Measurement problems encountered in TAT clinical practice

Medical Physics

Measuring the patient-specific and daughter-specific pharmacokinetics

Patient-specific dosimetry
Pharmacokinetics Imaging

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

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

Photon yield
Pharmacokinetics

Imaging

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

SPECT projection data

$^{225}\text{Ac}$ (440 keV) vs. $^{177}\text{Lu}$
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

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

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

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

- Current clinical qSPECT/CT protocol @ LMU for $^{225}$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 crucial
  - 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 $^{225}\text{Ac}$ 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
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)
Pharmacokinetics

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

Pre-therapeutic PET-CT

218 keV TDSC

218 keV TEW

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Liubchenko et al., EANM 2023
Pharmacokinetics

Patient example $[^{225}\text{Ac}]{\text{Ac}}$-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. $[^{177}\text{Lu}]\text{Lu-PSMA}$ for $[^{225}\text{Ac}]\text{Ac-PSMA}$ (Kratochwil et al. 2017), $[^{64}\text{Cu}]\text{Cu-FAPI-04}/[^{225}\text{Ac}]\text{Ac-FAPI-04}$ (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

Free $^{213}$Bi accumulates in kidneys!

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

$[^{177}$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)

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<thead>
<tr>
<th></th>
<th>$^{213}$Bi</th>
<th>$^{177}$Lu</th>
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<tbody>
<tr>
<td><strong>SUV$_{\text{mean}}$ (st. dev.)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Kidneys</td>
<td>2.3 (0.7)</td>
<td>1.7 (0.8)</td>
</tr>
<tr>
<td>lesions</td>
<td>1.6 (0.9)</td>
<td>1.5 (1.1)</td>
</tr>
</tbody>
</table>

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

![Graphs showing lesion and kidney uptake comparison](image)

*no recovery correction applied & images filtered to match SNR*

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Delker et al., EJNMMI 2023
Pharmacokinetics

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

Dry华echenko et al., under review, EJNMMI

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

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Pharmacokinetics Daughters

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

Significantly higher renal effective half-lives for $^{213}$Bi

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