

e-Poster: Tumour Dosimetry - It's a Gray Area: Analysing the Importance of Lesion-Level Dosimetry Methods in ^{177}Lu -PSMA Targeted Therapy

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Aim

With the expanding use of radioligand therapy (RLT), dosimetry is increasingly playing a role as a method for drug pharmacokinetic comparisons and as a potential predictor of efficacy. Large cross-trial dosimetry comparisons would permit more robust analysis, but their validity may be undermined by methodological inconsistencies, particularly in tumour selection and contouring. This work analyses a range of tumour dosimetry methods used across ^{177}Lu -PSMA-targeted RLT studies and evaluates their impact in the context of an ongoing Phase 1/2 study. While great strides have been made establishing standards for the acquisition of dosimetry data, particularly within the context of ^{177}Lu labelled radiopharmaceuticals, standards for contouring and selecting tumours are not yet well-established. The importance of this aspect of dosimetry is rarely discussed or assessed, therefore investigating this is important in assessing fairly the utility of cross-trial dosimetry comparisons.

Materials and Methods

Recent meta-analyses have collated ^{177}Lu -PSMA-targeted RLT dosimetry data from various studies¹. We categorized these studies by lesion dosimetry methods, focusing on lesion selection and contouring approaches. Absorbed dose estimates were compared across categories defined by significant methodological differences. These were methods which used anatomy, termed CT-guided/manual selection and contouring, and methods which used the functional activity imaging, termed activity-guided/threshold-based selection and contouring and finally an "other" category representing any alternative from these two or unknown approaches.

Separately, a phase I experience assessed the impact of dosimetry method on tumour dose estimates. Two approaches were used for tumour selection and delineation. The first was an anatomy-based method; up to 5 tumours were selected "blindly", without knowing the tumour avidity, on CT where no detail on PSMA expression was provided to the reader with contours defined by CT morphology. For the second approach, an activity-based selection and contouring method was used; up to 3 tumours were selected according to their relative uptake on the final SPECT-CT scan, tumour volume was determined using PSMA PET thresholding. The contour defined by PSMA PET thresholding was then transferred to the SPECT-CT scans where marginal adjustments were made to account for the limited spatial resolution of SPECT-CT in order to capture the majority of activity within the volume of interest.

The tumour doses in each of these methods, as well as the differences between the categories identified within the meta-analysis were then all compared to establish the potential impact of these methodologies on reported tumour absorbed doses.

Results

Of 16 dosimetry studies analysed, 5 used threshold-based contouring, 6 employed manual methods and 5 used alternative or unspecified methods. For tumour selection, 5 studies favoured avidity, 5 ignored avidity and 6 did not specify their approach. Whilst unknown methods limit statistical analysis of systematic differences, higher tumour absorbed doses were generated using threshold-based vs manual contouring. Figure 2 shows the estimated tumour specific absorbed dose coefficient in Gy/GBq by article referenced in the meta-analysis, alongside the results from the Phase I ^{177}Lu -rhPSMA-10.1 trial, BET-PSMA-121, with the method category.

In the Phase I dosimetry experience, significant differences were found between methods. The anatomy-based method mean tumour dose was 2.4 Gy/GBq (0.4-6.7) compared to the activity-based method equivalent of 8.9 Gy/GBq (2.0-25.6). This represented a 3.7-fold increase in tumour dose. In a minority of cases, where the same lesion was coincidentally selected for analysis by both methods, this was a 2.6-fold increase. This implies the majority of difference between the two methods was due to the contouring rather than selecting lesions of differing uptake.

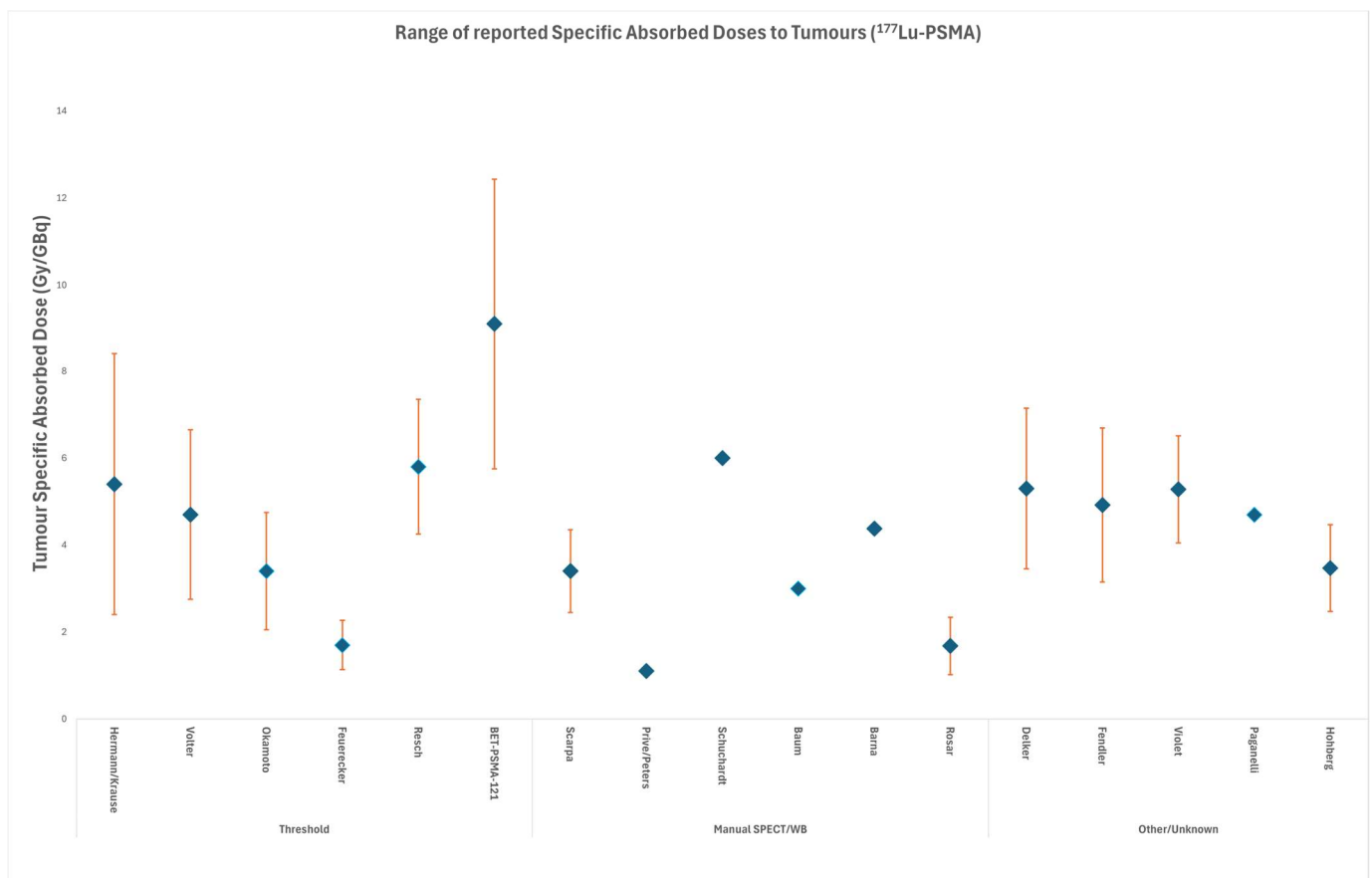


Figure 1: Range of reported specific absorbed doses to tumours (Gy/GBq) by article and contouring method. Error bars represent half a standard deviation.

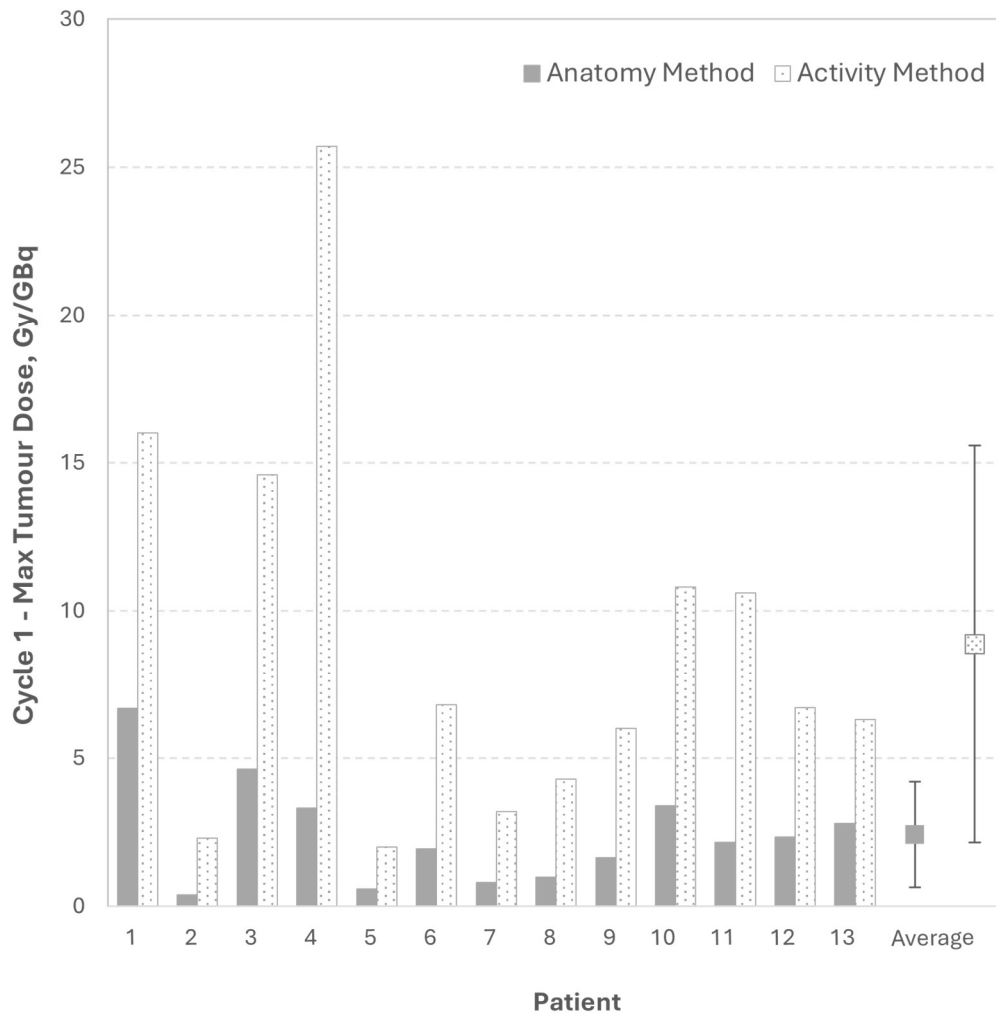


Figure 2: Tumour absorbed dose coefficients by method and patient.

Conclusion

These comparisons demonstrate the wide variance in dosimetry approaches and reporting as well as the significant impact these approaches can have on reported results. Without harmonisation of methods, the utility of dosimetry data, and the establishment of dose response relationships will remain confounded. Given the significant challenges establishing reliable tumour absorbed dose estimates given significant inter-patient biological variation, controlling for method is hugely important. At a minimum, studies employing dosimetry should clearly state their lesion selection and contouring methods to allow for more robust and unbiased comparisons.

References

[1] - Ells Z, Grogan TR, Czernin J, Dahlbom M, Calais J. Dosimetry of [^{177}Lu]Lu-PSMA-Targeted Radiopharmaceutical Therapies in Patients with Prostate Cancer: A Comparative Systematic Review and Metaanalysis. *J Nucl Med*. 2024 Aug 1;65(8):1264-1271. doi: 10.2967/jnumed.124.267452. Erratum in: *J Nucl Med*. 2024 Nov 1;65(11):1819. PMID: 38960712; PMCID: PMC11294071.