulmonary metastases, however, have reasonable response rates to ¹⁷⁷Lu-PSMA and do not confer a negative survival outcome.^{15,79} These differential responses based on metastatic site may be related to

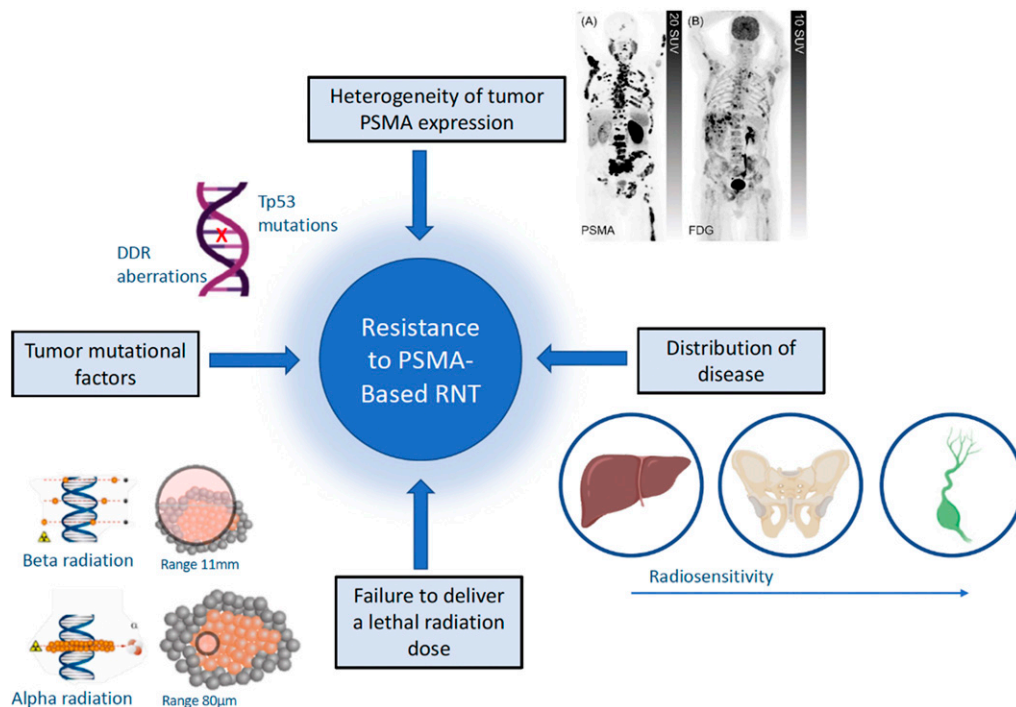


FIGURE 3. Mechanisms of Resistance to PSMA-Based Radionuclide Therapy

Abbreviations: DDR, DNA damage response; RNT, radionuclide therapy.

changes in the tumor microenvironment, with intertumor molecular heterogeneity common in advanced disease.⁸⁰ Tumor metastatic site appears to be a prognostic factor in men with mCRPC and hence is disease-specific rather than treatment-related.⁸¹ Strategies to increase the response of specific metastatic sites to ¹⁷⁷Lu-PSMA or other mCRPC systemic treatments are yet to be established.

Radioresistance Tumor mutational factors can also impact response to PSMA-based RNT. TP53 mutations, present in up to 43% of prostate cancer tumors, have been associated with radioresistance in several *in vivo* studies.^{82,83} The DNA damage response pathway is also implicated in radioresistance, with some DNA damage response aberrations being associated with poor responses to PSMA-based RNT.⁸⁴ DNA damage response alterations are present in up to 28% of prostate cancers.⁸⁵ Importantly, however, some DNA damage response alterations, such as BRCA2, increase responses to radiotherapy and possibly to RNT. To overcome radioresistance, combinatorial approaches of ¹⁷⁷Lu-PSMA with agents known to have radiosensitizing properties are currently under clinical investigation. These combinatorial approaches are discussed in the next section.

Combination Approaches

Combining PSMA-based RNT with potentially synergistic agents may improve responses. Mechanisms for this

include upregulating PSMA expression through androgen receptor-targeted agents, increasing tumor radiosensitivity through DNA repair inhibitors or agents causing additional DNA damage, targeting different PSMA-binding sites, and combining with immune checkpoint inhibitors (Fig. 4).⁸⁶ Several potential combinations are being evaluated in ongoing clinical studies (Table 1).

RNT may potentiate an immunogenic response leading to improved clinical outcomes when combined with immune checkpoint therapy. Prostate cancer is considered immunogenically “cold” with minimal T-cell infiltrates, leading to peripheral immune tolerance of the developing tumor.^{87–89} Several trials have evaluated PD-1/PD-L1 or CTLA-4 checkpoint inhibitors in patients with mCRPC, with limited clinical benefit.^{90–94} There is a need to convert the tumors from “cold” to “hot,” whereby tumor-infiltrating T cells increase to generate an antitumor response. Radiotherapy increases DNA damage and neo-antigen load through its direct cytotoxic effect, leading to increased immunogenicity.^{95–97} Some clinical studies support the hypothesis that radiotherapy combined with immune checkpoint therapy may improve outcomes in mCRPC.^{98,99} The phase I/II PRINCE trial (NCT03658447) evaluates the combination of pembrolizumab with ¹⁷⁷Lu-PSMA-617 in patients with mCRPC whose disease has progressed with a novel antiandrogen. An interim analysis found that this combination did not lead to increased toxicity

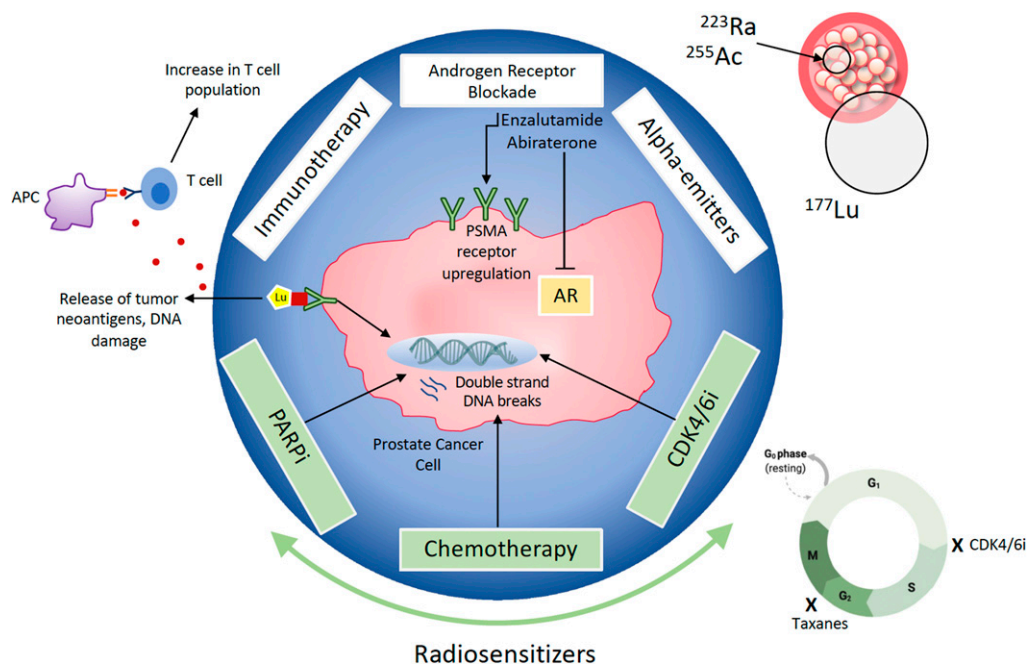


FIGURE 4. Mechanistic Rationale of PSMA-Targeting Radionuclide Therapy Combination Approaches

Abbreviation: PARPi, PARP inhibitor.

compared with either agent alone, though the results were not striking compared with ^{177}Lu -PSMA monotherapy, suggesting a need for additional checkpoint blockade to achieve synergy.¹⁰⁰ The EVOLUTION trial (NCT05150236), evaluating the triplet combination of nivolumab, ipilimumab, and ^{177}Lu -PSMA-617 in patients with mCRPC, will begin recruitment in 2022.

Inhibitors of DNA repair or DNA-damaging agents combined with PSMA-targeting RNT are likely to be synergistic. Radiation from PSMA-based RNT induces single-stranded DNA breaks and double-stranded DNA breaks by generating oxidative free radicals, activating DNA damage repair mediators such as PARP. Unrepaired double-stranded DNA breaks lead to mutagenic events and are highly cytotoxic. PARP enzyme inhibition has a radiosensitizing effect by preventing the repair of single-stranded DNA breaks and promoting cancer cell death through the accumulation of double-stranded DNA breaks.¹⁰¹ Several preclinical studies have demonstrated enhanced antitumor activity from the combination of PARP inhibitors and RNT.^{102–104} An ongoing phase I study is currently evaluating the safety and antitumor activity of olaparib in combination with ^{177}Lu -PSMA-617 in patients with mCRPC whose disease has previously progressed with novel antiandrogen therapy and docetaxel (NCT03874884).

Other agents with known radiosensitizing properties are currently being evaluated with β -emitting PSMA-based RNT. A phase I/II study is currently underway investigating the safety and preliminary efficacy of the CDK-4/6 inhibitor

abemaciclib, administered for 2 weeks before each dose of ^{177}Lu -PSMA-617 (NCT05113537). Preclinical studies have demonstrated that CDK-4/6 inhibitors sensitize cells to radiotherapy through inhibiting DNA damage repair and thereby enhancing apoptosis and blockade of cell cycle progression.¹⁰⁵ In addition, a phase I/II trial in men with mCRPC found that ^{177}Lu -PSMA-617 plus the radiosensitizer idronoxil (NOX66) is safe, although it remains unclear if this combination confers an additional antitumor effect.¹⁰⁶

Chemotherapy may improve the efficacy of RNT through treating non-PSMA-expressing sites of disease and by creating additional DNA damage.^{107,108} Taxanes, as microtubule-stabilizing agents, cause cell cycle arrest in the most radiosensitive part of the cell cycle (G_2 -M phase) and lead to tumor reoxygenation and apoptosis, thereby resulting in increased treatment potency when combined with radiotherapy.^{109,110} Previous studies have demonstrated that combining docetaxel with β -emitting PSMA-based RNT is safe and efficacious.^{111,112} A study is currently underway in Australia evaluating whether treatment with ^{177}Lu -PSMA-617 followed by docetaxel in de novo high-volume metastatic hormone-naive prostate cancer is superior to docetaxel alone (NCT04343885). In the mCRPC setting, a phase I/II trial is planned to open in 2022 in Australia, evaluating the combination of cabazitaxel chemotherapy and ^{177}Lu -PSMA-617.

Androgen receptor blockade may result in upregulation of PSMA receptor expression in castration-resistant disease, and therefore the combination with PSMA-targeted therapy

TABLE 1. Current PSMA-Targeting Radionuclide Therapy Combination Studies

Trial	Setting	Phase	Combination Strategy	Treatment
Immunotherapy				
NCT03658447	mCRPC	I/II	RNT + immune checkpoint inhibitor	¹⁷⁷ LuPSMA-617 + pembrolizumab
NCT03805594	mCRPC	I	RNT + immune checkpoint inhibitor	¹⁷⁷ LuPSMA-617 + pembrolizumab
NCT05150236	mCRPC	II	RNT + immune checkpoint inhibitor	¹⁷⁷ Lu-PSMA-617 + ipilimumab + nivolumab
NCT04946370	mCRPC	I/II	RNT + immune checkpoint inhibitor + antiandrogen therapy	²²⁵ Ac-J591 + pembrolizumab + AR pathway inhibitor (e.g., enzalutamide)
Radiosensitizers				
NCT03874884	mCRPC	I/II	RNT + PARP inhibitor	Olaparib + ¹⁷⁷ Lu-PSMA-617
NCT05113537	mCRPC	I/II	RNT + CDK-4/6 inhibitor	Abemaciclib + ¹⁷⁷ Lu-PSMA-617
NCT05340374	mCRPC	I/II	RNT + chemotherapy	Cabazitaxel + ¹⁷⁷ Lu-PSMA-617
NCT00916123	mCRPC	I	RNT + chemotherapy	Docetaxel + ¹⁷⁷ Lu-J591
NCT04343885	mHSPC	II	RNT + chemotherapy	¹⁷⁷ Lu-PSMA-617 followed by upfront docetaxel
PSMA Upregulation				
NCT04419402	mCRPC	II	RNT + antiandrogen	Enzalutamide + ¹⁷⁷ Lu-PSMA-617
Radionuclides				
NCT04886986	mCRPC	I/II	α - + β -RNT	²²⁵ Ac-J591 + ¹⁷⁷ Lu-PSMA-I&T
AlphaBet (planned)	mCRPC	I/II	α - + β -RNT	²²³ Ra + ¹⁷⁷ Lu-PSMA-I&T

Abbreviations: AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer; RNT, radionuclide therapy.

may be synergistic.^{113–117} A retrospective analysis of patients with mCRPC comparing those who received ¹⁷⁷Lu-PSMA alone versus in combination with abiraterone acetate found that survival outcomes were superior in the combination group.¹¹⁸ Androgen receptor pathway inhibitors were administered in combination with ¹⁷⁷Lu-PSMA-617 in 52.6% of patients in the VISION trial, and responses were most pronounced in this subgroup. The ENZA-p trial is currently recruiting and is evaluating the combination of enzalutamide with ¹⁷⁷Lu-PSMA-617 versus enzalutamide alone.¹¹⁹

RNT with α -particles targets micrometastatic disease more efficiently than β -particles and hence may improve the therapeutic effect of RNT. ²²⁵Ac-J591, a PSMA-directed monoclonal antibody radiolabeled with an α -emitter, is currently being studied with ¹⁷⁷Lu-PSMA-I&T ([NCT04886986](#)). The different binding sites of J591 and PSMA-I&T mean that theoretically additive radiation to PSMA-positive cells should occur when administered concurrently. A phase I/II study, the AlphaBet trial, evaluating the combination of ¹⁷⁷Lu-PSMA with ²²³Ra to target both the PSMA-expressing cancer cells and the bone microenvironment around the osseous metastasis, will start recruitment in 2022 in Australia.

Combining potentially synergistic agents with RNT has the potential for increased toxicity, and it is yet to be determined whether a combination or sequential approach

is more efficacious. There is an ongoing need for randomized controlled trials to assess this. The additional antiproliferative effect of some agents may also reduce cellular sensitivity to radiation; however, this is yet to be observed.⁸⁴

Clinical trials of RNT with ¹⁷⁷Lu-PSMA earlier in the prostate cancer disease course are ongoing. The LuTectomy trial¹²⁰ is evaluating the use of ¹⁷⁷Lu-PSMA-617 in the neoadjuvant setting in men with high-risk PSMA-positive prostate cancer who are undergoing surgery. The UpfrontPSMA¹²¹ and PSMAddition¹²² trials are evaluating ¹⁷⁷Lu-PSMA-617 in the metastatic hormone-sensitive space, whereas the ENZA-p,¹¹⁹ PSMAfore,¹²³ and [NCT04663997](#) trials are evaluating RNT in early-stage mCRPC. These trials may provide guidance for the optimal sequencing of ¹⁷⁷Lu-PSMA in prostate cancer. The impact on resistance mechanisms of applying PSMA-based RNT in these earlier stages is yet to be determined.

BEYOND LUTETIUM: NEXT-GENERATION RADIONUCLIDE THERAPEUTICS IN PROSTATE CANCER

¹⁷⁷Lu-PSMA-617 has shown promise in the theranostic approach to the treatment of prostate cancers but has its own limitations.^{9,124–127} As described above, α -emitters have advantages in their mechanisms of cell damage.⁵⁸ This

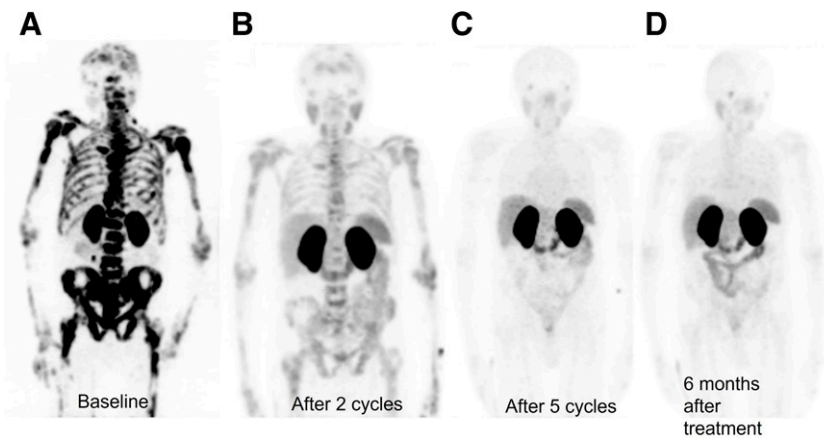


FIGURE 5. Case Example of PSMA-Targeted α -Radionuclide Therapy

A 69-year-old male with metastatic castration-resistant prostate cancer progressing after docetaxel was treated with five cycles of ^{225}Ac -PSMA-617. The patient experienced a remarkable response to targeted α -therapy by serum prostate-specific antigen (declining from 4,495 ng/mL at baseline to 18.51 ng/mL [−99%] after five cycles and 4.75 ng/mL [−99%] at 6 months after completion of treatment) and by PSMA PET [baseline ^{68}Ga -PSMA-11 PET/CT coronal maximum intensity projection (A) after two cycles of ^{225}Ac -PSMA-617, (B) after five cycles of ^{225}Ac -PSMA-617, (C) and at 6 months after completion of treatment (D)] without additional treatment.

Images courtesy of Mike Sathegke's laboratory and Ishmaheel Lawal, University of Pretoria, South Africa.

may be advantageous in diffuse bone marrow tumor infiltration and when prior RNT has failed owing to fewer off-target adverse effects. However, there is limited availability of α -emitters,¹²⁸ radiochemistry is more challenging, and the α -particles can have toxic effects if a healthy organ expresses the molecular targets (e.g., salivary gland toxicity with PSMA radioligands labeled with ^{225}Ac). Although they do not pose any external radiation hazard, α -particles can be dangerous if internalized, so proper radionuclide handling is important.¹²⁹ Most of the current limited sources of ^{225}Ac are obtained from thorium-229 generators derived from stockpiles of uranium-233.¹²⁸ Other potential production methods are currently being explored, with growing interest in targeted α -therapy.¹³⁰

Radium-223 Dichloride The first clinically approved α -emitter agent for mCRPC was ^{223}Ra -dichloride, offering a large improvement in quality of life and reduction in alkaline phosphatase and skeleton-related events, with some advantage in OS.⁵⁵ However, this bone-specific radionuclide has no effect on soft-tissue or circulating components of the tumor.

^{225}Ac -based targeted α -therapy The most studied targeted α -therapy in prostate cancer is ^{225}Ac -PSMA-617, a urea-based anti-PSMA small molecule using a DOTA chelator with good tumor cell internalization and low renal uptake. ^{225}Ac has a physical half-life of 9.9 days. Early studies indicate a good safety profile with low bone marrow toxicity even in patients with extensive osseous metastases.¹³¹ Among patients most often selected for ^{225}Ac targeted α -therapy,

multiple lines of therapies have often failed, including chemotherapy, androgen deprivation therapy, and/or ^{177}Lu -PSMA RNT, with PSMA PET/CT demonstrating radiotracer uptake within metastatic lesions. Treatment regimens vary from a standard fixed dose of 100 kBq/kg each cycle^{131,132} to a de-escalation approach starting at 8 MBq,¹³³ ranging from one to eight cycles approximately 8 weeks apart.

A systemic review and meta-analysis of ^{225}Ac -PSMA-617 targeted α -therapy in mCRPC including 141 patients showed advantages in PSA response and patient outcome with a low toxicity profile. Any PSA decline was reported in 83% of patients and $\geq 50\%$ PSA decline in 59% of patients. Molecular response was reported in 17% (Fig. 5). Advantages in survival (median PFS, 12 months) were observed. The most often encountered side effect was xerostomia (63%), followed by anemia (54%), fatigue (45%), grade 3 nephrotoxicity (5%), and grade 3 leukopenia/thrombocytopenia (0.9%).¹³⁴ Outcome appears to vary with treatment-resistant disease and prior treatment modalities.^{131,133,135–137} ^{225}Ac -PSMA-617/ ^{177}Lu -PSMA-617 tandem therapy methods in patients for whom ^{177}Lu -PSMA-617 RNT has failed are being explored with stable to partial treatment response in up to two-thirds of the patients, with authors reporting less severe xerostomia and hematotoxicity.^{138,139}

Other targeted α -therapy options²¹¹ At has favorable characteristics with a 7.2-hour half-life, and a urea-based small PSMA molecule is being studied. Preclinical studies have shown improved results in micrometastatic models.¹⁴⁰ Other agents being evaluated for PSMA-targeted

targeted α -therapy include lead-212–labeled small peptides, ^{213}Bi -labeled small molecules/nanoparticles, and PSMA-targeted thorium-227 conjugates.^{141–143}

Auger Electron-Based Therapy

Terbium-161 is a dual β /Auger emitter, with higher radiation-absorbed doses in modeling suggesting superior responses for micrometastatic disease in single-cell or cell cluster models.¹⁴⁴ These have been confirmed in survival viability, survival, and in vivo experiments in tumor-bearing mice.¹⁴⁵ Auger electron emitters such as ^{125}I are being explored when complexed to PSMA targets. In vivo studies evaluating a highly specific small-molecule ^{125}I -DCIBzL have shown antitumor effects with the potential for fewer off-target and on-target adverse consequences.^{146,147}

Radionuclide Vectors

The therapeutic and adverse effects of RNT are also dependent on the carrier molecule (i.e., vector), including the binding molecule and the chelator, especially with α -emitters such as ^{225}Ac , which has multiple decays and may dissociate from the chelator.⁵⁷ PSMA-targeting carriers include antibodies to PSMA, as well as urea-, phosphorous-, or thiol-based small molecules that interact with the PSMA transmembrane glycoprotein.¹⁴⁸ Antibody-based ligands such as J591 may have a more controlled biodistribution, thereby reducing radiation damage to normal tissues such as salivary glands because of relatively lower concentration in salivary tissue, but they can have hematotoxic effects due to longer circulation time in comparison with small molecules because of their size.^{57,149} Small molecules are cleared faster, demonstrate increased tumor penetration, and can overcome barriers to tumor drug delivery compared with larger molecules or antibodies, and they have advantages of better tumor penetration and faster clearance with lower bone marrow dose, especially in patients with bone marrow infiltration. However, strategies to decrease salivary gland damage from these molecules must be explored.^{59,149} These radiopharmaceuticals have a wide range of pharmacokinetics, and matching the physical half-life with the biologic half-life is crucial to balancing the therapeutic effects with potential toxicity.^{59,150} Using chelators such as albumin-based chelators can increase the biologic circulating half-life and tissue distribution of the RNT agents, resulting in increased and longer uptake in the tumor cells with reduced renal retention.¹⁵¹ Studies using radiopharmaceuticals other than the carrier PSMA-617 targeting small molecules/antibodies for RNTs include ^{177}Lu -PSMA-I&T,^{26,152,153} ^{177}Lu -rhPSMA,¹⁵⁴ Glu-urea-Lys target moieties such as ^{177}Lu -L1/ ^{225}Ac -L1,¹⁵⁵ ^{177}Lu -CTT1403, a peptidomimetic inhibitor of PSMA,¹⁵⁶ PSMA-targeted thorium-227 conjugate,¹⁴² ^{177}Lu -Ludodiapep (FC705),¹⁵⁷ ^{177}Lu -PSMA-R2,¹⁵⁸ and ^{177}Lu -EB-PSMA-617,¹⁵⁹ among others. Also underway are studies evaluating ^{225}Ac -

PSMA-J591, a human monoclonal antibody targeting the extracellular PSMA domain (see Table 1).^{160–162}

Potential Other Biologic Targets (Non-PSMA)

Potential non-PSMA targets are also being explored for prostate cancer RNT. Mitochondrial hexokinase-2 activity in prostate cancer cells has been seen in androgen-deprived cancer cells. Inhibiting hexokinase-2 may make these cells respond to androgen deprivation therapy and may be the basis of a new targeted RNT approach.¹⁶³

RNT targeting a serine protease enzyme, human kallikrein 2, is being studied with ^{177}Lu and ^{225}Ac -hu11B6 in prostate xenografts^{164,165} and in a phase I trial (NCT04644770). STEAP and DMT1 are overexpressed in many malignant tumor cells.¹⁶⁶ ^{89}Zr DFO-MSTP2109A, an antibody against STEAP1, is currently being studied.¹⁶⁷

Prostate cancer cells with neuroendocrine differentiation after treatment pose treatment challenges.¹⁶⁸ These cells preferentially express the inhibitory cell surface ligand δ -like ligand 3, which may be a potential biomarker target for non-PSMA-based PET detection using radiotracers such as ^{89}Zr -SC16.¹⁶⁹ Similarly, CEACAM5, a prostate neuroendocrine tumor-specific target, is being evaluated.⁶⁸ Somatostatin receptor-targeting theranostics approaches may be exploited in these patients if there is sufficient somatostatin receptor expression by these cells.^{170–172}

CONCLUSION

PSMA-based RNT is a novel therapeutic option and a new third-line treatment option for patients with mCRPC. As part of the theranostic approach, patients are being screened with PSMA PET/CT to confirm PSMA-positive disease. Standardized criteria for PSMA PET/CT–based patient selection have been developed. Addition of FDG-PET/CT as a screening procedure may increase therapeutic responses in more selectively treated patients, but its added value in the clinical setting requires further investigation. Predictive factors for outcome after ^{177}Lu -PSMA RNT were identified and incorporated in nomograms to assist during the patient selection process. Resistance mechanisms to PSMA-based RNT include low or heterogeneous tumor PSMA receptor expression, failure to deliver a lethal dose of radiation to metastatic sites, tumor microenvironment, and tumor biologic radioresistance. Combining PSMA-based RNT with potentially synergistic agents (e.g., immune checkpoint inhibitors, PARP inhibitors, antiandrogens, CDK-4/6 inhibitor, taxanes) or using PSMA-based RNT with α -emitters may improve therapeutic responses. Biologic targets other than PSMA are currently being investigated for potential theranostic applications in prostate cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_350946.

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SERMENT DES DOCTEURS

« En présence de mes pairs. Parvenu à l'issue de mon doctorat en **Imagerie et Physique Médicale**, et ayant ainsi pratiqué, dans ma quête du savoir, l'exercice d'une recherche scientifique exigeante, en cultivant la rigueur intellectuelle, la réflexivité éthique et dans le respect des principes de l'intégrité scientifique, je m'engage, pour ce qui dépendra de moi, dans la suite de ma carrière professionnelle quel qu'en soit le secteur ou le domaine d'activité, à maintenir une conduite intègre dans mon rapport au savoir, mes méthodes et mes résultats. »

DOCTORS OATH

« In the presence of my peers. With the completion of my doctorate in **Medical Physics and Imaging**, in my quest for knowledge, I have carried out demanding research, demonstrated intellectual rigor, ethical reflection, and respect for the principles of research integrity. As I pursue my professional career, whatever my chosen field, I pledge, to the greatest of my ability, to continue to maintain integrity in my relationship to knowledge, in my methods and in my results. »

