LMU KLINIKUM
Munich

Measurement problems encountered in TAT clinical practice

Medical Physics

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Measurement problems encountered in TAT clinical practice

Medical Physics

Measuring the patient-specific and daughter-specific pharmacokinetics

Patient-specific dosimetry

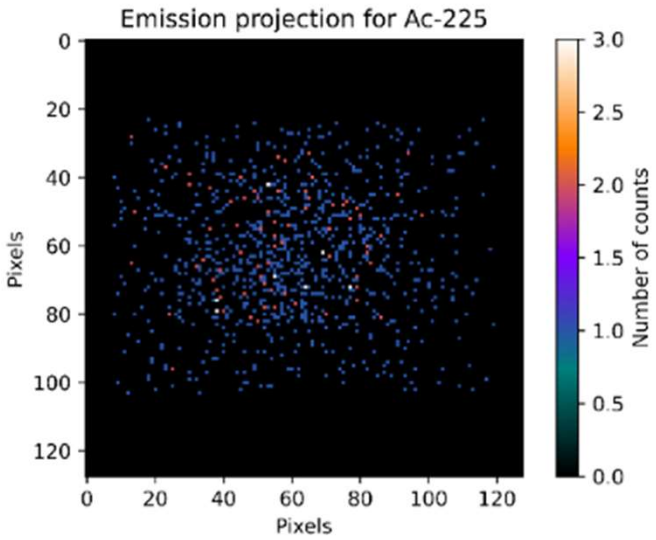
Pharmacokinetics
Imaging

	[^{177}Lu]Lu-PSMA-I&T	[^{225}Ac]Ac-PSMA-I&T	^{225}Ac vs. ^{177}Lu signal SPECT
Therapeutic activity	7.4 GBq	8 MBq	$\approx {}^{1}/_{1000}$
Photon yield	208 keV: 10 % (113 keV: 6 %)	218 keV: 11 % 440 keV: 26 %	$\approx {}^{1}/_{1000}$* $\approx {}^{1}/_{500}$* *compared to ^{177}Lu 208 keV

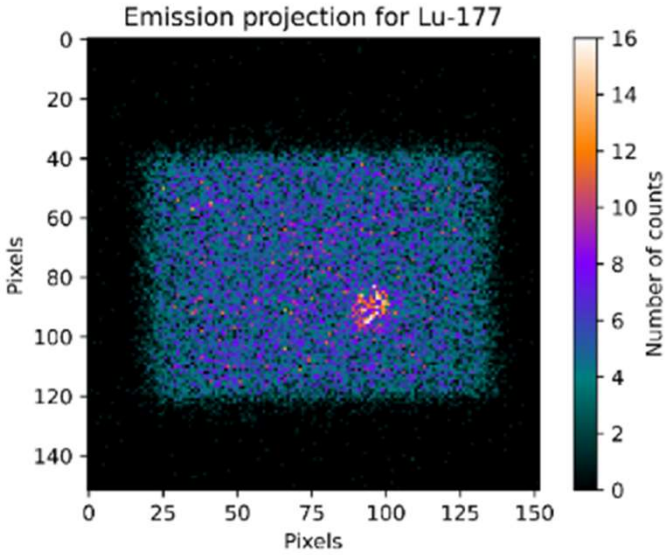
- Direct patient-specific imaging is doable but challenging in clinical routine
- Example for [^{225}Ac]Ac-PSMA:
  - Photon yield comparable to e.g. ^{177}Lu but
  - Low therapeutic activities limit signal strength for Gamma camera imaging
  - 440 keV challenging for a conventional gamma camera system

Pharmacokinetics
Imaging

- Comparison of SPECT projection data for NEMA phantom filled with clinically realistic activities



SPECT projection data
^{225}Ac (440 keV) vs. ^{177}Lu



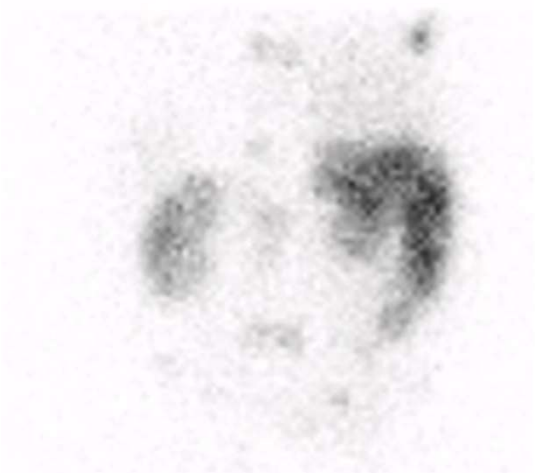
Pharmacokinetics
Imaging

- Comparison of SPECT projection data for combined ^{177}Lu/^{225}Ac-PSMA-I&T treatment (1000 MBq vs. 8 MBq)

^{225}Ac 440 keV (width 20 %)
3.5 minutes p. projection

SPECT projection data
^{225}Ac vs. ^{177}Lu

^{177}Lu 208 keV (width 15 %)
3.5 minutes p. projection



Pharmacokinetics

Current clinical qSPECT/CT protocol @ LMU for ^{225}Ac

- Current clinical qSPECT/CT protocol @ LMU for [^{225}Ac]Ac-PSMA-I&T and ^{225}Ac-PRRT
  - High-energy collimator, 3/8" crystal (Siemens Intevo T16 and Symbia T2 SPECT/CT)
  - 32 projections for 360°
  - 128 x 128 pixels (~4.8 x 4.8 mm²)
  - 210 sec per projection → ~ 1 hour total acquisition time!
  - 440 keV +/- 10 % (+ lower scatter), 218 keV +/- 10 % (+ lower/upper scatter), 78 keV +/- 25 %

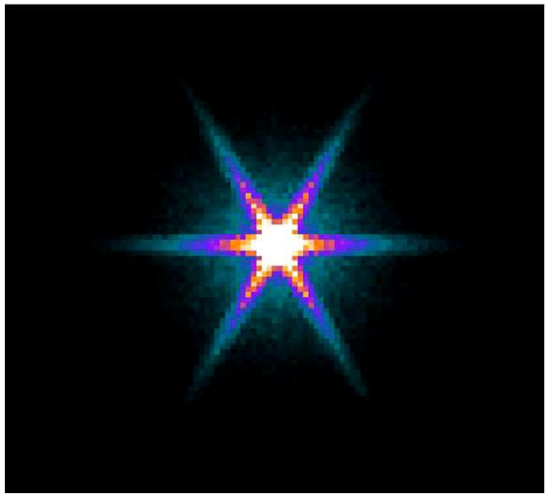
- **Current clinical restrictions**
  - Field-of-view is limited to one bed position only
  - Comfortable patient positioning is cruical
  - Imaging not available for all patients/all therapy cycles
  - Late imaging challenging

Pharmacokinetics

Current clinical qSPECT/CT protocol @ LMU for ^{225}Ac

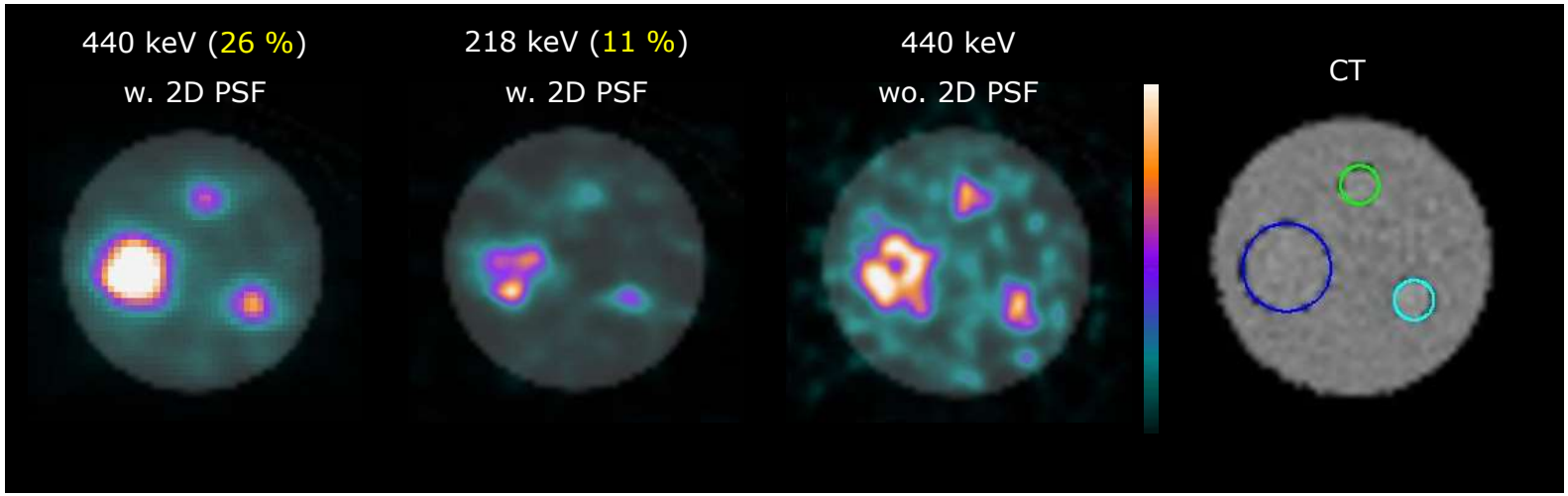
- Quantitative reconstruction
  - In-house MAP-EM (plus additional post-filtering)
  - 2D presimulated (SIMIND) point-spread-function set for resolution modelling (steps of 0.4 cm up to 60 cm distance; 10^{10} primaries for 128x128 pixel)
  - Transmission-dependent scatter correction

2D detector point-spread function
@ 440 keV



Pharmacokinetics

2D resolution modelling for ^{225}Ac qSPECT



- High count measurement: 30-fold higher activity concentration than expected in clinical routine (200 Bq/ml 72 h p.i. OAR)
- → total activity of approx. 2.8 MBq, ratio approx. 6:1

Pharmacokinetics
Measuring scatter for ^{225}Ac

Ann Nucl Med (2008) 22:549–556
DOI 10.1007/s12149-008-0170-z

ORIGINAL ARTICLE

Three-dimensional SPECT reconstruction with transmission-dependent scatter correction

Antti Sohlberg · Hiroshi Watabe · Hidehiro Iida

- Energy-window based scatter correction is likely to add additional noise (more severe for 218 keV)
- → Transmission-dependent scatter correction based on current image estimate (Sohlberg et al., Ann. Nucl. Med. 2008)

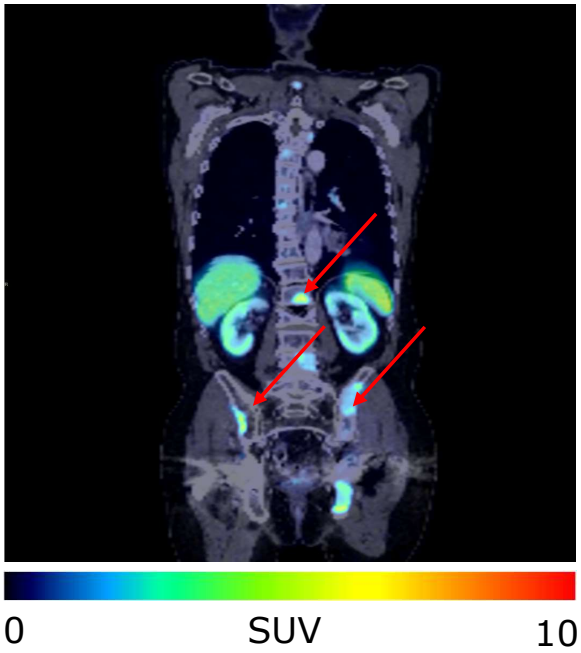
^{225}Ac 440 keV (width 20 %)
3.5 minutes p. projection

^{225}Ac 440 keV **lower scatter** (width 20 %)
3.5 minutes p. projection

Pharmacokinetics

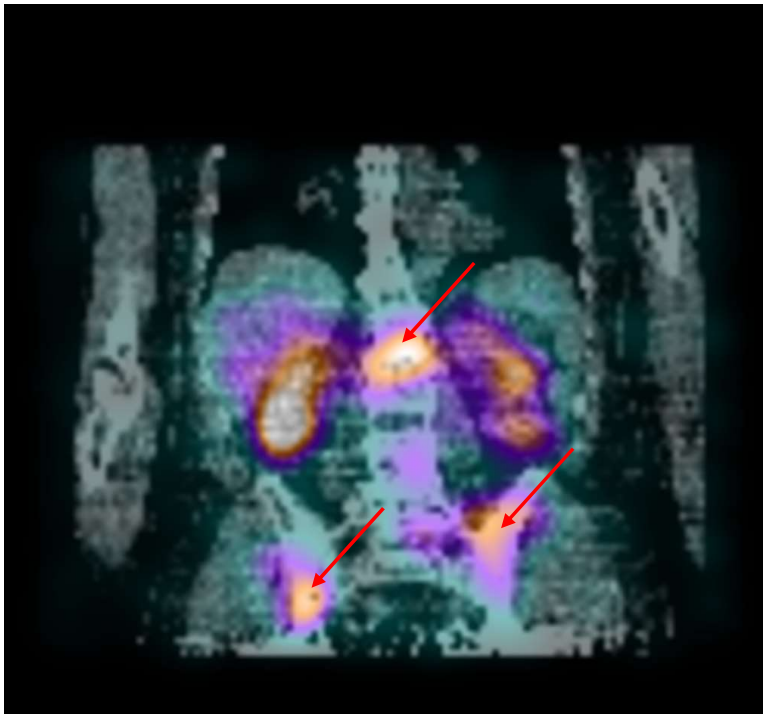
Patient example [^{225}Ac]Ac-PSMA-I&T SPECT/CT @ 24 h p.i. (8 MBq)

Pre-therapeutic PET-CT



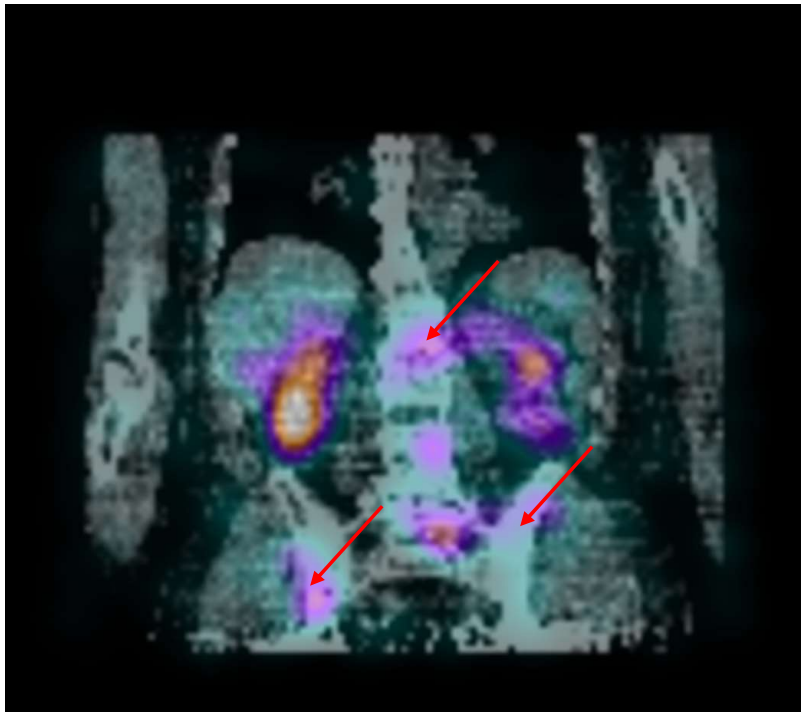
0 SUV 10

218 keV TDSC



0 Bq/ml 500

218 keV TEW

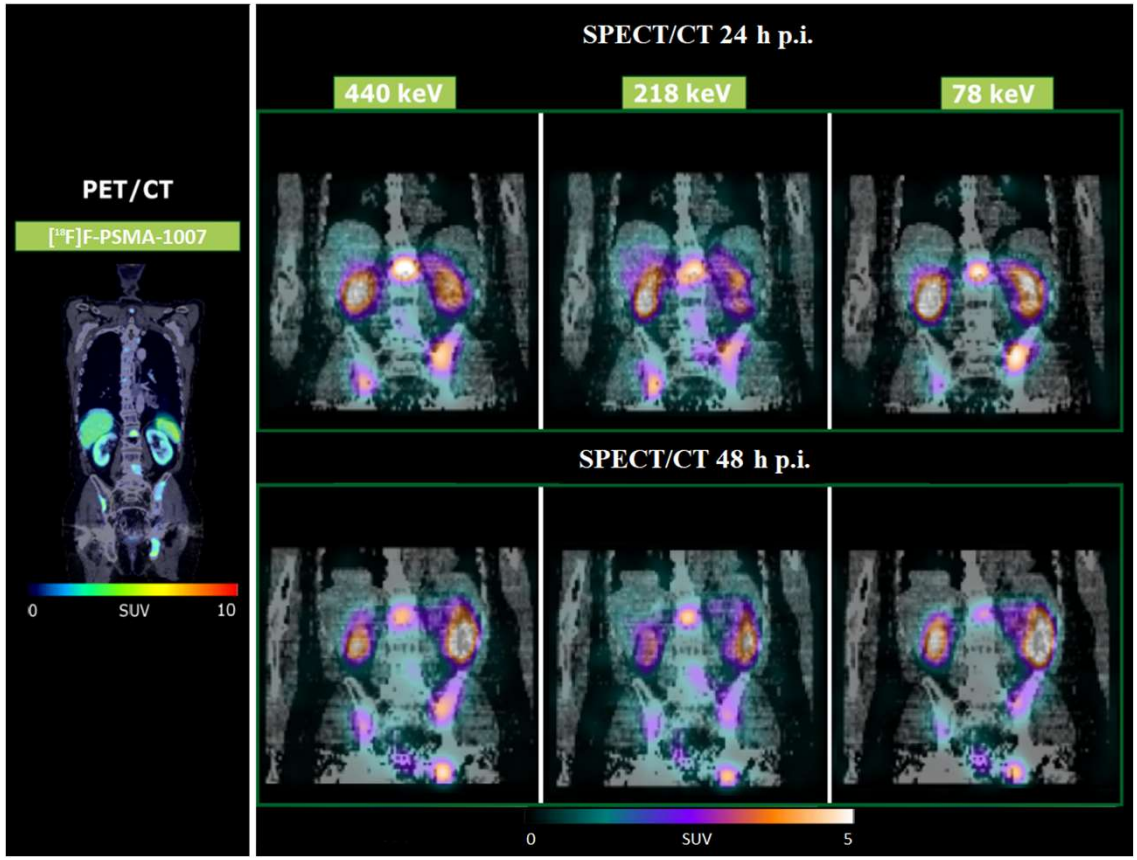


0 Bq/ml 500

Liubchenko et al., EANM 2023

Pharmacokinetics

Patient example [^{225}Ac]Ac-PSMA-I&T SPECT/CT (8 MBq)



Liubchenko et al., under review, EJNMMI

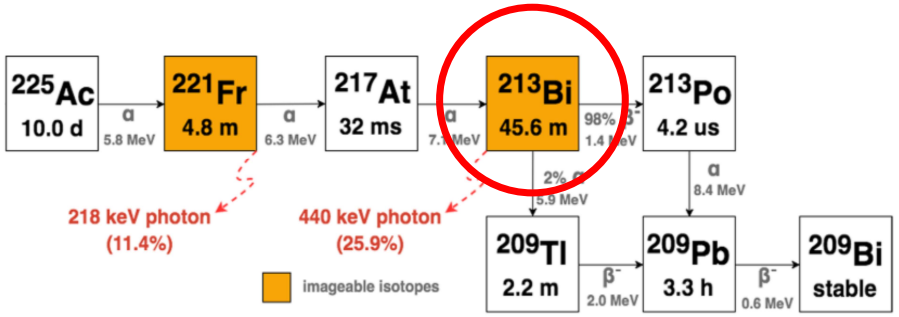
Pharmacokinetics

- Direct patient-specific imaging is doable but challenging in clinical routine)
- Surrogate imaging using theranostic pairs (e.g. [^{177}Lu]Lu-PSMA for [^{225}Ac]Ac-PSMA (Kratochwil et al. 2017), [^{64}Cu]Cu-FAPI-04/[^{225}Ac]Ac-FAPI-04 (Watabe et al. 2020)…)
  - → knowledge about target expression and target vector pharmacokinetics
  - → limited knowledge about daughter-specific pharmacokinetics
- In-vivo sampling (e.g. blood, urine)

Or combinations of both for more efficient and reliable protocols

Pharmacokinetics
Daughters

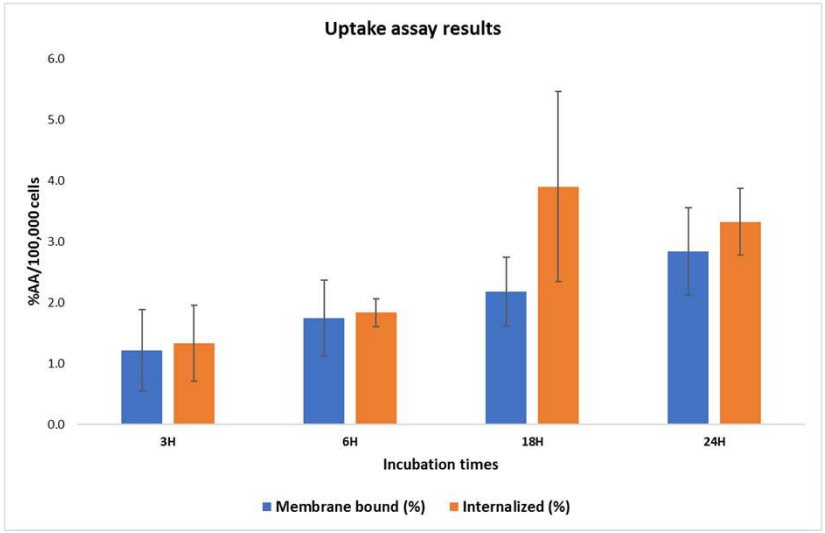
- ^{223}Ra, ^{225}Ac,… → long decay chains with alpha-emitting, long-lived daughters
- Ignoring free daughters can change tumor-to-OAR dosimetry
- Cell internalization is an important parameter



Robertson et al., PMB, 62 (11), 2017

Free ^{213}Bi accumulates in kidneys!

[^{177}Lu]Lu-PSMA-I&T in LNCaP

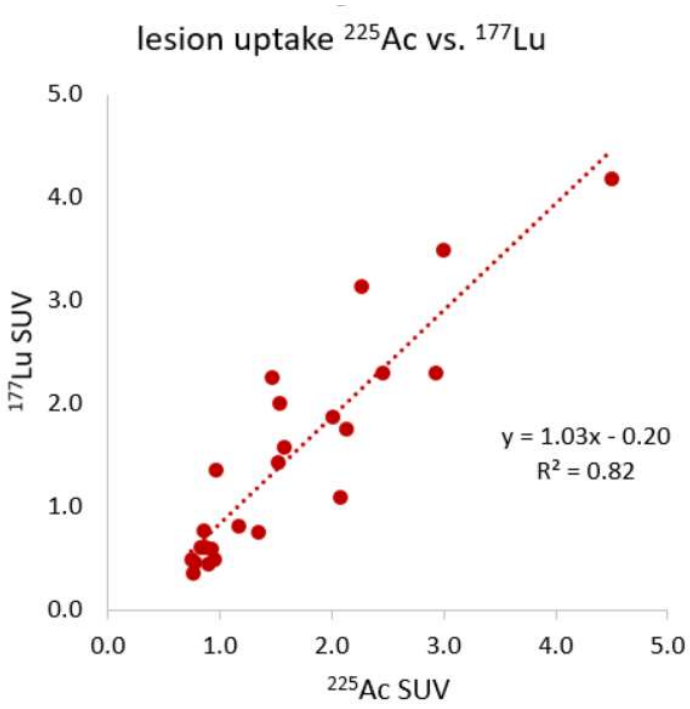


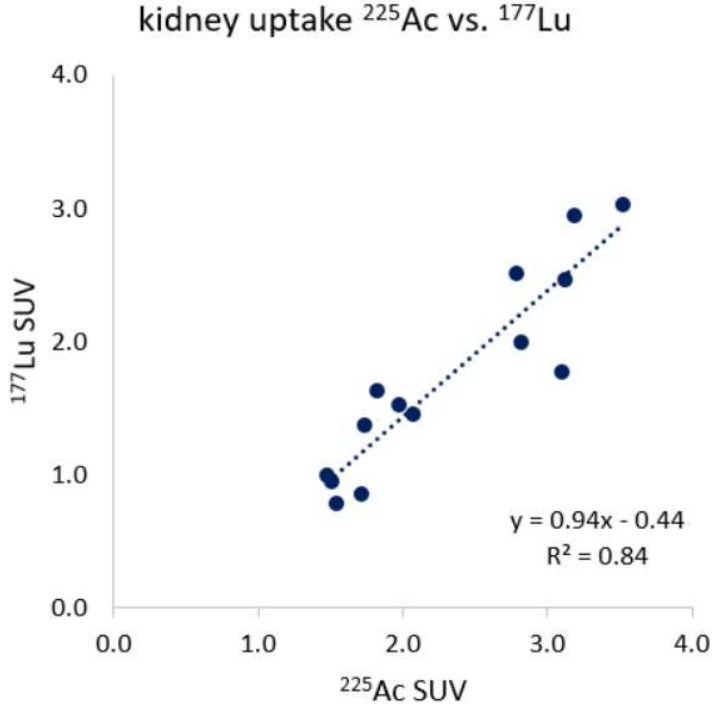
Hawarihewa et al., upcoming German congress (Nuklearmedizin 2024)

Pharmacokinetics

Multi-isotope SPECT for combined ^{177}Lu/^{225}Ac-PSMA therapy

- 7 patients w. SPECT imaging 24 h p. i. 208 keV (^{177}Lu) and 440 keV (^{225}Ac)
- → 14 kidneys and 24 lesions (bone and lymph node metastases)





	^{213}Bi SUV$_{mean}$ (st. dev.)	^{177}Lu SUV$_{mean}$ (st. dev.)
Kidneys	2.3 (0.7)	1.7 (0.8)
lesions	1.6 (0.9)	1.5 (1.1)

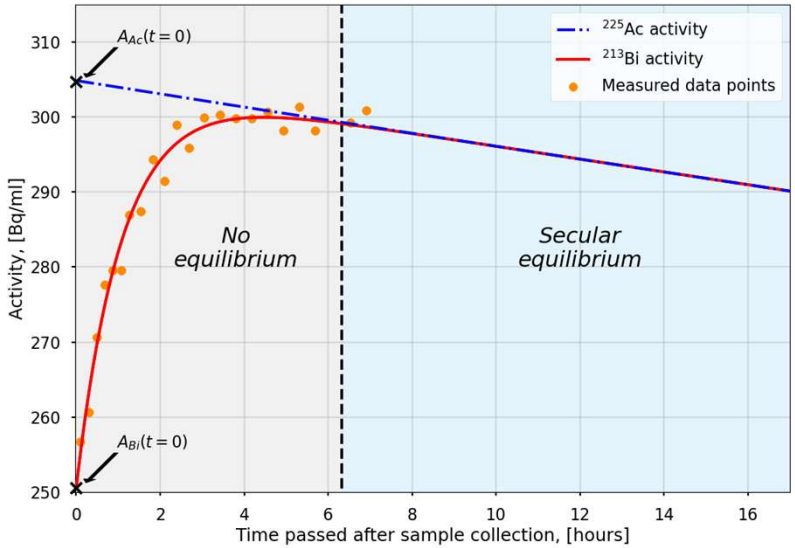
- Strong & significant correlation for both lesions and kidneys ($r>0.9$, $p<0.01$)
- Higher kidney uptake for 440 keV → free ^{213}Bi?

no recovery correction applied & images filtered to match SNR

Delker et al., EJNMMI 2023

Pharmacokinetics
Daughters

- Continuous urine sampling (sample collection along with each SPECT acquisition)



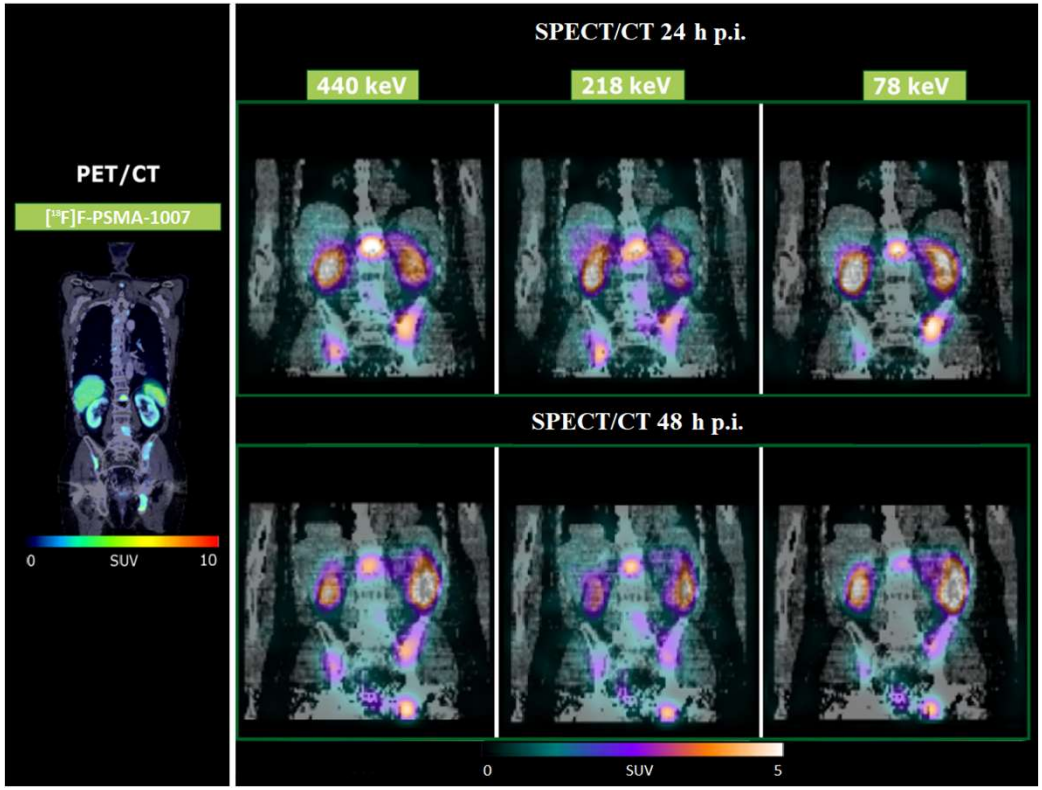
Urine & kidney pharmacokinetics [^{225}Ac]Ac-PSMA-I&T (5 patients)

	% increase from 24 to 48 h p.i.	24 h	48 h
^{213}Bi-to-^{225}Ac ratio urine	10±9	0.98±0.15	1.08±0.09
^{213}Bi-to-^{221}Fr renal ratio SUV_{mean}	9±8	1.08±0.10	1.18±0.10

Liubchenko et al., under review, EJNMMI

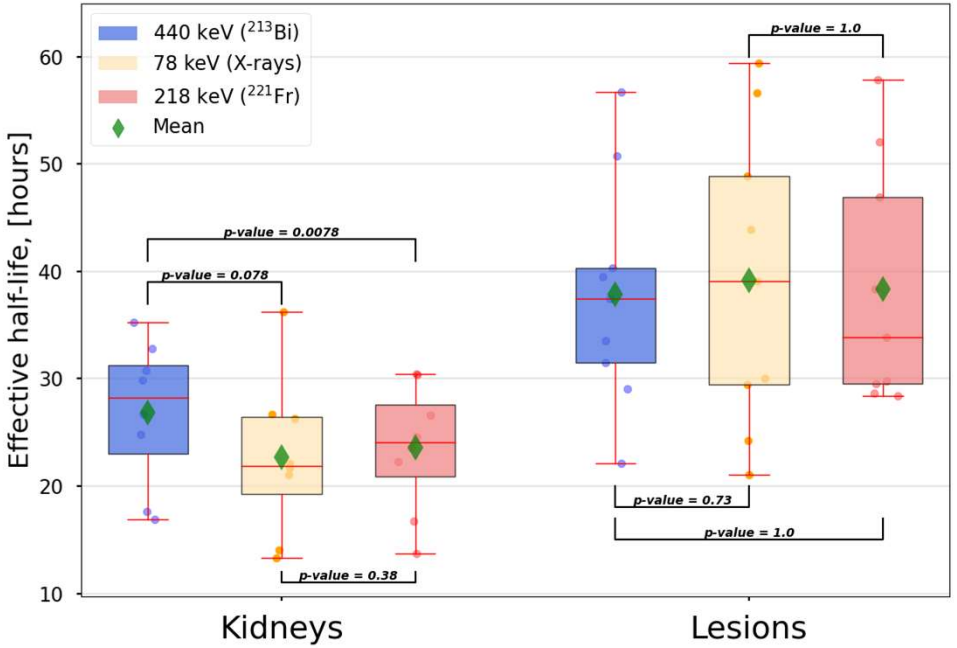
- Patient-specific blood sampling is challenging for 24 h p.i. and later

Pharmacokinetics
Daughters



Liubchenko et al., under review, EJNMMI

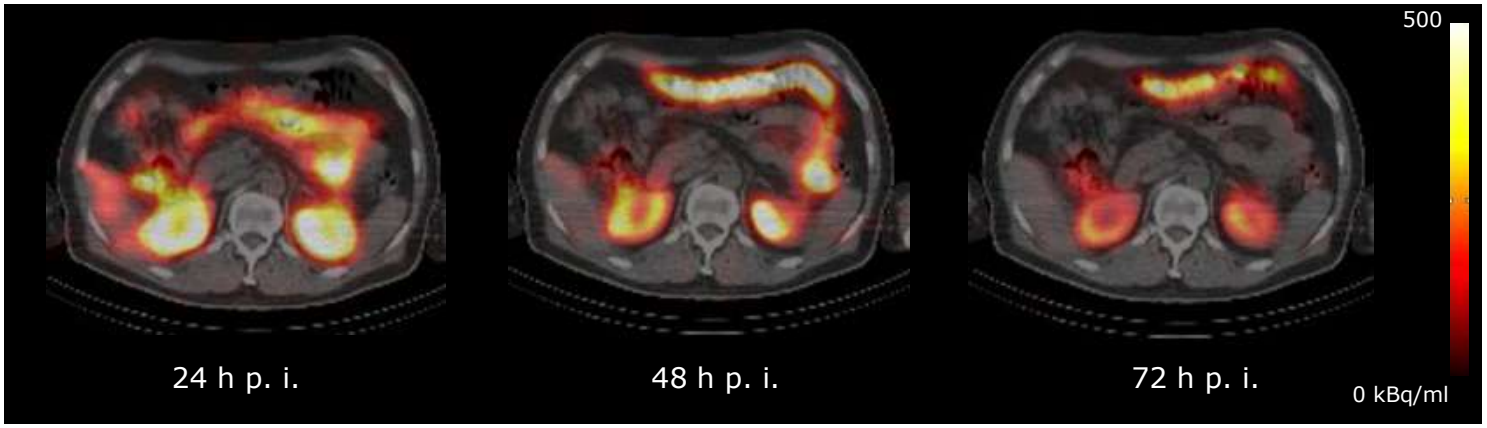
Five patients with [^{225}Ac]Ac-PSMA-I&T (8 MBq) qSPECT @ 24 and 48 h p.i.



- Renal effective half-lives and SUV show significant correlation for ^{213}Bi and ^{221}Fr
- Significantly higher renal effective half-lives for ^{213}Bi

From imaging to patient-specific dosimetry...?

- For alpha emitters, dosimetry requires knowledge of the cellular and subcellular pharmacokinetics
- Problem: clinical imaging devices are limited to a resolution of mm to cm



SPECT-based kidney dosimetry for [^{177}Lu]Lu-PSMA therapy (6 GBq)

$$RBE - weighted\ dose\ [Sv] = Absorbed\ dose\ [Gy] \times RBE$$?

Measurement problems encountered in TAT clinical practice

Medical Physics

Conclusion

- Measurement of the patient-specific and daughter-specific pharmacokinetics is doable, but
  - Long acquisition times → limited field-of-view, no. of time points/patients currently restricted
  - Late imaging particularly difficult for TAT with low activities
  - Reconstruction algorithms need to be adapted for low-count regime and high-energy gammas
  - Surrogate imaging needs careful interpretation for complex decay chains with long-lived daughters

- Clinical imaging limited to a resolution of a few mm up to cm → How to connect macro- and microdosimetry?
- Which RBE (tissue-specific, endpoint-specific,…)?

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