Abstract
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Modeling absorbed doses to tumors and at-risk organs from a novel PSMA-targeted radioligand labeled with Actinium-225

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BACKGROUND

- Dosimetry estimates for ^{225}Ac-labeled radioligands are impacted by low administered radioactivity and gamma yield, diminishing count rate for SPECT/CT and gamma camera acquisitions.[1] ^{225}Ac imaging is also confounded by radiation emitted by translocated daughter radionuclides[2]
- Absorbed radiation from ^{225}Ac-labeled radioligands can be estimated by dosimetry modeling of similar radioligands labeled with a more easily imaged radionuclide (e.g., ^{177}Lu)[3]

OBJECTIVE: Using data from an ongoing Phase 1/2 study of a novel ^{177}Lu-labeled, PSMA-targeted radioligand (^{177}Lu-rhPSMA-10.1) in men with PSMA-positive mCRPC,[4] we estimated absorbed radiation doses by extrapolating dosimetry estimates from ^{177}Lu-rhPSMA-10.1 to ^{225}Ac-rhPSMA-10.1

METHODS

^{177}Lu-rhPSMA-10.1 imaging
- Up to 3 cycles at 6-wk intervals (5.5–7.4 GBq; IV bolus)
- 4 SPECT/CT scans (at 3, 24, 48, and 168 h post-^{177}Lu-rhPSMA-10.1 administration)

^{177}Lu-rhPSMA-10.1 dosimetry in patients with mCRPC
- True TAC generated from 4 SPECT/CT scans
- Cumulative activities for tumors and normal (at-risk) organs
  - *Anatomy (CT), and activity (PET) contouring methods in tumors (different methods also included different tumor selection criteria)*
  - *Anatomy (CT) contouring in normal organs*
- Modeling of differences in physical half-lives of ^{225}Ac and ^{177}Lu

^{225}Ac dosimetry model estimates for tumors and normal organs

Manual mono-exponential model
- Alternative TAC at 3–24 and 24–168 h post dose, with 720 h cutoff
- Adjusted for physical half-life differences ^{225}Ac versus ^{177}Lu (not biological uptake/washout differences)
- Cumulative TIA (MBq*h) used to calculate absorbed dose if manual/theoretical models disagreed by ≤ 20%

Theoretical model[5]
- Plotted curve and integrated per LabPlot 2[6] fitting function
- 720 h cutoff
- For validation of manual model

Absorbed dose calculated for all organs and tissues using a derived S-value for ^{225}Ac for a 1 g sphere,[7] assuming a biological effectiveness factor of 5 for ^{225}Ac

RESULTS

Patient characteristics

- Data from the first treatment cycle in 13 patients were evaluated
- At screening, patients had a median age of 68 years and a median PSA level of 68 ng/mL
- **Figure 1** shows an example SPECT/CT scan acquired 24 h post-^{177}Lu-rhPSMA-10.1 administration

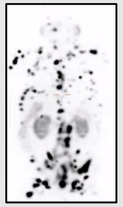


Figure 1. ^{177}Lu-rhPSMA-10.1 SPECT/CT scan (cycle 1) from a patient with a screening PSA level of 17 ng/mL

Absorbed dose estimates: tumor

- Our dosimetry modeling predicted a high absorbed dose to the tumor (**Figure 2**)
  - Absorbed doses were calculated using both anatomy (4.7 Gy_{RBE5}/MBq) and activity (6.6 Gy_{RBE5}/MBq) contouring to determine tumor lesion volume
- Absorbed doses in key dose-limiting organs for RLT were lower than those in similar PSMA-targeted radioligands; a lower tumor:kidney than tumor:salivary gland ratio was predicted for ^{225}Ac, though both were improved versus the values for the ^{177}Lu-labeled molecule (**Figure 3**)

Figure 2. Absorbed tumor dose estimates for ^{225}Ac-rhPSMA-10.1

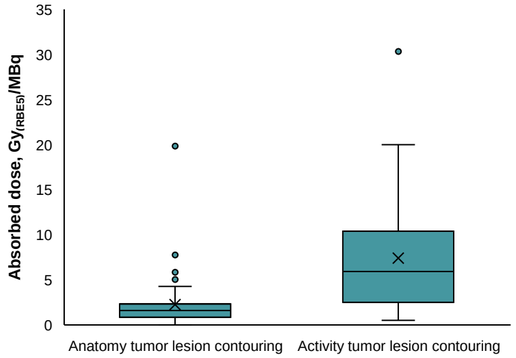
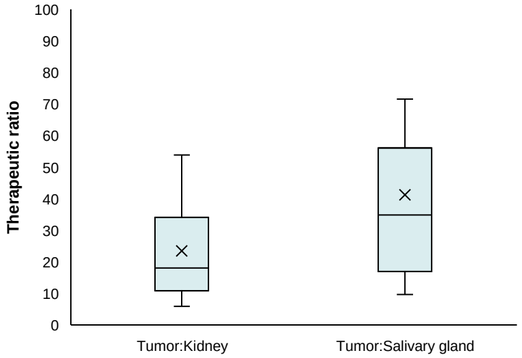


Figure 3. Tumor-to-normal organ ratios for ^{225}Ac-rhPSMA-10.1



Absorbed dose estimates: normal organs and tissues

- Low absorbed doses were predicted in all normal organs and tissues
  - Estimated absorbed doses in key dose-limiting normal organs are shown in **Figure 4**
  - Estimated absorbed doses to additional normal organs and tissues are shown in **Table 1**

Figure 4. Absorbed dose estimates for ^{225}Ac-rhPSMA-10.1 in key dose-limiting normal organs

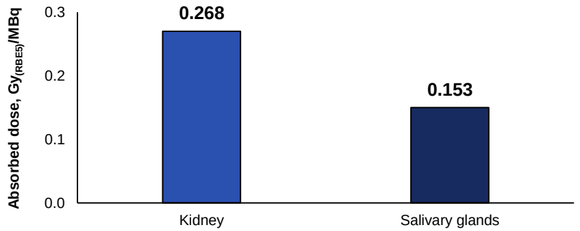


Table 1. Absorbed dose estimates for ^{225}Ac-rhPSMA-10.1 in additional normal organs and tissues

Organ or tissue	Absorbed dose, $Gy_{(RBE5)}$/MBq
Bone marrow	0.016
Brain	0.004
Heart	0.015
Intestines	0.183
Lacrimal glands	0.720
Liver	0.044
Lungs	0.072
Spleen	0.043

CONCLUSIONS

- **The favorable tumor-to-normal organ ratios in our dosimetry estimates of ^{225}Ac-rhPSMA-10.1 demonstrate its potential as a next-generation RLT in mCRPC**
- **Our model factored in all daughter decays but did not account for daughter translocation. The model was further limited by using a relative biological effectiveness factor of 5 to calculate $Gy_{(RBE5)}$/MBq, which has not been validated in clinical studies, to calculate absorbed radiation doses**
- **Further exploration of tumor-to-normal organ ratios of ^{225}Ac-rhPSMA-10.1 in prospective studies, including estimating daughter translocation, is warranted**

ABBREVIATIONS

^{177}Lu, Lutetium-177; **^{225}Ac**, Actinium-225; **CT**, computed tomography; **GBq**, gigabecquerel; **h**, hour; **IV**, intravenous; **MBq**, megabecquerel; **mCRPC**, metastatic castration-resistant prostate cancer; **PET**, positron emission tomography; **PSA**, prostate-specific antigen; **PSMA**, prostate-specific membrane antigen; **RBE5**, relative biological effectiveness factor of 5; **rh**, radiohybrid; **RLT**, radioligand therapy; **SPECT**, single-photon emission tomography; **TAC**, time–activity curve; **TIA**, time-integrated activity; **wk**, week

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