UCSF Helen Diller Family Comprehensive Cancer Center

Theragnostics and Novel Imaging in RCC

Arpita Desai MD

Assistant Professor

Medical Director GU Oncology

University of San Francisco California

Current Imaging Guidelines:

- MRI or Triple phase CT with IV contrast to characterize the kidney primary and assess for IVC thrombus
- CT chest to evaluate for metastatic disease
- Bone scan and MRI or CT of the brain if there are symptoms suggestive of metastatic disease
- Functional/theragnostic imaging not recommended yet based on consensus guidelines.

Arpita Desai/UCSF
@ADESAIONCMD
Ljunberg *et al* 2022
Motzer *et al* 2024

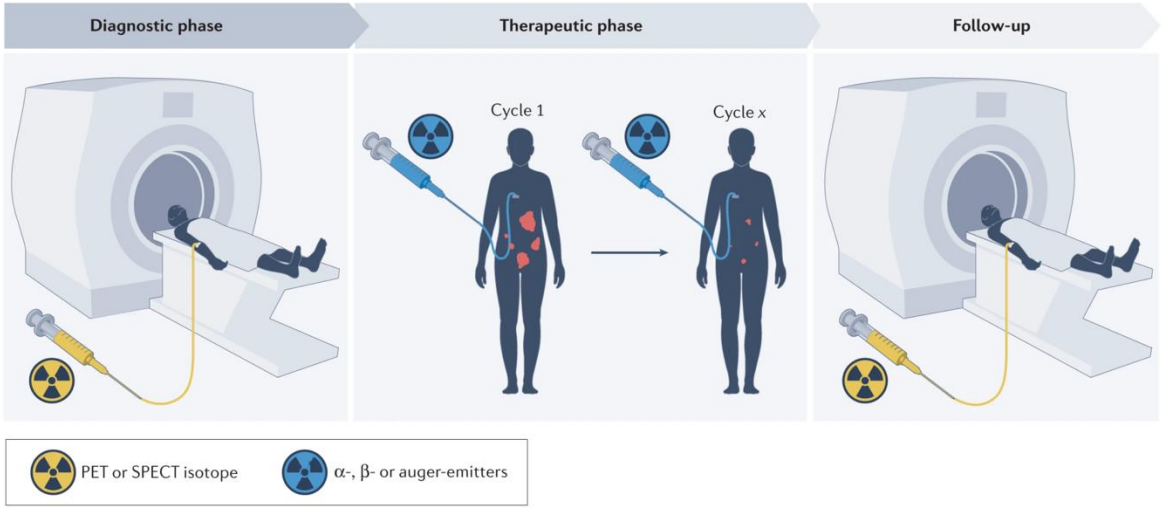
Challenges in RCC management

- Diagnostic Challenges:
  - Early detection difficulties
  - Differentiating benign from malignant tumors
  - Accurate staging and assessment of tumor burden
- Therapeutic Challenges:
  - Drug resistance
  - Side effects of systemic therapy
  - Lack of biomarkers

Arpita Desai/UCSF
@ADESAIONCMD

Theragnostics

Innovative approach that combines diagnostic and therapeutic capabilities in a single agent

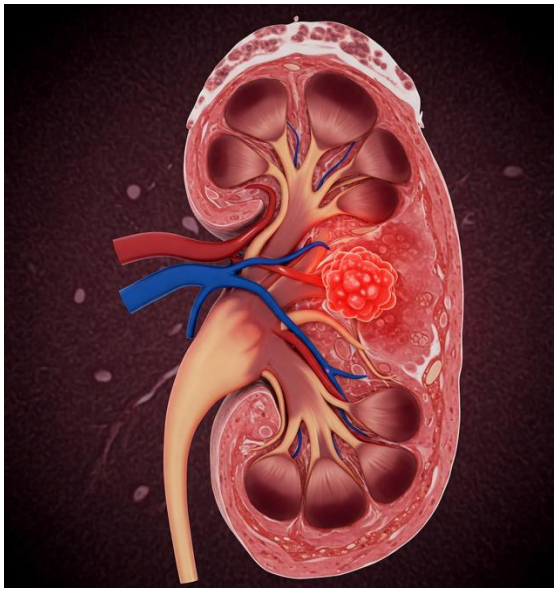


Arpita Desai/UCSF
@ADESAIONCMD

Bodei *et al* Nature rev Cli Onc 2022

Localized Kidney Cancer

- CA IX based
- Technetium Sestamibi

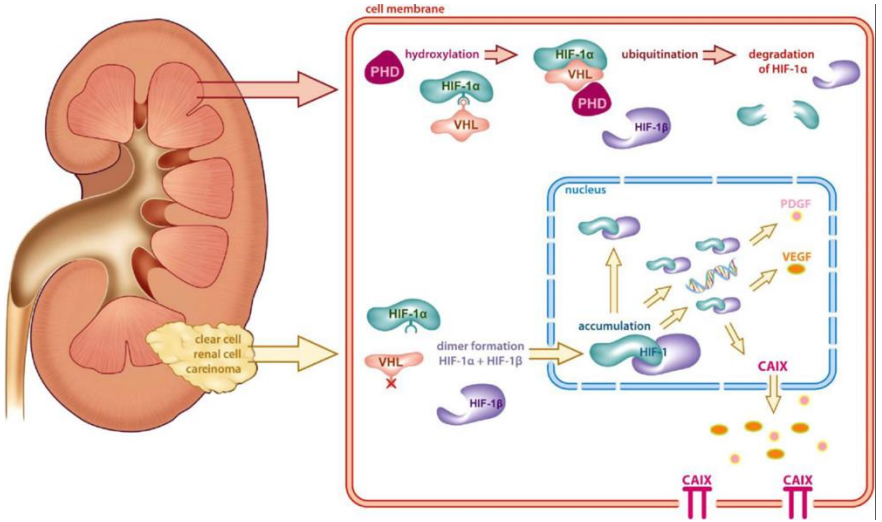


Arpita Desai/UCSF
@ADESAIONCMD

Image created with Gemini

Ca-IX

- ^{89} Zirconium Girentuximab
- ^{124}Iodine Girentuximab



Arpita Desai/UCSF
@ADESAIONCMD

Wu *et al* Mol. Pharmaceutics 2022

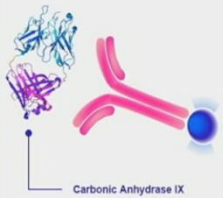
ZIRCON trial

Girentuximab

- IgG1 kappa light chain chimeric monoclonal antibody
- Girentuximab binds with high specificity to CAIX and is internalized
- Extensive safety experience with girentuximab in prior imaging and therapeutic studies
- Hepato-biliary excretion allows optimal renal visualisation

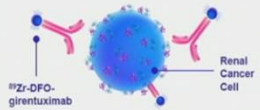
Payload: ^{89}Zr

- Positron emitter
- $T_{1/2}$ 3.3 days
- Suited for antibody-based imaging
- Hepatically cleared



^{89}Zr-DFO-girentuximab in CAIX expressing tumors

- Previous studies show feasibility imaging CAIX positive tumors (SPECT & PET)[1,2]
- ^{89}Zr-DFO-girentuximab (37 MBq [1 mCi] / 10 mg) was previously shown safe and allowed PET/CT imaging of ccRCC at 4-7 days after administration[3]



^{89}Zr-girentuximab administration
Initial sample size: n=252
Adapted size: n=300
Day 0

Abdominal PET/CT imaging[a]
*Blinded central image review**
Performed 5 ± 2 days post-administration

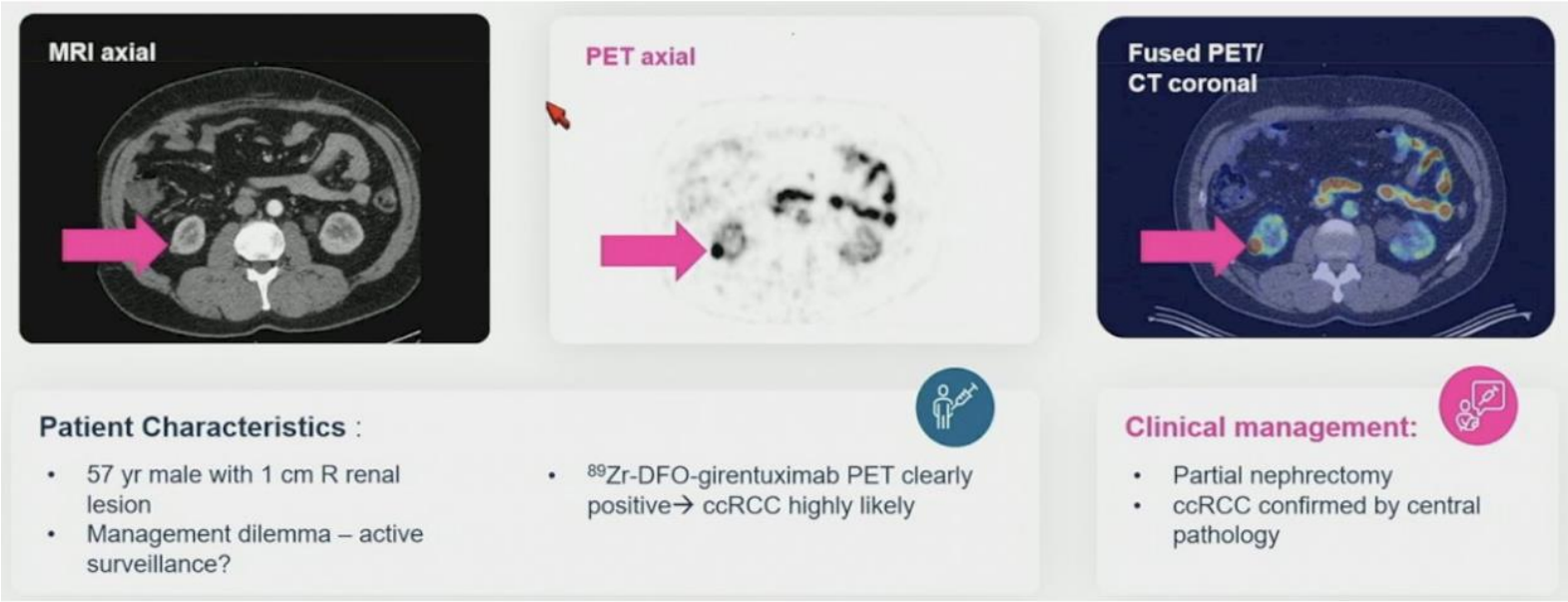
Partial/Radical Nephrectomy
*Central histology review**
Within 90 days post-^{89}Zr-DFO-girentuximab administration

Arpita Desai/UCSF
@ADESAIONCMD

Shuch *et al* 2023

ZIRCON trial

N= 284, Sensitivity= 85.5%, Specificity=87%, PPV%=93%, NPV%=86%



Arpita Desai/UCSF
@ADESAIONCMD

Shuch *et al* 2023

VOLUME 31 · NUMBER 2 · JANUARY 10 2013

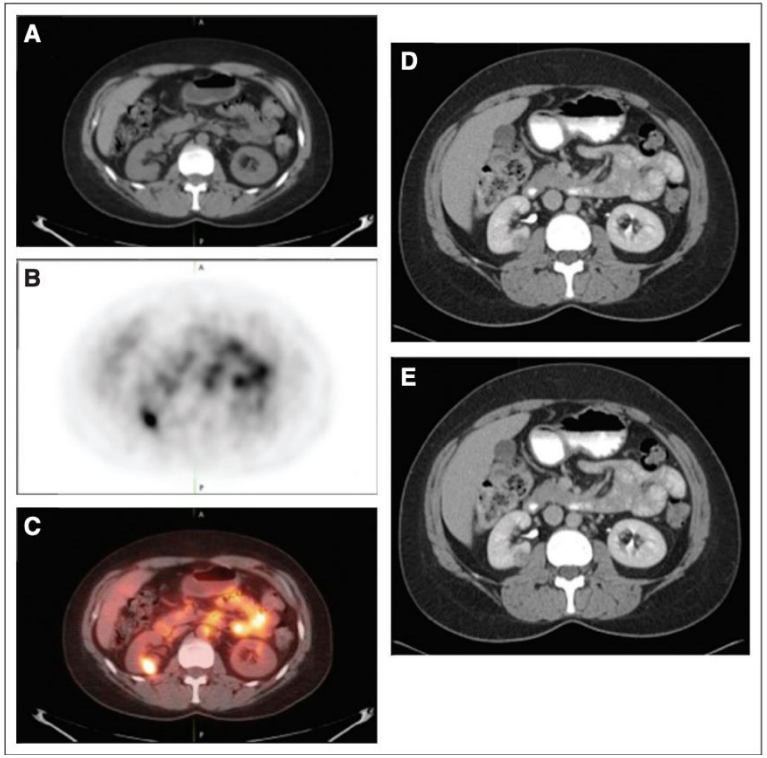
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

REDECT trial

Positron Emission Tomography/Computed Tomography Identification of Clear Cell Renal Cell Carcinoma: Results From the REDECT Trial

Chaitanya R. Divgi, Robert G. Uzzo, Constantine Gatsonis, Roman Bartz, Silke Treutner, Jian Qin Yu, David Chen, Jorge A. Carrasquillo, Steven Larson, Paul Bevan, and Paul Russo

- n= 195
- Sensitivity= 86.2%
- Specificity= 85.9%

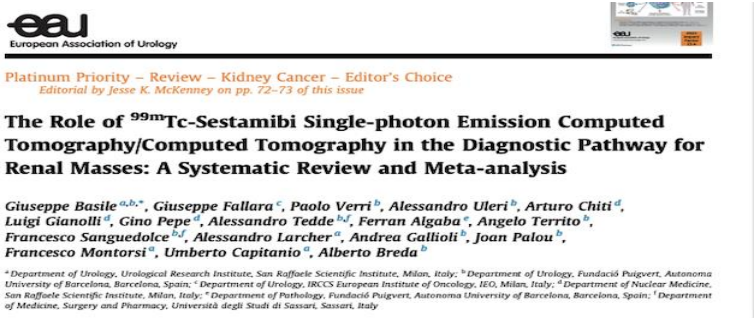


Arpita Desai/UCSF
@ADESAIONCMD

CA-IX based tracers

- Advantages:
  - Low background uptake in normal tissues
  - Increased sensitivity in detecting small /low grade RCC.
  - High specificity for Clear cell RCC
- Disadvantages:
  - Long scan time
  - Specialized facilities with long production time

Arpita Desai/UCSF
@ADESAIONCMD



European Association of Urology

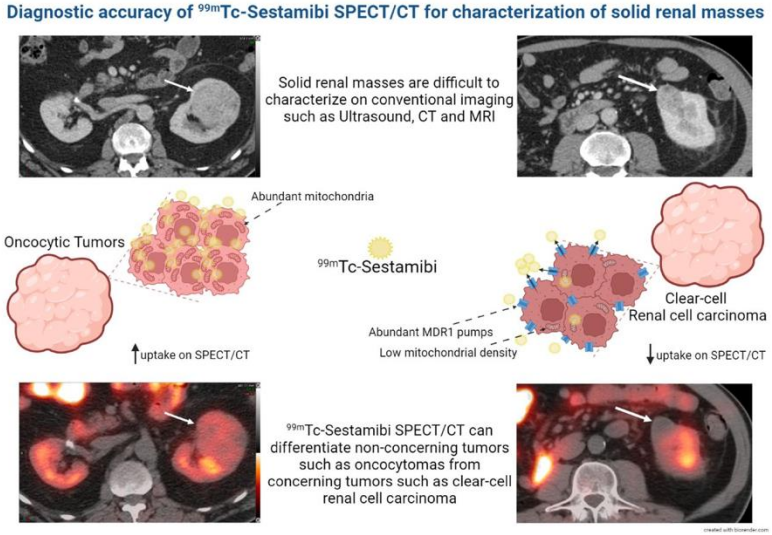
Platinum Priority – Review – Kidney Cancer – Editor's Choice

Editorial by Jesse K. McKenney on pp. 72–73 of this issue

The Role of ^{99m}Tc-Sestamibi Single-photon Emission Computed Tomography/Computed Tomography in the Diagnostic Pathway for Renal Masses: A Systematic Review and Meta-analysis

Giuseppe Basile [a,b,], Giuseppe Fallara [c], Paolo Verri [b], Alessandro Uleri [b], Arturo Chiti [d], Luigi Gianolli [d], Gino Pepe [d], Alessandro Tedde [b,f], Ferran Algaba [e], Angelo Territo [b], Francesco Sanguedolce [b,f], Alessandro Larcher [a], Andrea Gallioli [b], Joan Palou [b], Francesco Montorsi [a], Umberto Capitanio [a], Alberto Breda [b]*

[a] Department of Urology, Urological Research Institute, San Raffaele Scientific Institute, Milan, Italy; [b] Department of Urology, Fundació Puigvert, Autonoma University of Barcelona, Barcelona, Spain; [c] Department of Urology, IRCCS European Institute of Oncology, IEO, Milan, Italy; [d] Department of Nuclear Medicine, San Raffaele Scientific Institute, Milan, Italy; [e] Department of Pathology, Fundació Puigvert, Autonoma University of Barcelona, Barcelona, Spain; [f] Department of Medicine, Surgery and Pharmacy, Università degli Studi di Sassari, Sassari, Italy



- N= 489 (2016-2023)
- Sensitivity and specificity: 89%
- NPV: 98%
- Low specificity in differentiating oncocytoma
- from chromophobe RCC (46%)

Parihar et al JNM 2023

Metastatic Kidney Cancer

- PSMA PET
- FDG PET

Image created with Gemini

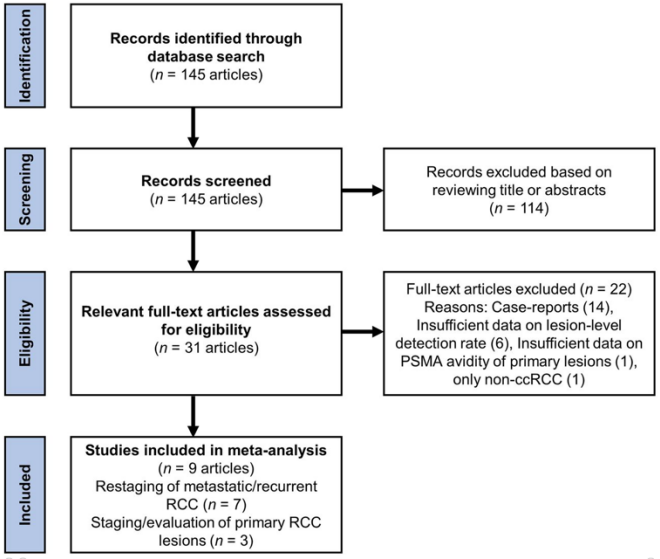
Arpita Desai/UCSF
@ADESAIONCMD

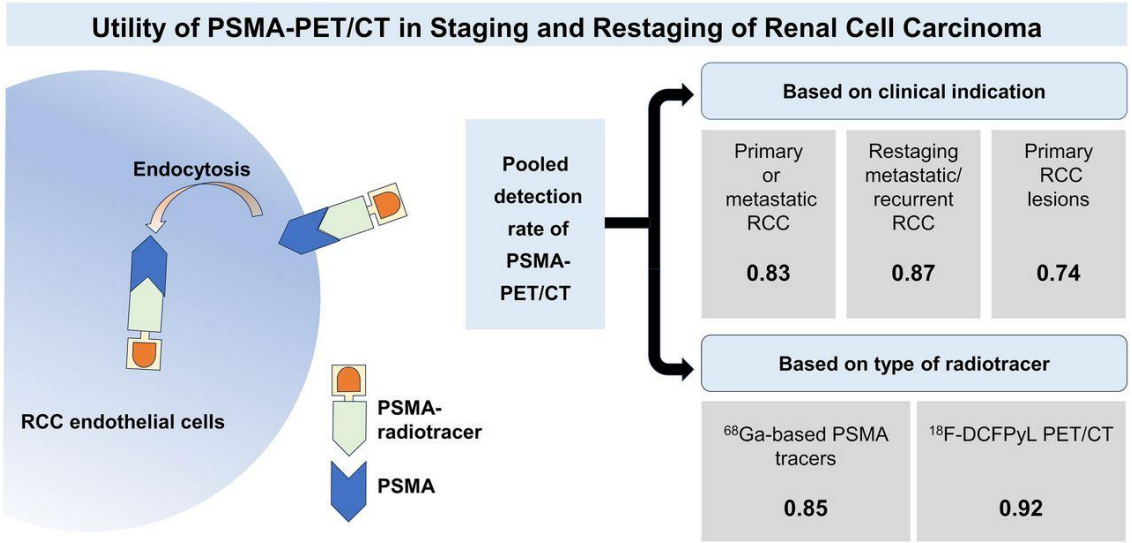
JNM The Journal of NUCLEAR MEDICINE

Utility of PSMA PET/CT in Staging and Restaging of Renal Cell Carcinoma: A Systematic Review and Metaanalysis

Moe S. Sadaghiani, Saradha Baskaran, Michael A. Gorin, Steven P. Rowe, Jean-Claude Provost, Iryna Teslenko, Roman Bilyk, Hong An and Sara Sheikhbahaei

Journal of Nuclear Medicine May 2024, jnumed.124.267417; DOI: https://doi.org/10.2967/jnumed.124.267417





ELSEVIER

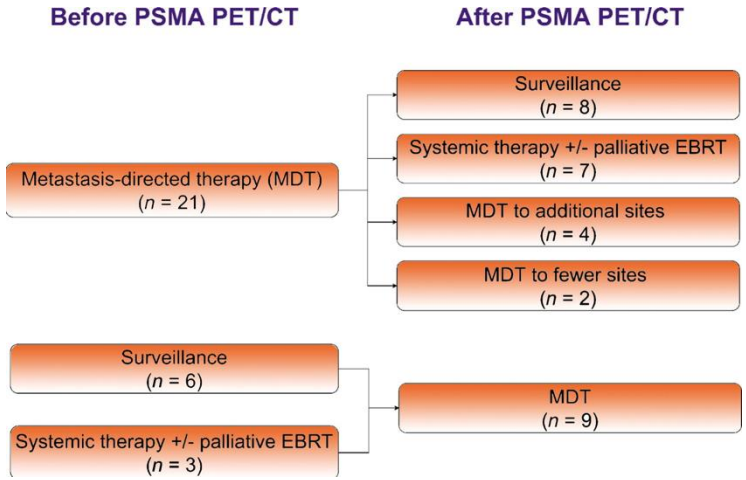
European Association of Urology

Kidney Cancer

Impact of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography in the Management of Oligometastatic Renal Cell Carcinoma

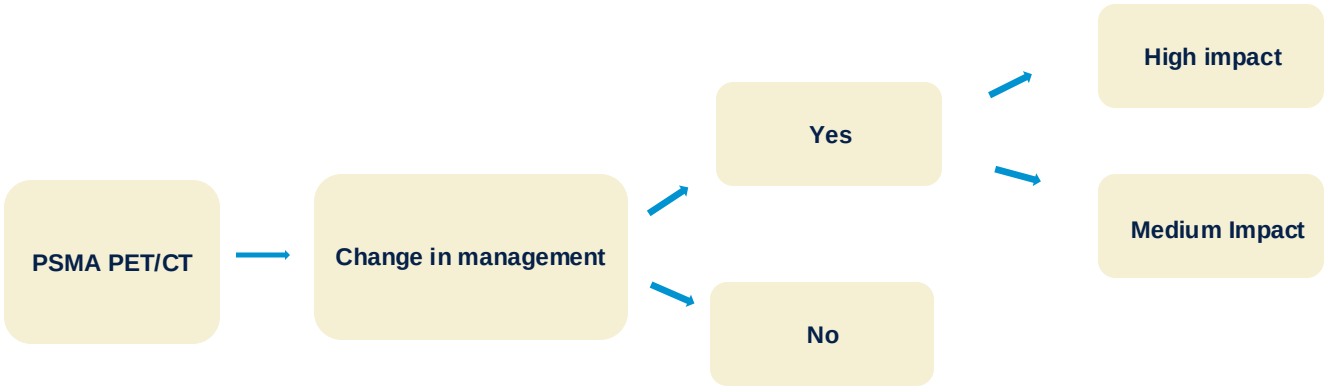
Cristian Udovicich [a,b], Jason Callahan [c], Mathias Bressel [d], Wee Loon Ong [a,e,f], Marlon Perera [g,h], Ben Tran [b,i], Arun Azad [b,i,j], Shankar Haran [a], Daniel Moon [k,l], Sarat Chander [a,m], Mark Shaw [a], Renu Eapen [l,n], Jeremy Goad [l,o,p], Nathan Lawrentschuk [l,q,r], Declan G. Murphy [l], Michael Hofman [b,c], Shankar Siva [a,b,]*

N=61	
Histology	Clear cell= 54 (89%)
	Non-Clear cell= 7 (11%)
PSMA positive	Yes 51 (84%)
	No 10 (16%)
No of PSMA positive mets	
0	10 (16%)
1	20 (33%)
2-3	18 (30%)
>3	13 (21%)



Impact on management

Impact	Description
High	Change in treatment intent, modality, treatment site
Medium	Change in treatment method but not intent, modality or site
Low	No change in treatment intent, method, modality or site



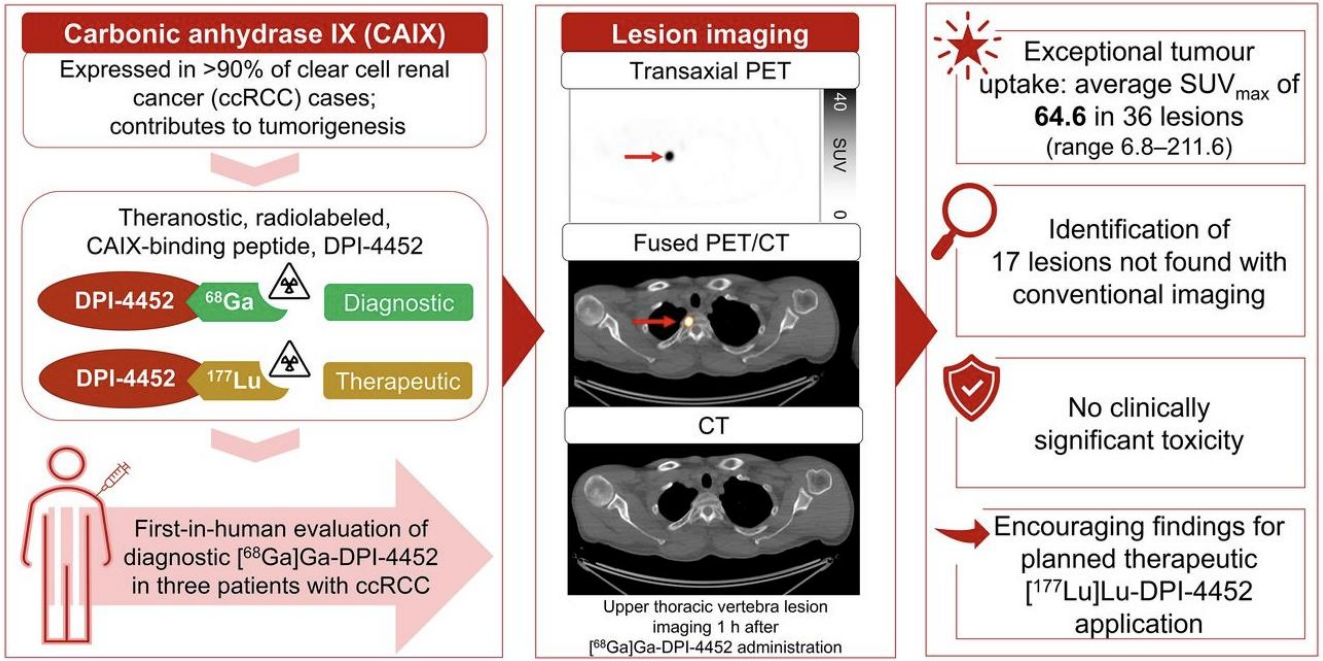
Arpita Desai/UCSF
@ADESAIONCMD
Udovicich *et al* 2022

PSMA in RCC

- Advantages
  - High sensitivity for clear cell RCC
  - Guide treatment options
  - Detect metastatic disease
- Disadvantages:
  - Not good for renal primary
  - Higher cost

Arpita Desai/UCSF
@ADESAIONCMD

DPI-4452 with ^{68}Ga



Arpita Desai/UCSF
@ADESAIONCMD

Hofman *et al* 2024

Functional imaging trials

Author, Year	Type/No.	Tracer	Molecular Target	Clinical Setting	Main Findings
Civan et al[46]	R/20	^{68}Ga-FAPI	FAP	Staging systemic disease	• Higher median tumor-to-background ratio for ^{68}Ga-FAPI-PET/CT compared with FDG-PET
Aggarwal et al[32]	P/37	^{68}Ga-PSMA	PSMA	Staging systemic disease	• Better in detecting marrow and equivocal bone lesions and worse in detecting liver lesions compared with CECT • Detected more lesions and showed significantly higher SUVmax than ^{18}F-FDG PET
Basile et al[16]	MA/489	^{99m}Tc-sestamibi	Uptake by cellular mitochondria	Oncocytoma and HOCT	• Pooled sensitivity and specificity of 89% oncocytoma and HOCT • Pooled sensitivity and specificity of 89% in differentiating pRCC and ccRCC from oncocytoma and HOCT
Shuch et al[13]	P/300	^{89}Zr-DFO-girentuximab	CAIX	Primary ccRCC	• Sensitivity 85% • Specificity 90%
Rizzo et al[31]	SR/331	^{68}Ga-PSMA ^{18}F-PSMA ^{18}F-DCFPyL	PSMA	Staging systemic disease	• Promising in detecting ccRCC lesions and discriminating the presence of aggressive phenotypes
Udovicich et al[35]	R/51	^{68}Ga-PSMA ^{18}F-DCFPyL	PSMA	Staging systemic disease and impact on management	• PSMA PET/CT detected additional metastases compared with CT in 25% of patients • Change in the treatment plan in 49% of patients, with the majority having a high impact
Mittlmeier et al[40]	P/11	^{18}F-PSMA	PSMA	Response assessment after systemic treatment	• Three CRs_{PET} and three PRs_{PET} compared with one PR on CT
Gao et al[23]	R/36	^{68}Ga-PSMA	PSMA	Primary ccRCC	• PSMA PET/CT can identify aggressive pathologic features of ccRCC
Verhoeff et al[33]	P/42	^{89}Zr-DFO-girentuximab	CAIX	Staging systemic disease	• Combined ^{89}Zr-DFO-girentuximab-PET/CT and CT detected more lesions than CT alone (91% *v* 56%) and more than CT and FDG-PET/CT combined (84%)
Siva et al[43]	R/7	^{68}Ga-PSMA	PSMA	Response assessment after SABR	• Demonstrate response earlier than morphological appearances on CT or MRI imaging
Divgi et al[14]	P/194	^{124}I-girentuximab	CAIX	Primary ccRCC	• Sensitivity 86.2% • Specificity 85.9%

Abbreviations: CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; CECT, contrast-enhanced computed tomography; CR, complete response; CT, computed tomography; DCFPyL, piflufolastat; FAP, fibroblast activation protein; FAPI, fibroblast activation protein inhibitor; FDG, fluorodeoxyglucose; HOCT, hybrid oncocytomic/chromophobe tumors; MA, meta-analysis; MRI, magnetic resonance imaging; P, prospective; PET, positron emission tomography; PR, partial response; pRCC, papillary renal cell carcinoma; PSMA, prostate-specific membranous antigen; R, retrospective; SABR, stereotactic body radiotherapy; SR, systematic review; SUVmax, maximum standardized uptake value.

Ali *et al* 2024

Take away points:

Functional imaging with PET is not yet standard of care

- Localized disease: Sestamibi, Girentuximab
- Advanced disease: PSMA, PET scan

Arpita Desai/UCSF
@ADESAIONCMD

UCSF Helen Diller Family Comprehensive Cancer Center