

Future imaging for RCC

Renal cell carcinoma

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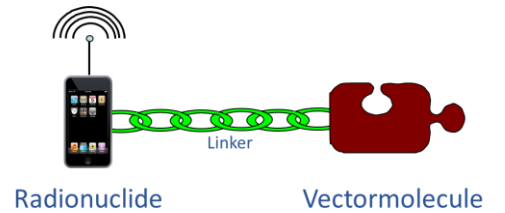
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Why do we need new imaging tools in RCC?

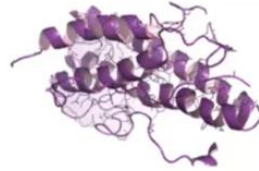
- Current standard imaging with CE CT and MRI provide structural information
- Limitations of CT/MRI
 - Difficult to distinguish benign/malignant masses
 - Not always accurate in subtype identification or in detection of small metastases
 - Limited insight into molecular/functional characteristics of lesions
- FDG PET in RCC
 - Measures increased glucose metabolism
 - Limited role in primary renal lesions due to renal excretion
 - More useful for extra-renal metastases and re-staging, but infrequently used due to lack in sensitivity

Building radiopharmaceuticals for imaging



Antibodies
MW 150 KDa

⁸⁹Zr-pembrolizumab



Peptides
MW 500-5000 Da

[⁶⁸Ga]Ga-DOTATATE



Small Molecules
MW <500 Da

[⁶⁸Ga]Ga-PSMA-11

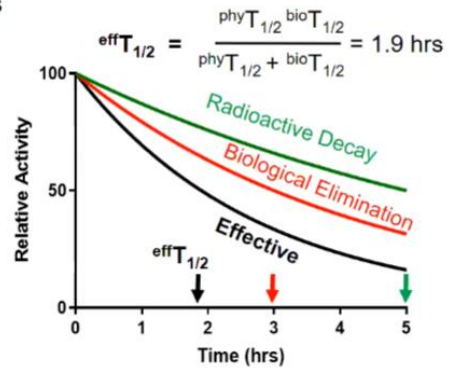
Radionuclide	Half-life	Imaging device
C-11	20.3 min	PET
Ga-68	68.3 min	PET
F-18	109.6 min	PET
Tc-99m	6 h	SPECT
Cu-64	12.7 h	PET
I-123	13 h	SPECT
Zr-89	3 d	PET

Physical (radioactive) Decay

$$\text{phy}T_{1/2} = 5 \text{ hrs}$$

Biological Elimination

$$\text{bio}T_{1/2} = 3 \text{ hrs}$$



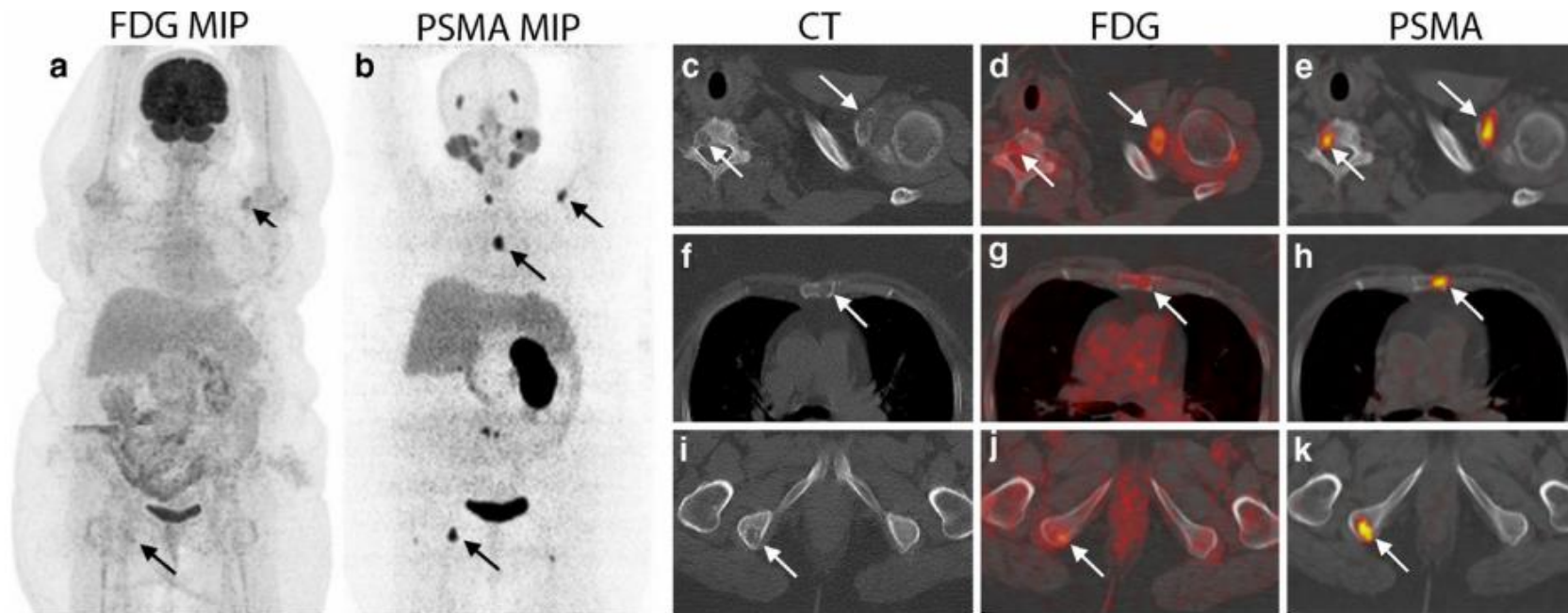
Half-life of diagnostic radiopharmaceuticals usually < 6 h (avoid unnecessary radiation dose)

PSMA

not only for prostate...

PSMA PET in RCC

- Cell surface protein, known for prostate cancer
- Also expressed in neovascularization of various solid tumors, including RCC (especially ccRCC (75-90%) and chromophobe RCC (30%-60%))
- Also expressed in proximal tubules of the kidney



PSMA PET in RCC

- Systematic review
 - Pooled detection rate in evaluation of primary or metastatic RCC 0.83
 - restaging of metastatic or recurrent RCC 0.87
 - staging or evaluation of primary RCC lesions 0.74 (physiologic uptake)

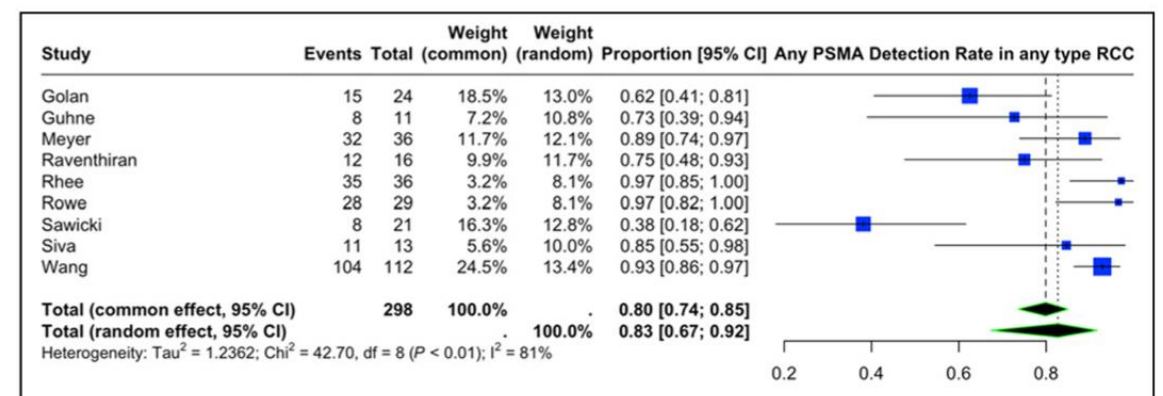


FIGURE 2. Lesion-based detection rate of PSMA PET/CT in staging and restaging of RCC (all included studies).

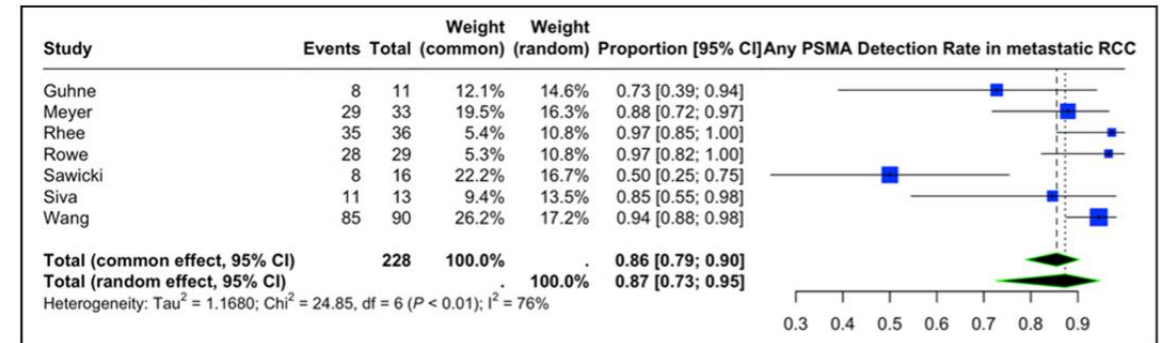


FIGURE 3. Lesion-based detection rate of PSMA PET/CT in restaging of patients with metastatic or recurrent RCC.

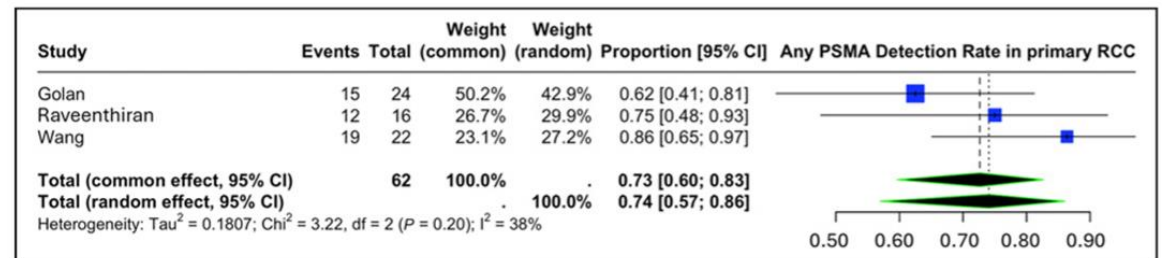


FIGURE 4. Detection rate of PSMA PET/CT in staging or evaluation of primary RCC.

PSMA PET in RCC

- Systematic review
 - Pooled detection rate of [^{18}F]F-DCFPyL PET/CT significantly higher than conventional imaging (0.92 vs 0.63).
 - Lesions detected that were missed on CT/MRI => change in staging and management
- PSMA PET may become a promising alternative imaging modality for evaluating RCC, particularly metastatic ccRCC
 - Large prospective studies warranted to confirm clinical utility in staging and restaging of RCC

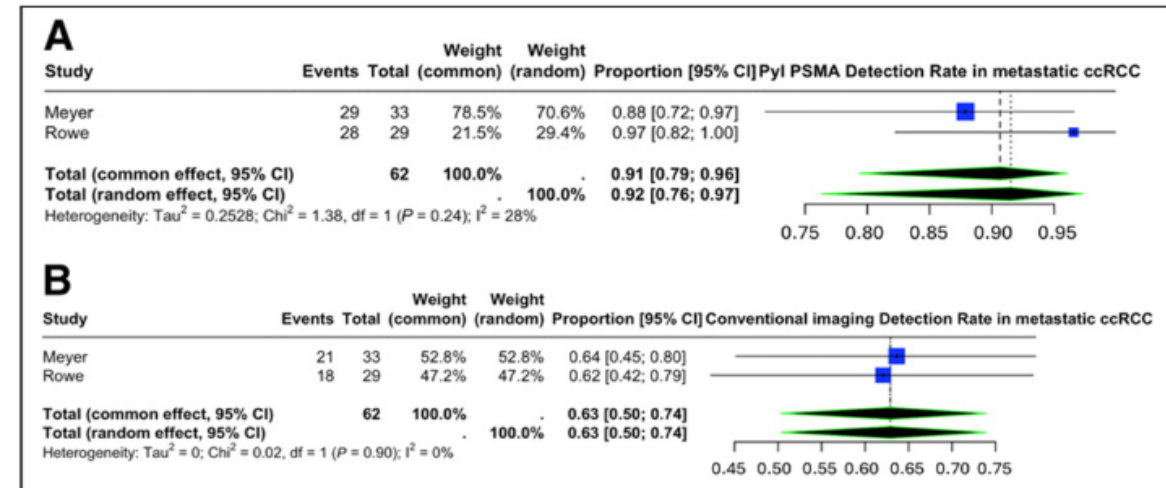


FIGURE 6. Lesion-based detection rate of ^{18}F -DCFPyL PSMA in restaging of metastatic RCC (A), in comparison with conventional imaging modalities (B).

CAIX

Carbonic anhydrase IX (CAIX) in ccRCC

CAIX is a cell surface, transmembrane protein induced by hypoxia^{1,2}

With hypoxia or VHL loss (~90% of ccRCC), CAIX is upregulated

CAIX is minimally expressed in normal tissue

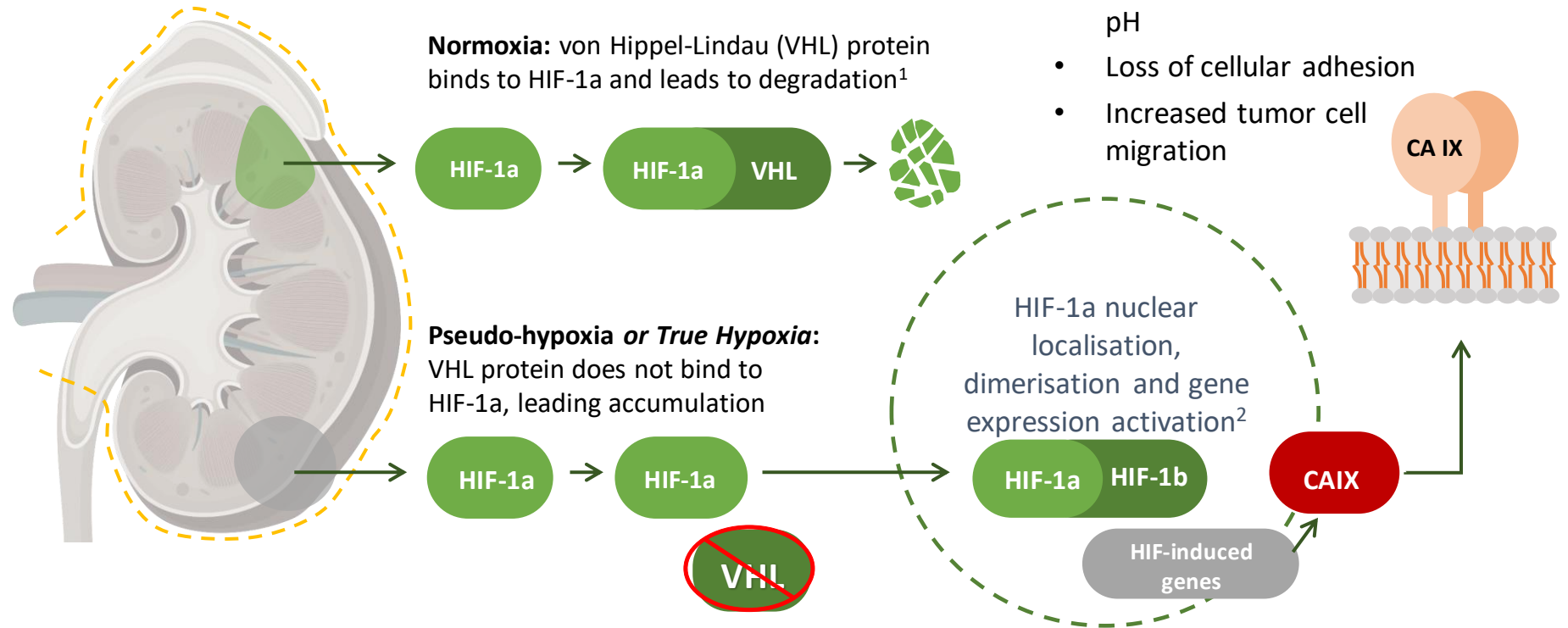


Illustration adapted from Stillebroer et al. 2010.

Abbreviations: CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; VHL, von Hippel-Lindau.

1. Aldera and Govender. *J Clin Pathol.* 2021;74:350-4.
2. Pastorekova and Gillies. *Cancer Metastasis Rev.* 2019;38:65-77.
3. Stillebroer et al. *Eur Urol.* 2010;58:75-83.

CAIX detection with ^{89}Zr -DFO-girentuximab

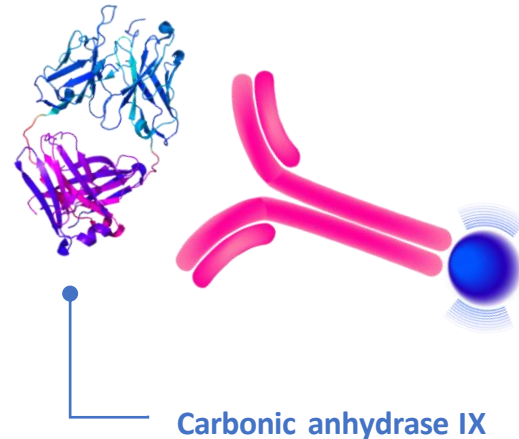
- Antibody-based PET imaging agent targeting CAIX

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

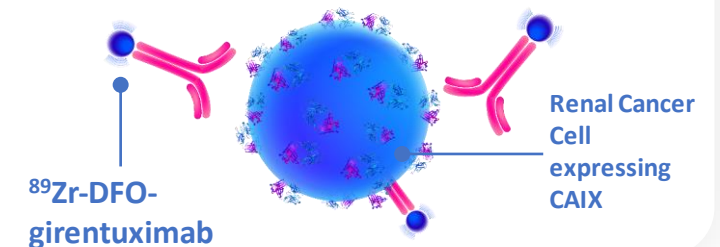
Payload: ^{89}Zr – ^{131}I – ^{124}I – ^{64}Cu

- Positron emitter
- 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 shown safe and allowed PET/CT imaging of ccRCC at 4-7 days after administration³



1. Oosterwijk-Wakka et al. *Int J Mol Sci.* 2013;14(6):11402-23.

2. Kulterer et al. *J Nucl Med.* 2021;62(3):360-5.

3. Merx et al. *Eur J Nucl Med Mol Imaging.* 2021;48(10):3277-85.

CAIX targeting

- 1993 – ^{131}I -mG250
 - 15 patients: 12/12 positive ccRCC lesions, 1/3 non-ccRCC lesions
- REDECT trial – ^{124}I -cG250 (^{124}I -girentuximab)
 - Ph III trial of ^{124}I -girentuximab vs CE CT in 195 patients with renal masses scheduled for surgery
 - primary renal mass ≤ 7 cm in diameter (T1b) in 81% and ≤ 4 cm in diameter (T1a) in 52%

	^{124}I -girentuximab	CE CT
Sensitivity	86.2 %	75.5%
Specificity	85.9 %	46.8 %
PPV	94.4 %	79.6 %
NPV	69.4 %	41.0 %

Detection of ccRCC

- No approval by FDA => confirmatory phase III trial => ZIRCON trial

ZIRCON – study design

Phase 3 clinical trial investigating ^{89}Zr -DFO-girentuximab for PET/CT imaging of ccRCC

Eligibility

Single indeterminate renal mass
 ≤ 7 cm (cT1) in diameter on CT or MRI
suspicious for ccRCC

Scheduled for surgical removal

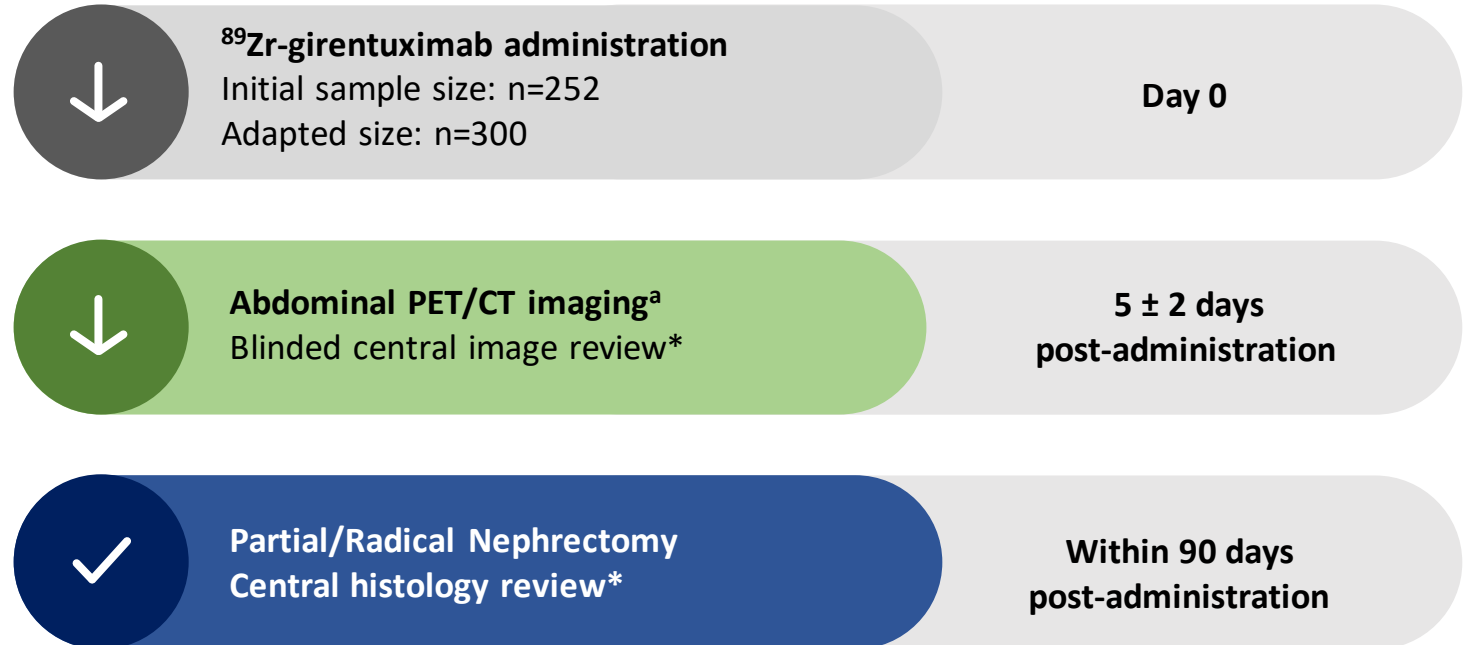
Endpoints

Co-primary endpoints

Sensitivity and specificity of
 ^{89}Zr -DFO-girentuximab PET/CT vs.
central histology (surgical
resection) in detection of ccRCC

Key secondary endpoints

Sensitivity and specificity of
 ^{89}Zr -DFO-girentuximab PET/CT in
cT1a (≤ 4 cm) subgroup



^a PET/CT imaging 20 mins single bed position - may be extended, at the discretion of the investigator, to whole-body imaging

Qualitative visual analysis, using histological results as standard of truth

ZIRCON – patient population

Patients with evaluable histology on surgical samples

Lesion characteristic	Total N = 288
Lesion median size, range (cm)	3.7 (0.9-7.7)
cT1a (≤ 4 cm) lesions, n (%)	179 (62)
cT1b (> 4 -7 cm), n (%)	109 (38)
lesions ≤ 2 cm	39 (13.5) [#]
(# local and ## central reading)	21 (7) ^{##}

Central histology	Total (N = 288)
ccRCC, n (%)	193 (67) 
other renal lesions, n (%)	95 (33)
malignant lesions	
pRCC	44 (15.3)
cRCC	22 (8)
spindle cell	4 (1.4)
sarcoma	2 (<1)
Other (mixed, rare,...)	14 (5)
benign lesions	
oncocytomas	9 (3)

* All patients who received 89Zr-DFO-girentuximab

** All patients with evaluable PET/CT imaging and confirmed histopathology (ccRCC/no ccRCC)

ZIRCON – co-primary endpoints

Sensitivity and specificity thresholds exceeded by all 3 independent readers*

	Reader 1	Reader 2	Reader 3	Overall % (95% CI)
Sensitivity, %	84.1	85.2	87.3	85.5
Lowest bounds, Wilson 95% CI	78.2	79.4	81.8	(79.8, 89.8)
Specificity, %	88.4	88.4	84.2	87.0
Lowest bounds, Wilson 95% CI	80.5	80.5	75.6	(78.8, 92.3)
Positive predictive value**, %	93.5	93.6	91.7	93.0 (88.0, 96.0)
Negative predictive value**, %	73.7	75.0	76.9	75.0 (66.0, 82.0)
Accuracy**, %	85.6	86.3	86.3	86.0 (81.5, 89.6)

* 95% CI had to be > 0.7 for sensitivity and > 0.68 for specificity, for ≥ 2 independent readers to declare the study positive

** Secondary objectives

Abbreviations: CI, confidence interval.

ZIRCON – key secondary endpoints: cT1a lesions

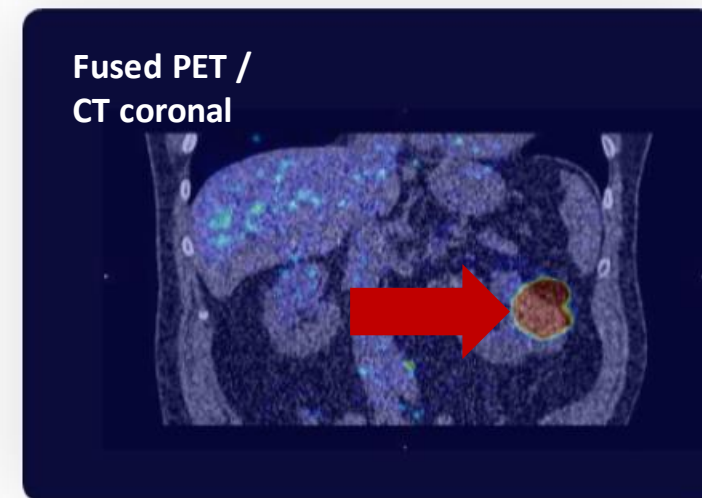
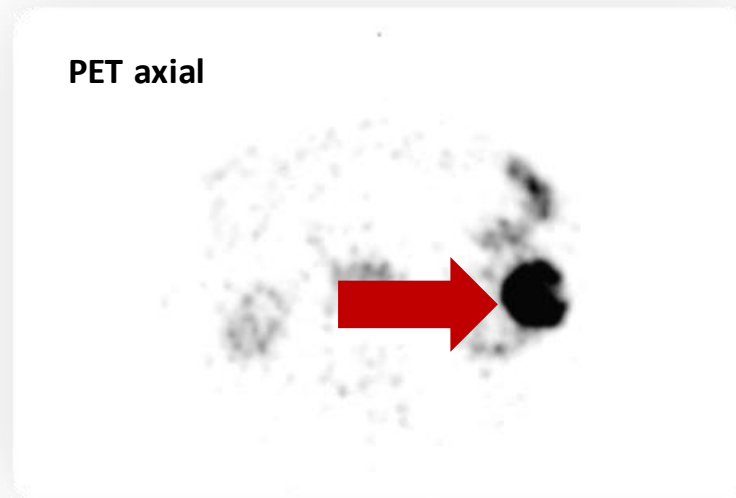
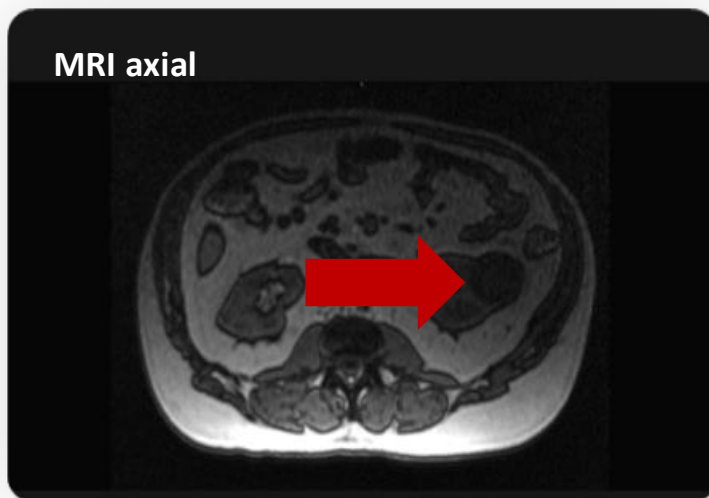
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Lowest bounds, Wilson 95% CI	75.3	77.8	77.8	(77.0, 91.2)
Specificity, %	90.7	90.7	87.0	89.5
Lowest bounds, Wilson 95% CI	80.1	80.1	75.6	(78.6, 95.2)
Positive predictive value, %	94.1	94.2	92.1	93.4 (86.1, 97.0)
Negative predictive value, %	76.6	79.0	78.3	78.0 (66.2, 86.5)
Accuracy, %	86.5	87.8	86.5	87.0 (80.6, 91.4)

Abbreviations: CI, confidence interval

ZIRCON – clinical case of complex cyst

Potential support for clinical decision making



Diagnostic challenge:

- 52 yr male
- 3.1 cm (cT1a) left kidney mass
- ^{89}Zr -girentuximab PET scan clearly positive → ccRCC highly likely

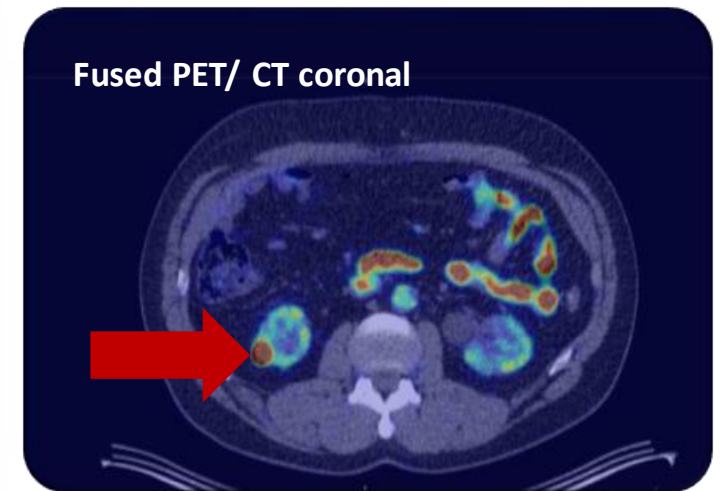
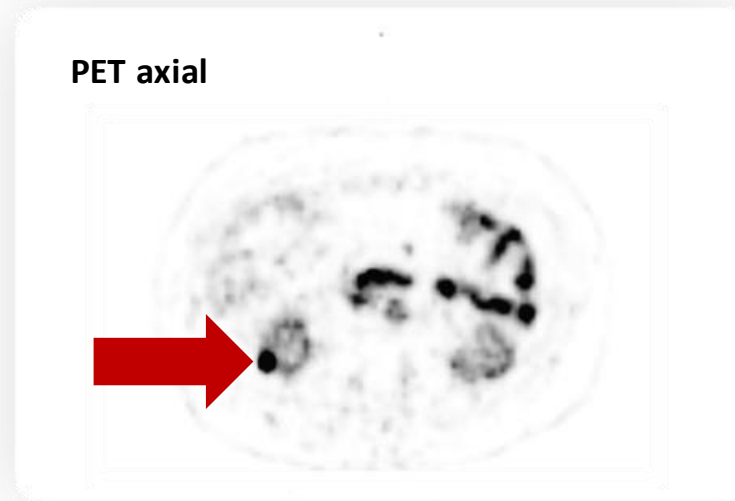
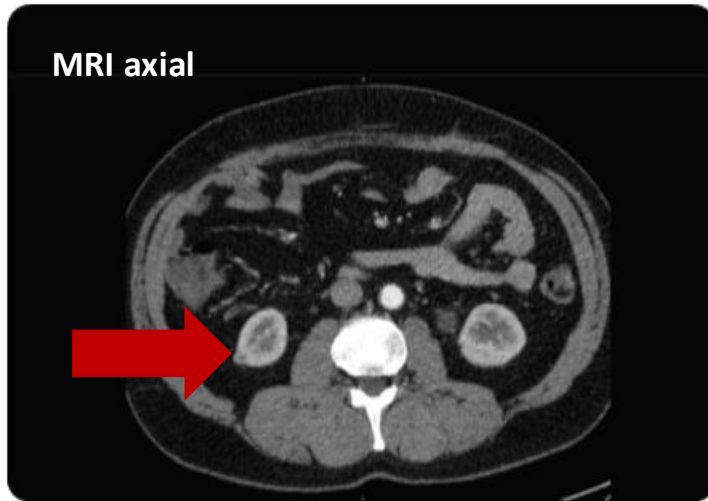


Clinical management:

- Surgery - radical nephrectomy
- ccRCC confirmed by central pathology
- Low/Focal CAIX expression by IHC



ZIRCON – clinical case of 1 cm mass



Diagnostic challenge:

- 57 yr male with 1 cm lesion found incidentally in right kidney
 - Management dilemma – active surveillance?
- ^{89}Zr -DFO-girentuximab PET clearly positive → ccRCC highly likely

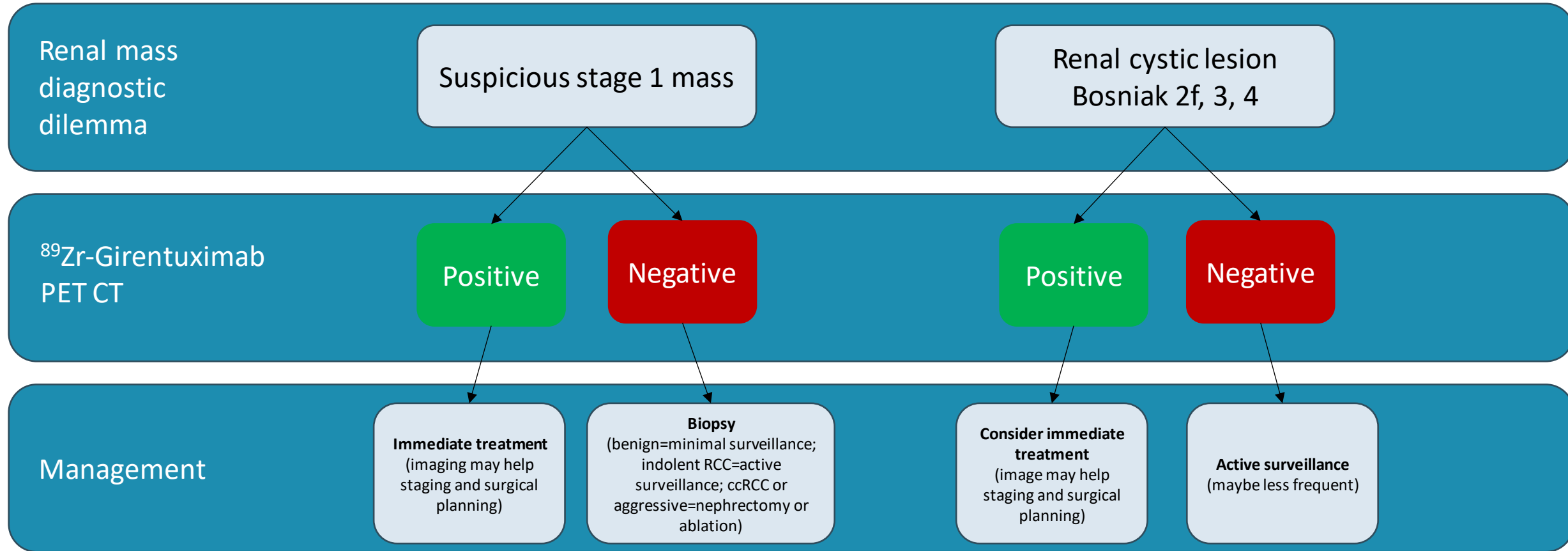


Clinical management:

- Partial nephrectomy
- ccRCC confirmed by central pathology

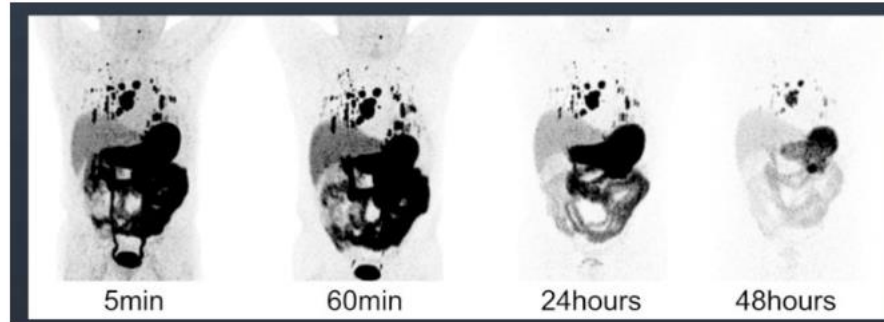


Potential pathways in candidates for treatment



Technical drawbacks of ^{89}Zr -DFO-girentuximab

- Long biological half-life of girentuximab and long physical half-life of zirconium
 - Long delay between injection and scan (4-7 days)
 - Low injected activity with higher radiation burden than typical PET-isotopes
 - Very long PET-acquisition
 - Relatively low image quality on standard PET scanner (LAFOV?)
- Evolution towards other isotopes and adapted antibody
 - [^{68}Ga]Ga-DPI-4452 (Debio 0328) - [^{68}Ga]Ga-NYM046 (NYM005)
 - ^{64}Cu -PD-32766 (Ph 0 data presented at ASCO GU 2025)
 - Scan 2h pi



Other targets

Other targets in RCC

- Receptor tyrosine kinase cMET
- HIF2alpha
- Fibroblast activation protein (FAP)
- Angiogenesis targets
- PD-1/PD-L1
- ...

[⁶⁸Ga]Ga-EMP-100

[¹⁸F]F-PT2385

[⁶⁸Ga]Ga-FAP

[⁸⁹Zr]Zr-bevacizumab

[⁸⁹Zr]Zr-labeled atezolizumab

To conclude...

- PSMA PET may become a promising alternative imaging modality for evaluating RCC, particularly metastatic ccRCC
 - Large prospective studies warranted to confirm clinical utility in staging and restaging of RCC
 - Theranostic approach towards ^{177}Lu -PSMA RLT
- CAIX imaging with [^{89}Zr]Zr-girentuximab PET/CT is a highly accurate, non-invasive imaging modality for detection and characterisation of ccRCC
 - Potential to be practice changing
 - Applications in other clinical scenarios?
 - Alternative CAIX-targeting radiopharmaceuticals to 'escape' zirconium
- Other new targets and radiopharmaceuticals are being explored in early phase clinical trials in RCC

